Correspondence Continuing Education Courses For Nuclear Pharmacists and Nuclear Medicine Professionals

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A Primer on Parenteral Radiopaque Contrast Agents

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A PRIMER ON PARENTERAL RADIOPAQUE CONTRAST AGENTS

STATEMENT OF OBJECTIVES

The purpose of this continuing education lesson is to increase the reader's knowledge and understanding of the clinical applications of parenteral radiopaque contrast agents.

Upon completion of this lesson, the reader should be able to:

1. Discuss in broad terms the clinical applications of contrast agents.

2. Explain the significance of iodine, its use in radiopaque contrast agents and the variations of carrier molecules used to deliver it.

3. Explain why relatively low osmolality and low chemotoxicity are desirable characteristics of contrast agents and describe how the structure of the contrast molecule influences these two characteristics.

4. Identify the risk factors for major reactions to contrast media and critically discuss pre-treatment protocols that minimize the probability of occurrence of such reactions.

5. Discuss the clinical manifestations and incidence of side effects and adverse reactions known to be associated with contrast media and identify their important causes and mediating factors.

6. Describe the manifestations and treatment of anaphylactoid reactions.

7. Discuss, in descriptive terms, contrast agent pharmacokinetics.

COURSE OUTLINE

A PRIMER ON PARENTERAL RADIOPAQUE CONTRAST AGENTS

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INTRODUCTION
The Term "Contrast"

The word "contrast" should be explained at the outset so that its use in the terms "contrast agent" and "contrast medium" is clearly understood. The term contrast is a photographic or, more generally, a medical imaging term. Contrast in an image of any kind is what allows detail to be discerned between two or more adjacent regions of the image. Black chalk on a blackboard cannot be seen because there is no contrast, however, white chalk on the same blackboard produces high contrast that is readily apparent to the human eye. Fortunately, there is some natural contrast in medical images of all kinds. If there were no contrast, medical images would be of little value. Thus in a computed tomography (CT) image (which has far better resolution and display of contrast than any ordinary x-ray film) darker blood vessels may be seen crossing a lighter liver. A tumor in the liver will frequently, but not reliably, be darker than normal liver and so will be readily apparent because of the natural contrast associated with this imaging technology. The purpose of a contrast-enhancing agent ("contrast agent," "contrast medium") is, as the name suggests, to enhance such natural contrast and render tissues of interest – usually those with pathology – more clearly visible. Now it must be said immediately that contrast agents do not always succeed optimally in this aim. Sometimes a tumor, to take the same example, may actually become less clearly visible after administration of a contrast agent. Clearly, much depends on the blood supply and other structural characteristics of normal tissue and tumor. However, such worsening of the observed contrast in an image is not the norm and usually contrast agents may be relied upon to improve the images and their information content by enhancement of relevant image contrast.

Sometimes reference is made to "negative" and "positive" contrast agents. This frequently causes confusion. As far as x-ray contrast agents are concerned "positive" agents are those that increase the absorption of x-rays while "negative" agents decrease x-ray absorption. The iodinated agents are positive contrast agents because iodine atoms, which are incorporated into their chemical structures, are efficient absorbers of x-rays in the diagnostic energy range. (So, incidentally, are the barium atoms in contrast agents used for studies of the gut.) Gases, such as air or CO_2, on the other hand, are negative agents as they do not significantly absorb x-rays and instead allow them to pass more readily. Thus, these gases may be very useful as well, for example, in providing the contrast necessary to differentiate the gastrointestinal tract from other adjacent anatomical structures.

Historical Development

Without the availability of good and relatively safe intravascular contrast agents, diagnostic radiology would not have come to occupy the central position it currently does in the medical diagnostic process. The great bulk of "interventional radiology" procedures would certainly not have emerged without the development of the contrast agent industry. The fact that most radiologists often take the contribution of the contrast agent largely for granted may be seen as a tribute to the excellent qualities associated with the current generation of these.

The need for intravascular contrast agents was realized very early in the history of radiology, as witnessed by the performance of angiograms on an amputated hand and on a cadaver kidney by Haschek and Lindenthal[1] and Hicks and Addison,[2] respectively, both within a month of Roentgen's report of the discovery of x-rays. The radioopaque suspensions used for these classic studies were not clinically practicable but the

achievements were remarkable. In subsequent years, various agents were used to opacify the gastrointestinal tract, the bladder, ureters, renal pelvis and lymphatics by direct injection, but little progress was made with the development of agents which could be safely injected into the circulation.

Berberich and Hirsch[3] used a strontium bromide solution for the opacification of the peripheral veins and, in the same year, Osborne, et al[4] at the Mayo Clinic noted opacification of the bladder in patients treated with intravenous (IV) solutions of sodium iodide for syphilis. They had unwittingly performed the first IV urogram. However, the delineation of the upper urinary tract was poor and sodium iodide solutions were rather toxic for general use for urography. Enough interest was generated, however, for Brooks[5] to try sodium iodide solutions for peripheral angiography and in 1927 for Moniz to apply them to carotid arteriography.[6] Both procedures had to be performed under general anesthesia and Moniz was so concerned about the toxicity of sodium iodide that he diverted his activity into one of the great dead ends or "cul-de-sacs" of radiological history, namely the use of colloidal thorium dioxide ("Thorotrast") as a contrast agent.[6] Thorium dioxide had the great advantage of being highly radio-opaque at a time when radiographic film and equipment produced relatively little image contrast, and the agent had virtually no known acute side effects upon injection. Unfortunately, thorium is radioactive, being an emitter of α-particles and having a half-life of 1.4×10^{10} years. It is permanently retained within the reticuloendothelial system, largely in the liver and spleen, and is associated with induction of malignancies, the first of which to be recorded in a human was a sarcoma of the liver some 20 years following its administration.[7] Other tumors described, and apparently related to the agent, include hepatoma, cholangiocarcinoma and myeloid leukemia. Retention of Thorotrast by urothelium following retrograde pyelography has also been associated with the development of transi-

tional cell carcinoma,[8] while local injections into breast and maxillary sinuses have been followed by carcinoma developing at these sites.[9] Perivascular extravasation of contrast is associated with local granuloma formation.

While inorganic iodide solutions were too toxic for general use, it was realized that elemental iodine is certainly an outstandingly good choice for x-ray absorption. The K-shell electron binding energy is approximately 33 KeV, which is lower than, but close to, the mean energy used in diagnostic x-ray work, thereby maximizing the cross-section for photoelectric interactions. All other considerations such as chemistry aside, iodine is an ideal choice of element for use in an x-ray contrast agent at the energies typically used clinically. Barium, incidentally, used in studies of the gastrointestinal tract is similarly an ideal choice in this same respect, having a K-shell binding energy of ~ 35 KeV.

If iodine was to be used, a suitable carrier molecule was clearly going to be necessary. The first such emerged in 1925 when Binz and Rath[10] synthesized a large number of compounds, some of them pyridone derivative containing iodine, in the quest for a

Figure 1. The contrast agents "Selectan neutral" and "Uroselectan." The first generation of pyridone-based agents.
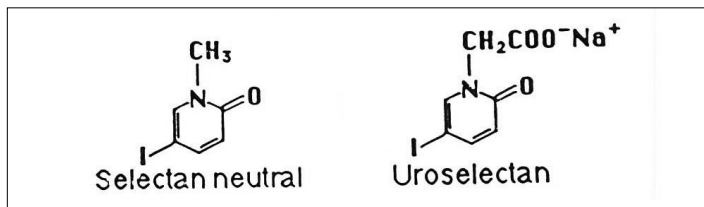
treatment of syphilis. Two compounds in this series became known as "Selectan neutral" and "Uroselectan" as they were partially selectively excreted in urine. These were used by a young American, Moses Swick, working under the supervision of, first, Lichtwitz and, subsequently, von Lichtenberg in Berlin, for IV urography in the years 1927 to 1929.[10] These mono-iodinated pyridone compounds (Figure 1) were

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superseded within 3 years or so by di-iodinated pyridones of higher solubility, which were also synthesized by Binz and Rath (Figure 2). These became the standard contrast agents for intravascular and other applications during the next two decades or more, until they were replaced in the early 1950s by the benzene ring based compounds. In fact, as early as 1933 Swick had suggested the use of iodinated benzene ring compounds

Figure 2. The contrast agents 'Uroselectan B' and "Diodone'. The second generation of pyridine-based agents.
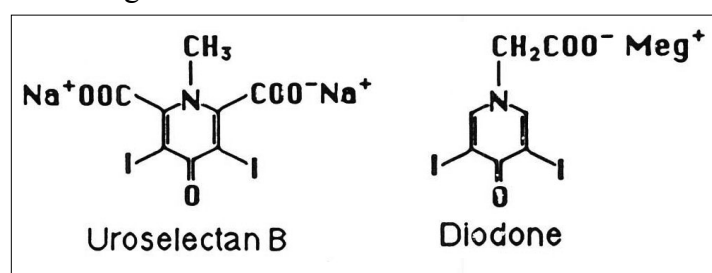
and had developed monoiodo-hippurate for this purpose. Unfortunately, the very addition of the iodine to the hippurate substantially increased the toxicity of the compound, a point developed below. The compound was, therefore, unsuccessful in its original intention but became an important tool in renal physiology and opened the way for the eventual development of successful contrast agents of this type in the 1950s.

