ON DESIGN, METHODOLOGY AND ANALYSIS: A RANDOMIZED CONTROLLED TRIAL OF RADIOCONTRAST MEDIA

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ON DESIGN, METHODOLOGY AND ANALYSIS: A RANDOMIZED CONTROLLED TRIAL OF RADIOCONTRAST MEDIA.

A THESIS FOR THE DEGREE OF MASTER OF SCIENCE IN COMMUNITY MEDICINE - CLINICAL EPIDEMIOLOGY.

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ABSTRACT

The preamble to this thesis describes the outline of a randomized trial which was performed to compare the incidence of adverse reactions to ionic high-osmolar and nonionic low-osmolar radiographic contrast media given by intravenous injection or during cardiac catheterization. The objective of the thesis itself is to describe the design, performance and analysis of this trial, while discussing methodologic issues that arose and flaws that occurred. The thesis will explore the consequences of the flaws and will seek to indicate how these might have been avoided or how they may be best dealt with now that they have occurred.

Chapter 1 provides a background description of radiocontrast media, the history of their development, and an explanation of some terms which are used in relation to contrast throughout the text.

Chapter 2 describes the scientific rationale for the study to compare the toxicity of ionic high-osmolar and nonionic contrast media. The literature review which forms the basis of this chapter was performed after the study had been completed. However, it is meant to indicate the sort of review which should precede the design of any substantial scientific research.

Chapter 3 describes the research questions which were posed. This chapter also outlines the relationship between the questions, existing knowledge about the toxicity of contrast

media, and a proposed strategy for the future use of these media.

Chapter 4 deals with the overall design of the trial and discusses the rationale for the choice of study population and interventions.

Chapter 5 is concerned with the processes of randomization and blinding that were employed in the trial. There were several deficiencies in the methods of the trial at this point. These are described, along with their possible consequences. Reference is made to methods which would have been more appropriate.

Chapter 6 discusses the choice of outcomes for the trial. Once again there were flaws in the methods. These are explored in this chapter. The handling of events is also discussed. The analysis and statistical methods used in the trial are discussed in Chapter 7.

Chapter 8 provides a general review of the methods of economic analyses of health programs. The chapter also discusses some existing economic analyses of the use of contrast media and outlines a proposed economic analysis which will use data from the trial described here. Chapter 9 discusses some ethical issues which arose in relation to the current study.

Chapter 10 summarizes the major methodological issues which were considered in the thesis.

PREAMBLE

The objective of this thesis is to discuss methodologic issues which arose during the design, performance and analysis of a study to compare the adverse effects of two classes of radiographic contrast media. The thesis will describe the methods of the trial and will indicate flaws therein. The possible consequences of these flaws will be discussed. The thesis will then outline how these flaws might have been avoided and how their effects can be dealt with after the fact. Reference will be made to methodology which might have been more appropriate.

The study upon which this thesis is based was performed between 1987 and 1991 at the General Hospital, Health Sciences Centre, in St. John's, Newfoundland. The study had the overall goal of establishing whether the nonionic low-osmolar radiographic contrast media were associated with a lower incidence of clinically important adverse events after contrast injection than ionic high-osmolar contrast media.

Since the low-osmolar media are ten times more expensive than the high-osmolar media in Canada, there was also interest in exploring the cost-effectiveness of the low-osmolar media. One question which arose was whether one could limit the increase in expenditure on contrast media in a radiology department by selecting only high risk individuals to receive the low-osmolar media if they were effective in preventing adverse events.

The reports of the results of the study are attached as Appendices A to C, but I will outline the study and it's major findings at this stage in order to orient the reader.

The study was designed as a randomized trial to compare the toxic effects of low-osmolar nonionic and high-osmolar ionic contrast media during cardiac angiography and intravenous injection. All patients having cardiac angiography were eligible for the study. Only those with one or more specified "high risk" characteristics having intravenous contrast were eligible. The study was performed in one hospital over a four year period. The randomization was performed separately in the patients having intracardiac and intravenous contrast.

Patients were excluded from the study if no suitable low-osmolar contrast was available, or at their own request. Furthermore the radiologists and cardiologists performing the imaging tests excluded others, whom they felt would be at excessive risk if given high-osmolar contrast. These patients were all followed in the same fashion as those who were randomized.

Simple randomization was employed and most of the outcomes of the trial were determined by individuals who were blind to the nature of the contrast given. Nevertheless there were flaws in the randomization scheme used and complete blinding was not achieved.

At the start of the study it was intended that the primary outcome would be the occurrence of a systemic reaction which was

severe enough to require therapy. It was intended that those having cardiac angiography and those having intravenous contrast would be combined for analysis of this outcome. The overall sample size estimate was based on this proposed analysis. As the trial progressed it became clear that it would be difficult, and probably unwise, to combine the patients having cardiac angiography with those having intravenous contrast. A separate primary outcome was then proposed for those having cardiac imaging. This was the occurrence of an adverse event (not necessarily systemic) which required therapy. The data upon which this outcome was based had been collected prospectively. The decision as to whether an outcome of this type had occurred was subsequently made by the investigators while blind to the type of contrast received.

As the trial progressed it became apparent that clinically important adverse hemodynamic events were occurring with a high frequency among those having cardiac angiography. This led to the analysis and subsequent termination of that arm of the study, while the intravenous arm continued.

Serial measurement of serum creatinine was employed to diagnose cases of contrast-induced renal failure in those with pre-existing renal impairment. The patients having intracardiac and intravenous contrast were analysed separately and then combined for this outcome. The frequency of significant acute renal failure after both high and low-osmolar contrast was low. The degree of pre-existing renal impairment and the presence of

diabetes were confirmed as risk factors for the development of a deterioration in renal function after contrast. There were insufficient patients in the study to allow definitive statements about the relative nephrotoxicity of the two classes of contrast media.

The findings of the trial indicated that low-osmolar contrast was significantly less likely to cause adverse events which led to therapeutic intervention after either intravenous or intracardiac injection. For those having cardiac angiography the low-osmolar contrast was also associated with a lower frequency of arrythmia requiring therapy and a lower frequency of significant hypotension. A retrospectively defined heterogenous category of prolonged or severe adverse events was also less commonly seen after the intracardiac injection of low-osmolar contrast. Most of the adverse events seen during cardiac angiography were cardiovascular in nature and some of these were severe enough to require a change in the level of care for the patient. The adverse events following intravenous contrast were mainly anaphylactoid in type and none were severe enough to require intensive treatment or hospitalization.

The study indicated that severe coronary disease and unstable angina were the best independent predictors of risk for an adverse event in those having cardiac angiography. A high risk group was identified retrospectively among those having cardiac imaging using these factors together with risk factors for a systemic adverse event. This grouping was then used for a

preliminary economic analysis of the selective use of low-osmolar contrast for cardiac catheterization.

Risk factors identified for the predominantly anaphylactoid adverse events seen in the patients given intravenous contrast included a history of prior adverse reaction to contrast, a history of allergy, and to a lesser degree cardiac disease, severe illness, renal impairment, anxiety, diabetes mellitus and asthma. A preliminary economic analysis of the selective use of low-osmolar contrast in high risk subgroups defined by some of these risk factors was performed.

I became involved in this study during it's design phase. This was soon after commencing my training in Nephrology at the Health Sciences Centre in 1987. I had not received any training in Clinical Epidemiology or in research design at that point. My involvement in this study was one of the factors which stimulated me to pursue training in clinical research methods, which I began in 1989. Dr. Patrick Parfrey was the coordinator of the study and my supervisor throughout this period. Following completion of my training in Nephrology in June 1990, I received a Fellowship from the Kidney Foundation of Canada, during the tenure of which, I played a major role in the analysis and reporting of the trial. Almost all of the data were collected and entered on computer for analysis by a dedicated group of research nurses and assistants without which the study would not have been possible. These personnel included Hilary Vavasour,

Gloria Kent, Jackie McDonald, Donna Hefferton, Frank O'Dea, and Roxanne Corbett.

CHAPTER 1 - INTRODUCTION

Modern radiology is highly dependent on agents known as radiographic contrast media. These compounds contain elements of high atomic weight which impede the passage of x-rays through otherwise radiolucent soft tissues. The contrast media can be given in a number of ways. Oral contrast, which may contain barium as the radiopaque element, can be used to outline the upper two thirds of the gastro-intestinal tract. Contrast media may also be given directly into body fluid compartments (as in myelography, where contrast is injected into the cerebro-spinal fluid), or into blood vessels by bolus injection or infusion. For parenteral use iodine usually serves as the radiopaque element. The iodine is incorporated into a variety of organic chemicals in order to reduce toxicity, improve iodine concentration (and thus diagnostic efficacy), and to provide diagnostic images with functional significance as the contrast is being excreted. An example of the latter use is intravenous pyelography. For this procedure the radiocontrast is injected intravenously and is then concentrated in the kidney producing an image known as a nephrogram. Subsequent excretion of contrast in the urine outlines the urinary collecting system, ureters and bladder.

The intravenous pyelogram (IVP) was one of the first successful examinations performed with intravenous contrast. By 1929 several compounds had been tested in Germany, one of the leading countries in organic chemistry at that time. Since then,

contrast media have been improved by the addition of more iodine atoms per molecule and by alterations in side chains to reduce toxicity. The basic pyridine ring was superseded by the benzene ring as an iodine carrier, and this feature is found in even the most recently developed contrast media. In 1954 sodium diatrizoate was introduced (Fig 1a). Along with its derivatives, iothalamate and metrizoate, this compound served as the standard medium for intravascular use prior to the advent of the low-osmolar media in the 1980's.

One of the problems with sodium diatrizoate and similar media is their very high osmolality in solution. This can be as high as 2200 mOsm/kg, over 7 times that of human extracellular fluid. This results from the requirement to deliver a threshold concentration of iodine to achieve opacification and the tendency of the compound to undergo ionic dissociation in body fluids. The dissociation yields a sodium ion and a diatrizoate ion, both of which contribute equally to the osmolality, even though the sodium does not enhance opacification.

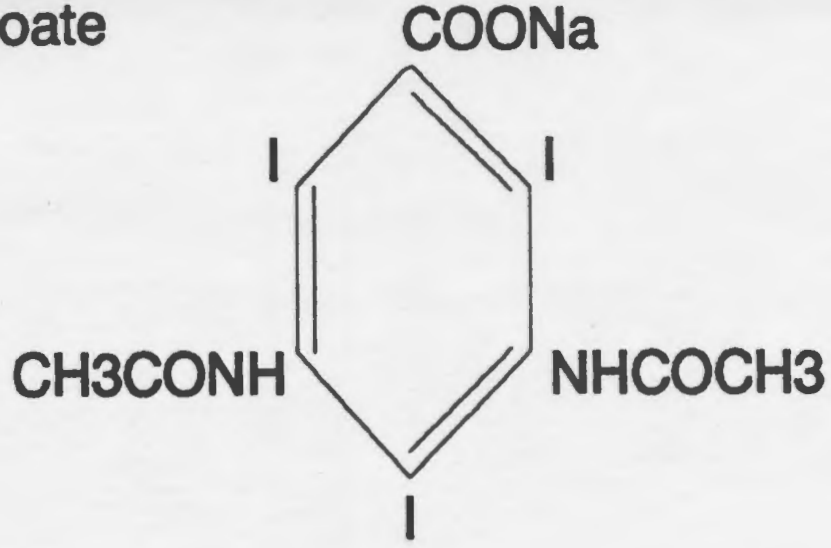
Although sodium diatrizoate is relatively non-toxic it can cause some adverse reactions when injected into humans. It is felt that the toxicity of diatrizoate results from two mechanisms. One is an effect of the hyperosmolality of the solution - so called "osmotoxicity", while the other is an intrinsic effect of the chemical structure and its interaction with body systems - so called "chemotoxicity".

In 1968 Torsten Almen proposed that replacement of the ionizing carboxyl group of diatrizoate by a nonionizing group, such as an amide, would halve the osmolality of the resulting solution without affecting the iodine content. He has recently summarized the development of the resulting low-osmolar media [Almen (1985)]. The high-osmolar media are also known as "ionics" because of their ionization property, and as ratio 1.5 media because there are 1.5 iodine atoms per particle in solution. The newer low-osmolar media have either a nonionic group replacing the carboxyl of diatrizoate (e.g Iopamidol and Iohexol Fig 1b and 1c) or are dimers of tri-iodinated benzoic acid derivatives, such as Ioxaglic acid (Fig 1d). All of these media are ratio 3.0 media and have osmolalities ranging from 600 mOsm/Kg (Ioxaglate) to 709 mOsm/Kg (Iohexol) [King (1989)].

Iohexol, Iopamidol and Ioxaglate were licensed for use by the FDA in the United States at the end of 1985, having been used in Europe for several years. Development continues, and many other compounds, including ratio 6.0 nonionic dimers such as Iotrolan, are undergoing preliminary testing [McClennan (1987)].

FIGURE 1

(a) Sodium diatrizoate



(b) Iopamidol

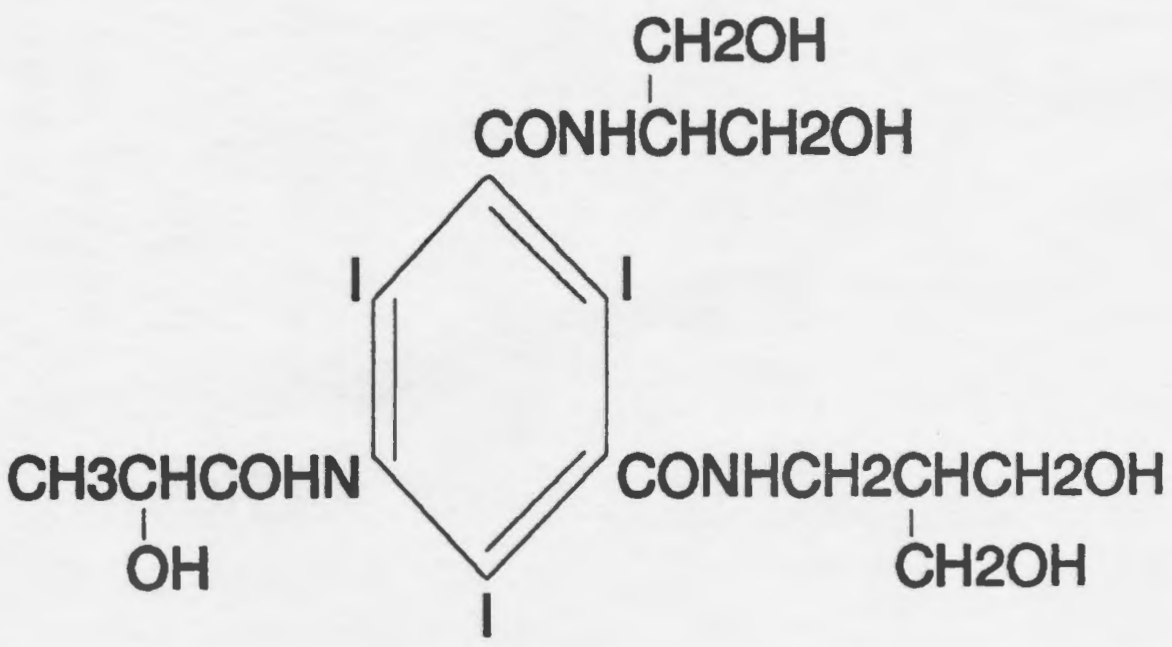
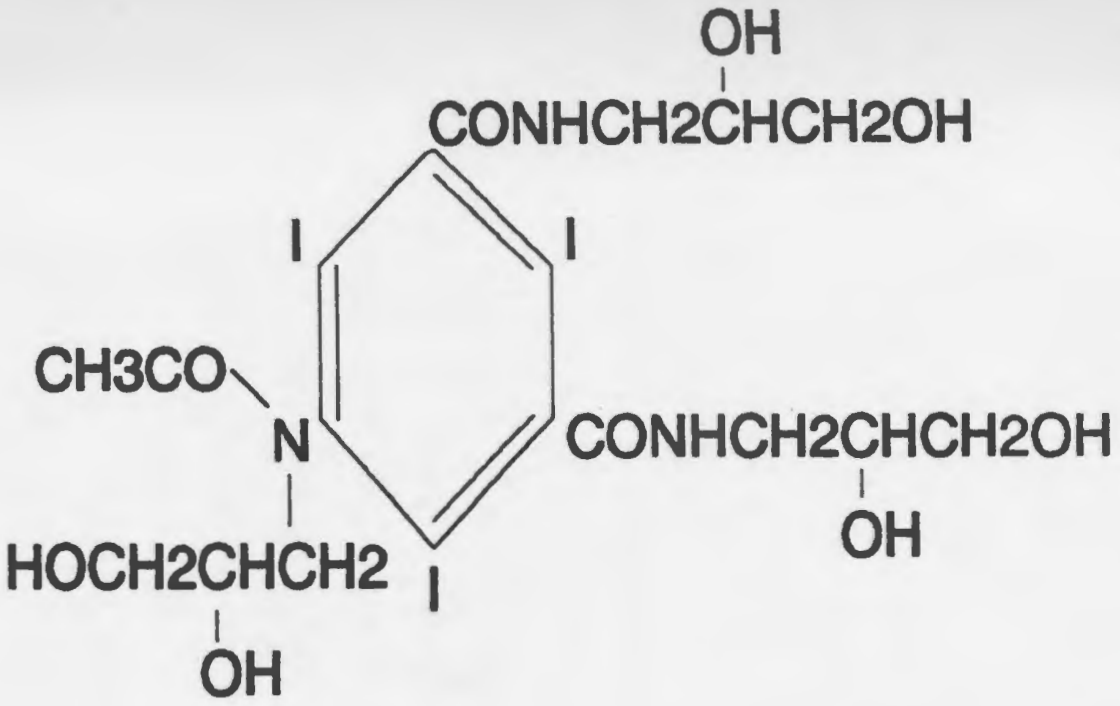
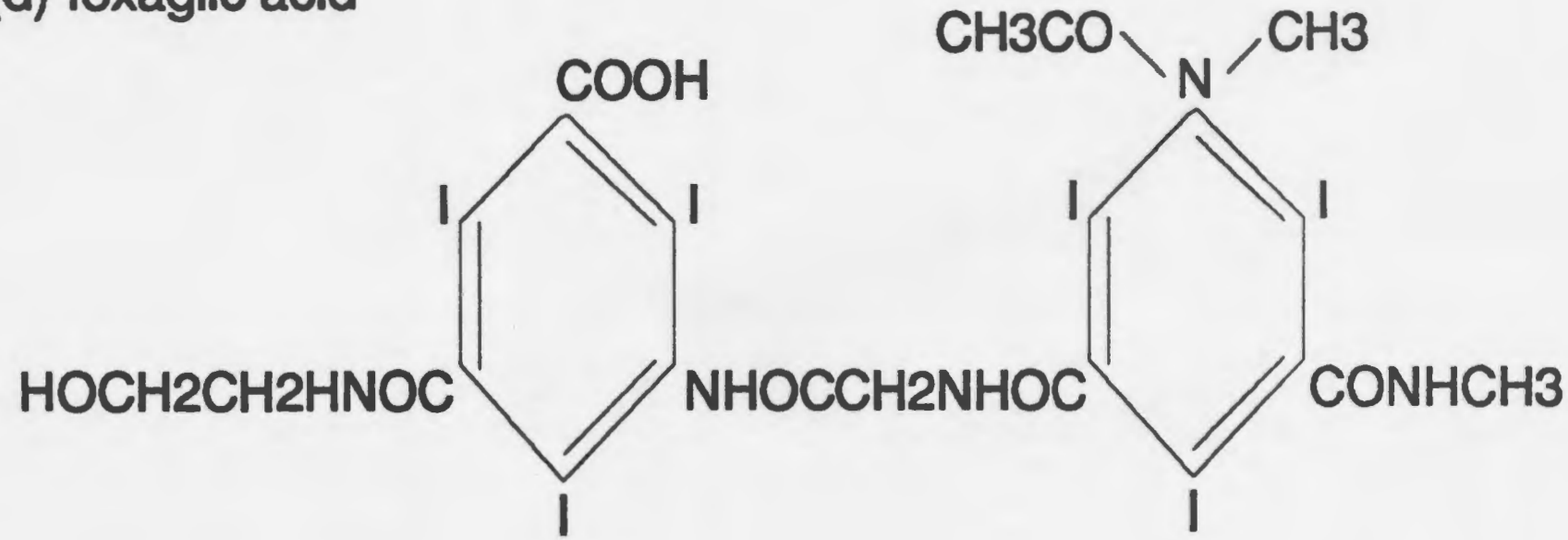


FIGURE 1

(c) Iohexol



(d) Ioxaglic acid



CHAPTER 2

RATIONALE FOR A STUDY TO COMPARE THE TOXICITY OF IONIC HIGH-OSMOLAR AND NONIONIC LOW-OSMOLAR RADIOCONTRAST DURING INTRAVASCULAR USE

It is important to review the existing literature about a topic carefully and critically prior to planning any scientific research. This review process helps to identify which research questions need to be answered. Analysis of how others have attempted to answer similar questions can also be helpful in deciding how to proceed with further research. This chapter will review the literature pertaining to the relative toxicity of ionic high-osmolar and nonionic low-osmolar radiocontrast agents during intravascular use. This particular review was performed after the trial which forms the basis for this thesis was underway. However, it is meant to represent the sort of review which should precede the planning of such a study.

2.1 The toxicity of ionic high-osmolar media:

These media have been in widespread clinical use for over 30 years and considerable experience of their efficacy and toxicity has accumulated. These media provide good diagnostic images in cases where the patient has been given a full dose and cooperates with the examination.

The toxic effects of these media can be classified in several ways. One method, widely used in surveys, is to classify reactions to the media in terms of severity. The classes are usually designated "mild", "moderate" or "intermediate",

"severe", "very severe" and "fatal". These terms lack precision and are defined differently in different studies. Comparison of event rates between studies is therefore difficult. Another disadvantage of such a classification scheme is that it does not specify the nature of the adverse event. This is an important disadvantage, as different adverse reactions probably have different pathogenetic mechanisms, and may be more or less likely to be improved by the newer contrast media.

Contrast related adverse events may also be divided into organ-specific and systemic or generalized reactions. This is more useful as it more clearly reflects the underlying pathogenesis and it allows a more accurate description of the nature of the adverse reaction. A severity classification can be superimposed on this form of classification if desired.

The route of administration of contrast is important and can best be considered in relation to the organ-specific and systemic generalized classification scheme. It appears that direct exposure of sensitive organs such as the kidney or the heart to large doses of radiocontrast will produce specific toxic effects in a predictable fashion. An adverse event might reasonably seem more likely to occur if the exposed organ is already diseased and thus less able to withstand the adverse effects of contrast media. Some individuals may also be idiosyncratically predisposed to organ specific toxicity, although this has not been proven.

The generalized or systemic adverse effects of radiocontrast may be equally likely regardless of the intravascular route of administration chosen. However, these effects can generally be divided into those that are at least partly predictable and those which are idiosyncratic, unpredictable, and possibly severe or fatal.

Our interest in the general question of contrast toxicity arose from the effects of contrast on the kidney. There had been considerable controversy in the literature regarding the incidence of contrast nephropathy and thus we performed a prospective controlled cohort study on this subject [Parfrey (1989)]. We studied hospital inpatients with a serum creatinine greater than 150 μmol/l, diabetes mellitus, or both. The study group were having intravascular radiocontrast while the control group were having abdominal ultrasound or CT scanning without contrast. The patients were examined before imaging and the serum creatinine was followed for three days to diagnose cases of contrast nephropathy. If the serum creatinine rose the patients were re-examined, without knowledge of whether contrast had been given, to determine whether definite precipitating factors for renal failure, other than contrast, were present. Using this data we were able to determine the risk for acute renal failure attributable to contrast in patients with various characteristics. The only group to have an excess of cases with an unexplained rise in serum creatinine of greater than 50% above baseline after contrast was the group with diabetes and

renal impairment. The incidence of such an event in this subgroup was 8.8% (95% confidence interval 1.9 to 23.7%). This was considerably less than the rates quoted in the literature for such patients prior to that. We also found that less severe changes in renal function after contrast were uncommon in patients with renal impairment alone and in patients with diabetes mellitus and normal renal function. After that study our interest generalized to the specific effect of contrast on other organs, such as the heart, and to the systemic adverse effects of contrast media. This interest was timely because of the growing controversy about the appropriate use of the new nonionic and low-osmolar contrast media.

2.2. The pathophysiology of contrast media induced adverse events:

Much work has been done to elucidate the mechanisms of contrast toxicity, but in many cases the data are incomplete. Based on the proposed mechanisms there are several situations where low-osmolar media might have advantages. In-vitro work has often shown that low-osmolar media have lesser effects on various biochemical and physiological processes as outlined below. Sometimes this work has been extended to animal models and even to humans. I will now briefly review what is known about the mechanisms of contrast toxicity. I will concentrate on systemic toxicity, cardiovascular toxicity, and nephrotoxicity as these represent our areas of interest.

2.2.1. Systemic idiosyncratic reactions:

The clinical features of these reactions may include rash, urticaria, bronchospasm, facial and laryngeal edema, hypotension, shock and death. These features suggest anaphylaxis as a mechanism. Anaphylaxis requires sensitization of the body to a foreign substance with the formation of IgE antibodies. On rechallenge, an IgE mediated release of histamine, serotonin, leukotrienes, and other mediators occurs and causes the clinical features mentioned above. There is little evidence of IgE antibody formation to contrast related antigens in humans [Lasser (1968), Lasser (1985), Brasch (1980)]. Recently it has been found that patients given both ionic contrast and interleukin 2 frequently develop rather severe, but delayed, reactions on re-exposure to the contrast [Zukiwski (1990), Oldham (1990)]. It may be that the contrast acts as a hapten and the IL-2 promotes an immune response which mediates the later reaction in an amnestic fashion. However, this does not necessarily indicate that more usual contrast reactions have an immunological basis. Nevertheless it is possible that the adverse reactions could still be caused by the mediators of anaphylaxis which are being triggered in a non-immunological fashion.

It is known that contrast media can release histamine directly [Lasser (1974), Rice (1983), Assem (1983)]. However, this occurs only with exposure of basophils to high concentrations of contrast in-vitro. Histamine release may be more pronounced in patients who have had a prior reaction to

contrast but this is not always so [Lasser (1985)]. Hemodynamic changes have not correlated with contrast induced increases in histamine levels in-vivo [Cogen (1979)]. Nonionic low-osmolar media have been shown to release less histamine from basophils in-vitro and this might indicate an advantage for these agents if histamine is an important mediator of contrast reactions [Amon (1989), Salem (1986), Dawson (1985)].

Contrast media can activate the complement system in-vitro and in-vivo. Direct activation occurs only with higher concentrations than occur in-vivo [Lasser (1985)]. It is also possible that contrast induced activation of complement is indirect, via damage to vascular endothelium [Lasser (1985), Grabowski (1989)]. Again, patients who have a history of prior reaction to contrast may have unstable complement systems, and thus be predisposed to contrast reactions [Greenberger (1984)]. However, complement levels may be increased by contrast without apparent clinical effect [Greenberger (1984)]. Nonionic low-osmolar agents appear to have less complement activating effect than ionic high-osmolar agents, which may relate to their lower osmolarity [Eaton (1990)]. Low-osmolar agents are also less toxic to endothelium [Laerum (1985)].

Endothelial damage may also activate Factor XII of the coagulation system [Lasser (1985), Cohan (1987)]. This in turn can activate pre-kallikrein which subsequently produces bradykinin. There is some evidence for more rapid pre-kallikrein activation in those with a history of prior reaction to contrast

but technical problems make this data suspect [Lasser (1985)]. The relevance of bradykinin to clinical events, and the effect of low-osmolar media have not been explored.

Lalli has suggested that contrast media, by gaining access to the central nervous system, stimulate a neurogenic response, which underlies contrast related adverse events [Lalli (1980)]. However, the evidence for this hypothesis is only circumstantial. Lalli had previously suggested that anxiety increased the frequency of reactions to contrast, and that this was mediated by higher centres augmenting the supposed contrast induced stimulation of the limbic system [Lalli (1974)]. In that study he tried to prevent contrast reactions by diazepam or hypnosis. Diazepam was ineffective but hypnosis appeared to reduce the frequency of contrast induced nausea and vomiting. The treatment groups were not randomly assigned, their baseline status was not measured, anxiety levels were not assessed and outcome assessment was not blind. These flaws in study design make interpretation of the results difficult. Whether nonionic low-osmolar media could reduce this type of effect has not been directly tested.

In summary, the mechanism of most idiosyncratic "anaphylactoid" reactions remains unclear. Even though nonionic low-osmolar contrast media do seem to have fewer deleterious effects on various physiological systems, it is not clear that this actually leads to a lower frequency, or severity, of idiosyncratic reactions when these media are used.

2.2.2. Cardiovascular toxicity:

Although intravenous contrast may have effects on the heart [Berg (1973), Pfister (1980), Mancini (1983), Heron (1984)], and cardiovascular collapse is a feature of some severe idiosyncratic systemic reactions, the direct cardiotoxicity of contrast is of most concern during cardiac angiography. Not only is the heart exposed to high local concentrations of the drug, but these patients are also likely to have cardiac disease and are thus less tolerant to a further cardiac insult. The cardiovascular effects of contrast media depend upon the site of injection, the osmolarity and inherent chemotoxicity of the media in solution, and also on the presence of additives, such as sodium, calcium or calcium binding compounds, in the contrast formulations [Hirshfeld (1990)].

The high osmolarity of ionic media may cause an acute rise in plasma volume by up to 20% after intravenous injection [Iseri (1965), Huet (1982)]. This, together with the effects of some contrast formulations on ventricular contractility as discussed below, might be enough to precipitate pulmonary edema during ventriculography in those with a predisposition to cardiac failure. Low-osmolar agents only increase plasma volume by about 8% [Dawson (1989)].

Hyperosmolar solutions may cause a concentration dependent decrease in myocardial contractile force [Kozeny (1985)]. However, the degree and direction of the change in contractility has varied in studies using nonionic solutions of mannitol or

glucose [Newell (1980), Atkins (1973), Wildenthal (1969)]. Exposure of the heart to solutions which contain sodium at concentrations higher than plasma depresses ventricular contractility [Kozeny (1985), Wolf (1973)], but the addition of small amounts of sodium to solutions of nonionic contrast media attenuated the depression of myocardial contractility that was otherwise observed in one study [Baath (1990)]. Solutions which bind calcium have negative inotropic activity [Drop (1981)]. These facts have to be considered when the cardiac effects of different contrast media are being compared.

All available formulations of ionic contrast media contain sodium at a concentration at or above that of plasma whereas there is virtually no sodium in the available formulations of nonionic media [Hirshfeld (1990)]. Some formulations of high-osmolar ionic contrast (Renografin-76 and MD-76) contain calcium binding additives [Hirshfeld (1990)]. These factors complicate interpretation of the literature comparing the cardiovascular effects of various contrast media.

In general, studies have shown that intracoronary injection of ionic high-osmolar contrast reduces the contractility of the left ventricle. Fleetwood has studied the cardiac effects of contrast in an isolated rat heart model [Fleetwood (1990)]. High ionic strength was associated with the fall in myocardial contractility. Nonionic low-osmolar media had little effect on ventricular contractility. The difference between the effect of high and low-osmolar contrast on ventricular function is

somewhat less evident when non-calcium binding formulations of high osmolar contrast are used [Murdock (1984)]. In fact it is hard to distinguish between an ionic medium which does not bind calcium and a nonionic medium such as metrizamide in terms of their effect on ventricular systolic function [Higgins (1978)]. Similarly in another study there was little difference between the effect of Renografin with added calcium and iohexol [Bourdillon (1985)]. Fleetwood et al. did find that coronary perfusion by an ionic medium without calcium binding additives (Angiovist 282) caused a greater fall in ventricular contractility than did perfusion with nonionic media in the Langendorff rat heart model [Fleetwood (1990)]. Klow et al. have studied the effects of various contrast media in the dog using an acute ischemic heart failure model [Klow (1990)]. They found that intracoronary injection of iohexol caused no change, ioxaglate a minor change and diatrizoate (as Renografin) a major depression in systolic contractile function. They did not comment on the possible role of calcium binding additives in relation to their result.

