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THE PHARMACOLOGY OF INTRAVASCULAR RADIOCONTRAST MEDIA

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INTRODUCTION

Radiopaque contrast media are used for many diagnostic procedures that require X-ray opacification of blood vessels or tissue. Contrast media are injected both intravenously and intra-arterially to achieve this purpose. An ideal contrast media would exert no effect on the physiologic state while achieving the desired opacification in the selected organ or vessel. As with all drugs the ideal has not yet been achieved; however, the current generation of contrast media are considerably less toxic than the original commercial agents. There are several thorough reviews of the development, utilization, and pharmacology of contrast media, therefore the emphasis in this review is on general characteristics and current or new contrast media molecules (1–6).

STRUCTURE

All the currently used intravascular contrast media are derivatives of triiodinated benzoic acids (7, 8). The iodine molecule is an effective X-ray absorber in the energy range where most clinical systems operate (9, 10). Figure 1 illustrates examples of the different contrast media molecules currently available. The anion diatrizoate is the most commonly used contrast media in the United States and is supplied as either a meglumine or sodium salt. Not shown in the figure are iothalamate and metrizoate, two similar ionic monomers. Metrizamide, iopamidol, and iohexol are nonionic molecules with an organic side chain replacing the carboxyl group. Ioxaglate is a "mono-acidic

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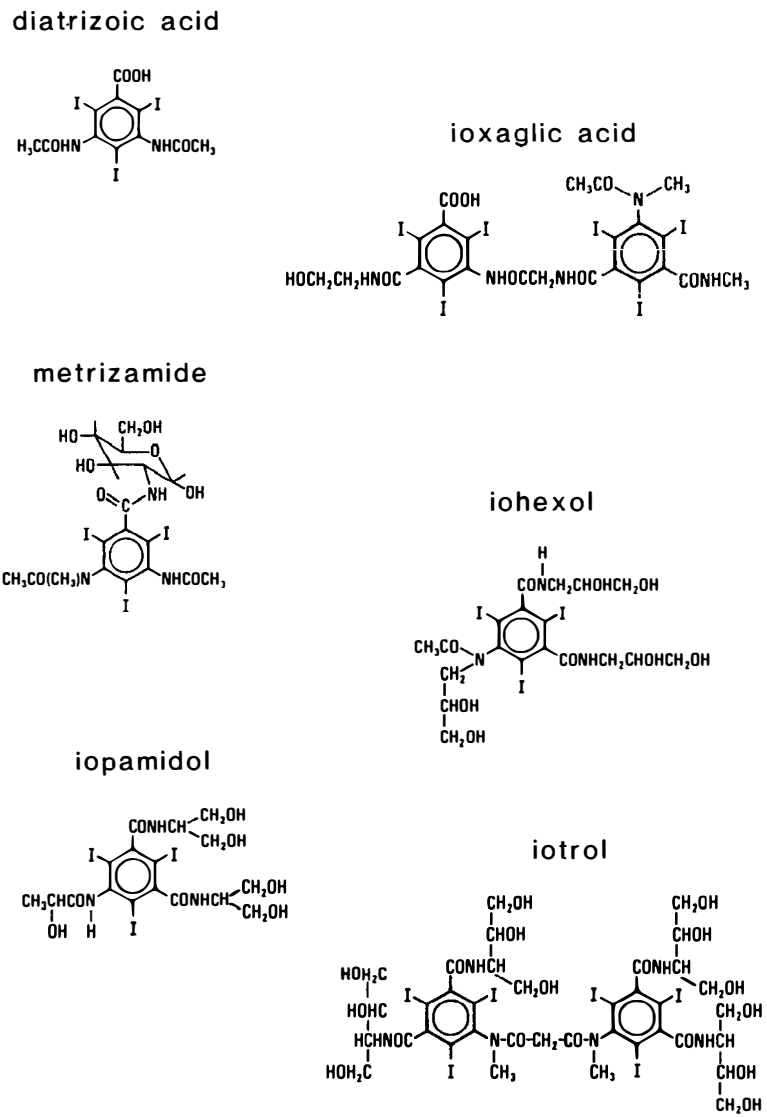