Figure 3. The structures of benzene ring-based contrast agents.

	R_2	R_3	Proper name	Commercial name
	H	$NHCOCH_3$	Acetrizoate	Urokon, Diaginol
	CH_3CONH	$NHCOCH_3$	Diatrizoate	Urografin, Hypaque
	CH_3CONH	$CONHCH_3$	Iothalamate	Conray
	CH_3CONH	$NCOCH_3$	Metrizoate	Isopaque, Triosil
		CH_3		

In 1952 Wallingford discovered that the introduction into the benzene ring of an amide side-chain with acetylation produced a low toxicity compound, acetrizoic acid (Figure 3).[11] Hoppe subsequently developed a doubly substituted molecule diatrozic acid[12] and closely related compounds, such as the iothalamates and metrizoates, followed. As can be seen from Figure 3, the various representatives of this type of contrast agent are all salts of the benzoic acids and differ only in minor ways in the substituent side-chains at the 3 and 5 positions on the benzene ring. The various competing commercial formulations differ in being sodium salts, meglumine (methylglucamine) salts or mixed sodium and meglumine salts, and in the concentrations available. For example, the iothalamate series is known commercially as the Conray range. Conray 280 is a pure meglumine salt at a concentration of 280 mg iodine/mL solution, whereas Conray 420 is a pure sodium salt at a concentration of 420 mg iodine/mL. The iothalamates are isomers of the diatrizoates with the $NHCOCH_3$ substituent group at position 5 merely changed to $CONHCH_3$. The diatrizoates are known as "Hypaque" when marketed by Amersham and as "Renografin" when marketed by Bracco. Urografin 370, for example, is a mixed sodium and meglumine salt at a concentration of 370 mg iodine/mL solution. Hypaque 270 is a pure sodium salt at a concentration of 270 mg iodine/mL solution.

The important points to consider in the choice of agent for a particular application are (i) the iodine concentration of the formulation, and (ii) the sodium and/or meglumine content. Sodium salts are more toxic to vascular endothelium and to blood-brain barrier and neural tissues and so should be avoided in venography and cerebral angiography. Meglumine salts should be used for these purposes. For cardiac work, a mixture of sodium and meglumine should be chosen (for example, Urografin 370), since both pure sodium and pure meglumine salts are more cardiotoxic and are associated with high levels of ventricular fibrillation. Some manufacturers have special formulations of their agents, with calcium and magnesium

Table 1. Iodinated Contrast Agents Available

Conventional (High Osmolality) Ionic Agents
Sodium/Meglumine Diatrizoate (Renografin), Bracco Inc, Princeton NJ, USA Sodium/Meglumine Metrizoate (Hypaque), Amersham plc, UK
Low Osmolality Non-Ionic Monomeric Agents
Iopamidol (Isovue) Bracco Inc, Princeton, NJ, USA Iopromide (Ultravist) Berlex Inc, USA Iohexol (Omnipaque) Amersham plc, UK Ioversol (Optiray) Tyco Inc, St Louis, USA
Low Osmolality Ionic Agents
Sodium Meglumine Ioxaglate (Hexabrix), Guerbet, France
Iso-osmolar Non-Ionic Dimeric Agents
Iotrolan (Isovist) Berlex Inc, USA Iodixanol (Visipaque) Amersham plc, UK

ions partially replacing sodium ions, in an attempt to reduce various aspects of toxicity. These ionic agents are sometimes referred to as "conventional" agents. Table 1 summarizes the proper names, commercial names and ionic content of a number of these agents still available in the USA.

Agents of this kind were used almost universally in diagnostic radiology for 30 years or so, from their introduction in the early 1950s until the introduction of the second-generation "non-ionic" agents (see later) in the early 1980s. Even today they are occasionally used but their only advantage over the non-ionic agents is lower price. They were used for all intravascular applications, arteriographies and venographies, and for body cavity studies such as cystography, arthrography, sinography and fistulography. They were not without their significant undesirable side effects (see next section). For myelography they were too dangerous, causing severe irritation of neural tissues and seizures. Iodine concentrations in commercial formulations range up to 370 mg iodine/mL and volumes used in various applications range from a few mL to 150 mL. The latter volume might be used to enhance a CT scan, for example. In complex angiographic procedures where the operator must guide himself by injecting small volumes repeatedly under fluoroscopy and must, additionally, take pictures, very large total doses may be given–up to 1000 mL of 300 mg iodine/mL strength. Of course, such doses are administered over a prolonged period of perhaps 2 hours or more. It would not be appropriate to give recipes for all contrast-enhanced radiological procedures, not only because of their number but because different radiologists tend often to do things differently (see Section VIII below). A tissue or blood concentration of at least 20 mg iodine/mL is essential to obtain sufficient enhancement effect.

DISADVANTAGES OF CONVENTIONAL IONIC CONTRAST AGENTS

An ideal contrast agent would provide a passive increase in x-ray absorption while having absolutely no effect on any body system or function, biochemical or physiological. The early agents and even those used up to the 1980s were far from ideal as these agents were often associated with both subjective and objective side effects of many kinds.

At the typical iodine concentrations used in many applications, 300-400 mg iodine/mL, the ionic contrast agents are substantially hyperosmolar with respect to plasma–up to seven or eight times in some

cases.[13,14] This hyperosmolality is associated with a number of adverse effects, both subjective and objective. Thus, when absolutely or relatively high doses of the contrast medium are injected into the circulation, as in many interventional studies or in cardiac studies in infants and small children, the osmotic load, may be a threat to the patient. Acute pulmonary edema is a risk. In fact, the plasma volume expands but this is partly compensated by the shrinkage of circulating cells. The effects of the hyperosmolar solutions on smooth muscle produce a generalized peripheral vasodilation with a sometimes profound fall in blood pressures followed by a reflex tachycardia, events which are poorly tolerated by some patients.[15] The subjective counterparts of this are the feeling of flushing and faintness experienced by many patients. Other unpleasant and subjective side effects, such as sensation of spontaneous bladder emptying and metallic taste, often cited by patients as most unpleasant, must be added.[13] Pain on arterial injection may be severe. Clinical bronchospasm is occasionally seen and may be severe (see anaphylactoid reactions below). Nausea is not uncommon; frank vomiting is less common but very important both for the patient and the technologists because it disrupts the examination.

At the microscopic level there may be injury to endothelial cells which is largely, but not entirely, mediated by hyperosmolality[16] and which on venous injection may lead to thrombophlebitis or frank venous thrombosis.[17] In arterial injections hyperosmolality may be a factor in the post-angiographic progression of stenosis to occlusion and to the failure, by early closure, of angioplasties. This injurious effect on endothelium is of particular significance in relation to the blood-brain barrier. There is considerable experimental work demonstrating the increased permeability of the blood-brain barrier and the transfer of contrast agent into the brain and into direct contact with neurons, which are very sensitive to contrast agents.[18] Indeed, one hypothesis holds that blood-brain barrier injury and subsequent neuronal irritation is the seat of all idiosyncratic anaphylactoid adverse reactions (see below) to contrast agents.

Contrast agents affect not only endothelial cells, but also erythrocytes, basophils and mast cells. Water is drawn out of erythrocytes by hyperosmolar contrast agents, so that they become shrunken and deformed and thus lose the flexibility essential for them to negotiate the capillary circulation.[19] The "sludging" of rigidified erythrocytes in the microcirculation of the lungs in pulmonary angiography has been related to the (usually) transient pulmonary hypertension associated with pulmonary angiography. Additionally, in selective renal angiography this sludging effect has also been cited as a factor in contrast agent-associated nephrotoxicity.

Basophils and mast cells are induced to release histamine, which may contribute to the subjective side effects experienced by patients and perhaps, although not certainly, to anaphylactoid reactions.[20]

In addition to the effects on the peripheral vasculature and on the expansion of the blood volume, the hyperosmolality of contrast agents is an important component of their cardiotoxicity (see below).[21]

Then there are a number of organ-specific toxic effects, which will be discussed below in Section VI. It may be wise to enter a caveat even at this stage. Osmolality is very important and in the next section we will discuss how it was reduced in newer contrast agent formulations. However, there are other factors contributing to the observed toxicity associated with these agents that will be discussed later. Meanwhile the reader should not take away an impression that high osmolality is the only issue or the only cause of the objective and subjective effects noted above.