Relatively few studies comparing intracoronary injection of high and low-osmolar contrast measure the effects on coronary tone or blood flow. High osmolarity seemed to be responsible for reductions in coronary resistance seen with contrast injection in the study by Fleetwood [Fleetwood (1990)]. It is known that hypertonic saline may cause coronary vasodilation after intracoronary injection [Wolf (1973)]. High-osmolar contrast

media exert a similar effect but the degree of vasodilation is much less marked with nonionic agents [Tragardh (1976), Gerber (1982)]. Reductions in coronary tone could shunt blood away from areas with fixed stenoses, and thus precipitate distal ischemia.

The overall hemodynamic response to bolus injection of contrast is complex. It depends on the site and rate of injection and the interaction of the effects of contrast on intravascular volume, myocardial contractility and systemic vascular resistance. The cardiac output may rise during coronary angiography. This increase in cardiac output is partly due to peripheral vasodilation. This in turn may be largely due to direct effects of hyperosmolar solutions on blood vessels [Marshall (1959), Dawson (1989)], and partly to the release of histamine [Dawson (1989)]. The vasodilation is generally associated with a fall in blood pressure which tends to return to baseline or above in 60 to 90 seconds [Hirshfeld (1983)]. These effects are generally less marked when low-osmolar media are used [Partridge (1981), Steiner (1980), Bettmann (1984), Hirshfeld (1989)]. The relative effects of calcium-binding and noncalcium-binding formulations of high-osmolar media on arterial pressure have not been well studied.

If contrast is injected at moderate rates and volumes into the left ventricle the immediate effect is usually a slight increase in ventricular volume and stroke volume [Hammermeister (1973)]. The major hemodynamic effect of ventriculography is not seen until the contrast reaches the peripheral circulation and

causes vasodilation as discussed above. At that point the blood pressure usually declines although the cardiac output remains high. If significant amounts of contrast reach the coronary circulation, and particularly if severe coronary disease is also present, the cardiac output may fall due to myocardial depression and bradycardia [Hamby (1977)].

Intracoronary injection of contrast has been noted to have direct and reflex mediated effects on sinoatrial nodal automaticity and AV nodal conduction [Higgins (1976), Higgins (1977)]. Calcium-binding ionic contrast media cause the most severe bradycardia, noncalcium-binding ionic media are intermediate in their effects, while nonionic agents cause the least slowing of the heart [Piao (1990)]. The tendency to bradycardia is much more profound following right than left coronary artery injections [Piao (1990)]. This is probably due to the fact that the blood supply to the sinus and AV nodes is from the right coronary artery in the majority of cases. Although the resulting bradycardia is usually transient and not accompanied by serious hemodynamic change, complete heart block and ventricular fibrillation may ensue [Piao (1990)].

The repolarization time of the myocardium is prolonged by contrast injection, and if this is not homogenous, there is a potential for tachyarrythmia and ventricular fibrillation [Hayward (1984), Hirshfeld (1990)]. Some of this effect may be due to hyperosmolarity [Hayward (1984)]. However, the calcium chelating effect of additives in some formulations of high-

osmolar contrast may also play a role [Murdock (1985), Zukerman (1987)]. While excess calcium in coronary blood tends to reduce fibrillation threshold, the addition of controlled amounts of calcium to calcium-binding formulations of ionic contrast media may reduce their tendency to lower the fibrillation threshold [Wolf (1980)]. Nonionic contrast may lower the threshold for fibrillation to a lesser extent than ionic media [Higgins (1985)]. This may translate into a lowered frequency of ventricular fibrillation during clinical use [Bashore (1988), Missri (1990)]. It should be noted that some of the potentially lethal arrythmias seen during angiocardiography may be related to procedural factors rather than contrast [Armstrong (1989)].

Nonionic media have been found to cause less ECG change than ionic media during intracoronary injection in some [Mancini (1983), Sullivan (1984)] but not all studies [Salem (1986)]. Similarly divergent findings have occurred with intravenous injections [Heron (1984), Foster (1987)].

In summary there is fairly strong experimental evidence that nonionic low-osmolar agents are less cardiotoxic than ionic high-osmolar media. The interpretation of much of the existing research is difficult given the disparate effects of the calcium-binding and noncalcium-binding formulations of high-osmolar media. The evidence that the lesser perturbation of cardiac physiology with nonionic contrast media translates into better tolerance in clinical practice will be reviewed in a later section.

2.2.3. The effects of contrast media on blood components:

Contrast media are not inert molecules and are capable of interaction with many biological structural proteins and enzymes. Such interaction may disturb the fine balance of integrated physiological processes and this has been termed a "chemotoxic effect" of the contrast media [Dawson (1985)].

Contrast media cause changes in red cell shape and deformability. Hyperosmolar contrast solutions with high ratios of contrast to blood induce the formation of "dessicocytes" which are similar to those produced by hyperosmolar saline and probably result from cellular dehydration [Aspelin (1978)]. Such changes are not seen with nonionic agents like metrizamide which have lower osmolarity [Aspelin (1978)]. Red cells with reversibly changed shape, called echinocytes, are seen even with iso-osmolar solutions of contrast media and are more prominent with metrizamide than with diatrizoate [Aspelin (1978)]. It has been suggested that the alterations in red cell shape result from an interaction of the contrast molecules with the surface membrane of the red cells [Aspelin (1978)]. The interaction of contrast with the surface of red cells may also be responsible for the formation of red cell aggregates when contrast is added to static blood. This has been observed particularly but not exclusively with nonionic media [Dawson (1988), Kimball (1988), Zucker (1988), Aspelin (1988)]. The resulting aggregates are easily disrupted by shear forces, such as that resulting from the injection of the mixture by syringe [Aspelin (1988)]. The

aggregates do not indicate coagulation and they can be prevented by the addition of low concentrations of saline to the blood/ contrast mixture [Kimball (1988), Zucker (1988)]. These aggregates may not have any clinical relevance.

Thromboembolism during coronary arteriography is rare but can have serious consequences [Davidson (1990)]. Concern has been expressed that this complication may be more common when nonionic contrast media are used [Grollman (1988)]. It has also been suggested that the effect of contrast media on the coagulation system, given it's complexity, may be a good way to assess the intrinsic chemotoxicity of contrast molecules [Stormorken (1986)].

Contrast solutions inhibit the coagulation system in vitro. Using global tests of the intrinsic and extrinsic pathways, the degree of inhibition has been found to be greater with the ionic high-osmolar than with nonionic media [Stormorken (1986)]. Much of the inhibition is not explained by either the ionic or osmolar strengths of the solutions and has been attributed to a direct effect of the contrast molecules [Stormorken (1986)]. However, it is unclear how blood samples were handled after collection in the study by Stormorken [Stormorken (1986)]. It has been suggested that when citrate is added to blood before contrast, the apparent anticoagulant effect of the contrast only reflects an inhibition of fibrin polymerization [Fareed (1990), Dawson (1990)]. Alterations in clot structure in the presence of ionic media indicate that these agents disturb fibrin

polymerization [Verebely (1969)]. However, others have shown that contrast media do not markedly alter fibrinogen structure but that they do block the conversion of fibrinogen to fibrin [Andes (1988)]. This effect is most marked with ionic media [Andes (1988)].

Binding of calcium must also be considered as a potential explanation for some of the apparent anticoagulant properties of ionic high-osmolar media [Morris (1982)]. Ionic media have actually been shown to be capable of activating the coagulation system by contact [Dawson (1989a)]. Nonionic media have been shown to allow thrombin generation while still displaying an overall anticoagulant effect in vitro [Kopko (1990)]. In experimental systems simulating cardiac catheterization nonionic media have been found to have less anticoagulant effect than ionic media [Hwang (1989), Hwang (1990)]. There seems to be agreement from several sources that in vitro nonionic media have less net anticoagulant effect than ionic media. However, the evidence available from in vivo work does not suggest that the coagulation system is disturbed systemically after the injection of either ionic or nonionic contrast [Stormorken (1986)]. Similarly the evidence is not firm that the lesser effect of nonionic media on the coagulation pathway translates into a clinically important risk for thromboembolism in patients treated with these agents [Davidson (1990)].

Contrast media inhibit collagen induced platelet aggregation in vitro [Stormorken (1986)]. While ionic and

osmolar strength may be more important in determining the degree of platelet inhibition than the degree of anticoagulation, there are still differences between agents which cannot be explained by these factors [Stormorken (1986)]. Grabowski has shown that platelet adhesion and aggregation are not inhibited by iohexol at a site of endothelial injury [Grabowski (1988)]. However, platelet aggregates do not form in the presence of contrast without endothelial injury and iohexol causes less alteration in endothelial monolayers than does either ioxaglate or diatrizoate [Grabowski (1989)]. The available evidence does not directly link these effects of contrast observed in vitro to clinical thrombotic events.

2.2.4. Contrast nephropathy:

This is usually defined as acute renal failure occurring after the administration of contrast in the absence of other causes of acute renal dysfunction. This definition, together with the difficulty in establishing a suitable animal model for contrast nephropathy, has hampered study of the frequency and pathogenesis of this disorder. Some have even questioned the existence of the condition [Katzberg (1989)]. Clinical experience does indicate the occurrence of otherwise unexplained renal impairment after contrast. The frequency of this event may be low, and it may only occur in the presence of other contributory factors, but there seems little doubt that the condition does exist [Parfrey (1989)].

It has been proposed that contrast could damage the kidney by: reducing renal blood flow and causing ischemia, a direct toxic effect on tubular or glomerular cells, obstruction of the tubular lumen by precipitating protein, or a combination of these mechanisms [Berns (1989)].

Vari studied rabbits in a sodium deplete state [Vari (1988)]. Acute renal failure consistently occurred when ionic contrast was given together with indomethacin. Neither contrast nor indomethacin alone were associated with renal failure in this setting. When the sodium deplete state was not present, even the combination of contrast and indomethacin was insufficient to produce renal failure. Acute saline or mannitol infusion was not sufficient to prevent the renal failure in sodium deplete animals. These results would seem to indicate that, in the rabbit at least, contrast may only be toxic when the kidney is exposed to a vasoconstrictive influence and its natural compensatory vasodilatory mechanisms are also impaired. These authors were unable to identify any histological correlates of the reduced renal function. Renal blood flow was normal even during the renal failure and there was no evidence for tubular obstruction. They found that the fall in glomerular filtration rate was due to a fall in the glomerular ultrafiltration coefficient.

Heyman performed a similar study in Sabra rats [Heyman (1988)]. These animals also developed acute renal impairment when salt depletion, indomethacin and ionic contrast were

combined. Necrosis of the medullary thick ascending limbs, tubular collapse and casts, and extensive vacuolization of proximal tubular epithelium accompanied the renal failure in these animals. There is no obvious explanation of why rats and not rabbits display these histological changes.

Vaamonde sought to induce contrast nephropathy in Sprague-Dawley rats [Vaamonde (1989)]. They studied rats rendered diabetic by streptozotocin and non-diabetic control rats under a variety of conditions designed to mimic the risk factors associated with contrast nephropathy in humans. They were unable to produce acute or delayed renal function changes with ionic contrast despite dehydration, partial renal ablation, and insulin use [Vaamonde (1989)]. The renal lesion in the rats differed from that seen in human diabetic nephropathy however, and it is the presence of this condition in patients which is associated with the greatest risk of contrast nephropathy [Parfrey (1989)].

It has been shown that contrast and other hyperosmolar solutions can cause a reduction in renal blood flow [Morris (1978)]. This vasoconstrictive response to contrast is only seen in the renal vessels. The change is maximal when the contrast is given directly into the renal artery. Similar changes of a lesser magnitude have been observed with intravenous contrast and may be absent with low-osmolar contrast [Russo (1990)]. Other mechanisms for contrast induced renal ischemia have been

reviewed but the relevance of these changes to contrast nephropathy remains unclear [Barrett (1991)].

The occurrence of enzymuria or tubular proteinuria after contrast injection has been taken as evidence of tubular injury [Kunin (1978)]. Several studies have compared the high and low-osmolar media in terms of their tendency to induce such enzymuria [Gale (1984), Albrechtsson (1985), Cavaliere (1987), Stacul (1987), Skovgaard (1989)]. These have not consistently indicated that the low-osmolar media are less toxic and the enzymuria did not usually indicate the occurrence of a clinically important renal injury. Other evidence for tubular toxicity includes the histological demonstration of tubular vacuolization associated with contrast in subjects with prior renal disease [Moreau (1986)]. This lesion can also be seen with low-osmolar contrast and with hyperosmolar solutions other than contrast [Allen (1962), Moreau (1986)]. The mechanism of production of the lesion is unknown and it does not correlate with renal functional impairment. Rabbit proximal tubular cells in-vitro display an impairment in cellular metabolism on exposure to diatrizoate, which is aggravated by hypoxia [Humes (1987)]. Iopamidol, a low-osmolar agent, was less toxic in this system.

Intratubular precipitation of urinary protein and uric acid have been suggested as mechanisms of contrast induced renal injury. Contrast media have been shown to precipitate Tamm-Horsfall protein in-vitro but it is unknown whether this occurs

in-vivo [Dawson and Freedman (1984), Dawnay (1985)]. Contrast media (especially those used for cholangiography) are uricosuric [Mudge (1971), Postlethwaite (1971)]. However only one case of contrast associated renal impairment has been described with the pathological changes of acute uric acid nephropathy [Harkonen (1981)]. Allopurinol prophylaxis did prevent the uricosuria, but was ineffective in preventing recurrent contrast nephropathy, in at least one patient with diabetic nephropathy [Feldman (1974)].

Thus it remains unclear how contrast may lead to renal injury and what other circumstances must prevail for contrast nephrotoxicity to be expressed. Although nonionic low-osmolar agents have shown some evidence of decreased toxicity when compared to high-osmolar media in experimental situations, there is insufficient evidence to state that they should be less toxic in routine clinical use.

2.3. The results of surveys of the toxicity of ionic high-osmolar media:

Following the initial introduction of sodium diatrizoate and related compounds, there were continuing concerns about the toxic effects of the then new contrast. There was also concern that no adequate means existed to measure the frequency of contrast related adverse events in practice. There had been several surveys of reactions to previously used media [Pendergrass (1942), Pendergrass (1955), Shehadi (1966)]. These surveys had been conducted by sending questionnaires to radiologists and asking them to describe their previous

experience with reactions to contrast. The response rate was low in this already selected group. In one study only 38.5% of those surveyed supplied useful information [Pendergrass 1955]. Thus these surveys were particularly liable to nonrespondent bias [Sackett (1979)], and it is possible that severe under-reporting could have occurred for minor or moderate level toxicity. An under or overestimate of fatalities could have occurred, because of inaccuracy in the estimate of either the number of deaths recorded or the number of injections performed in the same period.

Table 1 shows data derived from prospective studies of the toxicity of ionic contrast published between 1970 and 1990. The surveys were multi-institutional except for the two series from the Mayo clinic [Witten (1973), Hartman (1982)]. There were differing definitions of mild, moderate and severe reactions used in the various studies. Mild or minor adverse reactions were generally defined as events not requiring therapy but the nature of the events was almost never described. Moderate reactions were generally treated but seem to include very different types of events in the different studies. Severe adverse events were similarly diverse but generally required intensive treatment in a hospital setting. Some surveys grouped the adverse events seen after intravenous and intraarterial injections.

TABLE 1. THE FREQUENCY OF VARIOUS ADVERSE REACTIONS TO HIGH-OSMOLAR CONTRAST IN THE LITERATURE.

Study (year)	Design	Investigation	Reaction class	Incidence 95% CI (%)
Pendergrass (1955)	Retrospective	IVP	Death	0.0005-0.001
Ansell (1970)	Prospective	IVP, angiography	Moderate	0.04-0.05
			Severe	0.004-0.01
			Death	0.0008-0.004
Witten (1973)	Single institution series	Outpatient IVP	Minor	4.9-5.3
			Severe	0.06-0.12
			Death	0-0.009
Shehadi (1975)	Prospective survey	IVP	Mild	3.6-3.9
			Moderate	1.7-1.9
			Severe	0.01-0.03
			Death	0.001-0.01
		Angiogram	Mild	1.2-1.5
			Moderate	0.7-0.9
			Severe	0.02-0.07
			Death	0.003-0.03

TABLE 1. contd.

Study (year)	Design	Investigation	Reaction class	Incidence 95% CI (%)
Shehadi (1980)	Prospective survey	IVP	Mild	3.3-3.4
			Moderate	1.3-1.4
			Severe	0.04-0.06
			Death	0.002-0.009
		Cardiac angiography	Mild	0.7-1.1
			Moderate	0.8-1.2
			Severe	0.2-0.4
			Death	0-0.06
Ansell (1980)	Prospective survey	IV contrast Sample weeks	Mild	6.8-8.2
			Moderate	1.2-1.8
			Severe	0.04-0.02
		Nonsample weeks	Moderate	0.1-0.2
			Severe	0.01-0.03
			Death	0.00005-0.005
Hartman (1982)	Single institution series	IVP	Death	0.00003-0.003

TABLE 1 contd.

Study (year)	Design	Investigation	Reaction class	Incidence 95% CI (%)
Lasser (1987)	RCT steroid prophylaxis -placebo groups	IV contrast	Grade 1	4.1-5.9
			Grade 2	3.1-4.7
			Grade 3	0.3-0.9
			Treated reaction	1.6-2.7
Palmer RACR (1988)	Prospective survey	IV contrast "High risk"	Mild	5.9-8.7
			Moderate	1.9-3.7
			Severe	0.1-0.8
		"Low risk"	Mild	3.1-3.4
			Moderate	0.27-0.35
			Severe	0.06-0.1
			Death	0-0.006
Wolf (1989)	Prospective series	IV contrast	Mild	2.1-2.9
			Moderate	0.9-1.5
			Severe	0.24-0.56
			All treated	1.0-1.6

The study reported by Ansell in 1980 is interesting in that it discloses one of the problems with the survey type of study design [Ansell (1980)]. In that British survey of reactions to intravenous contrast over a one year period, the participating institutions were asked to report on all examinations and all reactions for two randomly selected weeks during the year. For the remaining 50 weeks the centres only reported reactions which were classified as being at least of moderate severity. As can be seen, the event rates were about 10 times higher during the two sample weeks as during the 50 non-sample weeks. This could either be due to severe under-reporting during the non-sample weeks or to over-reporting during the sample weeks. This kind of discrepancy throws considerable doubt on the accuracy of such survey results.

Shehadi reported a U.S. survey in 1975 and a further survey, including a large cohort of Italian patients, with Toniolo in 1980 [Shehadi (1975), Shehadi (1980)]. The definitions of reactions were the same in both studies and all patients having contrast were supposed to be reported. Intravenous and intraarterial contrast were studied separately. The event rates after IV contrast are very similar in both surveys. However, the frequency of mild and moderate reactions after cardiac catheterization may have been seriously underestimated, as such events occurred much more frequently during our randomized trial. The frequency of severe reactions after cardiac catheterization more than tripled from the first to the second

survey, while death rates declined. The event rates were low in both cases however, and this could represent a chance occurrence, a flaw in data reporting, or improved treatment for severe reactions.

The single institution series from the Mayo Clinic, reported by Witten and by Hartman, offer the advantages of more consistent reporting and the use of consecutive patients [Witten (1973), Hartman (1982)]. However, the definitions of reactions in the paper by Witten are rather diffuse, and I have attempted to draw information from the paper in order to make reasonably valid comparisons to the rest of the literature. The series reported by Hartman extends over an 18 year period and thus the effect of changes in practice on the likelihood of a fatal outcome to a contrast reaction, as well as changing diagnostic definitions, need to be considered.

In 1987 Lasser reported a randomized trial of steroid prophylaxis against reactions to ionic contrast [Lasser (1987)]. The rates of reaction quoted in table 1 are derived from all placebo patients. The reaction grading system is sensible and reflects the largely idiosyncratic, non-organ specific toxicity usually associated with intravenous contrast. Some patients with a history of prior reaction to contrast were excluded from the trial because they would receive steroid prophylaxis anyway. This might have reduced the incidence of reactions in the trial a little. Given that this trial extended over at least 6 years in 27 centres, it is surprising that only 6763 patients were

enroled. The baseline characteristics of the study population were not described. This leads to some doubts about the generalizability of the results. The comparability of the two randomized groups at baseline was not established either, which leads to questions about the internal validity of the study. Nevertheless, the incidence rates for various reactions in the placebo groups are largely in keeping with the rest of the literature quoted in Table 1.

The surveys by the Royal Australian College of Radiology [Palmer (1988)] and the Japanese Committee on the Safety of Contrast Media [Katayama (1990)] appeared after our own study was underway and have been very influential in determining the use of nonionic contrast media. Both were prospective surveys which sought to compare the incidence of adverse reactions to high and low-osmolar contrast.

Neither of these surveys showed that low-osmolar media significantly reduced deaths attributable to contrast. There were two deaths following ionic contrast and none following nonionic contrast during the RACR survey of 109,546 examinations. The Japanese reported one death after both high and low-osmolar contrast. Each medium had been given to about 150,000 persons. Neither of these deaths were thought to have been due to contrast. Given that death is so infrequently attributed to any kind of contrast medium, it would require a trial with millions of participants to show conclusively that

low-osmolar contrast significantly reduced the incidence of contrast related death.

The RACR and Japanese studies did suggest that the incidence of severe reactions was reduced by the use of low-osmolar contrast. However there are concerns about how patients were selected for entry into these studies and about whether bias could have influenced the reporting of adverse events.

2.4. A review of the evidence that low-osmolar contrast is safer than high-osmolar contrast:

The previous section has given some idea of the scope of the problem concerning toxicity of ionic contrast media. The nonionic media were first tested for safety in animals. It was found that a significantly higher dose (the so called LD 50) of nonionic than ionic contrast had to be given to kill 50% of a group of mice [Shaw (1985), Felder (1984)]. The in-vitro and animal studies cited above, in relation to the mechanisms of contrast toxicity, also provided some reasons to expect that nonionic media would be less toxic in humans.

Following the successful animal toxicology studies, the nonionic media were subjected to study in humans. Much of the initial work was carried out in Europe. The nonionic media were studied in small open-label studies and later in blinded randomized trials during various applications. I will limit my analysis to those studies which dealt with intravascular applications.

Two large international symposia were held in the United States in 1983 and 1984 to review cumulated experience with the nonionic agents iohexol and iopamidol. The proceedings were published as supplements to Investigative Radiology [Invest Radiol 1984;19(5) suppl , Invest Radiol 1985;20(1) suppl]. Both iopamidol and iohexol caused significantly less pain during peripheral angiography than ionic high-osmolar media [Bonati (1984), Newman (1984), Reidy (1984), Mills (1984), Wolf (1985), Dotter (1985)]. Ioxaglate has also been found to reduce pain during peripheral angiography [Murphy (1988)]. The nonionic agents caused smaller changes in heart rate, blood pressure, and pulmonary capillary wedge pressure than conventional ionic agents during cardiac angiography [Bettmann (1985), Newman (1984), Ciuffo (1984)]. These trials were small however, and did not show a significant reduction in clinically important events with nonionic media. Patients with severe or unstable cardiac disease had generally not been studied to see whether nonionic agents provided advantages in such cases. Intravenous iohexol for CT scanning or IVP was associated with some reduction in mild adverse reactions when compared to high-osmolar media [Holtas (1985), Rankin (1985)]. There were similar findings when iopamidol was evaluated for CT or digital subtraction angiography [Robbins (1984), Ford (1984)]. None of these studies established that nonionic contrast could reduce the incidence of clinically important reactions to intravenous contrast.

Many further studies of the relative toxicity of high and low-osmolar contrast were performed subsequently. Kinnison, Powe and co-workers performed an extensive literature search and reviewed all of the randomized trials, comparing high and low-osmolar media during intravascular use, which had been published between 1980 and 1987 [Kinnison (1989)]. Such randomized trials provide the strongest evidence by which to compare the clinical toxicity of contrast media.

The studies of contrast toxicity in humans which use non-experimental designs such as surveys, consecutive series and prospective cohort studies, may provide some data on the relative toxicity of high and low-osmolar contrast media, but by the nature of their design are open to several sources of bias [Sackett (1979)]. Sackett defines many such biases in his paper. For the sake of brevity I will not define them again but I will indicate how a few of them may apply to studies of contrast media.

Centripetal and referral filter biases could have led to patients who were at higher than average risk of an adverse event being over represented in the study cohorts. This would tend to exaggerate the incidence of adverse events reported. Diagnostic suspicion bias would be particularly important in unblinded comparisons of the incidence of reactions between "high risk" groups and others, or between ionic and nonionic contrast media. If this bias were operative the degree of risk associated with the risk factor, or the efficacy of the nonionic

contrast, would tend to be exaggerated. Procedure selection bias could operate if those patients at the highest risk for a contrast reaction were not given contrast or were given effective prophylactic therapy. This would tend to reduce the apparent incidence of contrast reactions. Missing clinical data bias would probably be important in the case of "risk factors". An accurate history of allergy, prior contrast reaction etc. may not have been taken in all cases, and may well have been collected after it was known whether a contrast reaction had occurred or not. This would tend to exaggerate the increase in risk associated with these factors.

Noncontemporaneous control bias is operative in the surveys by the RACR and the Japanese Committee on the Safety of Contrast Media [Palmer (1988), Katayama (1990)]. In these surveys the patients enroled early were more likely to have received ionic contrast, while those enroled later were more likely to have received nonionic contrast. Changes in factors other than contrast could have been at least partly responsible for the apparently lower incidence of adverse events seen with nonionic contrast. Therapeutic personality bias would be particularly likely to occur in the case of Lalli's work using hypnosis to prevent contrast related adverse events and might well be responsible for the apparent efficacy of that intervention [Lalli (1974)]. Data dredging bias probably applies to several of the surveys, where the influence of dose, speed and route of administration of contrast, along with numerous other factors,

were tested for association with contrast reactions and may have generated some spurious associations between these factors and adverse events.

Thus the results of the non-experimental studies have to be treated with caution, as the results can be greatly influenced by biases which are unpredictable in the magnitude of their effects and cannot be controlled for by any post-hoc form of analysis.

While performing a randomized trial does eliminate several sources of bias, there are several aspects of trial design that need to be considered when interpreting results. In particular, for the trials to be valid, subjects should have been truly randomly assigned, randomization and outcome assessment should have been performed blindly, the randomized groups should have been shown to be comparable apart from the intervention being tested, patients entered in the trial should all be properly handled in the analysis, and the clinical and statistical significance of the results should have been considered [Sackett (1981)]. For the results to be useful in practice, all clinically important outcomes should have been considered, patients included in the study should have been representative of the type of patients likely to require the intervention in practice, and the experimental therapy should have been applied in a way which is suitable for subsequent use [Sackett (1981)].

Chalmers has suggested criteria for evaluation of published randomized trials [Chalmers (1981)]. Powe et al. used these

criteria to evaluate the randomized trials of low and high-osmolar contrast media [Powe (1989)]. The instrument developed by Chalmers has been widely used but could be criticized as it's construct validity has not been fully established. The instrument weights some aspects of study design and analysis in arriving at a composite "quality" or "merit" score. The relative importance of these various aspects of study design needs to be established before the empirically assigned weights can be accepted. Nevertheless, the instrument does provide an overall assessment of the quality of randomized trials and can certainly be useful to point out gross deficiencies of trial design. There are two other factors to consider before a discussion of the results of the trials of contrast media. The first is that Powe et al. limited their analysis to trials which were reported in English at some point in time. This might have led to bias in their review since most of the early work on the toxicity of nonionic contrast was carried out in Europe. However, it is significant that no review in English has mentioned landmark studies which were only published in other languages. The second factor to consider is the general bias which exists against publishing negative studies. Many of the published trials included only small numbers of patients and it is possible that similar studies which had "true", or indeed "false", negative results were not published [Detsky (1985)]. This would bias the published literature in favour of nonionic contrast and make performance of an adequate meta-analysis of the data difficult.

Kinnison et al. identified 100 trials for inclusion in their analysis [Kinnison (1989)]. A total of 6398 patients were studied in the 100 trials. The number in each study ranged from 5 to 435. Thirty two trials used a crossover design. If one considers that reactions requiring therapy after ionic contrast occur with a frequency of about 2% [Lasser (1987)], then in order to exclude a 50% reduction in this incidence with nonionic contrast, negative trials would have to include more than 561 patients per group [Detsky (1985)]. Thus these trials were not nearly large enough to adequately examine such outcomes. This is not to say that a positive outcome would be invalid, but rather that it would be very unlikely, and a negative outcome would not carry much weight. Other adverse events (including those measured as continuous variables), which occurred with greater frequency, might well be adequately studied by some of the trials included in the analysis by Powe.

Powe found that the larger trials were more likely to have been rigorously performed. Recommendations were made by the authors of the trials irrespective of their quality. The attributes which were most often deficient in the studies were: documentation of exclusions, blinding of randomization, blinding observers to study results, tests of blinding, prior estimation of sample size, use of confidence intervals or mention of power post-hoc, assessment of subjective end points by more than one observer, documentation of study performance dates, and regression analysis of prognostic risk factors. Powe assessed

trials as being of "high quality", if they achieved a score of forty or more out of a possible 100, using the Chalmers grading system. This was close to the mean score of 39 achieved by the trials reviewed by Powe and also close to the mean of 42 for 376 randomized trials of various treatments reviewed by Lam [Lam (1987)].

Forty one of the trials compared intravenous injection of high and low-osmolar media. None of the trials, irrespective of quality, demonstrated an advantage with low-osmolar media in terms of clinically important renal, cardiovascular or laboratory test outcomes. Several studies did document less subjective heat, nausea and pain with low-osmolar media. No reduction in the incidence of urticaria was demonstrated.

Thirty four trials evaluated noncardiac intraarterial injections. Again these studies did not identify any advantage with low-osmolar media in terms of clinically significant renal dysfunction, cardiovascular disturbance, laboratory tests or urticaria. Low-osmolar media did seem to reduce the frequency of pain and warmth.

There were 25 trials evaluating the media during intracardiac injection. The high-osmolar media seemed to be more likely to reduce blood pressure, increase heart rate, increase left ventricular end diastolic pressure and prolong the QT interval. Most of these changes were minor however, and were not of real clinical importance. No clear advantage to low-osmolar media was identified in terms of arrythmia or renal dysfunction. There was

sometimes a reduction in heat, pain, and headache with low-osmolar contrast.

In all cases where it was examined, the image quality was as good, or better, with low-osmolar as with high-osmolar contrast. The trials did not comment on the relationship between patient variables (or so called "risk factors") and the incidence of adverse events. In fact, very few trials included many patients with characteristics which would traditionally have been associated with increased risk. Thus this body of data did not allow a sound identification of high risk subjects to be made. The relative advantage of the low-osmolar media, in subjects at higher than average risk, could not be deduced either.

Powe, Kinnison et al. conclude (as we had in 1987) that larger, properly performed, trials were indicated to clarify whether low-osmolar media could reduce the frequency of clinically important contrast related adverse events.

CHAPTER 3

DECIDING THE RESEARCH QUESTIONS

3.1. The primary question:

Following a literature review similar to that in the preceding chapter, the investigators who performed the trial which is discussed in this thesis felt that there was insufficient evidence available to indicate that low-osmolar agents were safer in many situations. Pursuit of the answer to this question would have had scientific merit on its own, but it might not have been easy to convince the medical community, or funding agencies, of the need for a further study of contrast safety. McClennan, in a "state of the art" paper in Radiology in 1987, took the view that enough evidence had been accumulated to warrant the use of low-osmolar contrast, at least in certain subgroups of patients [McClennan (1987)]. Apart from the literature to which I have alluded previously, a paper had been published describing experience with the use of iohexol for intravenous pyelography in a series of 50,660 patients [Schrott (1986)]. Fifty two percent of the patients in this series had one or more poorly described "risk factors" for an adverse reaction to contrast. Despite that, mild reactions occurred in 2.1%, moderate reactions in 0.9%, severe reactions in 0.01%, and there were no fatalities. There was no control group, but these figures were substantially lower than those quoted for high-osmolar contrast (Table 1). Although this study is open to many of the biases which I have mentioned above, it does at least

suggest that nonionic media might be safer in practice. Based on all this evidence, McClennan advised physicians to act as advocates for their patients and to encourage more widespread use of the nonionic media.

The major problem preventing widespread use of the new contrast media was their high cost. The nonionic media cost about 3 to 5 times as much as the ionic high-osmolar media in Great Britain and up to twenty times as much as ionic media in the United States [Fischer (1986)]. It has been estimated that complete replacement of high by low-osmolar media would cost about $1 billion per year in the United States alone [Jacobson (1988)]. This price differential caused some authors to question the wisdom of universal use of the new media [White (1986), Parfrey (1988), Evens (1988)]. It was argued that the limited resources available might be better spent on other needed forms of health care, such as radiological equipment and personnel [Grainger (1987)]. This aspect of the introduction of the new contrast media threw the question of the relative safety of nonionic and ionic contrast into sharp relief and made the need for a properly designed trial of the comparative toxicity of the contrast agents even more urgent. While several authors were sufficiently convinced of the lower toxicity of the nonionic agents to recommend their use in at least some situations [Dawson (1984), Grainger (1987), McClennan (1987)], there was widespread support in the literature for further studies of the toxicity of the new media [White (1986), Thompson (1986),

Bettmann (1987), Evens (1988)]. This interest in further research has continued during the performance of our trial [Bettmann (1990), King (1989)] despite the publication of large surveys by the RACR and the Japanese [Palmer (1988), Katayama (1990)]. Some authors now feel that there will be a gradual replacement of high-osmolar media by low-osmolar contrast despite the high cost [Grainger (1990)].

The primary research question is stated in questions 1 and 2 of section 3.3 below.

3.2. Evaluating strategies for selective use of low-osmolar contrast:

Because of the substantial financial implications of universal use of the new contrast media several groups have suggested that the low-osmolar agents be reserved for certain patients and examinations [Grainger (1984), Grainger (1987), Lasser (1987), Thompson (1986), Bettmann (1989), Fischer (1986), Dawson (1984)]. Grainger developed a comprehensive set of guidelines on behalf of the Royal College of Radiologists in the U.K. [Grainger (1984)]. These guidelines suggested that low-osmolar contrast be given to all patients who were to undergo arteriography which might be painful, and also to patients who were at increased risk of adverse reactions to the high-osmolar media. It was stated that the "high risk" patients were those with a history of prior severe reactions to contrast media, allergic subjects, and those with asthma, all of whom were at increased risk of an anaphylactoid reaction. Other "high risk"

groups were composed of infants and small children, patients with renal or cardiac impairment, diabetes, myelomatosis, sickle cell anemia or poor hydration, all of whom were felt to be at increased risk of an adverse reaction because of the high osmolality of the ionic media. In a 1987 article, Grainger also mentioned that "elderly" patients were considered to be at increased risk and thus should also be given low-osmolar media [Grainger (1987)]. Fischer concurred with Grainger's guidelines but also added very ill patients to the "high risk" group [Fischer (1986)]. McClennan used similar definitions of increased risk but specifically defined elderly as being aged over 50-60 years [McClennan (1987)]. Bettmann suggested using low-osmolar media in those with marked anxiety, and those in whom the side effects of pain, nausea and vomiting might be dangerous because of underlying cardiac, pulmonary, or nervous system disease [Bettmann (1987)]. He suggested low-osmolar agents for those with a history of reaction to contrast, asthma, or allergies only if time did not permit steroid prophylaxis. He also recommended that those with marked cardiac or pulmonary disease be given low-osmolar agents, while recognizing that such a recommendation was based largely on evidence other than trials in humans. Dawson stated that it was his policy to give the low-osmolar media to infants, elderly, frail, allergic or asthmatic patients and to those with cardiac disease [Dawson (1984)]. More recently the American College of Radiology have been reported as recommending nonionic contrast for painful examinations, those

where patient movement is undesirable, and in those with prior severe reactions to contrast, strong allergic history, asthma or defined severe cardiac disease [King (1989)].

There are problems with all of the guidelines however. Several questions need to be addressed before guidelines can be accepted as useful in practice. I will now discuss each of these questions in turn.

(a) Are patients with the specified characteristics actually at increased risk of an adverse event?

Table 2 shows the relative risk of various types of adverse reactions to contrast associated with several characteristics that have come to be called "risk factors". These data are derived from much of the same literature which was cited in Table 1. In most cases the relative risks were calculated by dividing the incidence of the specified adverse event in the subgroup with the risk factor by the incidence in the remaining subjects. The figure quoted from the case control study by Enright is actually an odds ratio rather than a relative risk [Enright (1989)].

TABLE 2. RISK FACTORS FOR VARIOUS ADVERSE REACTIONS TO HIGH-OSMOLAR CONTRAST IN THE LITERATURE.

Study (year)	Risk factor	Type of reaction	Relative risk
Ansell (1970)	Meglumine	Bronchospasm	3.5
	Infusion IVP	Moderate	2.5
	"	Severe	2.8
Witten (1973)	High dose	"Acute reaction"	1.6
	Allergy (incl. asthma + prior reaction)	"	2.5
	Asthma	"	3.5
	Prior reaction (mild)	"	1.04
	Prior reaction (severe)	"	20.0
Shehadi (1975)	Age > 50	All types	0.8
	Allergy (incl. asthma)	"	2.1
	Prior reaction	"	3.3
	IVP vs Arteriogram	"	2.5
	Slow injection	"	1.4
Ansell (1980)	Allergy (incl. asthma)	Mild	1.6
	"	Moderate	2.6
	"	Severe	3.9
	Asthma	Moderate	2.5
	"	Severe	5.0
	Prior reaction	Mild	6.8
	"	Moderate	8.7

TABLE 2 contd.

Study (year)	Risk factor	Type of reaction	Relative risk
Ansell contd.	Prior reaction	Severe	11.0
	High dose	Severe	2.0
	Cardiac disease	Mild	1.1
	"	Moderate	0.9
	"	Severe	4.5
	"	Fatal	8.5
	Indian race	Severe	8.0
	Age > 50	Moderate	0.5
	"	Severe	3.3
Shehadi (1980)	IVP vs arteriogram	All types	2.1
	Age > 50	"	0.9
	"Allergy"	"	2.4
Lasser (1987)	Prior reaction	All reactions	2.4
	Allergy	"	1.3
	Youth	"	1.4
	Prior reaction	Treated reactions	2.5
	Allergy	"	1.8
	High dose	"	2.0
Enright (1989)	Allergy	All reactions	2.0
Moore (1989)	Diabetes	Class II/III reaction	2.3
	Asthma	"	0.6
	Prior reaction	"	1.4

Assessing a risk factor is in some senses a study of prognosis. Such studies should have: assembled an inception cohort, described their referral pattern, completed follow up, performed objective outcome assessment blindly, and adjusted for extraneous prognostic factors [Sackett (1985)]. Most of the studies cited in Table 2 are prospective surveys or case series. In some ways they represent an inception cohort presenting for radiocontrast administration. In almost all cases the referral pattern is not described, and indeed we know little about the nature of the study population. In some of the studies several potential "risk factors" are lumped together, e.g. asthma and allergy in the studies by Ansell (1980), Shehadi (1975), and Witten (1973). This makes assessment of individual risk factors difficult.

While it is likely that adverse reactions would have occurred soon after contrast injection, it is far less likely that reporting was consistently complete, and thus follow up cannot be said to have been complete. In fact, since the investigators almost certainly knew some of the factors which were to be examined, they may have been more thorough in their reporting of reactions occurring in subjects with "risk factors". This would generally exaggerate the apparent strength of the factors as predictors of adverse events. In most of the studies rather imprecise definitions of adverse events were used. Since these often involved some degree of subjective judgement on the part

of the investigator, who was generally not blinded, there is also a potential for bias in the outcome assessment process.

It is not clear from most of the reports that the factors of interest were identified in advance. This would be important, as it would render a type I error more likely in the assessment of the statistical significance of the relative risks. Indeed some of the studies did not perform any statistical assessment of the strength of their risk factors at all and none reported confidence intervals for the relative risks. It is also clear that not all "risk factors" are relevant to all outcomes. In a recent study by Moore, one of the outcomes used was a Class II/Class III reaction [Moore (1989)]. Such reactions were very heterogenous, but were mostly cardiovascular reactions occurring during cardiac angiography. Thus it was inappropriate to examine IVP's together with cardiac catheterizations and to expect the same risk factors to be important in both groups given that they had different adverse events. The final problem with the studies is that very few used any kind of multivariate technique to simultaneously assess the independent strength of the various risk factors. Moore used a multiple logistic regression technique, but did not identify many risk factors in his study. The study population was small however, and no consideration was given to power.

Studies of risk factors can also be thought of as being similar to studies of causation in some respects. While the contrast exposure is certainly the proximate cause of the

contrast reaction, other characteristics of the examination and the patient can be thought of as contributory causes. Although some "risk factors" may actually be noncausal associations, the guidelines by which a study of causation can be assessed do still apply in part [Trout (1981)].

The strength of evidence for causation comes in large part from the basic study design. The strongest evidence comes from randomized trials. There are no trials where the supposed "risk factors" are randomly assigned. Indeed it would be impossible to randomly assign most of them as they represent inherent qualities of the subjects being given contrast. Allergy has been assessed as a risk factor in a case control study [Enright (1989)] and all the other studies are case series or surveys. The strength of association is indicated by the relative risk. This can be seen to vary depending on the outcome used and the risk factor assessed, but there is still some variation between studies even when these are taken into account. The strongest associations were generally found with allergy, prior reaction to contrast, and asthma. Since several of the studies found these characteristics to be "risk factors", this supports the reality of the associations. Being aged over 50 years was not seen to be associated with an increased risk in most studies, but was associated with an increased risk of severe adverse events [Lasser (1987), Ansell (1980)].

The temporal relationship between the "risk factors" and the reactions is as would be expected if the "risk factors" were in

fact causing the reactions. There are very little data by which to assess whether there is a relationship between the severity of the "risk factor" and the likelihood of a reaction. Similarly it is impossible to say whether the associations make epidemiological sense as there are no studies of the relative distribution of the "risk factors" and the reactions in populations. Several of the associations do make some biological sense, as was explained in Chapter 2 when the putative mechanisms of contrast toxicity were being discussed. The associations are not specific and cannot really be said to be analogous to previously proven causal associations.

Most authors attempt to define risk factors for contrast nephropathy separately from those for anaphylactoid reactions. Pre-existing renal insufficiency, diabetes, dehydration, old age, high dose of contrast, hypertension, congestive heart failure, route and site of injection, and myeloma are often stated to be risk factors [Berkseth (1984)]. The evidence for these is quite weak in most cases. I have previously reviewed this topic [Barrett (1991)] and we have studied the effect of renal insufficiency and diabetes ourselves [Cramer (1985), Parfrey (1989)]. It seems that there is an increase in the incidence of contrast nephropathy in subjects with pre-existing renal insufficiency with or without diabetes. Diabetics with normal renal function do not appear to be at increased risk, while diabetics with nephropathy probably have the highest risk [Parfrey (1989), Manske (1990)]. Dehydration may well be an

added risk in some cases, but this is often prevented now by hydration of patients before contrast, especially if they have other risk factors. The definition of high risk groups for contrast nephropathy may be of lesser importance to the strategy of selectively giving those at highest risk nonionic contrast because there is still little evidence that nonionic contrast is less likely to injure the kidney [Schwab (1989)].

(b) Do low-osmolar agents reduce adverse events in selected "high risk" patients?

There have been no studies, other than anecdotal reports, to specifically assess the efficacy of nonionic contrast in high risk patients. Holtas reported that 17 patients, who had had moderate/severe anaphylactoid reactions to ionic contrast in the past, received iohexol without adverse effects on up to three further occasions each [Holtas (1984)]. This incidence of 0 events in at least 17 trials yields an upper 95 percent confidence limit of about 17 percent for the incidence of recurrent anaphylactoid reactions after nonionic contrast in this select group with a history of prior reaction to ionic contrast [Hanley (1983)]. This is fairly impressive when one considers that the incidence of recurrent reactions to ionic contrast has been reported to be as high as 35% [Greenberger (1985)]. However, Shehadi found that serious reactions may be less likely to recur than less severe reactions [Shehadi (1982)], while Lalli was able to give a different ionic contrast to patients who had a history of prior shock reactions to ionic

contrast without any ill effects [Lalli (1975)]. Rapoport also found the low-osmolar agent metrizamide to be safe for imaging in patients who had a history of severe anaphylactoid reactions to ionic contrast [Rapoport (1982)]. All of the patients in this study had also received steroid and other prophylaxis. However, some of them had had reactions to ionic contrast in the past despite similar prophylaxis. These studies only provide weak evidence that low-osmolar media are specifically useful in patients with previous reactions to contrast.

After our study had been initiated Feldman et al. demonstrated that low-osmolar contrast was beneficial in patients with severe or unstable cardiac disease who were undergoing cardiac catheterization [Feldman (1988)]. Schrott gave low-osmolar contrast to "high risk" subjects of various types and observed a low rate of adverse reactions [Schrott (1986)]. This study was uncontrolled, however, and therefore relies on historical evidence that high-osmolar contrast would have led to more adverse reactions. Thus there are very little data available to justify the statement that low-osmolar contrast is of particular benefit to patients who might be at high risk.

(c) Can "high risk" patients be identified easily and reliably?

To identify those at high risk before contrast requires that the risk can be assessed by a history from the patient if possible. Hospital or other records are not always available at the time of imaging procedures and, if special tests or

examinations are necessary to identify which patients are at high risk, it may not be feasible to identify many such individuals in practice. While many of the traditionally quoted "risk factors" are identifiable by questioning the patient, there will almost certainly be differences of opinion as to what level of anxiety, what severity of asthma, what sort of allergy etc. actually carry a higher risk. This uncertainty must also have affected the studies which examined these characteristics as "risk factors" and in most cases there was no attempt to clarify what was meant by allergy, asthma etc. This makes it virtually impossible to state exactly what degree of risk is associated with various levels of most of the existing risk factors.

(d) Does exclusion of a large "low risk" group from the receipt of low-osmolar contrast fail to prevent many adverse events which continue to occur in the "low risk" group? Is the "high risk" group so large that cost savings, due to the use of low-osmolar contrast solely in the "high risk" group, are minimal?

The answers to these questions require knowledge of the sort of patients being treated in a cardiac catheterization laboratory or an X-ray department. This is likely to vary from place to place. Goel and colleagues asked their local radiologists for estimates of the proportion of the population being given contrast who had various "risk factors" [Goel (1989)]. It is not clear how their estimates were made, but it

would behove each centre to do a study of their own population to assess the likely local cost-effectiveness.

(e) Can less expensive measures, such as the use of steroid prophylaxis, achieve the same result as the use of low-osmolar contrast?

Prior to the trial of steroid prophylaxis reported by Lasser, there was no good evidence that any intervention could reduce the incidence of contrast related adverse events [Lasser (1987)]. Other workers had suggested that prophylaxis with medications or by minimization of anxiety could reduce the incidence of reactions [Greenberger (1985), Lalli (1975)]. The design of these studies precluded confidence in their conclusions however. Even though Lasser's study had faults (as I have discussed in Chapter 2) it provided reasonable evidence that steroid prophylaxis is efficacious. These authors found that the incidence of adverse events in their steroid treated patients was comparable to that which had been reported by Schrott in patients given nonionic contrast [Schrott (1986)]. Subsequently both Bettmann [Bettmann (1987)] and Lasser [Lasser (1990)] suggested that steroid prophylaxis might be as useful as, and cheaper than, the use of nonionic contrast in some patients. However there has never been a direct comparison of these strategies in any population.

3.3. A summary of the research questions:

Based on a review of much of the data discussed above, it was felt that several interrelated research questions should be

posed. The questions which were specifically addressed by the trial being discussed in this thesis were:-

(1) Is nonionic low-osmolar radiocontrast associated with a lower incidence of: (a) systemic anaphylactoid adverse reactions requiring therapy, (b) contrast nephropathy as defined by an unexplained increment in serum creatinine of at least 25% after contrast, (c) subjectively severe symptoms as assessed by a Likert-like symptom questionnaire completed by the patient immediately after imaging and (d) significant changes in heart rhythm or blood pressure, when compared to ionic high-osmolar radiocontrast given intravenously for CT or IVP in patients perceived to be at high risk of an adverse reaction to radiocontrast or into the heart during cardiac angiography?

(2) Is nonionic low-osmolar contrast associated with a lower incidence of adverse cardiovascular events which require therapy than high-osmolar ionic contrast after intracardiac injection of the contrast?

(3) What is the magnitude of the increased risk associated with the characteristics proposed in the literature as risk factors for adverse reactions to intravenous or intracardiac radiocontrast?

(4) Are there other demographic or clinical characteristics which are associated with an increased risk for the occurrence of such adverse reactions to radiocontrast given intravenously or by intracardiac injection?

(5) What is the incremental cost of using nonionic low-osmolar contrast rather than ionic high-osmolar contrast for patients of the type entered in the trial and, if nonionic contrast is effective in preventing adverse events, what does it cost to prevent one adverse event of specified type by use of low rather than high-osmolar contrast?

(6) Might the cost-effectiveness of the low-osmolar contrast be improved, without risking the occurrence of excessive numbers of potentially preventable clinically important adverse events, by the use of low-osmolar contrast only in a selected "high risk" population?

CHAPTER 4

RESEARCH ARCHITECTURE, INTERVENTIONS AND SUBJECT SELECTION

4.1. Research architecture:

The best way to determine if there is a difference between two "therapies" in terms of efficacy or toxicity is to administer them both to comparable subjects under the same conditions. This ensures that any subsequently observed differences between the groups are likely to be due to the "therapy" and not some other confounding factor. This could be achieved by giving both "therapies" to the same subject(s) at one or more different times (a crossover design), allowing only chance to determine the order of administration. In that situation each subject acts as his/her own control and thus the comparability of the subjects receiving each "therapy" is maximized. In trials of contrast media each subject is generally treated once and thus crossover designs or N-of-one studies [Guyatt (1986)] cannot be employed.

Comparability of the groups receiving ionic high-osmolar and nonionic low-osmolar contrast could be achieved by careful and extensive matching procedures. However, it would be difficult to arrange that all known prognostically important variables were matched and subject selection would become very difficult. It would not be possible to arrange matching for unknown prognostically important variables at all. To overcome these problems random assignment to treatment groups is often employed. If large numbers of subjects are randomly assigned to

two groups, chance alone should make prognostically important variables distribute equally across the groups. The current trial was therefore designed as a randomized comparison of low-osmolar with high-osmolar contrast media.

4.2. The interventions studied:

It was decided to compare the toxicity of ionic high-osmolar media to that of nonionic low-osmolar media in general. It would have been difficult to study specific products separately, as the differences between the various nonionic media would almost certainly be less than those between nonionic media in general and high-osmolar media. In practice the media used were those bought under contract by the hospital and the exact compound employed varied during the course of the study.

After the study had been completed we became aware of the possible difference between formulations of high-osmolar contrast which contain calcium binding additives and those which do not, in terms of their tendency to cause ventricular fibrillation [Murdock (1985), Zukerman (1987)]. The high-osmolar media used during the trial all contained calcium binding additives. However, ventricular fibrillation was only one of the clinically significant adverse events occurring less often after low-osmolar contrast in the trial. The literature comparing the two formulations of high-osmolar media does not contain enough data to prove that clinically important adverse reactions, other than ventricular fibrillation, are less frequent with formulations that do not bind calcium [Murdock (1985), Zukerman

(1987)]. The formulations of high-osmolar media which bind calcium are still in use for cardiac catheterization. It would have been better if the trial had compared non-calcium binding formulations of high-osmolar contrast with nonionic agents, but the differences that were observed between the high and low-osmolar media in terms of events other than ventricular fibrillation might still have been found. Therefore the comparison that was made still has implications for clinical practice.

It was decided not to study ionic low-osmolar media because this would have increased the heterogeneity of the interventions and there was little reason to suspect that ionic low-osmolar media would be less toxic than nonionic media. Ioxaglate, the only ionic low-osmolar medium marketed in Canada, is almost as expensive as nonionic media and thus there was no financial incentive to study it either.

Patients were randomly assigned to two equal sized groups. One group was given whatever ionic high-osmolar agent the doctor felt was best suited to the particular examination, while the other group was given a nonionic low-osmolar agent.

4.3. The study sites:

We were primarily interested in investigating the systemic toxicity of the two classes of contrast. We initially intended to study patients at the radiology departments of all three adult acute care hospitals in the city. This would have had the advantage of maximizing the generalizability of the results and

our sample size calculations indicated that we needed more patients than would be available in the radiology department of our own institution alone. It was eventually decided to limit the study to the General Hospital radiology department after it became clear that we could also study patients having cardiac catheterization at that institution and thus achieve our projected sample size.

The decision to study patients having cardiac angiography together with those having intravenous contrast was probably not sensible. These populations differ substantially in terms of their health status and their response to contrast media. The difficulties caused by the decision to study these populations together are further explored in Chapter 6.

The site chosen for the trial is the tertiary referral university centre for the province. It provided almost all of the computed tomographic imaging and all the cardiac angiography required by residents of the province during the study period. Thus the results in these subgroups at least should be quite generalizable. The advantages of a single institution design were that the study could be carried out by fewer staff, was less costly, and the conduct of the study could be more strictly controlled from day to day. All of the cardiologists and radiologists working in these departments agreed to participate in the study and thus again generalizability was maximized.

4.4. Selection of the study population:

It was decided not to include patients having peripheral angiography in the study, as there was already good evidence that low-osmolar contrast reduced the pain associated with this procedure [Bonati (1984), Newman (1984), Reidy (1984), Mills (1984), Wolf (1985), Dotter (1985)]. The same reasoning was applied to cerebral angiography. Venography was not excluded from the outset, but it was clear from the pilot study that relatively few venograms were done and, that as they were often arranged as emergencies, it would be difficult for the research nurses to enrol patients having this investigation. Furthermore, as we did not have facilities to investigate venogram-induced thrombosis we felt that our study would be unlikely to influence choice of contrast for venography.

Thus, in the radiology department, eligible subjects were drawn from the population presenting for intravenous pyelography or for contrast enhanced CT scanning.

All patients having cardiac angiography without angioplasty were eligible. Angioplasty was excluded as it was felt that technical factors, rather than contrast, might cause some of the adverse events during that procedure and that it would be difficult to decide which events were related to contrast and which were not. On the rare occasion when subjects were having complete angiography prior to a possible angioplasty, they were enroled and their involvement terminated prior to the commencement of the angioplasty.

4.5. Exclusions because of perceived excessive risk with high-osmolar contrast.

Before the trial started it was decided to exclude those with a history of severe prior anaphylactoid reaction to contrast. This was because the radiologists, and to a lesser extent the cardiologists, were uncomfortable with the use of high-osmolar agents in such patients. There were some reasons (reviewed in Chapter 3) to believe that low-osmolar contrast would cause fewer subsequent reactions in such patients. The final responsibility for deciding whether an individual patient could be entered in the randomized trial rested with the radiologist or cardiologist performing the imaging. This was necessary to allow these doctors to exercise their clinical freedom and to use their best judgement when treating an individual patient. This meant that the randomized groups were not entirely representative of the population presenting for imaging. This reduced the generalizability of the trial results. However, the internal validity of the trial was not compromised as all exclusions were made prior to random assignment of contrast and the exclusions could not bias the comparison of the randomized groups.

This selection process operated on a case by case basis and was difficult to predict. The participating doctors varied between and within themselves with regard to how they decided when a patient was suitable for inclusion in the randomized trial. There was a tendency to exclude a progressively greater

proportion of otherwise eligible patients as the trial progressed. This was particularly evident in the intravenous stratum where close to 30% of eligible patients were not being randomized by the time the trial was stopped. The major reasons given for exclusion were: prior reaction to contrast, allergy or asthma in the intravenous stratum, and suspected severe cardiac disease in the intraarterial stratum.

The principal investigators were unable to exert direct control over the subject selection process discussed above. Every effort was made to ensure that excessive numbers of patients were not excluded from randomization. A log was kept of all patients approached for primary interview during most of the trial. Note was made of how many met the eligibility criteria, how many refused randomization, how many were excluded by the radiologists and cardiologists, and the reasons for each exclusion. This accumulating information was regularly communicated to the collaborating physicians. These physicians were encouraged to maximize the number of eligible patients randomized. Latterly the publication of the results of the surveys by the RACR and the Japanese [Palmer (1988), Katayama (1990)] were quite influential in determining which patients were entered in the intravenous limb of the randomized trial. The bias of the participating radiologists in favour of low-osmolar contrast was strengthened by the results of these surveys. This was further augmented by a rather partisan

presentation by Professor Palmer of the results of the RACR survey during a visit to St. John's.

The cardiologists also excluded patients from randomization, particularly on the basis of suspected severe cardiac disease. The proportion of eligible patients not being randomized did not seem to increase over time to the same extent in those having intracardiac contrast as it did in those having intravenous contrast. The emerging evidence favouring low-osmolar contrast in subjects with severe cardiac disease [Feldman (1988)] did, justifiably, prevent some patients from being randomized.

4.6. Exclusions because of nonavailability of low-osmolar contrast:

Some patients, who were having CT scans which required a large volume of contrast, were not randomized and were given high-osmolar contrast. This was purely because there was no suitable, large volume, vial of low-osmolar contrast available locally during the early days of the study. These patients differed in some respects from those who were randomly assigned to high-osmolar contrast. However they appeared to have a similar incidence of contrast related adverse events to those who were randomized [Appendix B].

4.7. Selection of high risk subjects:

One of the aims of this research was to study the degree of increased risk associated with the "high risk" characteristics used in the many guidelines proposed by others (see Chapter 3). We wished to know whether it was possible to select a subgroup

of patients to preferentially receive nonionic contrast, and whether the guidelines suggested by others were optimal in that regard. The "risk factors" in the various guidelines included: a history of a prior reaction to contrast, a history of allergy, asthma, cardiac or renal impairment, diabetes, excessive anxiety and severe illness. To study these factors adequately one would ideally like to study all those having contrast enhanced imaging and then compare the incidence of adverse events in those with and without the various "high risk" factors.

However, the grant for this study did not cover the cost of contrast. If all patients attending for x-ray with contrast had been included in the study there would have been a substantial increase in the use of low-osmolar contrast, with an attendant increase in expenditure in the radiology department. It was felt that the department would not be able to afford to pay for the contrast for all those subjects. Therefore a decision had to be made as to how best to limit the use of low-osmolar contrast without compromising the major objective of determining the relative toxicity of high and low-osmolar contrast. If a clinically important benefit was not discernable amongst high risk patients, it was felt that it would be quite unlikely that such a benefit would be seen in a low risk group.

The estimated sample size (see Chapter 5) for the trial was large. Enrolment could not be limited to a proportion of eligible subjects in order to spread the cost of the low-osmolar contrast over a longer period, as to do so would have made the

duration of the study too long and would have introduced a possibility for bias in subject selection. Since the incidence of adverse reactions to contrast was likely to be lower in those without any "risk factors" it was decided to exclude such subjects. While this increased the likelihood of an event in those who entered the trial, and thus tended to reduce the required sample size, it complicated the assessment of the relative risk associated with various risk factors.

However, we hypothesized that several of the "risk factors" would not turn out to be very important. In particular it seemed likely that subjects who were aged over 50 years, but who had no other risk factors, would not have an excessive incidence of adverse events. Therefore we reasoned that if the incidence of adverse events did turn out to be lower in this subgroup than in others, that they could serve as a reasonable population against which to judge the effect of the other "risk factors". This approach was obviously not ideal as it would be impossible to say directly whether the observed incidence of adverse reactions in the subgroup aged over 50 was above or below that seen in other individuals felt not to be at increased risk. However, some information on the average incidence of specific adverse outcomes was available from the literature and served to compare with the observed incidence in our subgroup aged over 50 years.

All patients having cardiac angiography were eligible irrespective of whether or not they had any of the above "risk factors". This was because we were interested to know whether

those without cardiac disease at angiography would have as great an incidence of cardiovascular side-effects as those who had cardiac disease. In this way we could directly verify whether cardiac disease increased the risk of an adverse cardiovascular event after intraarterial contrast. It would also have been impossible to reliably identify those without cardiac disease for exclusion before the results of the cardiac catheterization were known.

One of the difficulties with deciding the eligibility criteria for this trial was deciding how to define each of the so called "risk factors". Most of these factors cannot be unambiguously defined. For example the decision as to whether someone is more than usually anxious is subject to considerable variability. Unless a standardized instrument for measuring anxiety is employed the decision is also highly subjective. This further increases the variability. Some of the factors, such as severe illness, are quite heterogenous.

Ideally the trial should have assessed the relationship of the severity of the risk factors with the likelihood of an adverse event. This was done in the case of renal impairment. The degree of pre-existing impairment, as reflected in the serum creatinine, was associated with the risk for contrast nephropathy. An attempt was made to assess the severity and etiology of prior reactions to contrast. This was necessary to allow the radiologists to decide whether patients should be randomized or not. Those with the most severe prior reactions to

contrast were excluded. However no attempt was made to consider the severity of prior reactions during the analysis of patients who were entered in the trial. This is a shortcoming that will be addressed in future work with this data.

It is difficult to measure the severity of some risk factors reliably. It might have been possible to scale the severity of anxiety or cardiac disease, but it would have been more difficult to measure the severity of an allergy history. The difficulty of these tasks is reflected by the fact that they have not generally been undertaken in other studies of contrast media.

Feasibility was also a major factor in deciding how to define the risk factors for this trial. The research nurses did not have time to perform extensive assessments of the severity of potential risk factors along with their other duties. It should also be emphasized that the results of the study were meant to be applicable in practice. Busy radiologists would not have time to perform lengthy or difficult assessments of the severity of risk factors either. If the factors were to be useful for identification of a high risk group for selective use of low-osmolar contrast, they would have to be identifiable by an easily administered screening process. Nevertheless this trial would have been enhanced by a formal attempt to measure and analyze the severity of at least some of the risk factors.

An informal attempt was made to prevent the inclusion of subjects with minimal degrees of allergy or trivial prior

reactions to contrast. The nurses collected details about the nature and severity of these factors. If there was doubt as to whether a patient should be coded as having the risk factor or not, these details were reviewed before a decision was made. It would have been better if more detailed explicit criteria as to what constituted eligible risk factors for the purposes of this trial had been uniformly applied. This would have helped others to interpret the results of the study.

The following operational definitions were used for risk factors which made patients eligible for inclusion in the trial of intravenous contrast: (1) Prior reaction to contrast was defined as a history from the patient or the medical record of an anaphylactoid or cardiovascular reaction, or severe symptoms following past administration of radiocontrast. (2) Allergy was defined as a history from the patient or the medical record of an adverse reaction to a drug, foodstuff or other contact, which was likely to have an immunological basis as determined by either the physician supervising the imaging or the principal investigator. (3) Asthma was defined as a history from the patient or the medical record of a respiratory disease with symptoms which were reversible either spontaneously or with bronchodilator therapy. (4) Cardiac disease was defined as a history of active angina, heart failure, myocardial infarction, congenital or valvular heart disease, or a history of cardiac surgery elicited from the patient or the medical record by the research nurse. In the case of patients having cardiac

catheterization it was possible to get specific information about the nature and severity of any existing cardiac disease from the cardiologist. His/her opinion was based on clinical information and the results of the cardiac catheterization. (5) Renal impairment was defined as a serum creatinine greater than or equal to 120 μmol/l in a sample taken within 24 hours prior to contrast administration. (6) Diabetes mellitus was defined as a history from the patient or the medical record of having that condition. Details of the duration of the condition and its therapy were also recorded. (7) Anxiety was recorded as present if the research nurse considered that the patient was unusually anxious as compared to other patients having that procedure. (8) Severe illness was defined as being confined to bed in hospital for acute medical reasons on the order of a physician. (9) Whether the patient was aged greater than 50 years was determined by asking the patient and examining the records.