LOW OSMOLAR AGENTS

The various important subjective and objective side effects of high-osmolar agents provided a powerful stimulus to formulate low-osmolar contrast agents. The obvious way to reduce the osmolality of solutions is

to dilute them, but this would also dilute the iodine concentration. Another approach was needed.
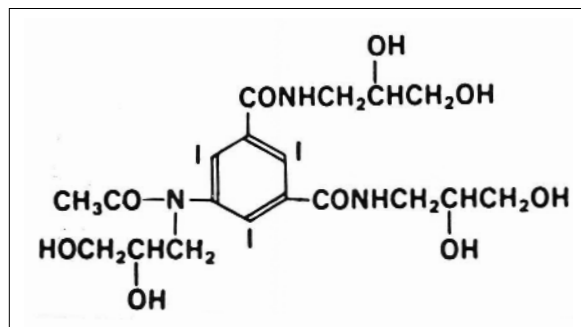
Non-Ionic Agents

Almen first suggested an approach to reducing the osmolality of contrast agents without diluting their iodine concentration.[22] He pointed out that the osmolality of any solution is proportional to the number of particles in that solution and that, by definition, ionic agents dissociate into two particles, anion and cation, and thereby, double their osmolality in solution. A non-ionic, non-dissociating agent theoretically should have half the osmolality at any iodine concentration of an ionic agent. The first practical result of this concept was metrizamide (Amipaque), produced by Nyegaard (subsequently Nycomed, then taken over by Amersham) in Oslo. This was a 1-substituted amide of metrizoic acid, a choice dictated by

the fact that Nyegaard was already a producer of metrizoates (Isopaque) contrast agents. The loss of solubility, inevitable with the elimination of the carboxyl group, was overcome by substituting a D-glucose group, which provided many hydrophilic hydroxyl groups (Figure 4). Metrizamide had the serious disadvantage of being unstable at high temperatures, making its sterilization by autoclaving impossible, requiring the agent to be produced as a lyophilized powder. Its instability in solution, even at room temperature, made it impossible to formulate ready-to-use solutions and the agent had to be made up at the time of use from a powder solute and a sterile solvent. It was therefore both expensive and inconvenient, and was not much used in intravascular applications. However, its low neurotoxicity, compared to the ionic water-soluble agents, led to a revolution in myelography. Although low-osmolar, non-ionic agents were otherwise little used in clinical practice, enough experimental and clinical work was performed to establish their considerable advantages in terms of
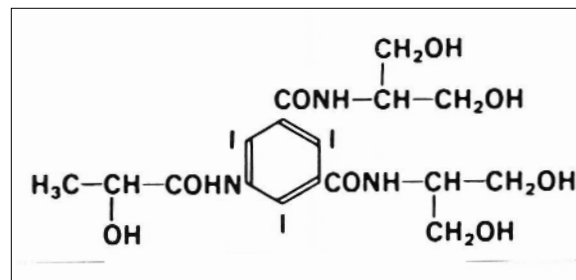
Figure 4. Metrizamide (Amipaque). The first non-ionic contrast agent.
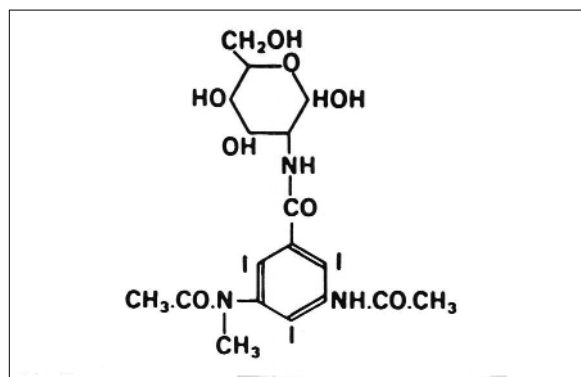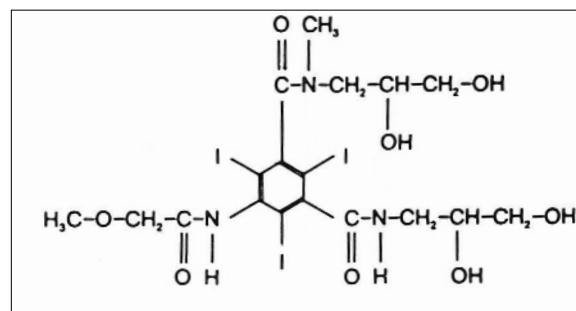

Figure 5. Metrizamide (Omnipaque). Second generation non-ionic agent.

Figure 6. Iopamidol (Niopam). Second generation non-ionic agent.

Figure 7. Iopromide (Ultravist). Second generation non-ionic agent.

reduced toxicity in a variety of applications, including coronary and carotid arteriography and peripheral venography. This stimulated the production of a second generation of non-ionic contrast media in ready-to-use formulations, of which there are now a number of representatives, including iohexol (Omnipaque, Amersham) (Figure 5), iopamidol (Niopam, Bracco) (Figure 6) and iopromide (Ultravist, Schering) (Figure 7). These second-generation compounds have the convenience of being in ready-to-use solutions and are considerably less expensive than metrizamide, although still significantly more expensive than the conventional ionic agents. They are all associated with a markedly reduced incidence and severity of all the objective and subjective effects discussed above. Cost is the only factor that has militated against replacing the conventional ionic agents with these second-generation non-ionic compounds completely for all applications.[23, 24]

A useful way to express the merits of any contrast agent, in terms of contrast-providing potential, relative to the disadvantages in terms of osmolality, is the ratio of iodine atoms provided per molecule (three in all cases so far considered) to the number of particles derived from a molecular unit (two in the case of the ionic agents and one, the whole molecule, in the case of the non-ionic agents). Thus, the ionic agents are sometimes referred to as 3:2 or ratio 1.5 agents and the non-ionic variety as 3:1 or ratio 3 agents. The higher the ratio the better, and 3:1 is clearly better than 3:2.

The non-ionic agents are formulated with a trace of calcium EDTA, which plays no role in any toxic effects. Its role is to chelate any traces of heavy metal contamination, which would promote degradation of the benzene rings with liberation of iodide.

Monoacid Dimeric Agents

If a linking bridge joins two tri-iodinated benzoic acid groups, the result is a dimeric acid. Thus, iocarmic acid, a meglumine salt of a dimer produced by linking two iothalamic acids, was introduced as "Dimer X" in 1970 and used, in spite of the fact that it was ionic and relatively neurotoxic, as a myelographic agent. The ratio of number of iodine atoms to particles in solution from each molecule in this compound was 6:3, an improvement on the 3:2 ratio associated with the conventional ionic monomeric contrast agents. Subsequently, one of the carboxyl groups of such a dicarboxylic acid was substituted with a non-ionizing group to produce a monoacid dimer. This is ioxaglic acid (Figure 8), which is produced in a commercial formulation as a mixture of sodium and meglumine salts of ioxaglic acid, known as Hexabrix. This has a high iodine to particle ratio of 6:2 (=3:1) and, while remaining an ionic agent, this compound succeeds, as do the non-ionic monomeric agents, in reducing osmolality to approximately half that of conventional ionic agents at any iodine concentration. The osmolalities for several contrast agents, plotted as a function of iodine concentration, are shown in Figure 9. Sodium iothalamate represents the conventional ionic agents in this figure. As can be seen, the reduction in osmolality, at any given iodine concentration, as compared with the conventional agent, is somewhat more than

Figure 8. Sodium meglumine ioxaglate (Hexabrix). A monoacid dimeric low-osmolality agent.
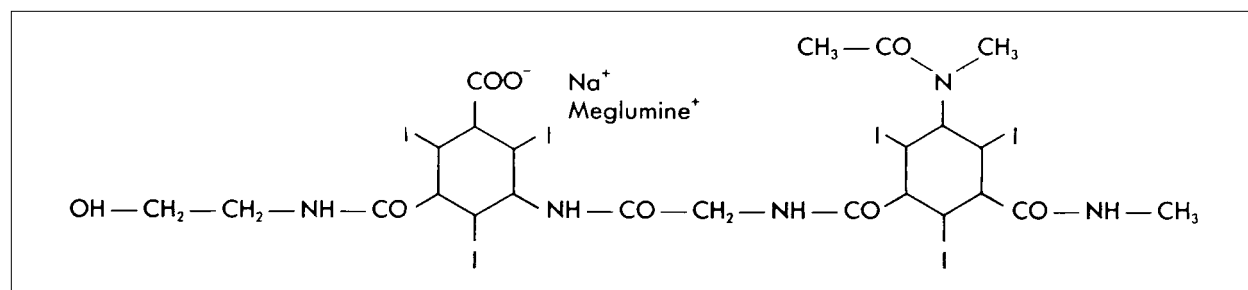
Figure 9. The osmolalities of some contrast agents as a function of iodine concentration at 37°C.

Non-Ionic Dimeric Contrast Agents

One obvious next step in contrast agent development, which has been taken both by Schering and Nycomed, is to combine the dimeric approach of Hexabrix with the non-ionic concept.[25] Simply taking a dimeric compound of the type discussed above and replacing both carboxyl groups with non-ionizing groups can do this. To maintain solubility, it is now essential to substitute around the molecule a large number of hydrophilic groups. The two commercial compounds of this type now available are illustrated in Figure 10. Iotrolan (Isovist, Schering) is available for myelographic and intravascular use and iodixanol (Visipaque, Nycomed) is available for intravascular use.

The osmolalities of such non-ionic dimers are lower than that of plasma (hypo-osmolar) at all iodine concentrations up to about 400 mg iodine/mL. This is the result of both a large molecular size and molecular aggregation producing a very high effective molecular weight and hence a lower than predicted osmolality. This problem of hypo-osmolality is a new concern for the contrast agent industry but is easily overcome. The addition of a little saline allows the osmolality to be adjusted upwards to become identical to that of plasma at any iodine concentration and this is done in the commercial formulations. The osmolality factor is thereby completely eliminated.