Only subjects with one or more of the above characteristics, who were having intravenous contrast for computed tomography or IVP, were eligible for inclusion in the trial.

CHAPTER 5

STRATIFICATION, RANDOMIZATION, BLINDING AND SAMPLE SIZE

5.1. Stratification before randomization:

Simple randomization does not always ensure that groups are completely comparable in all respects. It is possible for two randomized groups to end up with different proportions of individuals with some important characteristic. Although this is unlikely when large numbers are being randomized, the risk of imbalance can be minimized by stratification for the variables of interest before randomization. This is particularly helpful if there is a prognostically important variable which is likely to be present in only a small proportion of the population. In that situation chance might well give rise to groups imbalanced for the variable if simple randomization is used. This is avoided by employing a restricted or block randomization within the strata with and without the factor of interest. If there is more than one such factor present several stratification steps can be employed before randomization. The number of strata that can be used is limited in practice by the fact that the number of groups randomized separately at least doubles with the addition of each stratification factor. If imbalance between randomized groups occurs despite these precautions it can be addressed by stratified analysis.

Apart from ensuring comparability of randomized groups, stratification can also be useful if one expects that the

response to a given intervention might be different in quantity or, even more importantly, quality in different strata. Subgroup analysis within strata can be performed with greatest assurance of validity if the subgroups have been specified in advance and have been separately randomized with regard to the intervention.

Since there were major differences between patients in the intravenous and the intracardiac arms of the current study it was clear that patients would have to be stratified into those having cardiac catheterization and those having intravenous contrast prior to randomization. Within each of these strata there were several variables which could have a prognostic link to contrast-related adverse reactions. These variables included the factors which had been traditionally referred to as "risk factors".

In order to judge whether stratification by the presence of a particular "risk factor" would be required, it was necessary to know approximately how many patients with each of the "risk factors" would be available for study. A pilot study was performed before the trial proper was commenced. This indicated that there would probably be 1500 patients with a history of prior reaction to contrast, allergy, or asthma, 500 patients with renal impairment, 750 with diabetes, 750 with anxiety, and 2500 aged greater than 50 years available for study during the projected study period. Given these estimates further stratification of patients prior to randomization did not appear

warranted. It was hoped that the randomization process would generate comparable groups in terms of all of these variables.

5.2. The randomization process:

This trial used simple randomization within each of the two strata (i.e. cardiac and intravenous injection arms) in order to keep the process as straightforward as possible [Zelen (1974)]. This was necessary because there was very little time available to the research nurses between cases. The nurse was responsible for interviewing each patient attending for imaging, deciding eligibility, obtaining consent from both patient and doctor, and overseeing the randomization. All of this had to be done without imposing delays in the schedules of the imaging departments.

A block randomization scheme should have been used in this trial. This would have ensured that the groups remained comparable in terms of the number assigned to each treatment within the two strata as the trial progressed. However, the fact that a blocking scheme was not employed probably does not have serious implications for the validity of the randomization. There were several more serious limitations and deficiencies to the randomization process. In order to illustrate these I will first outline how the randomization proceeded in the current trial.

In the cardiac catheterization laboratory the research nurse was responsible for both patient recruitment and randomization. Randomization was done using a random number table, but a closed envelope system was not used. As a result the research nurse was

potentially aware of the group to which the prospective study patient would be assigned, at a time when the patient was being evaluated with regard to eligibility. The implications of this flaw will be discussed in the section on blinding later in this chapter.

In the radiology department the research nurse was responsible for patient recruitment and initially for randomization as well. A serious error occurred in the randomization process for this stratum during the first few months of the study. The error arose from the fact that some of the study staff were inexperienced in research methods and had not been adequately trained before they started to work on the trial. The error was also contributed to by inadequate formal detailed specification of how the randomization should be performed. This error could have been prevented by proper planning and by better training procedures. The error was compounded by the fact that patients entered in the trial were not recorded consecutively in a log at this stage. Such a record would have made it easier to recognise the error when it occurred. It would also have made it easier to deal with the error after the fact by allowing unambiguous identification of the subjects who had been inappropriately randomized.

The error to which I have been referring arose as follows. Nonionic contrast was not available in bottles containing more than 50 millilitres. Some investigations, such as CT of the abdomen or sinuses, routinely required a large volume of

contrast. The radiologists had decided that only ionic high-osmolar contrast would be employed for enhancement during those procedures. Thus it was not possible to randomly assign contrast to patients having these procedures. However, when such patients were otherwise eligible for inclusion in the trial, the nurse checked to see what contrast was indicated by the next random number to be used. If the random number indicated that high-osmolar contrast should be given, the patient received this and was recorded as having been randomized. If the random number indicated that nonionic contrast should be given then the patient was excluded from the randomized trial and received high-osmolar contrast. The random assignment to nonionic contrast was subsequently used for the next patient eligible for the randomized trial. This error may have introduced bias. Those patients who were having the procedures which required a large volume of contrast all received high-osmolar media. They would almost certainly have differed systematically from the next consecutive patients. These were given the nonionic contrast initially selected by the random number table for those having the procedure, for which only high-osmolar contrast could be employed. The resulting bias might have favoured the nonionic group because the patients having the high volume procedures tended to be at higher than average risk of an adverse reaction.

If the patients entered in the trial had been recorded consecutively in a log book it would have been possible to identify all those who had been inappropriately randomized.

These patients could then have been excluded from the analysis of the randomized trial. It was possible to identify the 220 patients who had investigations requiring a high volume of contrast before the error was discovered. These patients were removed from the randomized trial. They were analyzed together with others who were not randomly assigned a contrast medium. It was not possible to identify those who had been given the corresponding nonionic assignments and these patients were not removed from the randomized trial. This could also bias the comparison of the randomized groups because such patients might differ systematically in some way from the others in the trial. The direction and magnitude of such bias is difficult to judge without knowledge of the characteristics of the patients inappropriately randomized to the nonionic group.

An effort was made to determine if bias introduced in this way could have influenced the results of the trial. The event rates in the high and low-osmolar groups were determined separately for those entered in the randomized trial before and after the error was discovered. Among those entered in the trial before the error, and not subsequently excluded, 1.3% of those given high and 0.6% of those given low-osmolar contrast had an adverse event which required attention by a doctor. After the error such an event occurred in 5.6% of those given high and 1.7% of those given low-osmolar contrast. Given these numbers it seems unlikely that the adverse event rate was lower than average in the patients randomized to high-osmolar and subsequently

excluded, or higher than average in those inappropriately randomized to low-osmolar and not subsequently removed from the trial. If these assumptions are true then any resulting biases should tend to cancel each other out. In any case the difference between the ionic and nonionic groups randomized after the randomization was corrected is still highly significantly in favour of nonionic. Even if the patients entered before the error was discovered are not counted the conclusion of the trial remains unchanged.

A sure way to prevent the error in randomization from biasing the results of the trial would have been to exclude all of the patients entered in the intravenous limb of the trial before the error was corrected at the time that the error was discovered. Most of the patients thus excluded would not have been inappropriately included in the trial in the first place. However, all of these patients would have to be replaced by others who were correctly randomized. This would have been very costly but might have been worthwhile. Fortunately the analysis of the results before and after the error was corrected indicate that the potential bias does not invalidate the conclusions of the trial.

After the mistake in randomization was recognized, the whole randomization process in the radiology department was reviewed and improved. A sealed envelope system of random assignment was introduced. The nurse interviewed the potential subjects while blind to the next random assignment. She determined whether they

met the eligibility criteria. She then approached the radiologist to obtain permission to enter the subject in the randomized trial. If permission was granted, she handed the sealed envelope to the radiation technologist who prepared the contrast for injection. This randomization procedure should have been employed from the beginning of the trial. A log with consecutive numbering of the patients interviewed and of those entered in the trial was also maintained from this point.

5.3. Blinding procedures:

Blinding is an important technique that helps to control bias in randomized trials. Blinding can be applied at four stages [Chalmers (1981)]. The first stage at which blinding should be applied is when random assignments are being made. Chalmers has demonstrated that when the person responsible for recruiting subjects to a trial is aware of the next randomly determined treatment assignment, bias can play a role in determining the likelihood that a particular subject is entered in the study [Chalmers (1983)]. The result is generally an imbalance between the random groups in terms of some prognostically important variable. This complicates interpretation of the trial results and may even invalidate the study entirely.

Randomization was not performed blindly in the cardiac catheterization laboratory or during the initial phase of the trial in the radiology department. This could have influenced the nature of the patients assigned to the treatment groups. The problem could easily have been avoided by the use of a sealed

envelope system during randomization. The effects of the bias can be partially overcome by an analysis which standardizes or otherwise adjusts for factors, which are associated with the outcome, but which are not evenly distributed in the randomized groups.

The randomized groups appeared well balanced in terms of baseline factors among those having cardiac angiography. Therefore it seems unlikely that the unblinded randomization introduced major bias to this arm of the trial.

In the intravenous limb of the trial there appeared to be an excess of patients with cardiac disease randomly assigned to nonionic contrast. Whether this imbalance arose because of unblinded randomization is not clear. The results of the trial indicated that cardiac disease was associated with a higher likelihood of an adverse reaction requiring the attention of a doctor among patients receiving intravenous contrast. The excess of cardiac disease in the group assigned to intravenous nonionic contrast would thus tend to bias the trial against nonionic contrast. However, since the result of the trial was in favour of nonionic, this bias could only have reduced the apparent benefit of nonionic media. The logistic regression analysis adjusted for the presence of cardiac disease when it examined the relative risk for an adverse event associated with the nature of the contrast given [Appendix B].

The traditional use of the term "double blind" refers to the blinding of trial staff and subjects to the nature of the

assigned therapy. This is to ensure that measurement of outcome events is not influenced by bias on the part of the subject or others responsible for assessment of outcome.

In the initial phase of the study of intravenous contrast the patient, doctor, and radiation technologist were blind to the contrast given whereas the research nurse was not. The major outcome was the occurrence of an event which led to assessment or treatment of the patient by a doctor. The decision as to which patients should be assessed or treated was not made by the nurse and therefore these decisions should have been free from bias. Nevertheless it is possible that the nurse could have had some unintentional effect on the nature of the decisions taken and bias could thus have occurred. This situation could have been avoided by the choice of a better outcome measure as discussed in Chapter 6.

The research nurse in the radiology department was responsible for both measurement of the pulse rate and blood pressure after imaging and for interviewing the patient as to the presence and severity of subjective symptoms during the test. Therefore bias could have had a major effect in terms of these outcomes. The magnitude and direction of this bias cannot be reliably estimated and therefore the results of the analyses of these outcomes have to be interpreted with caution.

Blinding of outcome assessment was addressed when the randomization process in the radiology department was revised. From then on the radiation technologist prepared the contrast

and kept it hidden from all those who were responsible for assessing outcome. Thus the traditional "double blinding" of those who were assessing outcome was assured.

In the cardiac catheterization laboratory the patient and the cardiology staff were blind to the type of contrast given to randomly assigned patients throughout the study. The only person who knew the nature of the contrast assigned was the research nurse, who was not responsible for assessing major outcomes. The nurse did administer the subjective symptom questionnaire after the procedure and could have introduced bias to the assessment of this outcome. This is not critical to the major results of the trial, but it could have been avoided by having the questionnaire administered by a person who did not know which contrast had been given.

The final kind of blinding is that which applies during the analysis [Chalmers (1981)]. The analysis of this trial was not performed in a blind fashion. A pre-specified primary outcome and significance level were employed and should help to minimize bias at this stage in the study. Nevertheless it would have been preferable to perform the major analyses while blind to the contrast received by the groups being analyzed. It is unclear whether the results of this trial were affected in a major way by the lack of blinding during data analysis.

Chalmers has argued that not only should blinding be performed, but that a test of blinding should also be done [Chalmers (1981)]. This seems reasonable as it may be

unrealistic to claim the benefits of blinding when it is quite possible that the blinding process was ineffective. The effectiveness of blinding was not assessed at any stage in this study. A test of blinding could have been done by asking the cardiologists to say which contrast had been given at the moment they decided to treat an adverse event. Such events were often preceded by minor hemodynamic changes which, since these were more common with high-osmolar contrast, might have compromised the blinding of the cardiologist. If the cardiologists were found not to be blind, then the decision to treat could have been influenced by the nature of the contrast given and thus the primary outcome biased.

5.4. Sample size determination:

The required sample size was calculated separately for a number of outcome measures. These will be discussed in more detail in Chapter 6. The overall sample size was dependent on the estimated frequency of systemic idiosyncratic reactions requiring the intervention of a physician.

The formula used to calculate sample size was as follows:

$$\text{Number per group} = 2[(Z\alpha + Z\beta) \div (2\sin^{-1}\sqrt{\pi_1} - 2\sin^{-1}\sqrt{\pi_2})]^2$$

$Z\alpha$ is the standardized normal deviate of the chosen α level. $Z\beta$ is the standardized normal deviate of the chosen β level. π_1 is the expected incidence of the outcome of interest in the high-osmolar group. π_2 is the expected incidence of the outcome of interest in the low-osmolar group.

All calculations used a 1-tailed α level of 0.05 and a β level of 0.2.

The likely frequency of an anaphylactoid reaction requiring intervention after high-osmolar contrast was estimated at 2%, based on the event rates for placebo treated patients in the study by Lasser [Lasser (1987)]. To detect a reduction to 1% by use of low-osmolar contrast required a sample size of 1779 randomized subjects per group, or 3558 subjects in total.

The sample size in relation to contrast nephropathy assumed as an outcome a 25% rise in the serum creatinine above baseline within 72 hours of contrast exposure. It was estimated that this would occur in 10% of patients given high-osmolar contrast from the results of a previous study of the incidence of contrast nephropathy [Parfrey (1989)]. To detect a reduction in incidence to 5% by the use of low-osmolar contrast required 335 patients per group, or a total of 670 patients with both baseline serum creatinine greater than 120 μmol/l and a follow up value available.

A separate sample size was not calculated for cardiovascular outcomes in the stratum having cardiac catheterization as it was initially intended to combine these patients with those having intravenous contrast and to primarily examine their systemic idiosyncratic reactions. This was a major flaw in the design of the trial and will be more fully addressed in the following chapter.

CHAPTER 6

OUTCOMES AND EVENTS

6.1. The choice of an outcome for a trial of therapy:

The choice of an outcome is one of the important tasks faced during the design of a study. For a therapeutic trial the ideal outcome should provide a valid reflection of the effects of therapy. The outcome should be easy to measure. The measurement should be reproducible and associated with as few sources of variation as possible. This will maximize the probability of being able to detect the effects of therapy. The outcome chosen should be clinically meaningful if the study results are intended to influence medical practice or policy.

It is preferable to use a single outcome if possible. This prevents difficulty that may arise with interpretation if the analysis of several outcomes suggests several incompatible conclusions. Sometimes it is not possible to avoid the use of more than one outcome if all important effects of therapy are to be captured. In that situation it is important to specify a primary outcome before the study starts. Consideration should also be given as to how the results of the analysis of multiple outcomes will be interpreted. Decision analysis can be used to integrate the many good and bad effects of a therapy as measured in a trial. Another possible approach when a therapy can have many good or bad effects is to use a single composite outcome to measure all of the effects. However, care should be taken to

ensure that such an outcome is not too heterogenous to prevent sensible interpretation of the data.

6.2. The choice of outcomes for the trial of contrast media:

There was considerable difficulty in choosing an outcome for the trial of contrast media. Part of the difficulty related to the many possible adverse effects of contrast. This difficulty was compounded by the decision to study patients having both intravenous and intracardiac contrast together. Initially the focus was on the anaphylactoid systemic adverse effects of contrast. The importance of adverse cardiovascular events in patients having cardiac catheterization was not adequately appreciated. This reflected the fact that it was initially decided to study these patients in order to meet the sample size requirements for a comparison of the systemic anaphylactoid effects of high and low-osmolar contrast. Some of the resulting difficulties might have been avoided by a more careful review of the literature concerning cardiac catheterization and by more extensive involvement of individuals, familiar with the performance of this procedure, in the design of the trial.

Given the heterogeneity of the adverse effects of contrast media a decision was taken to use several outcome measures. Specific adverse effects were to be measured separately and a composite primary outcome was chosen. The primary outcome chosen was the occurrence of a systemic adverse event, which might be attributable to contrast, and which led to the use of a therapeutic intervention. This outcome was far from ideal in

many ways. The research nurses made a record of the nature of any adverse event which occurred, it's timing in relation to the administration of contrast and the details of any medical attention or therapy which followed. The decision as to whether the event might be attributable to contrast was made by the investigators after the fact. The need for this decision and the decision to give therapy made it possible for bias to be introduced. An attempt was made to control this by requiring that these decisions be made while blind to the nature of the contrast given. The subjective nature of the decisions to give therapy and to attribute an event to contrast tends to reduce the reproducibility of the outcome measure. It also makes it more difficult for a third party to interpret the results of the trial. A further problem was introduced by the lack of a precise definition of the term "systemic adverse reaction". This was almost certainly responsible for the designation of several episodes of chest pain after intravenous contrast as primary outcome events. It is not clear to me even now whether these events formed part of the intended primary outcome at the time when the trial was being designed.

The decision to study patients having cardiac catheterization led to some further difficulties in specifying an outcome for the study as a whole. Given the occurrence of many adverse cardiovascular events in the group having cardiac angiography, and the rather vague definition of the primary outcome for the intravenous stratum, it would have been almost impossible to

judge whether an adverse event which required therapy in a patient having cardiac angiography was one which qualified as a primary outcome event as intended for both cardiac and intravenous subgroups at the outset of the trial. This, together with differences in the nature of the subjects having cardiac and intravenous contrast, made it very unwise to even consider combining these two populations for analysis. These difficulties are discussed more for theoretical than practical reasons, as the cardiac and intravenous arms of the study were never combined for any analysis other than that dealing with contrast nephropathy.

When it was decided to study patients having cardiac angiography provisions were made for recording details of all hemodynamic changes during the catheterization. A semi-structured record was also kept of any serious events which occurred during or shortly after the angiography. Note was made of any therapy given and whether the cardiologist asked to be unblinded because of an adverse event. A distinct composite outcome for the patients having cardiac angiography was not specified until the trial was well underway. It was then decided that the primary outcome for the cardiac angiography patients alone would be the occurrence of an adverse event which led to the prescription of therapy or a request for unblinding by the cardiologist. This did not lead to difficulty in deciding the outcome of patients who had been studied before this outcome was chosen, because the data which had already been recorded was of

sufficient quantity and quality to make it easy to determine retrospectively whether such a primary outcome had occurred.

It is not methodologically correct to specify an outcome after a trial has started. This was a fairly major flaw in the current trial which could have been avoided by more careful planning. The retrospective classification of patients with regard to outcome again made it possible for bias to be introduced. An attempt was made to control this by keeping the nature of the contrast assigned hidden from those who were making the decision as to whether a primary outcome event had occurred or not.

The heterogeneity of the events which constituted a primary outcome for those having cardiac angiography also led to difficulty in interpretation of the trial results. These events varied from trivial angina to life threatening arrythmias. This led to the need to develop other categories of outcome, (such as that designated as "clinically important adverse events" in Appendix A), during the analysis of the trial to adequately describe the nature of the benefits of low-osmolar contrast.

In summary there were many flaws with the specification of major outcomes for this trial of contrast media. It would have been better if separate primary outcomes had been specified at the outset for the patients having cardiac angiography and intravenous contrast. These outcomes should have been precisely defined, based on objective events, more homogenous with regard to their severity, and more readily interpreted by consumers of the research findings.

6.3. Hemodynamic outcomes:

In addition to the composite primary outcomes already discussed, the occurrence of a number of pre-defined objective hemodynamic events was recorded routinely throughout the trial, both in patients having intravenous and intracardiac contrast.

The heart rate and arterial blood pressure of all subjects was recorded before and after the imaging procedure. This was done by counting the pulse and using a sphygmomanometer in the radiology department. Electrocardiographic recording and intraarterial pressure monitoring were used in the cardiac catheterization laboratory. Continuous monitoring of these parameters during contrast administration was only performed in the cardiac stratum.

For the intravenous stratum the pre-specified hemodynamic outcomes were the development of a new arrythmia or a change in the arterial blood pressure of more than 20 mmHg systolic or 10 mmHg diastolic. More severe or symptomatic cardiovascular disturbance would generally have required the attention of a doctor and, as such, would have been fully described.

For the cardiac stratum a number of specific adverse cardiovascular events were defined. These included (a) any new arrythmia after the administration of contrast, (b) the occurrence of asystole lasting 5 seconds or more, (c) a fall in systolic blood pressure of more than 20 mmHg lasting more than 1 minute or requiring therapy and (d) angina.

6.4. Symptomatic outcomes:

The presence and subjective severity of several symptoms occurring with contrast exposure was measured by asking all patients to complete a symptom scale after the procedure. The scale contained 9 items and each was scored separately. The items were the symptoms warmth, nausea, vomiting, itch, dyspnea, sneezing, pain, chest tightness, and any other symptom. The severity of each symptom was measured by using a 10 point Likert-like scale (Fig 2). The symptoms were all analysed separately as it did not seem sensible to combine them into a composite symptom index and there was enough data to analyse them individually.

The measurement of these subjective variables was not tested for reliability or validity. Ideally this should have been done. The lack of such testing would constitute a major flaw in any study which depended primarily on the use of an instrument with unknown psychometric properties to measure subjective states. Reliability could have been tested by having a number of subjects complete the symptom scale on two separate occasions. The degree of agreement between the two scores from each subject would give an estimate of the test-retest reliability of the scale. Alternatively we could have used a different method, known as the Discan method, to measure symptom severity [Singh (1989)]. This method would have established whether the measurement at least demonstrated internal consistency,a minimum requirement for any reliable measurement instrument. The method would have been too cumbersome to use in the current study.

FIGURE 2. The subjective symptom questionnaire.

Put a mark on each of the following lines to show the severity of the following symptoms that may have occurred after you had contrast infused into your blood vessels.

	NO PROBLEM										VERY SEVERE
PAIN	0	1	2	3	4	5	6	7	8	9	10
WARMTH	0	1	2	3	4	5	6	7	8	9	10
NAUSEA	0	1	2	3	4	5	6	7	8	9	10
VOMITING	0	1	2	3	4	5	6	7	8	9	10
SNEEZING	0	1	2	3	4	5	6	7	8	9	10
ITCHING	0	1	2	3	4	5	6	7	8	9	10
SHORTNESS OF BREATH	0	1	2	3	4	5	6	7	8	9	10
CHEST TIGHTNESS	0	1	2	3	4	5	6	7	8	9	10

The symptom scale responses were divided into 2 categories for analysis. Symptoms greater than or equal to 5 out of 10 were called severe. This cutpoint was arbitrary and led to a loss of power, but this was not serious because there were so many subjects with symptoms. In a study of smaller size it would be more efficient to treat the scale scores as ordinal values and to use a nonparametric test such as the Mann-Whitney-U test to analyze the data.

6.5. Contrast nephropathy:

There is no specific diagnostic test for contrast nephropathy. This remains a diagnosis of exclusion when acute renal failure occurs after the administration of contrast. Some authors have used changes in the level of various proteins and enzymes in the urine as indicators of renal damage. While these measures may be very sensitive, they are not specific and do not generally indicate the occurrence of a clinically significant renal injury. Therefore they were not used to diagnose contrast nephropathy in the current study.

Contrast nephropathy was diagnosed in this study by measuring serum creatinine before and after contrast. The serum creatinine is an indirect indicator of the glomerular filtration rate (GFR), and is widely used to assess renal function. Changes in the serum creatinine tend to lag behind changes in the GFR. This is not a serious problem if one repeats the measure at the appropriate time. This was done at 48 to 72 hours after contrast in the current study, as this is the time when the creatinine

most often reaches its peak with contrast induced renal damage [Mudge (1980)]. A more serious problem is posed by the fact that the serum creatinine changes less, in absolute terms, with the same change in GFR when renal function is nearly normal than it does when renal function is more impaired. Indeed, the serum creatinine rises in an exponential fashion as the GFR falls.

Some authors have used changes in the absolute level of serum creatinine to diagnose cases of contrast nephropathy. This is not appropriate as the apparent incidence of renal damage is then unduly influenced by the baseline renal function of the population studied. This hinders the comparison of the incidence and severity of renal damage in different populations.

A proportionate increase in the serum creatinine was used to diagnose a case of contrast nephropathy in the current study [Appendix C]. This is a more accurate reflection of the underlying change in the GFR than is the absolute change in serum creatinine. Logarithmic transformation of the serum creatinine values prior to further analysis is an even better way to compare changes in GFR in patients with varying existing renal function.

It is statistically inefficient to convert continuous data to categories for analysis. The change in serum creatinine after contrast is an example of a continuous variable. In the analysis of this study the mean change in serum creatinine after ionic and nonionic contrast was compared using a Student t test. This was done both with and without logarithmic transformation of the

serum creatinine values [Appendix C]. This method of analysis is not only the most statistically efficient, it also avoids the use of arbitrary definitions to categorize the occurrence of events.

The results of such parametric analyses are difficult to interpret from a clinical point of view. Clinicians are often more comfortable when confronted with data that state that a particular therapy causes fewer discrete adverse events than another. Therefore the number of specified discrete "cases" of contrast nephropathy seen with ionic and nonionic contrast was also reported for the current study. A "case" was defined by a rise in the serum creatinine to at least 125% of the baseline value. This makes some adjustment for the difference in the expected magnitude of response of the serum creatinine to similar changes in GFR in subjects with varying baseline levels of serum creatinine. The choice of a 25% change to represent a "case" was based on the fact that this degree of change is greater than would be expected to occur simply on the basis of test/retest variability in the assay for serum creatinine (coefficient of variation 3.9% at our own hospital laboratory), or even in the day to day variation in the serum creatinine of an individual without any real change in GFR (about 5.5%) [Young (1979)]. Of course one could have chosen any arbitrary higher cutoff to define a case. In our previous study we had used a 50% change to define a case [Parfrey (1989)]. This level of change is more clinically meaningful, but is much less frequent, and

would have required a vastly larger sample to be able to show a statistically significant difference between the contrast agents. Differing categorical definitions of "cases" have been partly responsible for the variation in the reported incidence of contrast nephropathy in the literature. Therefore care should be exercised when such categorically classified continuous data is being reported, compared or discussed.

Since contrast nephropathy remains a diagnosis of exclusion, even the documentation of a decline in renal function after contrast is not sufficient to diagnose a true case of contrast nephropathy. Acute renal failure is often multifactorial in origin and the precise role that contrast plays in a specific case may be hard to determine. In the initial analysis of this trial the incidence of renal function change, irrespective of the likely cause, after the two types of contrast agent was compared. This analysis is valid but is complicated by "noise" which makes it more difficult to discern any true difference between the contrast agents. Therefore the case records of all subjects who had a deterioration in renal function were reviewed. A decision was made as to whether contrast could have been at least partly responsible for the change. This decision was made by a nephrologist blind to the type of contrast given in order prevent bias [Appendix C].

6.6. Analysis of events:

How events are counted in the analysis of a trial can have profound effects on the results. There has been controversy as

to which events should be included in the analysis of a trial [Sackett, Gent (1979)]. There are two poles to the argument. On the one hand one would only like to count events that "make sense" and charge them to the "appropriate" regimen. However, to do so may risk invalidating the results of the trial. This happened in the case of the Joint Study of Extracranial Arterial Occlusion for example [Fields (1970)]. On the other hand one could perform an analysis by "intention to treat" and charge all events to the regimen to which the patient is initially randomized. Neither view is necessarily always correct [Sackett, Gent (1979)]. The choice of which events to include in the analysis depends on the nature of the research question, the perspective from which it is posed, and a concern to avoid specific bias [Sackett, Gent (1979)]. We considered these factors when deciding how to handle specific groups of events in this trial.

6.6.1. How crossovers were handled:

A subject in a randomized trial is said to have "crossed over" when he/she is switched from the intervention to which he/she was randomly assigned to receive the intervention which has been assigned to the members of another randomized group. If this happens it is difficult to know whether an outcome, which occurs after the cross over, is due to the action of the intervention to which the subject was originally assigned or to the intervention which was received after the cross over. The most robust way of dealing with patients who cross over is to analyze

them separately. If the conclusions of the study are not altered by assigning all of the events which occur after a cross over to any one specific randomized group, then the presence of cross overs is of minor importance, at least when interpreting the direction of the study results. The magnitude of any difference between the randomized groups is of course always sensitive to the presence of cross overs.

Cross overs posed a limited problem in the current trial of contrast media even though they were not always handled correctly in the analysis. None of the randomized subjects in the intravenous arm of the trial were switched from high to low-osmolar contrast or vice versa. In the cardiac catheterization arm many subjects randomized to high-osmolar contrast were switched to low-osmolar contrast during the procedure. This was not a problem in relation to the primary outcome of an adverse event which required therapeutic intervention because the requirement to switch to low-osmolar contrast was itself taken to constitute such an outcome. Therefore this outcome always happened before the cross over was made and the adverse event was always attributed to the high-osmolar contrast which had been given before cross over. This outcome was only counted once for each subject and therefore such an outcome could not be counted again after the subject had crossed over.

During the analysis of the cardiac catheterization arm of the trial a new category of outcome was created. This is designated as a "clinically important event" in Appendix A. This category

was created by combining events which had been recorded at the time of catheterization and counting the number of patients who had at least one such event. It was possible for these events to occur after a cross over. The effect of such cross overs was not initially considered in the analysis. This was an error which could have interfered with the interpretation of the results. The data were analyzed subsequently to assess the effect of the cross overs. Sixty four subjects who had a "clinically important" event also crossed over from high to low-osmolar contrast. However, none of those patients suffered their initial "clinically important adverse event" after the cross over. Therefore it was legitimate to attribute this event to the high-osmolar contrast they had received. The conclusion that high-osmolar contrast causes more adverse events of "clinical importance" is therefore not sensitive to the presence of, or the method of dealing with, the cross overs.

A similar problem exists with regard to the measurement of the subjective symptoms after cardiac catheterization. This measurement was made after cross over had taken place in some subjects. This problem should have been foreseen. The ideal way to deal with it would have been to administer the symptom questionnaire before the contrast was switched. However this would not have been feasible in practice. The subjective symptom data from the patients who crossed over should have been analyzed separately. This has not been done to date and therefore the results of the comparison of the high and low-

osmolar contrast, in terms of subjective symptoms, in patients having cardiac angiography, have to be interpreted with caution.

Although several patients were given both high and low-osmolar contrast for cardiac catheterization, only one such patient (nonrandomized) had a rise in serum creatinine after contrast, and in that case it was impossible to be sure which agent was responsible [Appendix C]. Given the fact that only one individual received both types of contrast and had a subsequent rise in serum creatinine, cross overs did not cause a major problem in the interpretation of the results of this part of the study.

6.6.2. How ineligible randomized patients were handled:

Events occurring after randomization but before contrast were not recorded as outcome events. Since such patients continued in the study and were given contrast, the exclusion of these events should not introduce bias.

I discussed a problem with the randomization procedure in the intravenous stratum in chapter 5. Patients were excluded from one group because they had been inappropriately randomized. Analysis of the baseline characteristics of all those who were nonrandomly given high-osmolar contrast revealed that they did differ in some respects from those who had been randomly assigned to high-osmolar contrast [Appendix B]. Thus the exclusion of the inappropriately randomized patients who received high-osmolar contrast could introduce a bias to the study results. However, as indicated in chapter 5, the major

conclusions of the trial are not altered by the complete exclusion of all patients randomized before the randomization process was corrected.

6.6.3. How dropouts were handled:

Because most adverse events occurred very soon after injection of contrast, there were few problems with dropouts or noncompliance in regard to the primary outcome. The only outcome which was affected by dropouts was contrast nephropathy. A second measurement of serum creatinine was obtained in about 80% of those who had cardiac catheterization and in about 55% of those who had intravenous contrast [Appendix C]. This was despite efforts to maximize the follow up of these patients. The problem arose largely with outpatients and patients who were discharged from hospital soon after their imaging test. Attempts were made to contact all such patients by telephone and arrangements were made for them to have their serum creatinine measurement repeated in a local hospital. Many patients could not be contacted or failed to have the test done. There are no data to indicate what happened to the renal function of those patients who were lost to follow up. It is unlikely that any of them required dialysis, as this therapy is only available at three institutions in the province and these cases would almost certainly have come to the attention of the investigators. There was no systematic difference at baseline between those who were lost to follow up and those who were not [Appendix C]. Those who were lost to follow up were derived equally from the groups

assigned to low and high-osmolar contrast. Therefore although it cannot be proven it seems unlikely that major bias was introduced by these dropouts. The occurrence of the drop outs seems to have been unavoidable given the nature of the population being studied.

CHAPTER 7

ANALYSIS

7.1. Data management:

The large number of subjects and variables in this trial resulted in an enormous amount of data. The data was stored on a database system known as Datatrieve [NMS, Vax Datatrieve V3, Digital Equipment Corp., Maynard, Massachusetts, 1984]. Each case was assigned a unique code number. Cases were entered as units. There were a few aspects of the data storage which could have been better organized. The patients in the cardiac and intravenous strata were entered in separate computer accounts. This was not a problem in itself, as the data could be transferred between accounts with little difficulty. However, the structure of the data and the names for the same variables were different in the two accounts. This was unnecessary and led to some difficulties in the analysis. There would have been even more problems if the two strata had been analysed together.

After data entry, and prior to any analysis, the data were checked for errors. This was done by looking for variables with impossible values and for logical inconsistencies in the data. For example a value of 2 μmol/litre for the serum creatinine would almost certainly represent an error. If a value for a variable was possible, albeit improbable, and existed on the original record it was retained. An example of a logical inconsistency would be a subject who was said to be taking an oral hypoglycemic agent but who was not diabetic. The data on

the computer was checked against the original data recording forms for virtually all variables used in the cardiac stratum and for all the major outcomes in the intravenous stratum.

7.2. Analysis of the strata:

It was initially intended to combine the results of the cardiac angiography and the intravenous strata for analysis of systemic reactions requiring therapy and to report the cardiac side-effects separately. However, the cardiac stratum was analyzed, without examining the event rates by the type of contrast assigned, when it appeared that clinically important hemodynamic events were occurring with a relatively high frequency. This analysis revealed that the incidence of adverse hemodynamic events requiring therapy was high enough that the trial, which had enroled 1490 randomized subjects having cardiac angiography up to that point, should be fully analysed. This analysis confirmed that nonionic contrast was significantly less likely to be associated with the occurrence of an adverse hemodynamic event severe enough to require therapy [Appendix A]. As a result it was decided that enrolment in the cardiac stratum would cease. Enrolment in the intravenous stratum continued until the total number of subjects in the two strata combined reached the sample size previously determined as necessary in relation to the primary outcome of treated systemic reactions.

When enrolment in the intravenous stratum was terminated we analysed the intravenous stratum alone initially. There was a statistically significant difference favouring low-osmolar

contrast in terms of systemic adverse events requiring therapy [Appendix B]. The trend for similar outcomes also favoured low-osmolar contrast in the cardiac stratum [Appendix A]. Therefore the two strata were not combined for analysis or reporting.

7.3. Descriptive statistics:

An initial step in analysis of the data was to determine the frequency distributions of the continuous variables prior to their statistical comparison. Counts were performed of the nominal variables. This description of the raw data gave a feel for its' structure. This was necessary to allow a correct choice of statistical techniques and also helped to identify when errors made during the more complex subsequent analyses. Continuous variables were presented as means and standard deviations or medians and ranges, depending on the frequency distribution of the variable. Nominal variables were presented as proportions, such as percentages.

7.4. Baseline comparisons:

The next step in the analysis was to examine the baseline characteristics of the subjects. A comparison of the randomized groups was made for a large number of demographic and clinical variables. This analysis included all variables which might have been related to the outcome, such as the "risk factors" already mentioned in chapter 3. This was to ensure that any difference in outcome between the groups was truly due to the contrast. We did not rely on the lack of a statistically significant difference in baseline variables between the randomized groups

to determine whether an important difference existed or not. It is an error to do so because a large and important difference may not be statistically significant even though it has an influence on the results [Altman (1985)]. It is also fallacious to test the comparability of properly randomized groups statistically as any difference that has arisen must have done so by chance [Altman (1985)]. However, statistical comparison can be justified in situations where bias might have influenced the assignment of subjects to groups. This is most likely to occur when the randomization is not performed blindly, as was the case in the current trial.

The analysis did reveal that there was an excess of cardiac disease in the patients who were randomized to nonionic contrast in the intravenous stratum [Appendix B]. The significance and management of this situation has been discussed in section 5.3 which deals with blinding.

The baseline characteristics of the subjects who were not entered in the randomized trial were compared to those of the randomized groups [Appendices A to C]. This was important for interpretation of the generalizability of the results. Those who had been excluded from randomization by the radiologists or cardiologists were predictably different from those who were enroled in the randomized trial. However, those who were not randomized because of the lack of availability of suitable nonionic contrast did not differ much from those who were randomized. Therefore one could argue that the exclusion of

these latter patients did not influence the results of the trial very much.

7.5. The choice of significance levels:

We chose to use a cut-off of 5% as a maximum chance of making a type I error in declaring a difference between contrast media statistically "significant" (i.e. $p < 0.05$ implies "significant"). The choice of a 5% level of significance is purely arbitrary, but this cut-off has now become well established in the literature as constituting one way to assess whether differences are meaningful or not. We reported the 95% confidence intervals for all differences and relative risks.

We chose to use a power of 80% for our sample size calculations so that the sample size would be reasonable, while not making a type II error excessively likely if the results of the trial failed to show a difference between the groups.

We planned to use one tailed tests to determine if any observed difference between the two media was statistically significant. There is controversy about whether one tailed tests of significance are appropriate in most situations. It would have been more methodologically sound if we had designed this trial to allow us to conclude that nonionic contrast was either more or less toxic than high-osmolar contrast. This would have required us to use a two tailed statistical test of significance to evaluate any difference in toxicity between the two media. However, there was little evidence in the literature to suggest that nonionic contrast was more toxic than high-osmolar

contrast. Even if nonionic contrast was only slightly less toxic than high-osmolar contrast it would not be widely used because of it's high cost. Therefore we were mainly interested in determining whether nonionic contrast was significantly and substantially less toxic than high-osmolar contrast. We were less concerned about being wrong if we declared that there was no difference between the media when in fact nonionic was more toxic than high-osmolar. Choosing to use a one tailed test of significance carried the advantage of allowing us to use a smaller sized sample, which was perceived as a major advantage when the feasibility of the study was being considered.

We reported the results of a two tailed test of significance for the outcome of the cardiac catheterization arm of the study [Appendix A]. A sample size had not been calculated in advance specifically for this stratum. We had not stated an intention to use a one tailed analysis in relation to the cardiac angiography patients alone. Therefore it seemed more legitimate to use a two tailed significance level in that situation. The results of the comparisons made in the intravenous arm of the study were analyzed using the one tailed tests of significance which had been planned at the outset.

7.6. Statistical tests:

Chi-squared tests for 2 by 2 tables were used to compare the distribution of binary variables between groups. In situations in which the expected values in any cell of the table were less than five, Fisher's exact test was used to determine

significance. This was because the chi-squared distribution is only approximately approached, at best, when being used to evaluate discrete data. The approximation becomes too crude in situations where there are small expected numbers and therefore the chi-squared distribution is an inadequate criterion to determine significance in those cases. The Fisher's test involves no such approximations and directly calculates the exact probability that the observed, or a more extreme distribution, occurred by chance, under the assumption that the null hypothesis is actually true.

The distribution of continuous variables in the high and low-osmolar contrast groups was compared using Student's t-test for unpaired data. Over the years this test has been found to be fairly robust to violations of the assumption that the frequency distributions of the variable in the two groups being compared are normal in character. Nevertheless, when there was a high degree of skew in the frequency distribution of the variables being tested, the Mann-Whitney-U test was employed to determine if a difference was statistically significant. The advantage of this approach is that the Mann-Whitney test is nonparametric and thus makes no assumptions about the distribution of the data. The disadvantage of nonparametric tests applied to interval data is that they do not use all of the information in the data and thus they lack power in comparison to parametric tests. This was not of practical concern in most of the analyses because most of

the differences were significant with the nonparametric analyses.

7.7. Multivariate analyses:

We were interested in determining whether it would be possible to identify a high risk group to selectively receive nonionic contrast. To do so we had to know which characteristics would define such a group. We had recorded whether each subject in the trial did or did not have each of a large number of characteristics, such as a history of prior reaction to contrast, allergy etc. We had not studied subjects without any apparent increased risk of an adverse event, apart from a few people with normal hearts having cardiac angiography. These individuals had a low rate of adverse events and served as a useful population to compare with others having cardiac angiography. Among those having intravenous contrast the subjects who were aged over 50 years, but who were otherwise not apparently at increased risk, had a low incidence of adverse events. Thus these individuals were used to gauge whether the incidence of adverse events was increased in those with any of a number of potential risk factors. Using this approach univariate analyses were performed and the relative risk of an adverse event in subjects with any given characteristic was calculated. These analyses did not simultaneously consider the independent effects of the characteristics being studied. When subjects had both asthma and a history of prior reaction to contrast it was impossible to determine which factor was most

responsible for the observed increase in the incidence of adverse events in such subjects. The relative importance of each of the factors can be determined in such situations by a multivariate analysis if the individual factors are not highly correlated.

The other situation which required a multivariate approach was the imbalance in the randomized groups in the intravenous stratum with regard to cardiac disease.

We performed a series of multiple logistic regression analyses using the BMDP LR program [BMDP Statistical Software, Dixon WJ ed, University of California Press, Berkeley, 1988]. It was necessary to use a logistic regression because the dependent variable was of binary type in all cases. In the case of the cardiac angiography stratum the dependent variable was the occurrence in a patient of a defined type of adverse reaction which was labelled "clinically important" [Appendix A]. In the intravenous stratum the dependant was the occurrence in a patient of an adverse event which required the attendance of a doctor. This was used instead of an event requiring therapy to increase the number of events available for the analysis. We analysed separately the randomized patients having cardiac angiography or intravenous contrast using the type of contrast, severity of cardiac disease, allergy, age etc. as independent variables. The exponential of the beta coefficients of the independent variables provided the odds ratio for event/no event associated with the presence or absence of the particular

characteristic being tested. A 95% confidence interval was constructed for the odds ratio using the standard error of the beta coefficients. Variables were entered into and removed from the models by both manual and automatic methods. In this way multicollinearity could be recognized by a change in the apparent importance of variables, when other correlated variables were entered into the model. Variables which had no significant effect were omitted from the "best fit" model. The goodness-of-fit chi-squared statistic was used to determine how well a given model fitted the data. The odds ratios quoted for given variables were those from the "best fit" model [Appendices A and B].

Within both the cardiac and intravenous groups separate analyses were performed for all patients receiving high-osmolar or low-osmolar contrast irrespective of whether they had been randomized or not [Appendices A and B]. This prevented exclusions from the randomized trial from weakening the relationship between certain characteristics and the likelihood of an adverse event. We were able to do this, as we had collected the same data on the cases who were not randomized as on those who were, and we did not try to compare contrast media in this analysis. These analyses identified those factors which were independently associated with the greatest increase in risk of an adverse reaction to contrast.

7.8. Multiple outcomes and comparisons:

This trial had several outcomes all of which were intended to indicate the relative toxicity of high and low-osmolar contrast. If some of the outcomes had indicated a benefit with low-osmolar contrast and some had not, it would have made a decision as to which contrast was superior more difficult. Such a problem did not actually arise because nonionic contrast appeared superior by all outcome criteria. There are several ways in which this problem can be handled in trials. One is to determine the relative importance of the various outcomes and to aim the analysis at a predetermined primary outcome. In using this approach it is important to be sure that the correct primary outcome has been chosen to avoid problems such as occurred in the trials comparing thrombolytic therapies for myocardial infarction [Sherry (1991)].

Another approach has been to develop mathematical models to describe a group of outcomes, and thus to derive a single global index of superiority of one treatment over another. These models have to be developed with a clear knowledge of what they are describing, and it is often not appropriate to try to arrive at a simple answer to a question of efficacy when the answer may actually be more complex. One therapy may only offer a limited advantage over another and even this may be limited to specific types of patients.

We reported several comparisons of the two types of contrast media in our report on the cardiac angiography stratum [Appendix A]. These comparisons were in terms of various types of adverse

events which required therapy. The comparisons were reported with statistical significance values. We used the Bonferroni procedure to adjust the significance level for the multiplicity of the comparisons [Miller (1981)]. This procedure requires that the p value associated with each of the individual pairwise comparisons of a set of multiple comparisons be multiplied by the number of comparisons made. This method of adjustment for multiple comparisons was chosen because of it's simplicity of calculation. The purpose of this adjustment was to protect against a type I error. When many comparisons are made, and particularly when they are unplanned and suggested by the results, the probability of a type I error is considerably above that implied by the nominal significance level. There are many techniques which aim to overcome this problem, but most of them suffer from the limitation that, while they protect against type I errors, they increase the chances of making a type II error [Steel (1980)]. This did not prove to be a problem in the present trial as the differences remained significant even after allowing for multiple comparisons [Appendix A].

7.9. Contrast nephropathy:

This trial showed a slightly lower frequency of contrast nephropathy with nonionic contrast, but the difference between the contrast media was not statistically significant [Appendix C]. However, the study ended without having enroled sufficient subjects to exclude or confirm that nonionic contrast can cause a 50% reduction in the incidence of contrast nephropathy, as

defined by a 25% rise in the serum creatinine. The parametric analysis also did not have a very high power. Therefore we are unable to either confirm or exclude the possibility that nonionic contrast is less nephrotoxic than high-osmolar contrast in subjects with renal impairment. The results of the study did confirm that the incidence of severe contrast nephropathy is low in subjects with moderate renal impairment and that the potential absolute benefit with low-osmolar contrast can thus be modest at best [Appendix C].

CHAPTER 8

ECONOMIC ANALYSIS

8.1. The role of economic analysis:

There has been increasing interest in health care financing in recent years. This has resulted in part from the development, and increasing demand for, new and expensive medical programs, and also from the limited availability of resources to pay for such programs. Economic analysis has a role in aiding the decision making process when health program planners are faced with choosing to supply some services at the expense of competing alternatives. The underlying assumption of all such economic analyses is that the aim of the decision maker is to provide the maximum aggregate health benefit to the target population using the resources available [Detsky (1990)]. In practice, factors other than this may be dominant in determining the distribution of scarce resources. Therefore economic analyses are only one contributory factor in any decision about health care delivery [Detsky (1990)].

Clinicians, in their relationships with individual patients, do not have the same aims as health program managers. In clinical practice the role of the clinician is to provide the best available care to the patient irrespective of cost. The clinician does not generally consider the possible effects of therapy for his own patient on the availability of resources to treat other patients. Therefore cost-effectiveness is not a factor in most decisions that doctors make when treating

individual patients. However, cost-effectiveness is relevant to doctors who are involved in decisions about how best to use available resources in a population setting.

Because cost-effectiveness is not a major consideration in the daily practice of many physicians, it's role in decision making has often been misunderstood by practising clinicians. This has led to calls for doctors to act as advocates for their patients as an unidentified group and not to be influenced by factors such as cost-effectiveness, even when they are acting in the role of advisors to health policy planners [McClennan (1987)]. This is not always appropriate and is more akin to sectional political lobbying than responsible medical practice. If doctors cannot function differently in their two separate roles as clinicians and as potential advisors to health policy planners, then they will be ignored in the latter role, probably to the ultimate detriment of their individual patients.

8.2. Classification of economic analyses:

Economic analysis of a medical program always involves a consideration of the costs of the program. However, to be considered a complete analysis, there have to be two other elements to the analysis as well. The first is a comparison of at least two competing programs and the second is a consideration of the potential benefits as well as the costs of each of the alternatives [Stoddart (1984)]. In situations in which the competing programs are not known to be either equally effective or equally costly, any less complete form of analysis

cannot provide all the economic data necessary to guide a decision as to which program provides the best "value" for money.

There are at least three forms of economic analysis which can be considered to be complete and useful in the above situation. These are cost-effectiveness, cost-utility, and cost-benefit analysis [Stoddart (1984)]. The difference between the three lies in how they express the non-monetary consequences of the competing programs. Cost-effectiveness analysis determines how much must be spent to achieve a unit of a given clinical outcome, such as a year of life saved, under the operation of each of the programs. Cost-utility differs in that peoples' preferences for given health states are taken into account and act as weighting factors in the calculation of the clinical outcomes, or "utilities", which arise from the operation of the competing programs. Thus in this form of analysis both quantity and quality of life are considered in measuring clinical outcomes. Cost-benefit analysis expresses both the costs and the outcomes of the competing programs in terms of monetary units, and thus leads to a dimensionless cost/benefit ratio.

Although cost-benefit analyses always involve a comparison between at least two program options, one of the options may be the implicit one of simply not providing the program being evaluated [Torrance (1986)]. In that way cost-benefit analysis can be considered to give rise to an estimate of the "absolute" value (or net social worth) of a program in terms of the

potential resources that it consumes or generates [Stoddart (1984)]. Therefore a decision might be made to fund only programs with a positive net social value [Torrance (1986)].

The form of analysis which is most appropriate in any given situation depends in part on the viewpoint from which the analysis is being undertaken. Cost-effectiveness does not necessarily reflect the health state preferences of the consumers of the health care programs. Therefore is not the best method to use when the analysis is being performed from their perspective. The viewpoint of the analysis also determines what costs should be included in the analysis. For example, if the analysis is being performed from the viewpoint of a health provider organization, it may not be relevant to consider whether one program is more likely than another to lead to less expenses for the patient in travelling to and from the health care facility. The same reasoning applies when considering which outcomes, or non-monetary benefits, to include in an analysis. These issues have been discussed by Drummond et al. [Drummond (1987)].

In our own situation we were mainly interested in the economic consequences of switching from high to low-osmolar contrast from the point of view of the health care system. We did, however, feel that it was important to consider the effect of the contrast-related adverse reactions on the patients quality-of-life, when determining the clinical consequences of the use of the two types of contrast. Therefore we aimed to perform both

cost-effectiveness and cost-utility analyses of the use of contrast media.

8.3. Incorporating quality-of-life in outcome measures:

Judgement of quality-of-life is largely subjective. It is often measured by determining the preference of individuals for various health states. The degree of preference is inversely related to the "quality" of the health state. There are four basic steps in determining the quality of a given health state. The first is to identify the state(s) to be rated. The second is to decide who will perform the rating. The third is to decide how the rating will be done. The final step is to aggregate the ratings in some fashion across all the raters to arrive at a more universal measure of the quality of the given health state.

The term "utility" has been used in many senses. In one rather broad usage the term is meant to imply a quality adjusted health state which results from the operation of a health care program. The term is used in this fashion in clinical decision analysis and in health program evaluation by cost-utility analyses. In a more narrow, but partly related, usage the term refers to von Neumann-Morgenstern utilities (vN-M utilities). These are specific weights applied to given situations (not necessarily health states) by individuals who express their preferences for the situations under conditions of uncertainty [Torrance (1989)]. Such values are based on a general utility theory developed by von Neumann and Morgenstern in the 1940's. This theory provides a normative model of how rational individuals

should make decisions under conditions of uncertainty [Torrance (1989)]. This is not to say that individuals do make decisions in such a fashion all the time. However, there is some empirical evidence that individuals follow the model in many situations [Torrance (1989)].

Confusion over the use of the term "utility" arises in part because utility theory provides the basis for the "standard gamble" approach to the measurement of health state preferences, called "utilities", which are subsequently used in the calculation of the quality-of-life adjusted outcome measures also known as "utilities".

Since such outcome "utilities" are measures which incorporate the preferences of patients for various health states, there is a need for a method(s) to measure these preferences in order to calculate the "utility" score for any given health state. Several such methods now exist. These include the standard gamble, time trade off, rating scale, magnitude estimation, equivalence, and willingness-to-pay methods [Froberg (1989)]. These methods are not all equivalent, often yield very different estimates of utility, and several have not been fully evaluated with regard to reliability and validity [Froberg (1989)].

The standard gamble is one of the better studied methods and is often considered to be the gold standard against which the other methods should be judged. This is because the standard gamble is directly derived from utility theory. It therefore provides a direct measure of preferences under conditions of

uncertainty. In the standard gamble method a rater is presented with a description of a given health state or is asked to imagine his own current health state. Suppose that this health state is preferred to death. Now the rater is asked to state whether he would prefer to stay in the given health state for a guaranteed specified period (say t years), or to take a gamble. The gamble is that he would live for the same time period in full health with probability p or die immediately with probability 1-p. The probability p is varied until the point is reached where the rater is indifferent to the alternatives of the gamble or the certainty of staying in the health state being rated. This value for p at indifference is the von Neumann-Morgenstern utility of the health state. This method can be difficult for people to understand, however, and therefore some of the other methods may be more feasible in practice.

The utility of the health states resulting from the occurrence of adverse reactions was not measured at the time that they occurred in the study which is discussed in this thesis. In fact, the cost-utility study was only designed after the trial proper was well under way. Telephone interviews were performed after the study to measure the quality of the health states resulting from minor contrast-related side-effects. It was felt that it would be impractical to use the standard gamble method with a telephone interview. The willingness-to-pay method to rate the quality of the health states was used and was found to

be feasible in practice. The details of the planned cost-utility study will be discussed later in the chapter.

The results derived with the various scaling methods may be influenced by the context in which the measurement is made, as well as by characteristics of the population studied [Froberg (1989a)]. For example, experience with an illness tends to increase the utility values assigned by raters to states associated with that illness. Health professionals often put lower values on health states than patients or the general public [Froberg (1989a)].

Health states are generally quite complex to describe and may have many attributes such as pain, loss of function, mood etc. Each of the attributes can have a varying number of levels. Such complex multi-attribute states can be rated as units or the individual elements that make them up can be rated separately and then combined. There are advantages to taking the latter "decomposed" approach. This increases the number of states that can ultimately be rated, and exposes the weighting factors that are applied to the various attributes by the rater in arriving at the final global assessment of the quality of the state [Froberg (1989b)]. It can also (with a functional measurement approach to a statistically inferred decomposed model) allow simultaneous validation of the derived scale values, along with a check for interaction between attributes at various levels [Froberg (1989b)].

Following measurement of the vN-M utility values of the various health states of interest, this measurement of the preference of individuals for the health state has to be incorporated in some way into the outcome, when evaluating health care programs. Doing so incorporates the concept of the quality of the health state in the outcome. One of the original, and still the most widely employed, ways to do this is to calculate a measure of outcome known as a Quality-Adjusted-Life-Year (QALY) [Torrance (1989)]. This is done by multiplying the time spent in a given health state by the quality adjustment factor derived from the measurement of the vN-M utility of the state. It should be noted that the weighting factor for the quality-of-life need not always be derived from empirically measured vN-M utilities. However, this is the best way to derive the weights if the quality adjustment is meant to reflect the true health state preferences of those likely to be in the health state [Torrance (1989)].

In calculating QALY's it is assumed that a prolonged but poor quality health state has the same "value" as a shorter but good quality one. It is also assumed that the gain of a QALY is always "worth" the same amount, no matter whether this gain is in the form of a minor increment in quality or quantity of life for a large number of people, or an equivalent major increment for a small number of people. In this sense QALY's are equitable measures. Another advantage of the QALY is the fact that it provides a unit of measure which allows comparison between

widely differing health care programs. This is of major importance when the programs are being competitively evaluated.

A major limitation of the QALY for comparison of various health states is the fact that the preference of the raters for given health states may not be mirrored by the relative number of QALY's assigned to the states. Situations have been discovered where raters have expressed a clear preference for one health state rather than another, but when the two states were compared by using the calculated QALY's, the least preferred state seemed superior [Mehrez (1989)]. This situation is obviously undesirable, but may not be all that common in practice. A more common situation would probably be that, while the order of preference for the health states is preserved in calculating the QALY's, the absolute value of each state is not directly reflected in the number of associated QALY's. This would be of importance when these states are being compared with others outside of the setting in which they were initially evaluated. This problem arises because QALY's are not the same thing as the vN-M utilities from which they may be derived. In order that the utility be properly reflected by the derived QALY value several assumptions have to hold. These are (1) that quality and quantity are mutually utility-independent (i.e. preferences for gambles on quality are independent of quantity and vice versa), (2) the trade off of quantity for quality exhibits the constant proportional trade off property (i.e. the proportion of remaining life that one would trade off for a

specified quality improvement is independent of the amount of remaining life), and (3) that for a given quality, utility is linearly related to quantity [Torrance (1989)]. Since these assumptions do not often hold in practice, QALY's are not the same as utilities [Loomes (1989)].

A further problem with QALY's is that they can only be used to rate a single chronic health state unless further assumptions are made. One such assumption is that the utility function of the individual over his or her lifetime health profile is additive in form. This assumption has no empiric basis and, since it is often more realistic to imagine that an individual will not remain in a given specific health state for a prolonged period of time, this constitutes a major limitation to the use of QALY's.

To overcome these problems with QALY's Mehrez and Gafni have developed a concept which they call the Healthy-Years Equivalents (HYE) [Mehrez (1989)]. This health state index incorporates elements of quality and quantity, and also allows comparisons across programs. Since it is directly derived from vN-M utilities and uses the rater's own utility function, it always reflects the health state preferences of the rater. The index is more difficult to calculate than the QALY, as it requires that, either the individual rater's utility function be known over the projected lifetime health profile in any situation where more than one period of less than full health is likely, or that the HYE value be obtained by using a multi-stage

lottery approach. In fact the latter approach can be used to measure the HYE value of a chronic health state, a particular lifetime health profile containing several different health states, and even the HYE values for many possible lifetime health profiles [Mehrez (1991)]. This approach has been proposed in relation to contrast media [Gafni (1990)]. Gafni states that the utility of a brief reaction to contrast can be rated using the standard gamble approach. Then the trade off of healthy years to eliminate the reaction can be measured in a second standard gamble measurement. This yields the Healthy-Years Equivalent of the life with the reaction directly and without any of the assumptions inherent in the use of the QALY measure.

8.4. A review of some existing economic analyses of contrast media:

There is a real dearth of complete economic analyses of the use of contrast media in the literature. Early considerations of the costs of contrast media were limited to estimates of the incremental cost of converting to the use of low-osmolar contrast media, generally for all patients. Sometimes this was combined with an estimate of the likely benefit of low-osmolar agents in reducing contrast related deaths; a benefit which has never actually been proven to exist. By this means estimates of the marginal cost-effectiveness of low-osmolar contrast, in terms of lives saved, were made [Jacobson (1988)]. These studies did not attempt to estimate the costs associated with nonfatal contrast reactions. Similarly, they did not attempt to view the

situation from the viewpoint of the person receiving the contrast. Powe et al. did measure the costs to a health provider of various nonfatal reactions to high-osmolar media [Powe (1988)]. This study did not consider the costs or benefits associated with the use of low-osmolar contrast. Thus it could not yield an incremental cost-effectiveness ratio of any kind.

Hlatky et al. recently reported a randomized trial of high versus low-osmolar contrast media for cardiac angiography [Hlatky (1990)]. This study considered the cost and the effectiveness of the two types of contrast. The viewpoint was that of the health care provider. However, they did not report a specific cost-effectiveness ratio and did not consider the option of a policy of selective use of low-osmolar contrast in high risk subjects. They did not consider any capital costs and only allowed for operating costs in their analysis. They did not consider any costs or effects that occurred more than 24 hours after the contrast had been given. The sources of the costs, and how these were measured, are not stated clearly in the paper. They did draw appropriately tentative conclusions and were aware of the problems regarding the generalizability of their results. Thus it can be seen that none of the published cost-effectiveness studies of contrast media have been methodologically rigorous.

Appel et al. reported a study in which they attempted to compare the incremental cost of low-osmolar contrast, for radiological examinations in general, with the amount that

people would pay to achieve specified reductions in the risk of contrast-related adverse effects [Appel (1990)]. This was done by selecting a group of outpatients, who were not going to have, and had not had an examination with contrast in the recent past. These raters were asked to state their willingness-to-pay specified amounts to be given low rather than high-osmolar contrast, while (a) imagining that they were about to be given contrast media and (b) while assuming that the low-osmolar media were less likely to cause specified adverse events. The low-osmolar media were stated to provide a specified reduction in risk of various minor and major adverse reactions. The raters considered how much they would pay to reduce the risk of each specific adverse reaction alone. They also stated how much they would pay to reduce the risk of all minor side-effects combined, and further, stated how much they would pay to reduce the risk of all major and minor side-effects simultaneously.

This study has several limitations. Firstly it does not address the question of the cost-utility of the two types of contrast media directly. Only one aspect of the cost of treating such patients with low or high-osmolar contrast is considered. The assumptions made with regard to the relative toxicity of the two types of media are based on the flawed studies which I have reviewed in Chapter 2. No attempt was made to allow for the uncertainty of those estimates by presenting the raters with more than one set of estimates of risk reduction. The health states which they described to the raters were contrived such

that none of the adverse reactions were assumed to lead to permanent, or even long term disability. Therefore the time horizon selected for this study was very short. This is not necessarily an accurate reflection of reality. The willingness-to-pay values derived from this study are probably not the same as those that would be derived from people who had recently experienced a contrast reaction. Such individuals would probably be in a better position to judge the utility of the health state related to any given type of contrast reaction. A further problem with the study is that the authors suggested possible responses to the willingness-to-pay questions to the raters. This is very likely to have had an anchoring effect and to have played a major role in determining the actual responses observed [Froberg (1989a)]. The authors recognized this limitation, but they state that they were obliged to use this approach because a pilot study had shown that raters had difficulty in providing answers to open ended questions about willingness-to-pay. This leads to a concern about the adequacy of the method used to determine the utilities. Furthermore the interviewer in this study perceived that 36% of the raters appeared to have difficulty understanding the concept of risks. If this is true it is not clear how the observed responses were obtained and whether these were true reflections of the incremental "utility" of the two kinds of contrast media. It would have been easier to measure the absolute utility of each of the states separately, and then to have used the published event rates associated with

each type of contrast, to derive an index of the utility of the two types of contrast. However, this approach would not capture the attitude to risk of the raters in making a decision as to which type of contrast to employ.

The most complete economic analysis of the use of contrast media was reported by Goel et al. [Goel (1989)]. These authors performed a cost-utility analysis of the use of low and high-osmolar contrast media. They did consider the alternative of using the low-osmolar contrast selectively in a high risk subgroup. The problem was structured as a decision tree and the final utilities associated with each decision option were expressed as QALY's. The major limitation of this analysis is the fact that it is based on assumptions regarding the relative toxicity of the two types of contrast media, and also about the quality of life associated with the health states which result from the occurrence of various contrast-related adverse reactions. No attempt was made to measure the vN-M utilities of these states. Reactions to contrast media are generally of very short duration in relation to the time horizon chosen in economic analysis (30 years in the study of Goel et al.). This means that even if they are associated with a major reduction in quality of life that they will not reduce by much the total number of QALY's for a person having such a reaction. Gafni pointed this out in commentaries on the Goel study and suggested that HYE's would be a better way of expressing the outcome of a future empirically based cost-utility study of contrast media

[Gafni (1990), Gafni (1991)]. The major difficulty was related to the relatively common minor adverse effects associated with contrast media. These effects should therefore be the ones most closely examined in any future empirical utility analysis. Goel et al., in their reply to the criticisms of Gafni, do not deny the problems associated with the use of QALY's, which I have discussed above. They do point out that any analysis that uses HYE's as the unit of outcome cannot be readily compared to analyses of other programs which were reported in terms of QALY's [Goel (1990)].