Such agents are more viscous than other contrast agents, largely because of their high molecular weight but when heated to body temperature (perhaps a good maneuver anyway) have acceptably low viscosities for clinical use.

the predicted 50% for all of the agents. This is partly the result of the large size of all these molecules and partly due to a degree of molecular aggregation in solution. The differences between the osmolalities of the various new agents are real but of little clinical significance. The fact that Hexabrix has a slightly lower osmolality at any iodine concentration than any of the other agents might suggest clinical advantages, even if small. Although Hexabrix is an acceptable arteriographic agent associated with reduced pain and discomfort, on IV injection it displays significantly greater toxicity, particularly in causing nausea and vomiting, than do the non-ionic agents. Therefore, it should not be used for enhancement of computed tomography (CT). This fact is, at first, surprising and the important reasons for this recommendation are discussed below. It must not be used for myelography.

It should be noted that, while the non-ionic monomeric agents and ioxaglate are described as low osmolality agents, this is a relative term. They are all hyper-osmolar with respect to plasma.
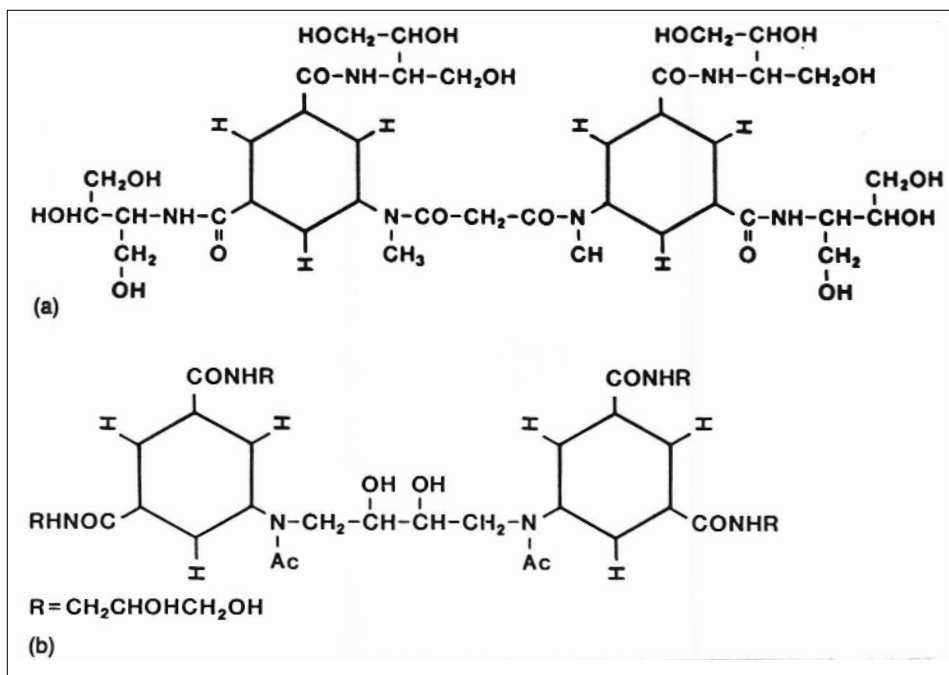
Figure 10. Two non-ionic dimeric contrast agents (a) iotrolan and (b) iodixanol. These prepared in formulations are iso-osmolar with plasma

It has been argued that the higher viscosity, combined with the lower diffusibility of such large molecules, is advantageous in myelography.

In summary, at this point, there are two kinds of non-ionic agents–monomeric and dimeric.

CONTRAST AGENT TOXICITY – THE CONCEPT OF MOLECULAR TOXICITY

Table 2 shows how LD_{50} has increased (toxicity decreased) since the early 1930s. This is a very crude, but important, measure of contrast agent toxicity. It reveals an interesting fact, namely that toxicity cannot be entirely a function of osmolality. Metrizamide and sodium meglumine ioxaglate are low-osmolality agents and, indeed, have somewhat lower osmolalities at any iodine concentration than do the second-generation non-ionic agents, and yet they have significantly lower LD_{50} (higher toxici-

ty). Furthermore, metrizamide is a non-ionic agent. It is clear that simply to be non-ionic is not enough, to be low osmolality is not enough, and to be low osmolality and non-ionic is not enough, necessarily, to achieve the lowest possible toxicity. The explanation is that contrast agents possess, by virtue of their chemical structure, an intrinsic toxicity that is sometimes labeled chemotoxicity.[26] This toxicity is agent-specific, unlike hyperosmolality-related toxicity, which is an entirely non-specific manifestation of the high-concentration solutions and can be mimicked by high-concentration solutions of other materials such as glucose. A clue is that when Swick, as discussed above, substituted an iodine atom in the hippuric acid structure, a marked increase in toxicity was the result. Iodine is a highly hydrophobic atom and it has long been known that the more hydrophobic agents have a greater toxicity than the more hydrophilic ones. The relative hydrophobicity/hydrophilicity is usually measured as a

Table 2. The LD_{50} Values for a Number on Contrast Agents From 1930 to the Present Day

Agent	LD50 (g iodine/kg mouse)
Sodium iomethamate (Uroselectan B)	2.0
Iodopyracet (Diodone)	3.2
Sodium acetrizoate (Urokon)	5.5
Sodium diatrizoate	8.4
Sodium meglumine Ioxaglate (Hexabrix)	12.0
Metrizamide (Amipaque)	14.0
Iopamidol (Nipam)	21.0
Iohexol (Omnipaque)	24.0

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partition coefficient, which correlates very well with various measures of toxicity. The addition of iodine to a benzene ring increases the hydrophobicity and therefore the partition coefficient.

Another parameter that correlates with the toxicity is the protein-binding capacity. None of these contrast agents possess much potential to bind to proteins but significant differences are to be found between different agents, particularly between ionic and non-ionic agents, and there is a close correlation between protein binding and toxicity. The higher binding agents are more toxic than the lower binding ones. The relationship between this observation and the partition coefficient has been explained in a synthesis of ideas as follows.

The chemotoxicity of contrast agents appears to be mediated by non-specific weak interactions between the agents and various biological molecules. This weak binding would not be of any significance if contrast agents were not used at such high concentrations and total doses as compared with any other type of drug. The interaction is mediated essentially by two elements.

1. There is a Coulomb (charge mediated) interaction in the case of the ionic agents that is obviously eliminated in the non-ionic agents.
2. There are hydrophobic interactions between hydrophobic portions of the molecule, mainly its benzene ring/iodine core, and hydrophobic portions of the biological molecules (the hydrophilic portions of both types of molecule being largely solvated by water molecules). The non-ionic agents have lower chemotoxicity, not only because they possess no charge, but also because of the many hydrophilic groups they carry. The addition of hydrophilic groups restores the solubility lost when the carboxyl group of the precursor ionic agent is eliminated and shields the hydrophobic core of the molecule, thus limiting its availability for hydrophobic interactions.

Several concepts can now be understood from this. The addition of iodine to the mol-

ecule renders it more toxic by enhancing the hydrophobicity of the molecular core. The non-ionic agents have lower chemotoxicity partly because they carry no charge to mediate Coulomb interactions and partly because they shield the hydrophobic core with their hydrophilic substituents. The protein-binding capacity of the molecule correlates with its toxicity because it is this binding, which mediates the toxicity. The partition coefficient correlates because the more the hydrophobic core of the molecule is shielded, limiting its interaction with biological systems, the more hydrophilic the contrast agent is overall and the lower, therefore, is its partition coefficient. Conversely, the less efficiently the hydrophilic substituents shield the hydrophobic core, the more the hydrophobic interactions can take place, the more hydrophobic the molecule the greater the partition coefficient. Furthermore, we can now see why metrizamide had such a relatively high toxicity for a non-ionic agent. All the hydrophilic groups are carried on a glucose substituent at position 1, rather than being distributed around the molecule, as is the case with the second-generation non-ionic agents. There is very little shielding of the hydrophobic core of the molecule, which therefore has a *relatively* high partition coefficient, high protein binding and high toxicity.

Figures 11 and 12 display the results of two *in vitro* studies of chemotoxic manifestations of contrast agents, namely the interactions with an enzyme and with structural proteins of platelet surfaces. The first results in an inhibition of the enzyme and the second in an inhibition of the aggregation of platelets on stimulus. As can be seen, in both cases there is a concentration-dependent effect (here expressed as iodine concentration) and there are marked differences between different agents. The same hierarchy of magnitudes is seen in both assays: the conventional ionic agents have the greatest effect, the non-ionic agents the least effect, and the monoacid dimeric low-osmolality ionic agent, Hexabrix, has an intermediate effect.

Figure 11. The inhibition of enzyme acetylcholinesterase by various contrast agents as a function of concentration.
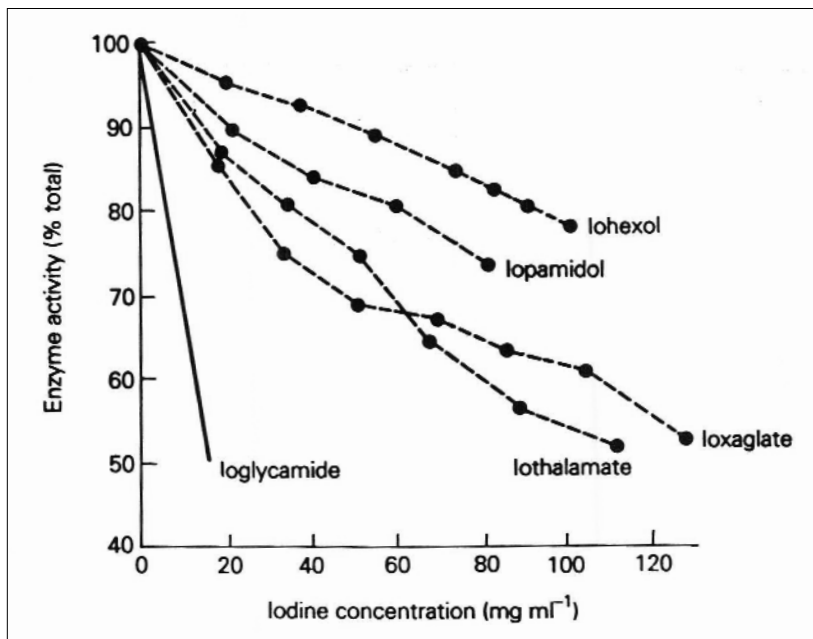
Figure 12. The inhibition of platelet aggregation by various contrast agents as a function of concentration (expressed as iodine).
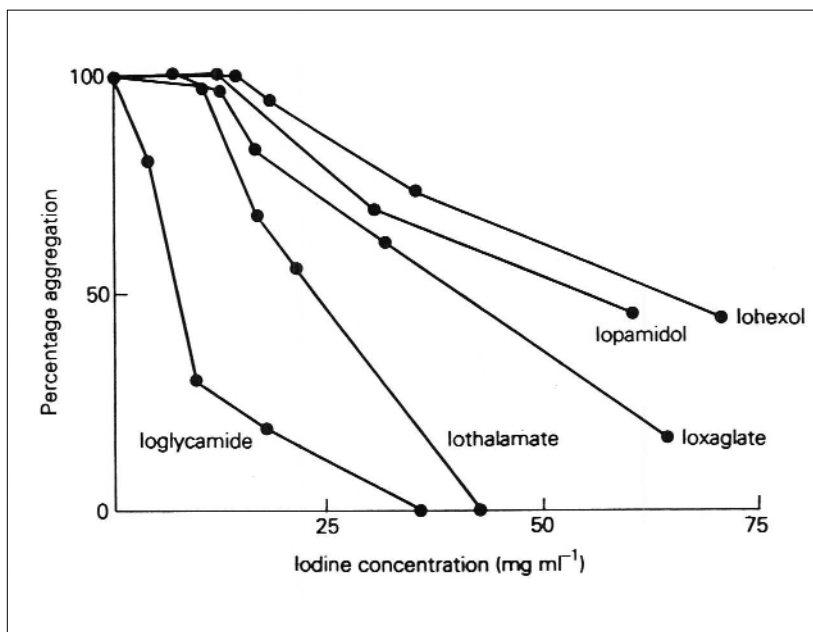
Although illustrations will not be given here, it may be noted that the low chemotoxicity of the non-ionic monomeric agents is shared, and perhaps shown to a greater extent, by the non-ionic dimeric agents.

The ideal contrast agent, it should be remembered, should have no effects of any kind on biological systems. Although not quite meeting this ideal, the non-ionic agents, monomeric and dimeric, represent the closest approach so far to the ideal.

PHARMACOKINETICS

The pharmacokinetics, fitting a two-compartment model, of the iodinated x-ray contrast agents are the same as those of the gadolinium chelates and technetium ^{99m}Tc-pertechnetate (DTPA).[27] The two compartments are plasma and interstitium (intra- and extra-vascular extra-cellular spaces). When contrast agent is delivered into the circulation it is diluted and mixed in the circulating plasma volume. There is a very weak tendency to bind to circulating proteins. The agents do not enter cells in the circulation to any significant degree. The agents bind minimally to plasma proteins. Being small, the molecules (or ions) also leak rapidly across normal blood vessels into the extra-vascular extra-cellular space. Cells such as hepatocytes may take up 1%-2%, although these agents, to a very good approximation are extra-cellular agents. They may be seen as extra-cellular space markers. The agents do not cross the blood-brain barrier unless it is damaged. (Such damage is the basis for contrast enhancement of brain pathologies.) There is no metabolism or significant breakdown of the molecules. Small amounts of free iodine in the iodide form [<0.005%] may be found in commercial preparations; levels rise if the

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containers are left in bright sunlight. However, there is no further significant iodine release in vivo. Excretion is by passive glomerular filtration with no active tubular excretion or reabsorption. The kidney may be viewed as a "target organ" in this sense. This route of excretion is the basis of the technique of intravenous urography. In the presence of renal impairment there may be a significant liver uptake and excretion in bile, but otherwise there is little liver uptake or excretion. The gall bladder is occasionally visualized on a plain abdominal film or CT scan the day after contrast administration in such patients. The gallbladder occasionally may be seen if normal function is impaired by the contrast agent (contrast agent associated nephrotoxicity).

Thus when a contrast agent is injected into the circulation by bolus or rapid infusion it mixes in plasma and leaks into interstitium everywhere in the body. As plasma levels fall – as a result of the mixing and dilution itself, as a result of the leak and, to a lesser extent, as a result of renal excretion – they eventually fall below the levels in the interstitium and then the agent leaks back into the circulation for ultimate excretion by the kidneys.

If contrast agent is injected into any body cavity, such as a joint, the spinal theca or an abscess cavity it will be reabsorbed into the circulation and excreted by the kidneys. There is no absorption from the normal, as opposed to perforated or inflamed, gut. The peritoneum allows rapid intravasation into the circulation. Thus if there is a gut perforation and oral contrast is administered, it leaks into the peritoneum, rapidly enters the circulation and may be seen if normal.

Only small amounts of contrast agent are found in breast milk. In any case, this seems to be of marginal importance since if this milk is given to a normal infant with a normal gut there will be no significant systemic absorption by the infant. Contrast agents are therefore not contraindicated in breast-feeding mothers.

OSMOLALITY, MOLECULAR TOXICITY, ORGAN-SPECIFIC TOXICITIES AND HIGH DOSE TOXICITY

We have seen above that both hyperosmolality and molecular toxicity contribute to the toxicity of iodinated contrast agents and that the non-ionic agents owe their reduced toxicity to a reduction in both. Some of the toxic effects have been described above, including injurious effects on endothelium. The endothelium is now viewed as an "organ," the largest in the body in fact, and this brings us to the important matter of other organ specific effects. Intravascular contrast agents have a variety of organ-specific toxicities.

Endothelium: (the largest organ in the body) Damage predisposes to thrombosis. There is one hypothesis that endothelial injury and its effect on various activation systems is the basis of major reactions.[26]

Cardiac: There are adverse effects on pump function and electrophysiology.[21]

Renal: There may be temporary or occasionally permanent impairment of renal function. The effect is thought to be more likely in older patients, in diabetics, in patients with already impaired renal function and in dehydrated individuals.[28-35]

Neural Tissues: The blood brain barrier protects the normal brain but contrast agents, particularly high osmolar ones, may damage the barrier and then pass. Injection into the spinal theca of course bypasses the barrier and brings contrast agent into direct contact with neural tissues.

Liver: Toxicity is not readily apparent but it should be noted that there is a general weak cytotoxic effect, greater with the ionic agents, on cells of all types.

In organ specific studies such as coronary angiography, cerebral angiography, renal angiography, low osmolality non-ionic agents tend to be used because of their lower toxicities.

Organ-specific toxicities are most obviously manifest in selective individual organ studies such as cardioangiography, cerebral

angiography, etc and, since they are dose-dependent, play a role in the high-dose systemic toxicity which is encountered in some circumstances as discussed below.