Irrespective of the criticisms of the studies which I have discussed above, the results of all of these analyses have indicated that the decision to use low-osmolar contrast has major cost implications. This is very important from the point of view of health care providers and continues to be emphasized in the literature. There is no agreement yet about the best way to use the low-osmolar contrast without causing huge increases in expenditure. The strategy of selective use of low-osmolar contrast for patients at high risk of a contrast-related adverse reaction may well be desirable from a cost-utility point of view. There continues to be sufficient uncertainty about the true cost-utility ratio associated with the use of low-osmolar contrast to justify further research in this area.

8.5. Economic analysis of our own study:

We have decided to perform the economic analysis of our study largely from the viewpoint of the health care system. This is

due to the fact that there is considerable controversy within the system as to whether nonionic contrast should be funded ahead of other programs, given the existing climate of fiscal restraint. Therefore our primary purpose is to provide data that might be useful in deciding whether to fund the use of low-osmolar contrast. It is necessary to perform a cost-utility or a cost-benefit analysis to achieve this objective, as the outcomes have to be expressed in a form that can be compared across disparate programs. A cost-utility analysis is also useful as both mortality and morbidity can be consequences of contrast-related adverse events [Torrance (1986)].

The current study was designed to address the question of whether a high risk subgroup could be identified. We aim to analyse the potential costs and consequences of a policy of selective use of low-osmolar contrast in such a high risk group only. Therefore we will perform both cost-effectiveness and cost-utility analyses of three competing program choices. The first choice is the continued use of high-osmolar contrast for all examinations of the type included in the current trial. The second is the universal use of low-osmolar contrast for all such examinations, while the third is the selective use of low-osmolar contrast only in those felt to be at high risk of an adverse reaction.

For economic analysis of the data from the trial itself only randomized patients can be included. Some patients had been excluded from the randomized trial because they were felt to be

at high risk of a reaction to high-osmolar contrast, but the doctors entering patients in the randomized trial did not only exclude individuals whom they felt were at increased risk of a reaction to high-osmolar contrast. The decision as to which patients were part of a high risk group was made after the study for patients in the cardiac catheterization arm. The records of all patients were reviewed, blind to whether they had suffered an adverse event. Those patients who had specified risk factors that could have been identified before contrast administration were placed in the high risk group. Since the assignment of high risk status was retrospective and the predictive ability of the risk factors has not been validated in a second independent testing set of patients, a policy of selective use might be more or less economically efficient than indicated by the results of the current analysis [Appendix A]. To allow for that we will perform sensitivity analyses of the proportion of patients included in the high risk group along with the likely incidence rates of adverse reactions in each high and low risk group combination during further cost-utility analyses. The actual costs and consequences of a policy of selective use of low-osmolar contrast will have to be measured in a further study. High risk patients will be selected in advance using specified criteria for receipt of low-osmolar contrast.

For the cost-effectiveness analysis of the current trial the incremental health care cost associated with the use of low-osmolar contrast was estimated. This served as the numerator for

the cost-effectiveness ratios [Torrance (1986)]. The denominators were the incremental numbers of adverse reactions of various types which had occurred. Ratios were calculated separately for the options of universal use of low-osmolar contrast and selective use of low-osmolar in defined risk groups only [Appendices A and B].

Data had not been collected regarding time spent by patients in the catheterization laboratory as a result of reactions. This made assignment of appropriate related costs difficult. Patients had not been followed up after they left the radiology or cardiology departments during the study. However the medical records of all those who had significant adverse reactions to contrast were examined to determine if any extra resources had been used in their care after they left those departments. In this way at least the hospital based resources consumed were identified. Capital and operating costs were included in the analysis, by using costs for inpatient care, which included these elements, as provided by the hospital administration. The cost figures used were those that were borne by the health care provider, as patients do not pay for health care at the point of delivery in Canada. Indirect costs or benefits applying to the patients as a result of the receipt of low-osmolar contrast were not considered. This is reasonable as the viewpoint is that of the health care system. Since all of the costs and consequences accrued very quickly after the contrast was given, we did not

have to allow for differential timing of the costs and benefits, or employ discounting [Appendices A and B].

The cost-utility analysis will be performed in collaboration with Dr. Allan Detsky in Toronto. The problem will be structured as a decision tree, much as in the study by Goel [Goel (1989)]. The cost-utility of low-osmolar contrast in high risk and low risk populations will be examined. Once again, sensitivity analyses will be performed for factors likely to affect the cost-utility of a policy of selective use of low-osmolar contrast in patients at high risk. The direct costs used in this analysis will be the same as those used for the cost-effectiveness study and will thus reflect costs to the health care system. There were no deaths and very few life threatening reactions during our study. The study was not designed to analyse such outcomes in any case. Therefore we will have to use figures from the literature to allow for the possibility of the occurrence of such adverse events.

We did not measure the vN-M utilities associated with severe reactions directly. To do so would have required a proxy population of raters and would not have been worth the effort in view of the very low frequency of such events and hence their limited impact on the final utility of any program chosen. The estimates required for the frequency and utility of severe reactions or death will be handled in a manner analogous to that used by Goel et al. [Goel (1989)].

As has previously been noted it is desirable to empirically measure the quality-of-life consequences of minor contrast reactions. This is because these reactions are relatively common and low-osmolar contrast is effective in reducing their incidence. Therefore they could have a considerable influence on the results of any cost-utility analysis.

We felt that those who had experienced the reactions were in the best position to judge their quality-of-life implications. It would have been best to perform the utility measurement of these reactions soon after they had occurred using the standard gamble method. Unfortunately we did not have the organization in place, or the resources available, to perform that measurement at such a time.

We performed telephone interviews with patients in the cardiac stratum who had had minor symptomatic reactions which did not necessarily require therapy. These were defined as the occurrence of symptoms graded as greater than or equal to 5 on the 10 point subjective severity scale (see Figure 3 above). The interviews were performed up to eight months after the cardiac catheterization had been performed. The results of these interviews are suspect because some patients may have forgotten some details of the event being rated. It will be necessary to make utility measurements in relation to adverse events by interviewing a separate cohort of patients soon after similar events have occurred.

In our initial telephone interviews we identified 384 subjects who had a minor symptomatic adverse reaction to cardiac angiography during the last 8 months of the study. We chose this time period to maximize the chance that the subjects would remember the symptoms and to ensure that we would have a sufficient number of raters to give reasonably reliable estimates of the quality-of-life implications of the symptoms. We arranged for each subject's cardiologist to send them a form letter informing them that we would call and of the reason for the call. One cardiologist, who had participated in the trial, decided not to collaborate in this part of the study. This led to the exclusion of about 10% of otherwise eligible subjects. A further number were unavailable for inclusion in this portion of the study because they had died or were otherwise uncontactable. These factors further limit the usefulness of the data because they reduce its' representativeness.

24 patients were contacted in an initial pilot study and were thus not used in the final analysis. Overall we were able to make contact with 229 of the original 384 subjects identified. Of these, 36 were either unable to remember the symptomatic adverse reaction or were unable to comprehend the nature of the questions asked. Therefore we had responses from 193 patients available for analysis.

Each subject was asked whether they remembered the adverse reaction, and if so, they were reminded of how they had rated its severity at the time of the trial. They were then asked to

imagine that they were about to have contrast again and that they were certain to have the same symptomatic reaction as they had previously. They were asked if they would pay any amount, out of their own pocket, to avoid the occurrence of the symptom. Subjects who had difficulty with the question were advised that they did not have to pay anything, if that was what they preferred, but they were not given any other anchor points in order not to limit the maximum possible value.

We also collected information about the income, education, and demographic characteristics of the subjects. These factors, together with the subjective severity of the symptom, were examined to determine if they had any influence on the amount that people were willing to pay. In fact they did not appear to do so.

The amount that someone is willing to pay to avoid the occurrence of a symptom is a measure of the net intrinsic benefit of avoiding that symptom. This is not exactly the same as the vN-M utility that someone would attach to the health state resulting from the existence of the symptom. The easiest way to handle the willingness-to-pay data in the cost-utility model is to consider it as an intangible benefit and to use it to offset some of the marginal net cost associated with the use of low-osmolar contrast [Torrance (1986)]. In this way the data are considered in the numerator of the cost-utility ratio.

Since we did not measure the utilities associated with more serious contrast-related adverse events (including reactions

requiring therapy in the cardiac catheterization stratum), we will have to make assumptions about the utility values associated with these states. This is probably reasonable in the case of the most serious reactions, as these are so infrequent that they will not influence the overall utility associated with any decision tree branch to a major extent. It will be necessary to measure the utility values for the states resulting from "intermediate" level reactions, as these may have more effect in the model. This may be done during a proposed study of the selective use of low-osmolar contrast. In the meantime we can still construct a cost-utility model by making assumptions about the utility of the "intermediate" level adverse events which are biased against high-osmolar contrast. If such a model still shows that selective use of low-osmolar contrast has a lower cost-utility ratio than universal use of low-osmolar, then we will still have an economic argument justifying the further study of that approach.

The final outcomes of the decision tree branches will be expressed in terms of QALY's initially, in order to facilitate comparison with similar data on other programs. The results could also be expressed in terms of HYE's, but only if further assumptions are made, which seems to negate some of the benefits of that approach.

CHAPTER 9

ETHICAL CONSIDERATIONS

9.1. Risks and benefits:

Before any research on human subjects is initiated there has to be a consideration of the risks and benefits of the proposed research. The major responsibility for this rests with the investigators, but research proposals are now generally subject to review by a separate institutional ethics review board before they are implemented. I have indicated that the investigators felt that there was insufficient evidence to justify the routine use of low-osmolar contrast prior to the commencement of the current trial. Therefore they did not think that it was unethical to withhold low-osmolar contrast from some subjects and to randomly assign them high-osmolar contrast. Furthermore high-osmolar contrast was in everyday use at the study institution anyway. The existing literature did not provide any evidence that low-osmolar contrast was more toxic than high-osmolar contrast. If anything there was a prevailing opinion that low-osmolar contrast should be more widely used in radiology. Therefore it was not felt to be unethical to expose subjects to the high-osmolar medium, or the low-osmolar medium for that matter, given the then prevailing state of knowledge of the relative toxicity of the two types of contrast.

Others did not hold the same views, however. Prior to the start of the current study there had been inquests in Ontario into the deaths of two young adults after receiving intravenous

contrast. The juries in those cases had recommended that there should be a substantial increase in government funding to allow the replacement of high-osmolar by low-osmolar contrast [Grainger (1987)]. This led to the virtual total replacement of high by low-osmolar media in that province. In Alberta the College of Physicians and Surgeons had reviewed the ethics and legalities of using low-osmolar media and concluded that only low-osmolar contrast should be used in that province [Parfrey (1988)]. These decisions had led to some problems because the high cost of the new media, combined with the lack of resources to pay for them, had required that expenditure on other forms of health care be curtailed [Linton (1990)]. The investigators interpreted this to mean that there was an even greater need for the study discussed herein to determine whether such policies could be justified by facts.

Such controversies led to an extensive debate over the ethical and legal implications of the research proposal for the trial. The local ethical review board did not object to the nature of the study and eventually the funding agency also agreed that the study met with acceptable ethical and legal standards. The opinion which was received from the Canadian Medical Protective Association assumed that the low-osmolar media were less likely to cause death and severe reactions [F. Norman Brown, M.D. Personal communication]. There is still no evidence to prove that the new media can prevent death and the evidence that they

may reduce the incidence of severe side-effects following intravenous use is mainly derived from surveys.

The study consent form did not state that the low-osmolar media were known to be less likely to cause death or severe reactions, as there was no evidence to say that this was so at the start of the study [Appendix D]. Neither was the study stopped on learning the results of the RACR and the Japanese surveys, as these studies did not provide the level of evidence that would demand such an action [Palmer (1988), Katayama (1990)]. Individual doctors differed in their interpretation of the available evidence. This was accommodated by providing the radiologists and cardiologists who took part in the study with the opportunity to use their best judgement as to whether a patient should be randomized or not. As I have stated in an earlier chapter, they did in fact exclude people, whom they felt to be at excessive risk of an adverse reaction to high-osmolar contrast, and treated them with low-osmolar contrast. This approach left the study entry criteria flexible enough that emerging evidence of the greater safety of low-osmolar media would prevent inappropriate inclusion of subjects in the study.

Apart from bearing the risk of a reaction to contrast (most of which would have existed anyway), the subjects in this study were also asked to provide some personal and medical information about themselves. This information was not of a sensitive nature and it's disclosure did not really constitute much of a material risk. The only other imposition was the requirement to have a

measurement of serum creatinine performed. The blood for this test was almost always taken at the time of insertion of the needle for injection of contrast and thus did not involve any increase in discomfort. Those with elevated serum creatinine were asked to have a second blood test done two days later, but this would have been done in some cases anyway and was not considered to be unreasonable from an ethical point of view.

The benefits arising from participation in the study included the receipt of low-osmolar contrast, which had been shown to reduce discomfort (see Chapter 2), by many subjects who would not otherwise have received these agents at our institution during the period of the study. The only other benefit to participants in the trial was the indirect one of knowing that one's participation might provide information leading to better health care in the future.

9.2. Stopping the trial:

The decision to stop a trial is influenced by many factors both internal and external to the trial itself. A trial is designed to answer a question and, to be ethically sound, should appear to be able to answer that question without exposing participants to excessive risk. Statistical considerations play a role in deciding how large a study has to be so that it is likely to detect a positive answer to the question posed. Such calculations are done before the study starts, but they rest on assumed event rates in at least one of the randomized groups. The ultimate intent is to have a study which is large enough to

exclude a benefit from the experimental treatment if one does not exist, and to be likely to detect such a benefit if it does exist. There is also a concern to determine the answer in as short a time as possible, so that others may benefit from the information. Finally, there is the concern that a minimum number of subjects should be enroled, and thus exposed to at least inconvenience, to achieve the research goal.

The ideal way to achieve those competing objectives would be to keep constant watch on the results of the study as it progresses. This would allow the study to be stopped as soon as it provided an answer to the question posed. The problem with this approach is that it introduces the "multiple peeks bias". This means that it hugely increases the chances of making a type I error and declaring a difference between treatments "significant" when in fact it is not. This situation is not desirable, as there is then the real possibility that patients subsequently will be exposed to useless or even harmful therapy.

To overcome these problems investigators have developed "stopping rules". These are prespecified guidelines as to when a trial should be stopped because a specific difference between treatments has been observed with a specified statistical significance level. Such rules need to applied by persons external to the trial itself to avoid all of the potential effects of the multiple peeks bias. This is generally done by having the results reviewed by a policy and data monitoring board. The board will generally include people knowledgeable in

the area of trial design and analysis, as well as persons expert in the field of the research question. These boards make decisions about the need to continue a study using the prespecified stopping rules, together with considerations of whether the research question has been answered by other investigations, whether the treatments under study appear to be as safe as expected, and whether the current study is enroling patients in the manner predicted. These topics have recently been nicely discussed [Browner (1991)].

Monitoring the accumulating data in a trial can be done by performing analyses at specified intervals or by examining the data continuously in a form of sequential analysis [Armitage (1975)]. The sequential analysis carries a high risk of making a type I error. To protect against that a very conservative significance level is used. This then reduces the power of the study. The most practical solution is probably to perform a limited number of analyses after specified numbers of subjects have been entered in the trial. The significance level for each of the analyses can be selected so as to maintain the type I error rate at a specified level at the projected end of the trial.

The organization of the trial under discussion here was not ideal in that a policy and data monitoring board was not set up. Repeated analyses of the accumulating data were not performed in order to prevent type I error. However, this delayed recognition that the low-osmolar media were substantially less likely to

cause an adverse hemodynamic event in those having cardiac angiography. An analysis of the overall event rate in the cardiac stratum was performed, when it was realized that the event rates were high. The result of this analysis was reviewed by an external advisor and, following the subsequent complete analysis of the data by contrast type, the decision was made to stop enrolment in the cardiac stratum. Enrolment in the intravenous stratum continued until the prespecified overall sample size was achieved. The trial was stopped at that point and the data were analysed. The results indicated that low-osmolar contrast was beneficial in reducing the incidence of adverse reactions requiring therapy, but the reactions which had occurred were not life threatening and the difference between high and low-osmolar contrast only just reached statistical significance [Appendix B]. Therefore an external data monitoring board might not have stopped this arm of the study before the point at which it was stopped anyway.

In summary the trial organization was not ideal in that formal processes for review of accumulating data were not established. However, the investigators did keep a close watch on the trial generally and were aware of the nature of the events which were occurring in the trial. As a result, analyses were performed in a timely fashion, and it does not appear that subjects were exposed to undue risk of harm. External factors were able to influence the trial as the radiologists/cardiologists were able to take account of the emerging evidence of the superiority of

low-osmolar contrast in the literature when deciding which patients to enter in the trial.

CHAPTER 10

SUMMARY AND CONCLUSIONS

This thesis has reviewed the design, performance and analysis of a trial comparing the toxicity of high and low-osmolar contrast media. The trial suffered from several flaws which mainly arose during it's design and the early phases of patient enrolment.

A thorough review of the literature should always be performed to determine what is already known about the subject for a research proposal. The review performed prior to this study should have been more comprehensive and careful in regard to the cardiovascular effects of contrast media, especially once it had been decided to include patients having cardiac catheterization in the trial. Such a review should have highlighted the differences between the formulations of high-osmolar contrast which bind calcium and those which do not. This might have led to the more clinically relevant comparison of nonionic and noncalcium-binding ionic high-osmolar media.

The most important problems with the design of the trial were in the areas of choice of major outcomes, randomization procedure and blinding. Furthermore it was initially intended to combine two fairly different populations to measure a single outcome. The initial primary question of whether low-osmolar media caused less systemic adverse events than high-osmolar media was not the most relevant question for the population having cardiac angiography. The fact that other outcomes were

more important for this group was not considered sufficiently before the trial began. A separate sample size for a relevant outcome was not calculated for the group having cardiac angiography. The trial was not monitored in a way that allowed for external unbiased consideration of the accumulating data. Therefore the cardiac angiography trial was terminated only after informal monitoring led to the analysis of the data for that group.

The flaws in trial design have implications for the interpretation of the results. It was intended that the trial would provide information about events of clinical importance so that the results might have an impact on clinical practice. The chosen major outcome for the cardiac angiography group proved too heterogenous in that regard. Fortunately the degree of detail in the information collected during the study did allow for post hoc construction of other outcomes which were somewhat more readily interpreted. It is uncertain whether the results of the trial of intravenous contrast will influence practice. Only a trial which examined more severe events or deaths would be assured of doing so and this type of trial would be a major undertaking. The economic analysis of the current trial is important however, because it illustrates the sort of trade offs that exist when a decision is made as to who should receive low-osmolar contrast.

The inadequacy of the randomization and blinding procedures employed make it imperative to consider whether bias could have

had a major influence on the trial results. I have indicated in the thesis how comparisons made during the analysis attempted to determine whether bias was operative. The results of these analyses were reassuring in that they did not provide evidence to support a conclusion that bias had been introduced. Neither did they suggest that the conclusions of the study would have been different if a more optimal design had been used. However one cannot be certain after the fact that bias was not at least partly responsible for the results obtained and therefore one always has to be cautious in the interpretation of the results of studies with major design flaws. It is always better to try to prevent bias by using a sound design than to have to consider whether it is operative after a study is complete.

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A COMPARISON OF NONIONIC LOW-OSMOLAR WITH IONIC HIGH-OSMOLAR RADIOCONTRAST AGENTS DURING CARDIAC CATHETERIZATION

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Running Head: Radiocontrast in cardiac angiography.

ABSTRACT

Background: A randomized trial was undertaken to compare the incidence, risk factors and costs of adverse events after ionic high-osmolar and nonionic low-osmolar radiocontrast media during cardiac angiography.

Methods: We compared the frequency of therapeutic intervention for adverse reactions, and the frequency and severity of specified hemodynamic, systemic and symptomatic side effects in two groups randomly assigned to ionic high-osmolar (N=737) or nonionic (N=753) radiocontrast, and also in 366 patients who could not be randomized.

Results: The randomized groups were well matched at baseline. Therapeutic intervention for adverse events was received by 213 of 737 (28.9 percent) patients after high-osmolar contrast, but by only 69 of 753 (9.2 percent) after nonionic contrast (95 percent confidence interval for the difference 15.8-23.6 percent). Hemodynamic deterioration and symptoms also occurred substantially more often after high osmolar contrast, as did severe or prolonged reactions (2.9 vs 0.8 percent, $p = 0.035$). Such severe reactions were virtually confined to those with severe cardiac disease. Multivariate analysis showed that severe coronary disease and unstable angina were predictors of adverse reactions of clinical importance. If all patients in our randomized trial had been given nonionic contrast, the incremental cost per procedure would have been Can $100. This cost would be higher in the USA.

Conclusions: Nonionic contrast is better tolerated than calcium binding ionic high-osmolar contrast during cardiac angiography. Should cost constraints deter universal use of nonionic contrast, selective use in those with severe cardiac disease could be considered.

Key Words: contrast media, diatrizoate, iohexol, iopamidol, toxicity, adverse effects, heart catheterization, random allocation, comparative study.

INTRODUCTION

The high osmolality of conventional contrast media may contribute to their adverse side effects. New iodinated contrast media have lower osmolality and some are nonionic. Low-osmolar agents cause less discomfort and may decrease objective side effects during cardiac angiography (1). Hypotension, cardiac arrhythmias, and pulmonary edema may be reduced in high risk patients such as those with recent myocardial infarction, unstable angina, hypotension, or severe heart failure (2). Unfortunately few high quality randomized controlled trials comparing intracardiac infusion of high-osmolar and low-osmolar media have been undertaken. Furthermore the number of patients enrolled in these studies has been small and some did not use clinically important outcome measures (3,4). Further trials have been recommended to determine whether nonionic media actually perform better than high-osmolar media and, if so, whether their benefits exist for all patients or only for high risk patients (5).

The major problem with the new contrast media is their cost - 10-20 times higher than conventional media in North America. Thus cost, as well as effectiveness, need to be considered in any decision as to which media should be used and for which patients (6). When all contrast requiring radiological procedures were considered and optimistic assumptions about the safety of nonionic media were made, it was found that the marginal cost of nonionic media was very high (7), amounting to $186 more per cardiac catheterization in a recent randomized trial (8).

Our randomized, controlled, double blind, clinical trial was undertaken (a) to compare the incidence of clinically important side effects following intracardiac injection of high-osmolar ionic and low-osmolar nonionic

contrast media,

(b) to determine whether it was possible to identify patients who were at high risk of adverse reactions, and

(c) to determine the cost-effectiveness of the nonionic versus the high-osmolar media.

METHODS

For 17 months prior to August 1990 one thousand eight hundred and fifty six consecutive adult patients having cardiac catheterization without angioplasty during the research nurses' working hours were considered for entry to the study. The only pre-specified exclusion criteria were (a) history of prior anaphylactoid reaction to contrast (N=32) and (b) a cardiac condition severe enough for the cardiologist to insist upon nonionic contrast. These conditions included low output left ventricular failure, unstable angina, or myocardial infarction in the previous week (N = 188). It should be noted that not all those with these clinical conditions were excluded from the randomized trial. However, refusal by the cardiologist to enter the patient for reasons other than (a) or (b) occurred in a further 125 instances and refusal by the patient to enter the study occurred on 21 occasions. 267 of 366 (72.9 percent) non-randomized patients received nonionic contrast, 56 (15.3 percent) received low-osmolar ionic contrast and the remainder high-osmolar contrast. All non-randomized patients were followed in the same manner as the randomized groups.

737 patients were randomly assigned to receive high-osmolar contrast (Renografin 76 or MD 76 in all cases) and 753 to receive nonionic contrast (Iohexol N=33, Iopamidol N=721). Outcomes were determined by the doctor, cardiopulmonary technician and patient, all of whom were blind to which

contrast was prescribed. The research nurse was responsible for the allocation of contrast and was also an unblinded recorder of events that occurred during and after the procedure, as reported by the patient, doctor and technician. Informed consent was obtained from each patient. A questionnaire containing demographic data (age, sex), clinical history (prior reactions to contrast, allergies, asthma, cardiac disease, renal impairment, diabetes mellitus, anxiety, other illnesses) and medication history was completed by the research nurse before random allocation of contrast.

Serum creatinine was measured on the day of the procedure. As the risk of clinically important contrast nephropathy is low in patients with normal renal function (9) a repeat serum creatinine was obtained 2 days after the procedure, only if the pre-contrast level was greater than 120 umol per liter (1.36 mg per deciliter). One hundred and fifty three patients had an elevated serum creatinine on the day of the cardiac catheterization and a follow-up level was obtained in 123 (80%) patients. A more detailed analysis than presented in this report will be provided in another paper where the data from both the cardiac and an intravenous contrast trial will be combined.

Following insertion of the catheter, arterial blood pressure, cardiac rate and rhythm were recorded continuously. The type and dose of contrast was recorded, as was the duration of catheterization. Following contrast infusion the development of asystole, hypotension, angina, arrhythmias and other adverse

reactions was recorded, as was the type of therapeutic intervention which resulted from these reactions. After the procedure the results of the coronary arteriogram and left ventriculogram were obtained. On leaving the cardiac catheterization laboratory the patient was asked to complete a short questionnaire containing Likert scales (graded from 0 [no symptoms] to 10 [the most severe imaginable]) related to the presence and severity of 9 symptoms: pain, warmth, nausea, vomiting, sneezing, itching, shortness of breath, chest tightness and any other symptom. Any side effect which occurred during the 30 minute period after the procedure terminated was also recorded.

The research protocol was approved by the Human Investigation Committee of Memorial University of Newfoundland.

CATEGORY OF REACTIONS

1. Therapeutic intervention by a doctor: This was the primary outcome of interest and was assigned if the patient received a medical intervention because of an adverse reaction to contrast. A reaction severe enough to necessitate unblinding of the cardiologist was considered to have been one requiring a therapeutic intervention. We did not use standard criteria to determine who required medical intervention.
2. Clinically important adverse events: Reactions potentially related to contrast, that were either life-threatening themselves, might presage a life-threatening event, or were of sufficient severity to be likely to interrupt or delay the completion of the angiography. Such clinically important events were defined as follows: (a) angina which was not relieved by one nitroglycerine tablet (b) tachyarrythmias of new onset

requiring treatment (c) bradyarrythmias or conduction system disturbance of new onset requiring treatment (d) a fall in blood pressure to less than 80 mmHg systolic for longer than 1 minute or which required therapy.

3. Subjectively severe symptoms: One or more symptoms rated greater than or equal to the arbitrary cutpoint of 5 on the Likert scale.

4. Severe, prolonged reactions: Unlike categories 1-3 these reactions were judged retrospectively by the investigators blind to the type of contrast prescribed. They included angina requiring multiple drugs, ventricular fibrillation or severe tachyarrhythmia requiring medical intervention, prolonged hypotension requiring multiple interventions, prolonged cardiac arrest.

EFFECT OF PATIENT DESCRIPTORS ON INCIDENCE OF REACTIONS

Potential covariates were examined to determine whether they influenced the reaction rates. These included sex and age; history of prior reaction to contrast, allergy, asthma, diabetes mellitus, renal impairment (serum creatinine > 120 umol per liter), anxiety, severe illness, cardiac failure, myocardial infarction, hypertension, intermittent claudication and transient ischemic attacks; presence and severity of coronary artery disease, left ventricular dysfunction and valvular disease as determined by the catheterization; dose and type of contrast infusion. Anxiety was recorded as present only if the research nurse considered it severe. Severe illness was

defined as being bed-bound in hospital by order of a physician for acute medical reasons. The effect of the potential covariates was analysed by examining incidence rates of therapeutic intervention in the subgroups with each of the covariates and also by combining them in a multivariate analysis.

COST ANALYSIS

The records of all randomized patients having a significant reaction during cardiac catheterization were reviewed to determine what changes in medical care occurred as a result. The additional days spent in coronary care or on the ward as a result of an adverse reaction to contrast were assessed blind to the type of contrast prescribed, as were the many different medications, balloon pumps and pacemakers. The average cost to the hospital of extra days spent in coronary care or on the ward was assigned for each patient, as was the actual cost to the hospital of resources consumed to treat an adverse event. The average marginal cost to the hospital of a day spent in coronary care rather than on a ward was used when such an event occurred. Thus all costs are based on hospital costs in 1991 Canadian dollars.

STATISTICAL ANALYSIS

Continuous variables are presented as medians or means and standard deviations. All statistical tests were 2 tailed with a significance level of 0.05. The Bonferroni procedure was used to adjust for multiple comparisons

(Table 3). Incidence rates and relative risks are presented with 95 percent confidence intervals. The effect of nonionic contrast on the rate of reactions and the effects of binary covariates were assessed by the chi-squared test or Fisher's exact test. Continuous variables were compared by t-tests or Mann-Whitney U tests depending on distribution. A stepwise multiple logistic regression, using the BMDP software (1988 version), was performed to assess the effect of several potential predictors on the incidence of clinically important adverse events. The variables were added to and removed from the models singly by both automated and deliberate stepping procedures to allow detection of multicolinearity. All variables of potential clincial importance were so examined. The interaction of several variables were also assessed in the models. The odds ratios presented are those from a final model using all independent variables previously found to have a predictive effect.

At the outset it was intended that the patients in this trial be combined with those in a trial of intravenous contrast (manuscript submitted for publication) to investigate the systemic toxicity of the contrast agents. The overall required sample size was estimated to be 3543. During enrollment of the patients having cardiac angiography it became apparent that there was a high frequency of adverse cardiovascular events requiring therapy, noted before analysis by contrast assignment. This high frequency in 1490 patients was reported to the external advisor (Dr. JD Harnett). He advised full analysis of the data, following which the cardiac catheterization arm of the trial was stopped.

RESULTS

Patient status at baseline

Randomized trial: Table 1 shows the demographic data, clinical

information, dose and type of contrast, while Table 2 shows the results of the cardiac catheterization for patients in the randomized study. The two randomized groups were well matched for all demographic and clinical variables, drug prescription (Table 1) and for the degree of cardiac disease observed at catheterization (Table 2).

Non-randomized patients: Those patients, who were excluded from the randomized trial for medical reasons, had more severe previous cardiac illness (previous myocardial infarction 63 percent (N=140); unstable angina 66 percent (N=146), were more likely to be severely ill [43 percent (N=95)], or to have a history of prior contrast reaction [16.3 percent (N= 36)], than those in the randomized trial.

Effect of nonionic contrast in randomized trial

Therapeutic intervention: The number of patients receiving a therapeutic intervention by the cardiologist as a result of adverse reaction to contrast was high (28.9 percent) after high-osmolar contrast, and the relative risk for such an intervention was 3.1 times (95% confidence intervals: 2.5-4.1) that in the nonionic group (Table 3). A switch to a low-osmolar contrast was the only intervention in 29 cases assigned to high-osmolar contrast. In addition, the incidence of clinically important angina, hypotension and bradycardia was substantially higher in the high-osmolar group (Table 3). Urticaria occurred in 20 (2.7 percent) and was treated in 9 (1.2 percent) patients assigned to high-osmolar, while only 1 case (0.1 percent $p < 0.0001$) given nonionic had urticaria and this was not treated. Nonionic contrast was associated with a lower incidence of symptoms particularly pain, chest tightness and nausea (Table 4).

Severe or prolonged reactions: These events (category of reaction 4)

occurred in 2.9 percent of the high-osmolar group and in 0.8 percent of the nonionic group (Table 3). In the former group these severe reactions included angina requiring multiple drugs (N=11), ventricular fibrillation (N=5), prolonged hypotension requiring multiple interventions (N=4) and a prolonged cardiac arrest (N=1). In the comparable nonionic group 4 of the 6 patients had angina requiring morphine (one of whom had an intraprocedural myocardial infarct), one had ventricular tachycardia requiring lidocaine, and one atrial fibrillation requiring verapamil and digoxin.

All but 3 of those having severe or prolonged reactions had severe coronary disease, advanced valvular disease or poor left ventricular function. 22 of the 27 severe events were in people who could have been identified as at high risk in advance because of unstable angina, current heart failure, previous coronary artery bypass grafting or known 3 vessel coronary disease. There were no deaths related to the procedure and no episodes of permanent disability or damage attributable to contrast administration in the study.

Procedure time: The average time from insertion to removal of the catheter was not longer in those who received high-osmolar contrast (13.7 $\pm$ 8.8 vs 13.6 $\pm$ 10.6 minutes). The number of abbreviated procedures was few: three patients randomly allocated high-osmolar and one nonionic contrast.

Contrast nephropathy: Sixty-four patients who received high osmolar contrast, had an elevated serum creatinine on the day of the cardiac catheterization, and also had a follow-up level taken. Three (4.7%) of this group developed greater than 25% but less than 50% rise in serum creatinine,

and a further 3 (4.7%) patients had greater than 50% rise. Of 59 patients, who randomly received non-ionic contrast and had pre-serum creatinine greater than 120 umol/l, 2 (3.4%) patients experienced greater than 25% but less than 50% rise in serum creatinine, and 1 (1.7%) patient had greater than 50% rise. Given the relatively small sample size and low incidence rates of contrast nephropathy these differences were not significant.

Non-randomized patients: Those who had been excluded from the randomized trial for medical reasons had a higher incidence of most adverse reactions than those randomly allocated nonionic contrast. A therapeutic intervention was required in 17 percent versus 9.2 percent (p=0.002). It should be noted that, despite being at higher risk, those excluded for medical reasons had a lower incidence of adverse reactions than those who were randomized to high-osmolar contrast.

Effect of covariates

Univariate analysis of all the covariates mentioned in the methods revealed that the only patients with a higher than average relative benefit from nonionic contrast, in terms of events requiring therapeutic intervention, were those with diabetes mellitus (relative risk 6.6, 95 percent CI 2.7-16.3) and those with a history of prior reaction to contrast (relative risk 7, 95 percent CI 1-50). Those who were severely ill had a greater incidence of therapeutic intervention after both types of contrast (40.5 percent after high-osmolar and 12.6 percent after nonionic). There was a gradual increase in the number requiring therapeutic intervention with increasing severity of coronary

disease in those receiving either high-osmolar or nonionic contrast (one vessel 27.1 versus 4.2 percent, 2 vessel 35.7 versus 11.1 percent, 3 vessel 39.1 versus 17.9 percent, left main 38.2 versus 22 percent).

Multiple logistic regression was used to further assess the linear associations between many subject and investigation related characteristics and the occurrence of an adverse event. The dependent variable used was the number of patients with clinically important adverse events (see category of reactions (2) in methods for definition). The type of contrast was one of the independent variables in each model.

The independent variables found not to be associated with adverse events of clinical importance in these models included age, sex, a history of prior reaction to contrast, allergy or asthma, the presence of renal impairment (serum creatinine $\geq$ 120 umol/l), valvular heart disease, diabetes, the degree of left ventricular dysfunction, or dose of contrast.

Severe illness was associated with an increase in the risk of a clinically important adverse reaction (odds ratio 1.36, 95 percent confidence interval 1.1 to 1.7) but this association was no longer significant when the degree of coronary disease was taken into account. The best predictors of an adverse reaction of clinical importance were the presence of severe coronary disease (left main, three vessel or coronary artery bypass grafts present) (odds ratio 1.5, 95 percent confidence interval 1.2 to 1.8) and unstable angina (odds ratio 1.2, 95 percent confidence interval 1.03 to 1.5). The interaction of these variables had little extra association with the occurrence of an adverse reaction.

Cost Considerations

The length of hospital stay was the same in those randomly allocated high-

osmolar contrast as in those given nonionic contrast (median stay 5 days in each case). The length of stay was significantly longer in those excluded from the randomized trial for medical reasons (median 11 days, $p < 0.0001$ relative to randomized groups).

The differences between the high-osmolar and nonionic groups in terms of medical care for adverse events potentially related to contrast included: 20 days spent in coronary care rather than on a ward, 1 day on a ward rather than as an outpatient, insertion and maintenance of 2 pacemakers, and many different medications. The cost of all these interventions was Can $6,742. Contrast for the high-osmolar group cost Can $18,352 (including nonionic in those crossed-over), while contrast for the same number of patients in the nonionic group cost Can $98,700. Thus the incremental cost of nonionic contrast was Can $73,606, or Can $100 per patient undergoing the cardiac catheterization procedure. Thirty-nine percent of patients in the randomized study had current heart failure, myocardial infarction within previous 2 weeks, unstable angina, previous coronary artery bypass grafting, known 3 vessel coronary disease or advanced valvular disease. If only patients in this "high risk" group were given nonionic contrast the marginal cost would be $128 per "high risk" patient having cardiac catheterization. Data on the number of patients needed to treat to prevent a reaction and the marginal cost per event prevented, if all patients or only "high risk" patients in the trial were given nonionic contrast, are reported in Table 5.

DISCUSSION

There have been consistent requests for trials to provide better information about the benefits of the expensive nonionic contrast media. To date few large scale randomized trials have been reported (3) and many did not comment on the clinical consequences of the adverse reactions reported following contrast. To our knowledge our study is the largest randomized trial yet reported comparing intracardiac high-osmolar and nonionic contrast.

We observed a high frequency of adverse effects requiring therapeutic intervention after high-osmolar contrast. This event rate is higher than that reported for a similar population given high-osmolar contrast by Hirshfeld et al (5). This may be due to the fact that we included treatment of angina, bradycardia and requests for unblinding as events. In fact many of the adverse effects seen with contrast in our trial were relatively minor and short lived. Nevertheless more clinically important adverse events also occurred (see category of reactions 2 in methods). The incidence rates for serious arrythmias and prolonged angina seen in our study are similar to those noted by others (5,10). Severe prolonged reactions (see category of reactions 4) were infrequent but were also more likely to be seen with high-osmolar contrast.

The particular formulations of high-osmolar contrast used in our trial contained calcium chelating additives. These media have been associated with a significantly greater incidence of ventricular fibrillation than similar high-osmolar media which do not chelate calcium (11,12). Although use of a non-calcium chelating formulation of high-osmolar contrast might have prevented some of the episodes of ventricular fibrillation seen only after high-osmolar contrast in our study, there is no evidence that the non-calcium chelating high-osmolar media can prevent other adverse reactions to contrast. Neither

has there been any adequate comparison of nonionic contrast, which we found to be associated with a lower incidence of all contrast related adverse events, and non-calcium chelating formulations of high-osmolar agents.

Virtually all patients having cardiac catheterization were eligible for inclusion in this trial but the cardiologists excluded a sizeable number because they felt that they would be at excessive risk with high-osmolar contrast. These patients were more ill and did have more adverse events than those randomized to the same nonionic contrast. However, they had less adverse events than those who received high-osmolar contrast in the randomized trial. Virtually all of the most serious adverse reactions, to either contrast, occurred in those with advanced cardiac disease, and the multivariate analysis of those in the randomized trial identified the severity of coronary disease and the instability of angina as risk factors for clinically important adverse events in this already selected group.

We found that universal use of nonionic contrast for the type of patients in our randomized trial, who are served by the Canadian health care system, would cost an extra Can $100 per patient undergoing the procedure. In the United States nonionic contrast is up to twice as expensive compared to Canada. Therefore the figure of US $186 higher for use of iopamidol rather than diatrizoate in a recent US trial (8) would be comparable to our predictions. Of course if nonionic contrast were selectively given only to those at higher risk for adverse reactions the cost-effectiveness would improve.

The results of this trial illustrate the problem that faces health policy decision makers when a new therapy is found superior to an established one, but is also associated with a substantial increase in cost. There are no agreed formal guidelines to aid a decision as to how much society would be willing to

pay to achieve a given degree of improvement in the health status of individuals. Cost-effectiveness analyses alone cannot usually be used to compare disparate and competing health care programs. Decisions as to which programs should be funded are often not influenced solely by even cost-benefit considerations (6,7).

Thus we conclude that nonionic contrast is better tolerated during cardiac angiography than a calcium chelating formulation of high-osmolar contrast, but universal use of nonionic contrast is expensive. It may be possible to select those at highest risk of serious adverse side-effects on the basis of some clinical variables. Therefore selective use of these agents may, at least, be more economically attractive. Should the price of nonionic media decrease, their universal use would be more attractive in the cardiac catheterization laboratory.

TABLE I: DESCRIPTION OF PATIENTS AT BASELINE

	Randomized			
	High-Osmolar		Nonionic	
	N	%	N	%
Total	737	100	753	100
Male	520	70.6	514	68.3
Prior reactor to contrast	33	4.5	21	2.8
Allergic	171	23.2	170	22.6
Asthmatic	50	6.8	46	6.1
Diabetic	115	15.6	115	15.3
Renal impairment	90	12.2	80	10.6
Aged >50 years	516	70.0	522	69.3
Severe illness	74	10	95	12.6
Anxious	300	40.7	313	41.6
Medical History				
Myocardial infarction	310	42.1	322	42.8
Heart failure	100	13.6	108	14.3
Intermittent claudication	219	29.7	236	31.3
Hypertension	357	48.4	371	49.3
Transient ischemic attacks	41	5.6	42	5.6
Drugs:Nitrates	429	58.2	412	54.7
Calcium Channel Blockers	403	54.7	409	54.3
Antiplatelet Agents	358	48.6	349	46.3
Beta Blockers	294	39.9	270	35.9

TABLE I: DESCRIPTION OF PATIENTS AT BASELINE (CONT'D)

Premedication given	681	92.4	701	93.1
Unstable Angina as indication for catheterization	278	37.7	287	38.1

	MEAN ± SD	MEAN ± SD
Volume of contrast (ml)	122 ± 43	127 ± 35
Age (years)	56 ± 11	55 ± 11
Pulse rate before procedure	68 ± 25	69 ± 13
Systolic blood pressure before procedure (mmHg)	139 ± 25	138 ± 26
Diastolic blood pressure before procedure (mmHg)	71 ± 13	70 ± 14

TABLE 2: RESULTS OF CARDIAC CATHETERIZATION

	Randomized			
	High-Osmolar		Nonionic	
	N	%	N	%
Valvular heart disease	65	8.8	62	8.2
Left ventricular dysfunction				
-Mild	209	28.4	219	29.1
-Moderate	90	12.2	99	13.1
-Severe	26	3.5	30	4.0
Coronary disease				
-Left main	55	7.5	41	5.4
-One vessel	170	23.1	167	22.2
-Two vessel	126	17.1	153	20.3
-Triple vessel	192	26.1	179	23.8
-Coronary bypass grafts present	31	4.2	24	3.2

TABLE 3: THE NUMBER OF CASES WITH SPECIFIED ADVERSE REACTIONS TO CONTRAST IN THE RANDOMIZED TRIAL.

Adverse Reactions	High-Osmolar N=737	%	Low-Osmolar N=753	%	P*	95% CI Difference%	RR	95% CI RR
[1]Category 1: Cases who required therapeutic intervention	213	28.9	69	9.2	$<10^{-7}$	15.9-23.6	3.1	2.5-4.1
[1]Category 2: Clinically important adverse events	124	16.8	25	3.4	$<10^{-8}$	10.5-16.5	5.1	3.3-7.7
Angina relieved by 2 nitroglycerine tablets (GTN)	23	3.1	6.0	0.8	0.014	0.9-3.7	3.9	1.6-9.6
Angina requiring more than 2 GTN	31	4.2	12	1.6	0.028	0.9-4.3	2.6	1.4-5.1
[1]Clinically important hypotension	40	5.4	3	0.4	$<10^{-7}$	3.3-6.7	13.6	4.2-44
Treated bradycardia	63	8.5	6	0.8	$<10^{-7}$	5.6-9.9	10.7	4.7-25
[2]Treated Tachyarrythmia	6	0.8	2	0.3	NS	-0.1-1.3	3.1	0.6-15
[1]Category 3: Subjectively severe symptoms, excluding warmth	189	25.6	70	9.3	$<10^{-8}$	12.6-20.1	2.8	2.1-3.6
[1]Category 4: Prolonged/severe event	21	2.9	6	0.8	0.035	0.7-3.4	3.6	1.5-8.8

*The P values were adjusted for multiple comparisons by Bonferroni correction.

[1] These adverse events are defined in the text.

[2] Ventricular fibrillation in all cases after high-osmolar, 1 episode of ventricular tachycardia and one of atrial fibrillation after nonionic.

TABLE 4: THE INCIDENCE OF SYMPTOMS SUBJECTIVELY RATED AS GREATER THAN OR EQUAL TO 5 ON A 10 POINT SEVERITY SCALE IN THE RANDOMIZED TRIAL.

	High-osmolar		Nonionic		P	Relative	95%
	N	%	N	%		Risk	CI RR
Warmth	527	71.5	443	58.8	<0.0001	1.2	1.1-1.3
Pain	79	10.7	34	4.5	<0.0001	2.4	1.6-3.5
Chest tightness	75	10.2	32	4.2	<0.0001	2.4	1.6-3.6
Nausea	79	10.7	26	3.5	<0.0001	3.1	2.0-4.8
Vomiting	13	1.8	11	1.5	NS	1.2	0.5-2.7
Dyspnea	17	2.3	12	1.6	NS	1.4	0.7-3.0

TABLE 5: COST EFFECTIVENESS OF NON-IONIC CONTRAST IN RANDOMIZED TRIAL.

Category of Reaction	If all patients given nonionic		If high risk[a] patients only given nonionic	
	Number needed to treat to prevent one reaction	Marginal cost for use of nonionic per event prevented	Number needed to treat to prevent one reaction	Marginal cost for use of nonionic per event prevented
1. Therapeutic intervention	5.1	$510	4.2	$541
2. Clinically important adverse events	7.4	$740	6.8	$871
4. Severe, prolonged event	50	$5,000	27	$3,464

[a]High risk: current heart failure, myocardial infarction within previous 2 weeks, unstable angina, previous coronary artery bypass grafting, known 3 vessel coronary disease, or advanced valvular disease.

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A RANDOMIZED TRIAL OF NONIONIC LOW-OSMOLAR VERSUS IONIC HIGH-OSMOLAR RADIOCONTRAST FOR INTRAVENOUS USE IN PATIENTS PERCEIVED TO BE AT HIGH RISK

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Running Head: Radiocontrast for intravenous use.

ABSTRACT

Background: Nonionic low-osmolar radiocontrast may be better tolerated than ionic high-osmolar radiocontrast following intravenous injection but its cost-effectiveness has not been examined in a large randomized trial. Selective use of expensive nonionic contrast has been advocated in groups perceived to be at high risk of an adverse reaction, but the costs and consequences of various strategies need to be examined.

Methods: We randomly assigned 955 patients to receive high-osmolar and 1158 to receive low-osmolar intravenous contrast, all of whom had 1 or more of the following perceived "risk factors" for adverse reactions to radiocontrast: prior reaction to contrast, allergies, asthma, diabetes, cardiac or renal disease, anxiety, severe illness or age greater than 50 years. Demographic and clinical data were collected before contrast was given. The occurrence of any adverse event, requirement for therapy and subjective symptoms was assessed in a double blind fashion after contrast.

Results: In the randomized trial an adverse reaction requiring the attention of a doctor occurred in 3.9 percent after high-osmolar and 0.9 percent after low-osmolar contrast ($p < 0.000005$). Therapy was given to 1.4 percent and 0.5 percent respectively ($p = 0.035$). The difference was due to a reduction in urticaria and other mild anaphylactoid reactions. In those receiving high-osmolar contrast the following factors increased the risk relative (RR) to those aged over 50 alone: prior reaction (RR = 7.4), allergy (RR = 4.4), cardiac disease (RR = 3.1), severe illness (RR = 3), renal disease (RR = 2.4), anxiety (RR = 2.2), diabetes (RR = 1.9) and asthma (RR = 1.4). In a multivariate analysis only prior reactions and allergy were independent risk factors. The marginal cost of nonionic contrast was Can $ 72.77 per patient in

the randomized trial. If all patients in the randomized trial were given nonionic contrast it would cost Can $2679 to prevent 1 reaction. If only those with prior reactions, allergy or asthma were given nonionic contrast it would cost at most Can $1211 to prevent 1 reaction and at least 67 percent of reactions would be prevented.

Conclusions: The frequency of reactions requiring medical attention and therapy, after intravenous use of high-osmolar contrast, in patients perceived to be at high risk, is low. Nonionic contrast significantly reduces this incidence, but at high cost. Selective use of nonionic contrast is a viable strategy.

Key Words: contrast media, ionic, nonionic, toxicity, adverse effects, intravenous, risk factors, cost-effectiveness, random allocation, comparative study.

INTRODUCTION

The high osmolarity of conventional radiographic contrast media may contribute to their toxicity. This led to the development of nonionic and dimeric-ionic contrast media which have lower osmolarity (1). These new compounds have also been shown to have lesser effects on many physiological processes and are thus said to be less chemotoxic (2). It was expected that these advances would improve on the already good safety profile of conventional high-osmolar radiocontrast media.

The low-osmolar agents have been available for use in North America since 1986 and in Europe for several years longer. These newer agents were quickly shown to be superior in terms of minor adverse effects following intravenous administration (3). Large scale prospective surveys have been published more recently and suggest that more serious adverse events may also be less frequent with low-osmolar media (4,5). Such surveys are subject to several sources of bias because of study design. Adverse events of "intermediate" severity (6) have not been very well studied in randomized clinical trials (7). Such evidence is desirable to confirm or refute the impression derived from the surveys. Death and the most severe adverse events are so infrequent that it is unlikely that a large enough randomized trial will be conducted to study them.

The low-osmolar contrast media are between ten and twenty times more expensive than high-osmolar media in North America. If low- rather than high-osmolar media were used for all radiological procedures in the United States, it has been estimated that the extra expenditure would amount to at least $1.1 billion per annum (8). Partly as a result of these economic considerations, some have suggested selective use of the low-osmolar media in patients perceived to be at high risk (9). Such a policy of selective use is much more

cost effective (10) but depends on accurate information as to what constitutes a high-risk subject.

Thus we performed this randomized, double blind, clinical trial (a) to compare the incidence of moderately severe adverse events following intravenous injection of high-osmolar ionic and low-osmolar nonionic contrast media in patients perceived to be at high risk (b) to determine the relative risk for such events associated with various clinical characteristics and (c) to examine the cost-effectiveness of low-osmolar nonionic contrast in a selected "high-risk" population.

METHODS

Inclusion and Exclusion Criteria: Subjects were considered for entry to the randomized trial if they were having intravenous contrast for computed tomography (CT) of the head or body or intravenous pyelography at the Health Sciences Centre, St. John's. This is a tertiary referral centre for the province. Only those patients who had one or more "high risk" characteristics were eligible (6,11). These included (a) prior mild adverse reaction to radiocontrast (b) "allergy" to drugs, foods or other substances (c) asthma (d) cardiac disease (angina, heart failure, myocardial or valvular disease) (e) diabetes mellitus (f) chronic renal failure (g) age greater than 50 years (h) severe illness (bed-bound in hospital for medical reasons) and (i) excessive anxiety as judged by the interviewing nurse.

Subjects were excluded from the trial in the absence of any of the above characteristics and for three other reasons: (1) patient refusal, (2) non-availability of low-osmolar contrast in a form suitable for the patient's investigation, (3) at the request of the radiologist because of a perception that the patient would be at excessive risk if high-osmolar contrast were

given.

Subjects and Contrast Media: In the three years prior to February 1991 three thousand one hundred and sixty seven consecutive eligible patients were identified during the research nurses working hours. This represented 49.5 percent of those having intravenous contrast for similar investigations over the same time period. Of these 2113 (66.7 percent) were entered in the randomized trial. 955 were randomly assigned to receive ionic high-osmolar contrast and 1158 to receive nonionic low-osmolar contrast. The contrast used was that bought under contract by the hospital. Overall 163 patients were given Iopamidol, 1329 Iohexol, 12 Ioxaglate, 613 meglumine Iothalamate and 1050 sodium/meglumine diatrizoate in various concentrations. In the early months of the study some patients, having CT of the body, for which no appropriate infusible formulation of nonionic contrast was available locally, were inappropriately entered in the randomized trial. Such individuals (N = 220) who had received high-osmolar contrast were subsequently identified and removed from the trial. The corresponding assignments to nonionic contrast had been used for the next available patient. These subjects could not be reliably identified after the error was discovered and remain in the randomized trial. 58 patients refused to enter the trial, 612 were excluded because of non-availability of appropriate nonionic contrast and 216 were excluded at the request of the radiologist because of asthma, allergies and previous reactions to contrast. A further 168 were not randomized for miscellaneous reasons. All non-randomized patients were followed in the same fashion as the randomized groups. The only patients who received steroid prophylaxis were 5 patients with a history of prior serious reaction to contrast. All were nonrandomized and given nonionic contrast. None had any adverse events with the current

examination.

Protocol: The research nurses briefly interviewed all patients to determine eligibility. Informed consent was sought and a questionnaire containing demographic data (age, sex), clinical history (prior reactions to contrast, allergies, asthma, cardiac disease, renal impairment, diabetes mellitus, anxiety, other illnesses) and medication history was completed by the research nurse. The nurse then approached the radiologist who made the final decision as to whether contrast type could be assigned at random. A radiation technologist prepared the randomly assigned contrast. The research nurse, radiologist and patient remained blind to the type of contrast administered.

The nurse recorded the patient's pulse and blood pressure before and immediately after the radiological procedure as well as recording any adverse events which occurred after contrast and before the patient left the radiology department. Whether the radiologist was required to review a patient because of an adverse event was also noted, including any therapy prescribed. Before leaving the department the patient completed a questionnaire containing Lichert scales (graded 0 to 10) relating to the presence and severity of 9 symptoms: pain, warmth, nausea, vomiting, sneezing, pruritus, dyspnea, chest pain and any other symptom. The serum creatinine was measured on the day of the procedure and if it exceeded 120 umol per liter (1.36 mg per deciliter) a repeat serum creatinine was sought 2 days later. This data will be analysed in a separate paper.

This research protocol was approved by the Human Investigation Committee of Memorial University of Newfoundland.

Outcomes:

1. The primary outcome was the occurrence of an adverse event after contrast

which was sufficiently severe for the doctor to treat the patient.

2. Hemodynamic deterioration defined as a change in blood pressure from baseline of greater than 20 mmHg systolic or 10 mmHg diastolic.
3. The occurrence of symptoms subjectively rated as severe (greater than or equal to 5 on a scale of 0 to 10) by the patient.

Analysis and Statistics:

Continuous variables are presented as medians and ranges or means and standard deviations. All statistical tests had a significance level of 0.05 which was 1-tailed for outcomes. Incidence rates and relative risks are presented with 95 percent confidence intervals. Categorical variables were compared by the chi-squared or Fisher's exact test. Continuous variables were compared by t-tests or Mann-Whitney-U tests depending on distribution.

A stepwise multiple logistic regression, using BMDP software (1988 version) was performed to assess the effect of various risk factors on the primary outcome.

We used a 2 percent incidence of reactions requiring therapy after high-osmolar contrast, as found by Lasser (12) to estimate sample size. We wished to be able to detect at least 50 percent reduction in risk with low-osmolar contrast with a maximum 1-tailed Type I error rate of 5 percent and a Type 2 error rate of 20 percent. This suggested that we required 3543 subjects in total. We had intended to combine the subjects in this report with a previously reported group having cardiac catheterization (13) and we stopped patient accrual when the total predicted sample size was achieved.

RESULTS:

Baseline Comparison: The randomized groups were well matched apart from a greater prevalence of previous cardiac disease in the group assigned to low-

osmolar contrast (Table 1). The volume of high-osmolar contrast given was higher, which is partly due to the lower iodine content of the high- than the low-osmolar contrast (141 versus 300 mg per milliliter) used for infusion, and partly to the regular use of larger vials of high- than low-osmolar contrast (300 versus 100 milliliters) at our institution.

Those excluded from the randomized trial by the radiologists, and given low-osmolar contrast, had the expected significantly higher proportion of prior reactors, allergic and asthmatic patients (all $p < 10^{-8}$ relative to the randomized group) (Table 2). Eczema, rhinitis, and use of antihistamines or bronchodilators were all more common in these selected patients as well. This group was significantly younger than the randomized groups ($p < 0.0001$).

Table 2 also shows the baseline characteristics of the patients who were excluded largely because of non-availability of low-osmolar contrast, and who received high-osmolar contrast. The only differences between these patients and those who were randomized to high- osmolar contrast were a slightly lower prevalence of prior reactors (1.1 versus 2.7 percent, $p = 0.02$) and a higher prevalence of diabetics (15.6 versus 12 percent, $p = 0.03$), very ill patients (7 versus 3.5 percent, $p = 0.001$), anxious patients (43.9 versus 26.6 percent, $p < 10^{-8}$), and patients on diuretics and steroids in the non-randomized group.

Outcomes in the randomized patients: Therapy was given for a contrast reaction 2.6 times more often in those assigned to high-osmolar contrast (Table 3). Adverse events requiring attention by the radiologist were 4.5 times more frequent in those randomly assigned to high-osmolar contrast. Table 3 also shows that urticaria alone or other mild anaphylactoid reactions accounted for most of the difference between the groups. The remainder of the reactions were varied but consisted of severe vomiting in 5 (0.5 percent) cases given

high- and none given low-osmolar contrast. There were no life-threatening reactions. We did not show any difference in hemodynamic responses to contrast, with a fall in blood pressure greater than 20/10 mmHg occurring in 97 of 955 (10.2 percent) of those receiving high-osmolar and in 104 of 1158 (9 percent, p = NS) receiving low-osmolar contrast. Angina was more frequent (0.5 percent versus 0.3 percent, p = NS) in those given low-osmolar contrast but this may reflect the more severe cardiac history in those patients. Several subjectively severe (greater than or equal to 5 on the 10 point scale) symptoms were significantly more common in those given high-osmolar contrast (Table 3).

Outcomes in the non-randomized patients: Despite being at apparently higher risk, those excluded from the randomized trial and given low-osmolar contrast had a lower frequency of reactions requiring the attention of a doctor than those given high-osmolar contrast in the randomized trial (1.5 versus 3.9 percent, p = 0.05) (Table 4). Predictably, when all patients given low-osmolar contrast are considered, those excluded from the randomized trial had more such reactions (1.5 versus 0.9 percent, p = NS).

The adverse event rates in those receiving high-osmolar contrast were the same irrespective of whether they were randomized, apart from a lower frequency of subjectively severe warmth in those not randomly assigned (Table 4).

Assessment of Risk Factors: We did not specifically study patients felt to be at low risk of adverse events. Thus it is not possible to define the relative risk of our "high risk" categories directly. However the patients who were aged more than 50 years and were without any other risk factor had the lowest frequency of adverse events requiring a doctor's attention (1.6 percent of those given high- and 0.3 percent of those given low-osmolar contrast). These patients thus serve as a useful population against which to assess other risk

factors. Table 5 shows the results of a univariate analysis of risk factors within each contrast group.

To further assess the independent effects of these and other potential risk factors we performed a series of multiple logistic regression analyses. In each case the dependent variable was a reaction requiring attention by a doctor. All 3167 patients were included for one analysis and all those receiving high-osmolar contrast were included in a separate analysis. The results are shown in Table 6. As can be seen a history of previous adverse reaction to contrast, a history of allergy and cardiac disease increase the risk of an adverse event. A high volume of contrast was also associated with a small independent increase in risk. None of the other "risk factors" which made patients eligible for the randomized trial had independent predictive power for adverse events requiring the attention of a doctor.

All of those at increased risk benefited from the use of low-osmolar contrast. The relative reduction in the incidence of an adverse reaction requiring the attention of a doctor, by use of low-osmolar contrast, ranged from a two-fold reduction in those with cardiac disease, to a 4.1 fold reduction in those with a history of prior reaction, to an 8.9 fold reduction in those with a history of allergy.

Cost Considerations: The high-osmolar contrast for the 955 patients in the randomized trial would cost at least Can $8,197 at local prices in 1991. The cost of the drugs used in treating adverse reactions was negligible. All patients who had an adverse event requiring a doctor's attention remained in the radiology department for between 10 minutes and 2 hours until they were judged stable. None of the patients required admission to hospital or a change from a ward to an intensive care bed as a result of a reaction. None of the

reactions required the attendance of an anaesthetist. 1 patient required assessment in the emergency department after high-osmolar contrast and 5 patients were similarly assessed after low-osmolar contrast. Thus the marginal cost of treating adverse reactions related to high-osmolar contrast was very small and can be ignored for this analysis.

The cost of providing nonionic low-osmolar contrast to a group of 955 patients in the randomized trial was Can $77,699. Thus the marginal cost of nonionic contrast for this group was Can $ 69,502 or Can $72.77 per patient on average.

If all patients in the randomized trial were given nonionic contrast then 49.5 percent of those being given intravenous contrast in our X-ray department would receive nonionic. This would increase the cost of contrast in our radiology department by 948 percent over use of only ionic media and it would cost Can $2679 to prevent 1 reaction severe enough to require the attendance of a doctor. Universal use of nonionic contrast would further substantially increase the cost of preventing 1 reaction.

If those aged over 50 years, but without other risk factors, were not given nonionic contrast, and if this was given to all others eligible for our trial, then 38 percent of those getting intravenous contrast would receive nonionic contrast. This would increase contrast cost in our radiology department by 244 percent over use of only ionic contrast and it would cost Can $1998 to prevent 1 reaction, while 86 percent of preventable reactions would be prevented. If only those with a history of prior reaction to contrast, allergies or asthma were selected to receive nonionic contrast then 19 percent of those being given intravenous contrast would receive nonionic contrast. This would increase the cost of contrast by 183 percent over use of only ionic

media, and cost Can $1211 to prevent 1 reaction, while 67 percent of preventable reactions would be prevented.

Because some prior reactors to contrast, allergic patients and asthmatics were excluded from the randomized trial, the cost to prevent a reaction in this type of patient is probably overestimated and the proportion of potentially preventable reactions prevented is probably underestimated. Since nonionic contrast is nearly twice as expensive again relative to ionic contrast in the United States the above costs could be doubled in that country.

DISCUSSION

Our results indicate that nonionic low-osmolar agents are associated with a significantly lower frequency of "moderate" or "intermediate" level adverse reactions than ionic high-osmolar agents, when given intravenously to a selected "high risk" population. We have also confirmed the impression of many others that selected symptoms like warmth, nausea, and vomiting are ameliorated by low-osmolar contrast. It should be noted that steroid or other prophylactic therapy was not given to patients in our randomized trial. The exclusion of some patients from the randomized trial did not prevent us from using these patients to assess risk factors as we collected the same data on all patients.

The adverse events which constituted our primary outcome were generally not long-lasting or severe but were sufficiently worrisome for a doctor to treat them. The decision to treat these reactions was taken before unblinding in virtually all cases and therefore the difference in the number of treated reactions is likely to be due to a difference in toxicity.

The frequency of reactions requiring a doctor's attention (1.6 percent) in those who were over 50 years of age but had no other risk factor, and who were given high-osmolar contrast, is comparable to the frequency of fairly similar

events in the literature. Such events occur in between 1.2 and 2 percent of unselected cases in prospective surveys (12,14-18). Thus this category of patients might be considered to be at average risk, at most, for these "intermediate" level reactions.

A history of prior reaction to contrast media, or allergies did behave as risk factors for "intermediate" level adverse reactions to high-osmolar media in our trial. This is similar to the general experience and the relative risks are comparable to those seen in the Japanese survey in relation to overall and severe adverse events (5). Our multivariate analysis showed that the independent effect of each of these risk factors may be a little lower than the usual univariate analyses might suggest. Despite accepted opinion (5) we were unable to identify asthma as a major risk factor for adverse reactions. Exclusion of the most severe asthmatics from the randomized trial cannot explain this as asthma still fails to act as a major risk factor when these excluded patients are also considered. However, in this study the presence or absence of asthma was dependent only on the patient's own history and a greater risk associated with true atopy may have been diluted. Anxiety and other clinical conditions are, at best, weak risk factors for these "intermediate" reactions. The increase in risk associated with higher doses of high-osmolar contrast supports the recent literature (5).