High-Dose Toxicity of Contrast Agents

While much energy has been expended on the problem of idiosyncratic/anaphylactoid reactions to contrast agents (see below), particularly with regard to the elucidation of their underlying mechanisms, their prediction and their prophylaxis and management, much less attention has been paid to the problem of the dose-dependent side effects of the agents. In terms of frequency, dose-dependent effects are of greater importance than idiosyncratic reactions in a number of patient groups who are well represented in radiology, such as those with poor cardiac reserve, impaired renal or hepatic function, and multi-system organ failure.[36] Serious idiosyncratic reactions are uncommon (see below) but higher and higher doses of the agents are being used in more and more patients in the field of interventional radiology. Even without such obvious underlying risk factors, many patients may be at risk from dose-dependent contrast medium toxicity, including sodium and/or osmotic overload in complex or prolonged procedures involving large total doses of contrast medium.[36]

Theoretical Considerations

In a typical IV urogram, 300 mg iodine/kg may be used. For a 70-kg man this represents 21g iodine, which could be provided, for example, by 50 mL of sodium iothalamate containing 420 mg iodine/mL. Several rules of thumb are in use to define an upper limit for the total contrast medium dose. A maximum dose for a healthy adult of some three times the above level, which is 1000 mg iodine/kg, is sometimes suggested. This may be compared with the measurement of the LD_{50} of ~ 8000 mg iodine/kg for conventional contrast agents, a comparison of uncertain relevance to the clinical situation but the only guide available. There would appear to be some safety margins here, giving scope for higher doses to be used if the examination is vital and demands it. There is clearly a question of clinical judgment to be exercised in the context of the individual patient, the importance of the procedure and the consequences of not proceeding with it. The time over which the total dose is to be administered is also clearly an important consideration, remembering that the half-life of contrast agents in the circulation is approximately 90 minutes.[27] One other important factor now is the availability of the better low-osmolar non-ionic contrast agents. These have a higher LD_{50}, present a lower osmotic load and contain little or no sodium. Whatever arbitrary upper limit in mg iodine/kg is set for the conventional agents, it seems likely that twice or three times this dose of a new agent can be used. Thus if 1000 mg iodine/kg may be given in the form of a conventional agent, possibly 2500 mg iodine kg^1 of a new agent may be given. If this is in the form of, say, Omnipaque 300 (Iohexol 300 mg iodine/mL), this would mean a volume dose for a 70-kg man of $(2500 \times 70) / 300 \approx 600$ mL.

Even higher doses may presumably be used if the contrast medium is administered over an extended period, for example in a 2 or 3 hour long complicated procedure. Such high doses should never be given without serious thought but, if the procedure is vital for diagnosis or therapy considerations, they may then be given with caution, detailed decisions being tailored to the individual patient. A reasonable precaution, with the risk of renal function in mind, is to make sure that the patient is well hydrated at the start of the procedure (see below). Note that even a modest dose of a low osmolar agent may put patients with poor cardiac function into pulmonary edema.

ANAPHYLACTOID/IDIOSYNCRATIC REACTIONS

Idiosyncratic reactions may occur following the administration of any contrast agent.[27] Clinical manifestations include severe bronchospasm, angioedema and car-

diovascular collapse. They have close parallels with anaphylactic responses and may be clinically indistinguishable from them but they are not anaphylactic. For this reason they are sometimes described as anaphylactoid reactions. Although unpredictable, such reactions are more likely to occur in certain patient groups: (i) those that have reacted on a previous occasion to a contrast agent (the recurrence rate at a second contrast agent administration is thought to be only ~ 20%), and (ii) those with established allergies to other drugs or agents and (iii) asthmatic and atopic individuals. Whether or not cardiac disease is a risk factor is controversial with different studies reaching different conclusions. These reactions are essentially dose-independent and may even occur following subcutaneous or intradermal test doses. Occasionally, reactions follow non-vascular procedures such as percutaneous transhepatic cholangiography, arthrography and hysterosalpingography, presumably as a result of intravasation in these cases. It is important to realize that such reactions may be delayed up to 30 min and the patient should never be left entirely unsupervised during or immediately following a procedure.

The mechanisms of these reactions remain obscure in spite of a considerable amount of study and the elaboration of a number of hypotheses. Apart from the citing of various mediators of the immune system a role has been suggested (supported by a great deal of anecdotal evidence) for anxiety and the possibility that a substantial proportion of those events involving cardiovascular collapse are of primary cardiac rather than allergic origin. However, it has now been clarified that the non-ionic monomeric contrast agents are associated with a significantly reduced risk of such reactions, particularly in definably at-risk patients. This certainly is the outcome of large-scale clinical trials of ionic versus non-ionic contrast agents in Japan[38] and Australia.[39] It can be firmly stated, as a consequence, that non-ionic agents should be used in all cases when the patient is definably at increased risk of such a reaction.

Prophylaxis of Anaphylactoid Reactions

If anxiety does have a role to play, simple reassurance may achieve worthwhile results. The role of corticosteroids as prophylaxis against such reactions in at-risk patients has been the subject of considerable controversy.[40] It is widely believed that corticosteroids are effective in this regard but the evidence for it is not substantial. The paper by Lasser and colleagues[41] describing a multicenter study in the USA is usually cited, but this paper has not been without its critics. It has been argued that even if its evidence is accepted at face value, the reduction in risk is little more than 50%, whereas a 6-10 fold decrease in risk is achieved by using non-ionic contrast agents.[40] Some, as yet inconclusive, evidence has been claimed for the efficacy of antihistamines as prophylaxis. Since anxiety is said to play a role, reassurance to the patient may be as valuable as any other maneuver.

Treatment of Anaphylactoid Reactions

If a patient collapses following contrast agent administration, first principles must be applied – clear and maintain the airway and perform CPR. Rapid plasma volume expansion is known to be effective. A first line drug in cardiovascular collapse and severe bronchospasm in these circumstances is adrenaline (1:1000 deep intra-muscular or, with care, 1:10,000 (suitably diluted) intravenously and titrated against effect). Corticosteroids are not front line drugs but may have a useful and rapid effect on bronchospasm and cardiovascular collapse. A variety of other drugs may also have a role. The reader is referred for details of recommended management to Guidelines issued, variously, by The American College of Radiology and The Royal College of Radiologists in the UK. The following, originally developed by the author and reproduced with permission, is taken from the latter guidelines.

Management of Adverse Reactions to Intravascular Contrast Agents

Conventional ionic iodinated intravascular contrast media have been available for over 35 years and have proved to be very safe and effective with a quoted adverse reaction rate of 5.8%, the vast majority being of a minor nature. The adverse reaction rate associated with the newer non-ionic agents is generally considered to be of the order of one

Table 3. Management of Adverse Reactions to Intravascular Contrast Agents

Symptoms	Treatment
Nausea/vomiting	Reassurance Retain intravenous (IV) access and observe Anti-emetics rarely necessary
Mild scattered hives/urticaria	Routine treatment not necessary Retain IV access. Observe. If troublesome, antihistamine – chloropheniramine maleate 10-20 mg or promethazine hydrochloride 25-50 mg (max 100 mg) by slow IV injection
Severe generalized urticaria	IV antihistamines as above. With addition of IV Hydrocortisone 100 mg IV
Mild wheeze	100% oxygen by MC mask (unless evidence of chronic obstructive airways disease with hypercapnia) Beta-2 agonist by inhaler e.g. salbutamol by nebulizer (5 mg in 2 ml saline). Repeat as necessary.
Hypotension with bradycardia (vasovagal reaction/faint)	Raise the patient's feet 100% oxygen by MC mask (unless evidence of chronic obstructive airways disease with hypercapnia) IV fluids (preferably colloid e.g. Gelofusine – 10 mL/Kg rapidly. THE HELP OF AN ANESTHESIOLOGIST SHOULD BE REQUESTED IF RESPONSE IS NOT RAPID. ECG monitoring and oximetry should be instigated. Atropine 0.6mg IV. Repeat at 5 minute intervals up to 3 mg total.
Hypotension alone – not vasovagal but no other signs anaphylactoid reaction	100% oxygen by MC mask IV fluids rapidly rapidly as above of Ephedrine 30 mg diluted and given incrementally to response. It is usually given in 3 to 6 mg increments providing that the patient is not tachycardic. (In tachycardia methoxamine 5-10mg IV at rate of 1 mg/min may be more appropriate.) IF THERE IS NO RESPONSE THE CRASH TEAM SHOULD BE SUMMONED TO DIRECT THE SUPERVISION OF PRESSOR AGENTS: Vasopressor, e.g. dobutamine 2.5-10 micrograms/kg/min or dopamine 2-5 micrograms/kg/min titrated to response. ECG Oximetry and blood pressure monitoring should be established.
NOTE ANTIHISTAMINES AND HYDROCORTISONE SHOULD NOT BE MIXED IN THE SAME SYRINGE. IF THIS IS DONE, IT CAUSES PRECIPITATION (***Continued on next page***)	

fifth that with the older conventional ionic agents. Uncommonly, a patient will develop a more serious reaction to either type of agent that may prove life-threatening and which must be treated quickly and appropriately.

The exact mechanisms of contrast reactions remain undefined, but several factors may contribute, with the individual patient's 'reactivity' being the most important.

Table 3. Management of Adverse Reactions to Intravascular Contrast Agents (*continued*)

Symptoms	Treatment
Angioedema/ Urticaria/ Bronchospasm/ Hypotension proceeding to Anaphylactoid reaction	IV fluids Beta-2 agonist by nebulizer as above IV antihistamines IV hydrocortisone 500 mg ECG monitoring, oximetry, and blood pressure monitoring should be established. CALL THE CRASH TEAM* The crash team will then consider the use of adrenaline 1 mL of 1 in 10,000 [100 microgram by slow IV injection (10 microgram/min); in severe cases further aliquots up to a total of 1 mg may be required.]**
*The use of adrenaline when appropriate should not be delayed if there are medical staff in attendance. **The use of IV (1/10,000) vs deep IM (1/1,000) adrenaline is controversial. Some authorities advocate the IM route. Others argue that if medically qualified staff are in attendance the IV route should be used with due caution.

Unconscious/
Unresponsive/
Pulseless/
Collapsed patient
	Standard cardiopulmonary resuscitation
	measures must be employed
	1. CRASH TEAM summoned
	The crash team will then institute standard resuscitation
	procedures:
	2. Establish airway
	3. Initiate ventilation
	4. Precordial thump followed by external cardiac massage
	5. IV fluids established
	6. Cardiac monitoring by ECG
	7. DC cardioversion if in ventricular fibrillation
	   (200 to 360 joules)
	8. IV adrenaline/isoprenaline/lignocaine/calcium chloride
	   as necessary
	9. Consider administration of hydrocortisone/antihistamines
	   during course of a successful resuscitation.

Seizure	May be the consequence of hypotension and primary treatment should be on above lines. 100% oxygen by MC mask. If convulsions continue, anticonvulsant may be given – e.g. diazepam IV 5-10 mg, initially although much higher doses may be needed. Second-line drugs such as thiopentone may be required but by this time the patient should be intubated and ventilated.

Anecdotally, stress and fear increase a patient's susceptibility to a contrast reaction. Histamine release, complement activation, coagulation and fibrinolytic system activation and prekallikrein to kallikrein transformation with bradykinin generation may all be elements involved. Central nervous system direct toxic effects have also been cited as a primary trigger. The very diversity of postulated reaction mechanisms appears to have produced confusion about management. Identification and symptomatic characterization of a reaction are the key first steps and should be followed by ad hoc management based on general principles.

Symptom complexes are listed together with their suggested management. They are placed in approximately ascending order of severity, no attempt being made to integrate symptomatology into a coherent etiological scheme.

DRUG DOSAGES WHERE GIVEN ARE APPLICABLE TO ADULTS. SUITABLE ADVICE SHOULD BE TAKEN IN PEDIATRIC PATIENTS. (Anti-emetics may be dangerous in children as there is a high incidence of extra-pyramidal side-effects to such drugs as perphenazine.)

General Comments

Corticosteroids are, quite correctly, thought of as slow-acting drugs with a lag time after injection of at least 6 hours. However, there is no doubt they may work very rapidly indeed when administered intravenously in severe asthma and in bronchospasm related to drug reactions and should therefore not be withheld.

IV adrenaline is sometimes considered a dangerous drug associated with cardiac arrhythmias. This is true and it should not be used in minor reactions but only in severe life threatening bronchospasm and/or cardiovascular collapse when the potential benefits greatly outweigh the risks. Doses may have to be high and may need to be repeated. Under normal circumstances Adrenaline should only be given by a medical or other suitably trained practitioner.

Aminophylline is an agent that has fallen into disrepute in recent years since it may be associated with hypotension and collapse and may only serve to exacerbate the situation.

General Points Worth Reinforcing

Depending on the severity of the reaction and the length of treatment required, an intravenous cannula should be inserted as soon as is practicable and drugs administered through this rather than the needle, which carries the risk of cutting out.

Contrast agents should not be injected in an isolated clinical setting. Facilities for resuscitation should be available if required. Non-ionic contrast medium should be used if a full cardiac arrest team is not available.

The patient should never be left alone following injection particularly during the first 10 minutes. Remember serious reactions may sometimes by considerably delayed.

Equipment and drugs routinely used in the management of medical emergencies should be immediately available. One trolley serving a unit with scattered rooms on several floors is not acceptable.

Equipment and drugs should be regularly checked by a designated person(s) and recorded as checked.

All persons involved in the daily running of a department should be aware of the site of resuscitation equipment.

All personnel should attend a basic resuscitation course on a regular basis.

Each department should have a specific protocol for dealing with various reactions, which should be updated periodically.

The person who administers the contrast should have a basic medical history about the patient, particularly relating to previous allergies and be adequately trained in resuscitation procedures.

Suggested drugs for the emergency box to be placed in each room where intravenous contrast agents are used:
➢ Chlorpheniramine maleate
➢ Promethazine
➢ Hydrocortisone

➢ Atropine
➢ Salbutamol inhaler
➢ Salbutamol nebulizer
➢ Ephedrine
➢ Normal saline
➢ Gelofusine

The following will usually be reserved for use by the crash team:

➢ Methoxamine
➢ Dobutamine
➢ Dopamine
➢ Adrenaline (1 in 10,000)
➢ Adrenaline 1 in 1,000, at least 10 ampules

The advice of the local consultant anesthesiologist designated to take responsibility for anesthesiology matters within the radiology department, should be sought when formulating local policies.

A NOTE ON THE CLINICAL USE OF CONTRAST AGENTS

It is difficult to convey in a short survey the range of application and enormous importance of contrast agents in clinical practice. Other than in such simple imaging as chest or bone x-rays, scarcely an x-ray image is ever obtained without the concomitant administration of a contrast agent, intravascular, oral or both. Direct injection into blood vessels via a variety of catheter techniques makes blood vessels clearly visible. This whole field is called angiography. Injection into natural body cavities, such as joints (arthrography) or the spinal theca (myelography) helps delineate normal and abnormal anatomy. Iodinated intra-vascular agents are handled and excreted almost exclusively by the kidneys and during their excretion following a simple intravenous injection render the whole renal tract – kidneys, ureters, and bladder – visible on x-ray images (Intravenous Urography – IVU). Virtually all body CT scans are "enhanced" by the administration of both an intravascular contrast agent and an oral agent. This not only helps clarify which soft tissues are blood vessels or gut but, because normal and abnormal tissues (such as, say, tumors) handle contrast agents somewhat differently (because of their differing capillary permeabilities and sizes of vascular and interstitial spaces) it also usually increases the contrast between normal and abnormal. In other words, the agents enhance what is really important, namely the conspicuity of abnormalities in the image.

A BRIEF NOTE ON COAGULATION AND PLATELETS

All intravascular x-ray contrast agents inhibit coagulation and platelet aggregation.[42] Historically, this has been thought advantageous in angiography since it helps prevent formation of clots in catheters and syringes, which might be accidentally injected into the patient sometimes with catastrophic results. The non-ionic agents have a less anticoagulant properties than do the ionic agents. This caused a considerable controversy, more in the United States than elsewhere because of the medico-legal climate, with some expressing anxieties that non-ionics might be unsafe in angiography. It has even been erroneously suggested that non-ionic agents have some positive pro-coagulant or pro-thrombotic effect. The simple facts are that anticoagulant properties are a function of chemotoxicity. Therefore, the greater the anticoagulant properties are, the more toxic the contrast agent. The key to safe angiography lies not in a return to more toxic agents but in the use of less toxic non-ionic agents together with good technique.[42]

THE METFORMIN ISSUE

The biguanide agent for the treatment of NIDDM, Phenformin, was associated with a significant incidence of Type B lactic acidosis. The mortality of this condition is some 50%.[43] The drug was withdrawn in 1977. The related drug, Metformin, is also a recognized cause of this serious condition but much less frequently than Phenformin. The incidence is reported to be ~0.03 per 1000 patients years.[44] In the reported cases there do almost invariably exist contraindications to the very use of Metformin.[44-47] Nevertheless, when the drug was introduced into the USA, the manufacturer, Bristol Myers Squibb, put a warning into the package insert regarding the co-

administration of contrast agents, a warning based on the idea that contrast agents are thought associated with renal function impairment, the sine qua non of lactic acidosis. The medico-legal context, in which American medicine is conducted, combined interestingly with the Internet, generated and spread anxiety rapidly. These anxieties then spread to the United Kingdom, notwithstanding the fact that Metformin had been in use there for many years. In response to many enquiries the Royal College of Radiologists felt obliged to put out some guidelines in 1996. These guidelines caused a great deal of controversy since they considerably complicated the lives of radiologists dealing with such patients who are by no means rare. Was all this necessary and was there a real problem?

Theoretical Mechanisms

Theoretically the combination of Metformin and x-ray contrast agents may have adverse effects because contrast agents supposedly impair or further impair renal function and hence Metformin excretion.

➢ Metformin is a well-recognized cause of Type B lactic acidosis in which mortality is greater than 50%.[43] Type B lactic acidosis is much less likely to occur with Metformin than its predecessor, Phenformin, which was withdrawn in 1977.

➢ The causal mechanisms may be related to increased peripheral anaerobic glycolysis, and inhibition of hepatic gluconeogenesis from lactate, associated with a reduction in hepatic intracellular pH. The latter might further compromise hepatic lactate metabolism.

➢ Metformin is excreted unchanged by the kidney and reduced renal function is a sine qua non for the development of lactic acidosis. Mild degrees of liver dysfunction do not appear to substantially predispose to lactic acidosis in general. Arterial pH is often raised in hepatic failure because of respiratory alkalosis. Nonetheless, because chronic liver disease is associated with reduced rates of

lactate clearance, liver dysfunction may increase the risk of lactic acid accumulation in patients taking Metformin. This is particularly likely if the clearance of the drug is reduced by renal disease or if cardiac impairment reduces renal perfusion.

➢ The renal function of patients undergoing contrast enhancement may become impaired, particularly if there is preexisting renal disease.[48] Patients with diabetes are more likely to have some degree of impairment of renal function than the normal population and are said to be at greater risk of contrast nephropathy.

Is there a risk in practice?