Nonionic contrast for intravenous use has not been shown to reduce mortality (5). Severe or life-threatening reactions to contrast are very rare and probably have the same risk factors as the less severe reactions occurring during our trial (5,6). Even these "moderate" reactions are infrequent and do cluster in high risk groups. Provision of nonionic contrast to our study population (about half of the total population receiving intravenous contrast)

would be very expensive. Prevention of what are really quite mild reactions to ionic contrast will be prohibitive in many institutions. Provision of nonionic contrast to those with a prior reaction to ionic contrast, an allergic history or asthma is more cost-effective but still quite expensive. This is even more so in the United States, where nonionic contrast costs more than in Canada.

If the cost differential did not exist, few would oppose universal use of nonionic contrast. In addition to reduced use of procedures requiring contrast and a reduction in volume infused, the ideal solution to the current dilemma would be a reduction in the cost of nonionic contrast. Every effort should be made to encourage the pharmaceutical companies to do this. The use of steroid prophylaxis might reduce the incidence of reactions to high-osmolar contrast by as much as nonionic contrast does (12) but we did not examine that approach in our trial. No direct comparison of the strategies of steroid prophylaxis versus use of nonionic contrast has been made and to do so would require a large trial. Steroid prophylaxis is cheap and might be a reasonable alternative to the use of nonionic contrast in many cases. In the interim we feel that a policy of selective use of nonionic intravenous contrast in patients with a history of prior reaction to contrast, allergy or asthma can be justified.

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TABLE 1: BASELINE CHARACTERISTICS OF THE RANDOMIZED GROUPS

	High-Osmolar		Low-Osmolar	
Total	N = 955	% = 100	N = 1158	% = 100
Male	487	51	566	48.9
Potential Risk Factors				
Prior reaction to contrast	26	2.7	37	3.2
History of allergies	273	28.6	332	28.7
Asthma	53	5.5	79	6.8
History of cardiac disease	139	14.6	226	19.5
Renal impairment	94	9.8	140	12.1
Diabetes	115	12.0	143	12.3
Age > 50 years	774	81.0	975	84.2
Age > 50 years only	274	28.7	307	26.5
Anxious	254	26.6	337	29.1
Very Ill	33	3.5	32	2.8
Medical History				
History of Heart Failure	16	1.7	35	3.0
Hypertensive	309	32.4	403	34.8
History of transient cerebral ischemia	46	4.8	59	5.1
Eczema	41	4.3	54	4.7
Rhinitis	37	3.9	44	3.8

TABLE 1: BASELINE CHARACTERISTICS OF THE RANDOMIZED GROUPS (CONT'D)

	High-Osmolar		Low-Osmolar	
	N=955	%=100	N=1158	%=100
Drug History				
Digoxin	39	4.1	58	5.0
Beta Blocker	70	7.3	100	8.6
Nitrate	32	3.4	61	5.3
Anti-histamine	15	1.6	18	1.6
Steroid	32	3.4	51	4.4
Bronchodilator	39	4.1	65	5.6
	Mean ± SD		Mean ± SD	
Age (years)	59.2 ± 14.3		60.3 ± 13.1	
Heart Rate (beats/min)	78.3 ± 11.9		78.1 ± 12.5	
Systolic blood pressure (mmHg)	135.9 ± 21.3		137.0 ± 22.4	
Diastolic blood pressure (mmHg)	83.4 ± 11.7		82.4 ± 11.4	
	Median (Range)		Median (Range)	
Contrast Volume (mls)	100 (40-750)		50 (1-400)	
Serum Creatinine (umol/l)	84 (27-1823)		85 (43-991)	

TABLE 2: BASELINE CHARACTERISTICS OF PATIENTS EXCLUDED FROM THE RANDOMIZED TRIAL.

	High-Osmolar		Low-Osmolar	
Total	N = 716	% = 100	N = 338	% = 100
Male	349	48.7	145	42.9
Potential Risk Factors				
Prior reaction to contrast	8	1.1	136	40.2
History of allergies	183	25.6	171	50.6
Asthma	37	5.2	105	31.1
History of cardiac disease	125	17.5	57	16.9
Renal impairment	87	12.2	39	11.5
Diabetes	112	15.6	37	10.9
Age > 50 years	625	87.3	185	54.7
Age > 50 years only	167	23.3	11	3.3
Anxious	314	43.9	114	33.7
Very Ill	50	7.0	18	5.3
Medical History				
History of Heart Failure	23	3.2	13	3.8
Hypertensive	217	30.3	96	28.4
History of transient cerebral ischemia	33	4.6	13	3.8
Eczema	23	3.2	36	10.7
Rhinitis	22	3.1	51	15.1

TABLE 2: BASELINE CHARACTERISTICS OF PATIENTS EXCLUDED FROM THE RANDOMIZED TRIAL (CONT'D)

	High-Osmolar		Low-Osmolar	
	N=716	%=100	N=338	%=100
Drug History				
Digoxin	41	5.7	9	2.8
Beta Blocker	45	6.3	23	6.8
Nitrate	30	4.2	11	3.3
Anti-histamine	19	2.7	13	4.0
Steroid	54	7.5	32	9.8
Bronchodilator	36	5.0	88	26.0
	Mean ± SD		Mean ± SD	
Age (years)	60.4 ± 12.8		51.3 ± 17.5	
Heart Rate (beats/min)	78.9 ± 11.6		81.1 ± 13.4	
Systolic blood pressure (mmHg)	134.4 ± 21.4		131.4 ± 21.7	
Diastolic blood pressure (mmHg)	78.1 ± 11.1		83.3 ± 12.2	
	Median (Range)		Median (Range)	
Contrast Volume (mls)	300 (26-650)		100 (20-400)	
Serum Creatinine (umol/l)	86 (36-1375)		84 (43-654)	

TABLE 3: DESCRIPTION OF ADVERSE REACTIONS TO CONTRAST IN THE RANDOMIZED TRIAL.

	High-Osmolar	Low-Osmolar	P
Reactions requiring therapy	13 (1.4%)	6 (0.5%)	0.035
Reactions requiring attention of a doctor	37 (3.9%)	10 (0.9%)	<0.000005

Nature of reactions requiring attention by a doctor

			Treated			Treated
	N	%	N	N	%	N
Urticaria alone	18	(1.9)	7	0	(0)	0
Other anaphylactoid	6	(0.6)	4	3	(0.3)	1
Angina	3	(0.3)	0	6	(0.5)	5
Other cardiovascular	2	(0.2)	1	0	(0)	0
Neurological	2	(0.2)	0	1	(0.1)	0
Severe vomiting	5	(0.5)	1	0	(0)	0
Other	1	(0.1)	0	0	(0)	0

Subjectively severe symptoms (≥ 5 on a scale 0 to 10)

Warmth	167	(17.5)	87	(7.5)	<0.000001
Nausea	69	(7.2)	25	(2.2)	<0.000001
Vomiting	21	(2.2)	8	(0.7)	0.0015
Pruritus	29	(3.0)	6	(0.5)	<0.000005
Pain	13	(1.4)	12	(1.0)	NS
Dyspnea	9	(0.9)	12	(1.0)	NS
Chest Pain	6	(0.6)	11	(0.9)	NS

TABLE 4: ADVERSE EVENTS ASSOCIATED WITH CONTRAST IN PATIENTS EXCLUDED FROM THE RANDOMIZED TRIAL.

Adverse Event	High-Osmolar		Low-Osmolar	
Total	N=716	%	N=338	%
Reaction requiring therapy	11	(1.5)	1	(0.3)
Reaction requiring attention	22	(3.1)	5	(1.5)
Urticaria	9	(1.3)	2	(0.6)
Angina	5	(0.7)	0	(0)
Subjectively severe symptoms ($\geq$ 5 on a scale 0 to 10)				
Warmth	59	(8.2)	29	(8.6)
Nausea	37	(5.2)	10	(3.0)
Vomiting	16	(2.2)	2	(0.6)
Pruritus	11	(1.5)	4	(1.2)
Pain	8	(1.1)	4	(1.2)
Dyspnea	7	(1.0)	4	(1.2)
Chest Pain	8	(1.1)	1	(0.3)

TABLE 5: THE RISK, RELATIVE TO THOSE AGED OVER 50 YEARS AND WITHOUT OTHER RISK FACTORS, ASSOCIATED WITH VARIOUS CHARACTERISTICS BY UNIVARIATE ANALYSIS.

	High-Osmolar		Low-Osmolar	
Characteristic	Relative Risk	95% CI	Relative Risk	95% CI
Prior reaction to contrast	7.4	2.3-24	9.2	1.1-78
History of "allergy"	4.4	2.0-10	2.5	0.3-22
Cardiac disease	3.1	1.2-8	7.9	0.9-63
Severe illness	3.0	0.9-10.1	6.4	0.4-100
Renal Impariment	2.4	0.9-6.8	3.5	0.3-39
Anxiety	2.2	0.9-5.2	3.5	0.4-30
Diabetes Mellitus	1.9	0.7-5.5	1.8	0.1-28
Asthma	1.4	0.3-6.6	1.7	0.1-27

TABLE 6: FACTORS ASSOCIATED WITH ADVERSE REACTIONS TO CONTRAST BY MULTIVARIATE ANALYSIS.

All Patients

Risk Factor	Odds Ratio	95% Confidence Interval
High/Low osmolar contrast	2.2	1.6-2.9
Prior reaction/No prior reaction	1.8	1.2-2.7
Allergy/No allergy	1.6	1.2-2.0
Cardiac disease/No cardiac disease	1.4	1.1-1.9

Patients given high-osmolar contrast only

Prior reaction/No prior reaction	1.8	1.0-3.1
Allergy/No allergy	1.8	1.4-2.3
High volume of contrast/ Low volume of contrast	1.3	1.0-1.7

THE INCIDENCE OF CONTRAST NEPHROPATHY AFTER IONIC HIGH-OSMOLAR AND NONIONIC LOW-OSMOLAR RADIOCONTRAST IN PATIENTS WITH IMPAIRED RENAL FUNCTION: A RANDOMIZED TRIAL

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The cardiologists who participated in this trial were Drs. E Stone, C McCallum, B Sussex, M Furey, A Williams, B Rose, and S Missan.

The radiologists who participated in this study were Drs. R Reddy, P McManamon, M Mangan, T Cummings, S McMaster, P Collingwood.

Running Head: Contrast media and nephrotoxicity.

ABSTRACT

Background: Prescription of low-osmolar contrast to prevent nephrotoxicity in subjects with pre-existing renal impairment is costly and has not been clearly shown to be effective.

Methods: 366 subjects with a pre-contrast serum creatinine greater than 120 µmol/l having cardiac catheterization or intravenous contrast had serum creatinine repeated 48 to 72 hours after contrast. 249 of these were randomized to receive high or low-osmolar contrast.

Results: In the randomized study the serum creatinine rose by at least 25 percent after contrast in 8 of 117 (6.8 percent) given high and in 5 of 132 (3.8 percent) given low-osmolar contrast ($p > 0.05$, 1-tailed 95 percent confidence interval for the difference 3 to 7.8 percent). More severe renal failure (greater than 50 percent increase in serum creatinine) after contrast was uncommon (3.4 percent with high and 1.5 percent with low-osmolar contrast). A rise in serum creatinine after contrast was significantly associated with the severity of the pre-contrast renal impairment and the presence of diabetes mellitus. Diabetics with a serum creatinine greater than 200 µmol/l pre-contrast had the highest risk of deterioration in renal function after contrast.

Conclusions: Clinically important nephrotoxicity is uncommon after high-osmolar contrast and is not completely prevented by low-osmolar contrast in subjects with renal impairment. Larger studies will be required to define the precise role of low-osmolar contrast for prevention of contrast nephropathy, particularly in diabetics

with renal impairment.

Key words: contrast media, adverse effects, high-osmolar ionic, low-osmolar, kidney failure (acute), random allocation, comparative study.

INTRODUCTON

Contrast nephropathy may be defined as an acute toxic nephropathy due to radiographic contrast media. There has been considerable confusion in the literature about the incidence of the condition (1). We have previously shown that it is not common with normal pre-existing renal function, but that it is more frequent in patients with renal impairment, especially when due to diabetic nephropathy (2,3).

There has been difficulty in establishing an animal model of contrast nephropathy (4). This has hindered efforts to investigate it's pathogenesis and has led some to question the existence of the condition (5). Nevertheless, contrast has been shown to have toxic effects in rabbits whose kidneys have been subjected to other stresses (6).

It was expected that nonionic low-osmolar contrast would be less nephrotoxic than ionic high-osmolar media. Some (7-9), but not all studies (10,11) of contrast-induced enzymuria and proteinuria have suggested that low-osmolar media may be less nephrotoxic. A randomized trial in humans, mostly with normal renal function, did not find that low-osmolar media were less nephrotoxic (12). In a noncomparative study, low-osmolar contrast was associated with a 50 percent incidence of a 25 percent rise in serum creatinine after cardiac catheterization in patients with advanced diabetic nephropathy (13). A randomized trial in patients with pre-existing renal impairment undergoing cardiac angiography found a statistically significantly smaller rise in serum

creatinine at 24 hours after nonionic contrast than after ionic contrast (14). The authors of the study concluded that the nonionic contrast was less nephrotoxic than the ionic, although there was not a significant reduction in the incidence of clinically important episodes of nephrotoxicity and no benefit was seen in insulin requiring diabetics (14).

Because low-osmolar contrast is 10-20 times more expensive than high-osmolar contrast and because patients with impaired renal function have an increased risk of contrast nephropathy, we performed a randomized controlled clinical trial to examine the relative nephrotoxicity of the two classes of contrast media in patients with high serum creatinine levels.

METHODS

Research design and study population:

This study was one component of a large randomized trial comparing ionic high-osmolar to nonionic low-osmolar contrast (15,16). The trial was performed over the three years prior to February 1991 at a university based tertiary referral centre. Patients having cardiac catheterization, intravenous pyelography, or CT scanning with contrast were eligible. All subjects entered in the trial had their serum creatinine measured within 24 hours prior to contrast administration and, if this exceeded 120 µmol/l, were included in the study of nephrotoxicity. The protocol included repeated measurement of serum creatinine in all such subjects at 48 to 72 hours after contrast.

The subjects were stratified into those having cardiac

angiography and those having intravenous contrast before randomization. No attempt was made to stratify for other factors related to nephrotoxicity.

Some subjects were excluded from the randomized trial (15,16). No subject was excluded because of a perceived risk of nephrotoxicity. To allow recognition of bias we followed all subjects irrespective of randomization status. Table 1 shows the number of subjects who were eligible for entry to this portion of the study, along with the number of subjects who had a second measurement of serum creatinine after contrast.

Many subjects were outpatients and were not seen by a nephrologist prior to contrast. No routine prophylactic measures against nephrotoxicity were employed before or after imaging. Before randomization, details of demographic, clinical (including any renal or cardiac disease and diabetes mellitus), and medication history were recorded by the research nurse. Subjects who had a 50 percent or greater rise in serum creatinine were seen by a nephrologist after imaging. The medical records of all subjects with at least a 25 percent increase in serum creatinine were reviewed by a nephrologist, blind to the contrast administered, to determine whether contrast was likely to have caused the increase.

Outcomes:

Serum creatinine was measured by autoanalyser in several different laboratories, as outpatient subjects attended their local hospitals for follow-up. We defined a case of contrast nephropathy as the unexplained occurrence of a 25 percent or greater increment

in serum creatinine at 48 hours after contrast. We also report more severe degrees of deterioration in renal function. To facilitate comparison with other studies (12,14), we report the number who had a rise of at least 44 μmol/l in serum creatinine, and the mean change in serum creatinine after each type of contrast.

Statistics and sample size:

Incidence rates, means and standard deviations, medians and ranges are used as appropriate to describe the data. The frequency of events in the groups receiving high- and low-osmolar contrast was compared by Chi-squared tests or Fisher's exact tests for 2 by 2 tables. Means were compared by t-tests for unpaired data, while medians were compared by Mann-Whitney-U tests. We used a 1 tailed α of 0.05 to declare significance and we report one tailed 95 percent confidence intervals for differences between the randomized groups. We used multiple logistic (BMDP LR program, 1988) and multiple linear regression (SPSS-X, 1988) models to examine, and adjust for, the effect of covariates on the outcomes. Crossovers were handled by intention-to-treat analysis, but only one randomized subject received both types of contrast and had a subsequent rise in serum creatinine.

Before the study we estimated that the incidence of a 25 percent rise in serum creatinine after high-osmolar contrast would be 10 percent (2). To detect a 50 percent reduction in this incidence with low-osmolar contrast, with a 1 tailed α of 0.05 and a β of 0.2, we required to randomly assign 332 subjects to each type of contrast. However, enrollment in this component of the

study was stopped when the objectives of the two associated trials were achieved (15,16). Although the size of the sample that could be analysed was less than anticipated, and thus prone to type II error, we felt that the data collected on these 366 subjects with renal impairment should be reported now.

RESULTS

Baseline comparison:

Table 2 shows the baseline characteristics of the randomized subjects who had a measurement of serum creatinine after contrast. By chance more diabetics were given low-osmolar contrast, while cardiac angiography was the investigation performed in a greater proportion of those given high-osmolar contrast.

Table 3 shows the same profile of baseline characteristics for the subjects who were not entered in the randomized trial, but who did have a second determination of serum creatinine. In the early part of our study infusable low-osmolar contrast was not available for CT of the body (16). These patients were more likely to have diseases associated with renal impairment. The profile of the subjects who had low-osmolar contrast reflects the fact that a majority had severe cardiac disease and had cardiac angiography. Therefore it is not surprising that both groups had higher serum creatinine levels than the corresponding randomized groups.

We examined the characteristics of those subjects who failed to have a second serum creatinine determination. In the randomized study these subjects differed from those having follow up in that a greater proportion had intravenous contrast (76.2 percent), and

were outpatients, while a lesser proportion (7.1 percent) had a serum creatinine greater than 200 µmol/l.

Outcome of the trial:

The difference between the two randomized groups, in terms of any of the outcome events, failed to reach statistical significance (Table 4). Although the incidence of minor changes in renal function after contrast was greater in the subjects who were not randomized, more severe acute renal failure was not significantly more common in these subjects (Table 4).

Following review of the records, it was felt that contrast was unlikely to have been responsible for the 25 percent rise in serum creatinine after contrast in one subject randomized to high-osmolar contrast, in two subjects nonrandomly receiving high-osmolar contrast, and in one subject nonrandomly given low-osmolar contrast. When these cases were excluded, the incidence of a 25 percent increment in creatinine was 6 percent (95 percent CI 2.4-11.9) in those randomized to high-osmolar, and 3.8 percent (95 percent CI 1.2-8.6) in those randomized to low-osmolar contrast. The corresponding figures for the non-randomized groups were 18.6 percent (95 percent CI 8.4-33.4) with high-osmolar and 9.5 percent (95 percent CI 3.9-18.5) with low-osmolar contrast.

The mean change in serum creatinine by 48 to 72 hours after contrast was 3.5 µmol/l in those randomized to high-osmolar and -1.5 µmol/l in those randomized to low-osmolar contrast (95 percent confidence interval [CI] for the difference -6.1 to 16.1). The corresponding figures for the non-randomized groups were 17 µmol/l

in the high-osmolar and 4 µmol/l in the low-osmolar group. Because serum creatinine is not linearly related to glomerular filtration rate, we also compared the response to the two types of contrast after inverse and logarithmic transformation of the data. This analysis also failed to reveal any statistically significant difference between the high- and low-osmolar media.

Multivariate analysis of the effect of contrast:

Given the lack of statistically significant benefit with low-osmolar contrast, and the difference in the randomized groups at baseline which might have contributed to this situation, we analysed the randomized subjects by multiple linear regression analysis. The change in serum creatinine after contrast served as the dependant. The independent variables used were the type and route of administration of contrast, presence of diabetes, and the pre-contrast serum creatinine. The type of contrast did not not significantly predict the change in serum creatinine in these models.

Risk factors for contrast nephropathy:

In order to identify factors which might predispose to contrast nephropathy and to examine the effect of low-osmolar contrast in various risk groups we stratified the randomized subjects into four groups: those with a pre-contrast serum creatinine between 120 and 200 µmol/l with and without diabetes, and those with a pre-contrast serum creatinine greater than 200 µmol/l with and without diabetes. The incidence of contrast nephropathy, as defined by a 25 percent increment in serum

creatinine after high- or low-osmolar contrast, in each of the strata is shown in table 5. These results suggest that those with more severe renal impairment, especially when due to diabetic nephropathy, are at the highest risk of contrast nephropathy. There is not a consistent trend to a lower incidence of contrast nephropathy with low-osmolar contrast across the strata but the lower incidence with low-osmolar contrast in the group with advanced diabetic nephropathy is interesting given the results of another recent trial (14).

When the data for all subjects, irrespective of randomization or type of contrast prescribed, was stratified and analysed in the same fashion as for the randomized patients the results suggested even more strongly that the degree of renal impairment, especially in diabetics, is predictive of the risk for contrast nephropathy. The serum creatinine rose by more than 25 percent after contrast in 16 of 266 (6 percent) with a serum creatinine less than 200 µmol/l without diabetes, in 4 of 36 (11 percent) diabetics with a serum creatinine less than 200 µmol/l, in 8 of 48 (16.7 percent) of those with a serum creatinine greater than 200 µmol/l without diabetes, and in 5 of 15 (33.3 percent) diabetics with a serum creatinine greater than 200 µmol/l.

In a series of multiple linear and logistic regression models the only variables which were statistically significantly associated with a rise in serum creatinine after contrast were the severity of the pre-existing renal impairment and the presence of diabetes. In these models the type, volume, and route of

administration of contrast did not add to the prediction of contrast nephropathy.

DISCUSSION

This study shows that the level of renal impairment, especially in diabetic patients is the most significant predictor of contrast nephropathy and that the incidence of clinically severe contrast nephropathy (greater than 50 percent rise in serum creatinine) is low whether high- or low-osmolar contrast is prescribed.

The randomized study failed to confirm a clinically important role for low-osmolar contrast in prevention of contrast nephropathy in subjects with renal impairment. This is compatible with the results of an earlier study which largely examined subjects with normal renal function (12). However, as the overall incidence of contrast nephropathy was lower than we had predicted, this study does not have sufficient power to exclude a 50 percent reduction in the incidence of contrast nephropathy, as assessed by any outcome, with low-osmolar contrast. Given the results, we would have required a sample size of over 1300 subjects per group to exclude such a benefit, using a rise of 25 percent in serum creatinine to diagnose a case of contrast nephropathy (17). The study did have a power of greater than 0.8 to detect a true difference of at least 10 μmol/l in the change in serum creatinine after contrast between high- and low-osmolar media, and no such difference was found. This is contrary to the findings of another recent trial (14).

Although the data suggest that low-osmolar media may have some benefit, we cannot conclude that low-osmolar contrast prevents contrast nephropathy in subjects with impaired renal function. If the point estimates of incidence in our randomized trial are correct one would need to treat 53 subjects of the type in our randomized trial with low-osmolar contrast at a marginal cost of Can $4770 to prevent one case having a 50 percent rise in serum creatinine after contrast. If low-osmolar contrast was reserved for those with a pre-contrast serum creatinine of greater than 200 µmol/l with or without diabetes one would only need to treat 8 such subjects at a marginal cost of Can $720 to prevent one such event.

It is of interest that the incidence of contrast nephropathy was low in our subjects who did not receive any prophylactic treatment. In fact, our results are similar to those of others who employed a prophylactic fluid loading regimen (12). While avoidance of dehydration is desirable the benefits of intentional fluid loading or any other prophylactic measure need to be established by adequate randomized controlled trials before routine use can be recommended.

We chose to use serum creatinine to measure outcome, even though it is an insensitive measure of renal function, as it has the advantages of being easy to measure and of being able to detect clinically important changes in renal function. Others have used enzymuria to compare the nephrotoxicity of high- and low-osmolar contrast, but the results have not been consistent and were often of dubious clinical relevance (7-11).

We conclude that the incidence of clinically important contrast nephropathy is low after both high and low-osmolar contrast media in subjects with moderate pre-existing renal impairment. Larger studies will be required to define the precise role of low-osmolar media for prevention of contrast nephropathy in subjects with more severe impairment of renal function. Since those with diabetic nephropathy seem to be at greatest risk (13), it would make most sense to conduct any further trials in such patients.

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TABLE 1. Patients with pre-contrast serum creatinine greater than 120 µmol/l who underwent cardiac angiography or had a procedure requiring intravenous contrast.

	Randomized			Non-randomized		
	Cardiac	IV	Total	Cardiac	IV	Total
Eligible	153	222	375	57	105	162
Serum creatinine repeated after contrast	123 (80%)	126 (57%)	249 (66%)	50 (88%)	67 (64%)	117 (72%)

TABLE 2. Baseline comparison of the randomized groups with post-contrast serum creatinine available.

	High-osmolar		Low-osmolar	
Total:	N=117	%	N=132	%
Male	99	86.6	92	69.7
Diabetic	12	10.3	24	18.2
Creatinine > 200 µmol/l	17	14.5	18	13.6
History of cardiac failure	18	15.4	20	15.2
Hypertensive	61	52.1	77	58.3
Bed bound in hospital	11	9.4	14	10.6
ACE inhibitor	13	11.1	15	11.4
Calcium channel blocker	49	41.9	48	36.4
Nonsteroidal anti-inflammatory	15	12.8	15	11.4
Diuretic	30	25.6	31	23.5
Type of investigation:				
Cardiac catheterization	64	54.7	59	44.7
Intravenous pyelogram	19	16.2	34	25.8
Computed tomography	34	29.1	39	29.5
	Mean ± SD		Mean ± SD	
Age (years)	64.3 ± 10.7		64.0 ± 12.3	
Systolic blood pressure (mmHg)	140.6 ± 26.5		142.8 ± 23.6	
Diastolic blood pressure (mmHg)	75.9 ± 12.1		78.2 ± 13.0	

TABLE 2. continued.

	High-osmolar		Low-osmolar	
	Median	(range)	Median	(range)
Serum creatinine (µmol/l)	138	(120-685)	138	(120-572)
Serum urea (mmol/l)	9.8	(4-47)	9.9	(4.7-44)
Contrast volume (mls)	120	(50-400)	100	(40-400)

TABLE 3. Baseline characteristics of the non-randomized groups with post-contrast serum creatinine available.

	High-osmolar		Low-osmolar	
Total:	N=43	%	N=74	%
Male	36	83.7	47	63.5
Diabetic	4	9.3	11	14.9
Creatinine > 200 µmol/l	13	30.2	15	20.2
History of cardiac failure	8	18.6	25	33.8
Hypertensive	20	46.5	51	68.9
Bed bound in hospital	5	11.6	22	29.7
ACE inhibitor	3	7.0	12	16.2
Calcium channel blocker	5	11.6	32	43.2
Nonsteroidal anti-inflammatory	9	20.9	10	13.5
Diuretic	13	30.2	29	39.2
Type of investigation:				
Cardiac catheterization	1	2.3	49	66.2
Intravenous pyelogram	2	4.6	9	12.2
Computed tomography	40	93.1	16	21.6
	Mean	± SD	Mean	± SD
Age (years)	66.4	± 11.4	67.0	± 11.8
Systolic blood pressure (mmHg)	136.0	± 20.1	142.0	± 29.5
Diastolic blood pressure (mmHg)	79.0	± 11.7	75.0	± 15.3

TABLE 3. continued.

	High-osmolar		Low-osmolar	
	Median	(range)	Median	(range)
Serum creatinine (µmol/l)	159	(120-502)	141	(120-654)
Serum urea (mmol/l)	11.8	(6-32)	10.3	(5-66)
Contrast volume (mls)	300	(50-400)	122.5	(45-400)

TABLE 4. The incidence of outcome events in the trial before removal of cases where contrast was not felt to be the cause of the acute renal failure.

Randomized subjects:

	High-osmolar N = 117	%	Low-osmolar N = 132	%	95% CI For The Reduction With Low-osmolar (%)
Scr rise of ≥ 25%	8	6.8	5	3.8	3.0 to 7.8
Scr rise of ≥ 50%	4	3.4	2	1.5	1.9 to 5.2
Scr rise of ≥ 44 µmol/l	7	6.0	7	5.3	0.7 to 5.6
Dialysis required	1	0.8	0	-	0.8 to 2.1

Non-randomized subjects:

	High-osmolar N = 43	%	Low-osmolar N = 74	%
Scr rise of ≥ 25%	10	23.3	8	10.8
Scr rise of ≥ 50%	2	4.7	3	4.1
Scr rise of ≥ 44 µmol/l	7	16.3	8	10.8
Dialysis required	0	-	2	2.7

Scr = serum creatinine. Note that the 95 percent confidence intervals for the differences between the randomized groups are one tailed.

TABLE 5. The incidence of a 25 percent rise in serum creatinine with high- or low-osmolar contrast in the randomized trial after stratification by serum creatinine and the presence of diabetes mellitus.

Stratum	High-osmolar		Low-osmolar	
	N	%	N	%
Nondiabetic with serum creatinine < 200 µmol/l	3/91	3.3	1/97	1.0
Diabetic with serum creatinine < 200 µmol/l	0/18	-	2/17	11.8
Nondiabetic with serum creatinine > 200 µmol/l	1/13	7.6	1/11	9.1
Diabetic with serum creatinine > 200 µmol/l	3/4	75.0	1/7	14.3

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CONSENT TO PARTICIPATE IN BIOMEDICAL RESEARCH

TITLE: The side effects of non-ionic compared to ionic contrast medium

INVESTIGATORS: Dr.'s Parfrey, P. McManamon, E. Stone

You are going to have an imaging procedure which requires injection of contrast material into your blood vessels. You are being asked to participate in a research trial of 2 different types of constrast material. Participation in this study is entirely voluntary. You may decide not to participate or may withdraw from the study at any time without affecting your normal treatment.

Confidentiality of information concerning participants will be maintained by the investigators. An investigator will be available during the study all times should you have any problems or questions about the study.

1. Purpose of study: To determine whether the non-ionic contrast medium is safer than the usually prescribed ionic contrast material.

2. Description of procedures and tests: You will be given either non-ionic or ionic contrast and neither you or your doctor will be aware which one it is. You will complete a short questionnaire before and after your test. At the time a needle is inserted to give the contrast, a blood test may be taken and this will be repeated 2 days later, if the initial test shows abnormal kidney function.

3. Duration of subjects participation: Ten minutes before and thirty minutes immediately after your imaging test, and 5 minutes 2 days later.

4. Foreseeable risks, discomforts, or inconveniences: As the first blood sample will be taken at the time a needle is inserted to give contrast, no extra discomforts should arise other than those usually associated with having the imaging test. The new contrast medium is likely to be at least as safe than the regularly used medium. If your initial blood test shows abnormal kidney function than a second blood sample will be taken 2 days after your imaging test and may leave a small bruise.

5. Benefits which the subject may receive: The new non-ionic contrast may produce less discomfort than the regularly used ionic contrast.

6. Alternative procedures or treatment for those not entering the study: Your imaging test will be undertaken using the regularly used ionic contrast.

7. Any other relevant information: As the newer medium is 10-15 times more expensive we want to be sure that it will be safer than the regularly used ionic contrast.

I, _____, the undersigned, agree to (my child's, relative's or ward's_____) participation in the research study described above.

I acknowledge that a copy of this form has been offered to me. I understand that there is no guarantee that participation will be beneficial.

_____ _____
(Signature of Participant) (Date)

_____
(Signature of Witness, optional)

To be signed by investigator:

To the best of my ability I have fully explained to the subject the nature of this research study. I have invited questions and provided answers. I believe that the subject fully understand the implications and voluntary nature of the study.

_____ _____
(Signature of Investigator) (Date)

If appropriate:

_____
(Signature of Minor Participant)

Relationship to participant named above _____