➢ As long ago as 1977, sporadic cases were reported of lactic acidosis in patients receiving Metformin.[49,50] The cases were apparently precipitated by the administration of iodinated x-ray contrast agents. The cause then suggested was as indicated above: that contrast agents impair, or further impair, renal function and hence Metformin excretion.

➢ Further cases have been reported occasionally throughout the 1980s and 1990s.[51, 52]

McCartney et al carefully reviewed the literature in this field.[53] They found that in more than a quarter of a century there were only 18 reports of Metformin-induced lactic acidosis (MALA) after contrast usage. In only one case was renal function normal at the start of the examination. They concluded that at least 16, and probably 17, had contraindications to Metformin use in the first place. Their conclusion was essentially that the problem almost invariably lies in the prescribing of Metformin rather than in the use of the contrast agent.

What should be done?

Modified RCR guidelines suggest discontinuation of Metformin at the time of the investigation and withholding it for 48 hours. For those with abnormal renal function it should only be reinstated when the renal function is found to be normal. This at least

has the merit for the radiologist of passing the responsibility to the physician.

McCartney and associates[53] suggest what, in effect, is another way of passing responsibility and inconvenience to the referring clinician. They suggest that since no patient with impaired renal function should be on Metformin the clinician be asked to state that the patient is on Metformin <u>and</u> has normal renal function. In this case, they argue, there is no evidence of a need to stop Metformin. If the renal function is not normal the physician should be assessing whether Metformin is appropriate therapy anyway. Emergency patients should undergo the study and the Metformin should be stopped as a precaution. Further management again will revert to the clinical team. This all seems eminently sensible from the radiologist's point of view.

CONCLUSIONS

The water-soluble intra-vascular iodinated x-ray contrast-enhancing agents are essential tools in medical imaging. Their chemistry and pharmacokinetics are very simple and, superficially speaking, they may be said to have no pharmacology. Their manufacturers prefer us to think of them as something other than "drugs" – hence the term "agent". However, as has been described, they have a considerable variety of interesting and clinically important effects that should be understood by anyone administering them. Indeed they are associated, albeit rarely, with significant morbidity and mortality. However, their enormous usefulness in adding value to x-ray examinations outweighs the very small risks associated with their use.

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QUESTIONS

1. Iodine is an ideal element for use in x-ray contrast agents because:
   a. its atomic number is high
   b. it is a halogen
   c. it is non-reactive chemically
   d. it has an appropriate K-shell binding energy
   e. it is a β emitter.

2. Which of the following **is not** a common side effect of intravascular x-ray contrast agents?
   a. metallic taste
   b. flushing
   c. bronchospasm
   d. vomiting
   e. pain on arterial injection

3. Which of the following **is not** a clear-cut risk factor for anaphylactoid reactions to intravascular x-ray contrast agents?
   a. a previous reaction
   b. asthma
   c. cardiac disease
   d. allergies to other drugs or agents
   e. atopy

4. Intravascular iodinated x-ray contrast agents:
   a. distribute themselves between cells and interstitium
   b. distribute themselves between plasma and interstitium
   c. are taken up avidly by hepatocytes
   d. are excreted by renal tubules
   e. break down in the body

5. Which of the following **is not** thought to be associated with intravascular contrast agent nephrotoxicity?
   a. dose-dependent
   b. more likely in the elderly
   c. more likely in patients with pre-existing renal disease
   d. more likely if the patient is dehydrated
   e. more likely in patients taking aspirin

6. Which of the following statements regarding intravascular x-ray contrast agents **is not true**?
   a. inhibit coagulation
   b. inhibit platelet aggregation
   c. non-ionics are better anticoagulants than ionics
   d. ioxaglate is a better anticoagulant than the non-ionics
   e. anticoagulant effect is a marker for toxicity

7. On intrasvascular contrast agent pharmacokinetics. The agents:
   a. can readily negotiate the blood brain barrier
   b. may be found in high concentrations in bile
   c. are described by a 2-compartment model
   d. are reabsorbed by renal tubular cells
   e. take part in an enterohepatic circulation

8. Intravascular x-ray contrast agents
   a. are strongly bound to circulating plasma proteins
   b. stimulate histamine release
   c. are blood pool agents
   d. are not significantly excreted by the liver in renal failure
   e. contain no free iodine

9. Organ-specific toxicities of intravascular x-ray contrast agents include:
   a. cardiotoxicity
   b. hepatotoxicity
   c. nephrotoxicity
   d. neurotoxicity
   e. endothelium toxicity

   a. all of the above
   b. a, b, and c only
   c. a, b, and d only
   d. a, c, d, and e only
   e. c, d, and e only

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10. On intravascular contrast agent chemotoxicity. This is:
    a. mediated by hydrophilic substituents
    b. mediated by hydrophobic parts of the molecule
    c. higher in non-ionic agents than the ionic agents
    d. higher in non-ionic dimers than monomers
    e. mediated by additives in the formulation

11. High osmolar intravascular x-ray contrast agents:
    a. expand the plasma volume
    b. cause red cells to expand
    c. inhibit histamine release
    d. do not predispose to venous thrombosis
    e. do not cause arterial pain

12. The structures of modern intravascular contrast agents are:
    a. based on the pyridone ring
    b. based on the benzene ring
    c. relatively hydrophilic
    d. all dimeric

    e. relatively hydrophobic
    a. a. a and b only
    b. b and c only
    c. c and d only
    d. d and e only
    e. none of the above

13. Which of the following statements regarding intravascular contrast agent toxicity **is not true**?
    a. mediated by high osmolality
    b. a function of charge
    c. a function of hydrophobicity
    d. decreased by addition of iodine to the molecule
    e. dose-and concentration-dependent

14. Intravascular iodinated x-ray contrast agents:
    a. are absorbed from the normal gut
    b. are absorbed across the peritoneum
    c. freely cross the normal blood brain barrier
    d. freely enter normal cells
    e. freely enter abnormal cells

15. Regarding 'low osmolality' intrasvascular x-ray contrast agents, they are:
    a. always non-ionic
    b. always dimeric
    c. always iso-osmolar with plasma
    d. monomers are always hyperosmolar with respect to plasma and body fluids
    e. formulation additive free

16. Concerning ionic intravascular contrast agents:
    a. these should be used for myelography
    b. pure sodium salts should be used for neuroangiography
    c. pure meglumine salts are ideal for coronary angiography
    d. meglumine salts are more painful in arteriography than sodium salts
    e. meglumine salts are less irritant to veins than sodium salts

17. Concerning 'low osmolar' intravascular x-ray contrast agents:
    a. non-ionic monomers are iso-osmolar with body fluids
    b. ioxaglate should be used for myelography
    c. ioxaglate is best used intravenously
    d. not all ionize in solution
    e. are never hyperosmolar with respect to body fluids

18. Intravascular x-ray contrast agents are:
    a. readily absorbed across inflamed gut
    b. not absorbed from joint spaces
    c. excreted by the kidneys following interthecal injection
    d. found in high concentrations in breast milk
    e. taken up avidly by hepatocytes

    a. a and b only
    b. a and c only
    c. b and c only
    d. b and d only
    e. d and e only

19. Anaphylactoid reactions to intrasvascular x-ray contrast agents:
    a. occur more commonly in asthmatics
    b. are more likely with non-ionic agents
    c. have a 90% recurrence rate after a previous major reaction
    d. corticosteroid prophylaxis reduces the risk by a factor of 10
    e. non-ionics are never associated with them

20. Toxicity of intravascular x-ray contrast agents **is not** mediated by:
    a. hyperosmolality
    b. molecular weight
    c. chemotoxicity
    d. charge
    e. all of the above

21. Idiosyncratic reactions to intravascular x-ray contrast agents are:
    a. anaphylactic in nature
    b. all due to cardiotoxic effects
    c. dose dependent
    d. more common in atopic individuals
    e. usually predictable

22. Which **is not true** regarding treatment of major anaphylactoid reactions?
    a. corticosteroids are the first line treatment
    b. adrenaline is the first line treatment
    c. fluid replacement is important
    d. maintenance of airway and CPR are of secondary importance
    e. adrenaline may be given intra-venously or intramuscularly

    a. a and d only
    b. b and c only
    c. c and a only
    d. d and e only
    e. all of the above

23. Which of the following **is not true** regarding prophylaxis against major reactions?
    a. corticosteroids have an undisputed role to play
    b. antihistamines may be useful
    c. reassuring the nervous patient may be helpful
    d. the best 'prophylaxis' is the use of a non-ionic agent
    e. if corticosteroids are used they may be given just before the contrast agent

    a. a and b only
    b. b and d only
    c. a and e only
    d. c and d only
    e. b and e only

24. On additives in intravascular x-ray contrast agents:
    a. non-ionic agents contain no formulation additives
    b. EDTA is added to all agents
    c. Ca EDTA is added to non-ionic agents
    d. non-ionic dimers are additive free
    e. all of the above.

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25. Regarding high dose and relatively high doses:
    a. 1000 mgI/Kgms is a typical dose in IV urography
    b. high doses may cause acute pulmonary edema
    c. renal function is not a concern in high dose
    d. hepatic function is a concern in high dose
    e. ionic agents are safer if high doses are to be used

<u>NOTES</u>

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