Figure 1 The structure of six different molecules currently in use in Europe or the United States illustrates the four classes of media available. All of the intravascular contrast media are derived from tri-iodinated benzoic acid precursors.

dimer" in which two of the "monomer" molecules have been linked to form a monovalent anion while iotrol is a nonionic "dimer." Iohexol, ioxaglate, and iopamidol contrast media are available for intravascular use in Europe and their approvals are currently pending in the United States. Intravascular injections of iohexol, iopamidol, and ioxaglate have been shown in numerous animal and

clinical studies to be less toxic than the currently used anion "monomers" (11–13). Metrizamide is currently approved in the United States for intrathecal use while iohexol, iopamidol, and iotrol approvals are pending for that route of administration.

As shown by the intravascular LD_{50} data in Table 1, contrast media are among the most inert compounds biologically and most of their physiologic and pharmacologic effects are related to their high concentration and, more specifically, to their high osmolality. The different media are often grouped according to the number of iodine molecules divided by the number of particles in an ideal solution. Thus the ionic monomers yield a ratio of 1.5 iodine molecules for each particle in an ideal solution; the nonionics and mono-acidic dimer have ratios of 3 to 1.

CONCENTRATION AND COLLIGATIVE PROPERTIES

Most intravascular drugs achieve their primary function at doses in the μg/kg range. Contrast media must absorb X rays to perform their function and are therefore generally used in dose ranges measured in g/kg and in concentrations as high as 1.5 Molal, or 10 times higher than the concentration of body fluids. At these high concentrations the colligative properties of these contrast media solutions are very important. Osmolality and viscosity are shown as a function of concentration (in mgI/ml) in Figure 2 and 3 for three types of contrast media. The osmolalities of contrast media solutions are considerably lower than expected for ideal solutions. Thus a 1.5 Molal solution of diatrizoate has an osmolality of only 1.7 rather than 3.0 Osmoles/kg. The viscosity of the concentrated solutions is higher than that of blood and plasma, and contrast media can produce alterations in local blood flow.

DIAGNOSTIC UTILIZATION

There are three general modes of utilizing intravascular radiopaque contrast media in clinical practice. The first is the direct injection of the media into a vascular structure to provide opacification of the vascular lumen. This procedure is performed at injection rates sufficient to replace blood flow through the structure. If the X-ray images are being recorded directly on film, concentrations from 280 to 370 mgI/ml are used. More recently the development of computerized tomography (CT) and digital subtraction angiography (DSA) have made it possible to visualize vascular structures with concentrations as low as 2 to 8 mgI/ml.

A second mode of using contrast media is to visualize and monitor their distribution in body fluid compartments. This is primarily used in contrast-enhanced CT studies. The X-ray absorbance of soft tissues is low and only small differences are observed in normal and pathologic tissue. The use of

Table 1 Comparisons of several parameters for six different contrast media molecules

Contrast media	Molecular weight	Moles of iodine per mole particles in solution	Type of Molecule	Acute LD_{50}[a] in mice (gI/kg)	Half time[b] in man (min)
Diatrizoate	636	1.5	ionic, monomer	7.5 (14)	101 (15a)
Ioxaglate	1269	3.0	ionic, dimer	13.4 (14)	92[c]
Metrizamide	789	3.0	nonionic, monomer	18.6 (14)	75 (15b)
Iohexol	821	3.0	nonionic, monomer	24.2 (14)	121 (15b)
Iopamidol	777	3.0	nonionic, monomer	22.1 (14)	128 (15c)
Iotrol	1626	6.0	nonionic, dimer	26.0 (15)	—

[a]Acute lethal dose 50 following intravenous administration in units of grams of iodine per kilogram body weight. Numbers in parentheses are references.
[b]This time is calculated from a 2-exponential model and represents the half time of the slow excretion component.
[c]Half time supplied by Guerbet Laboratories.

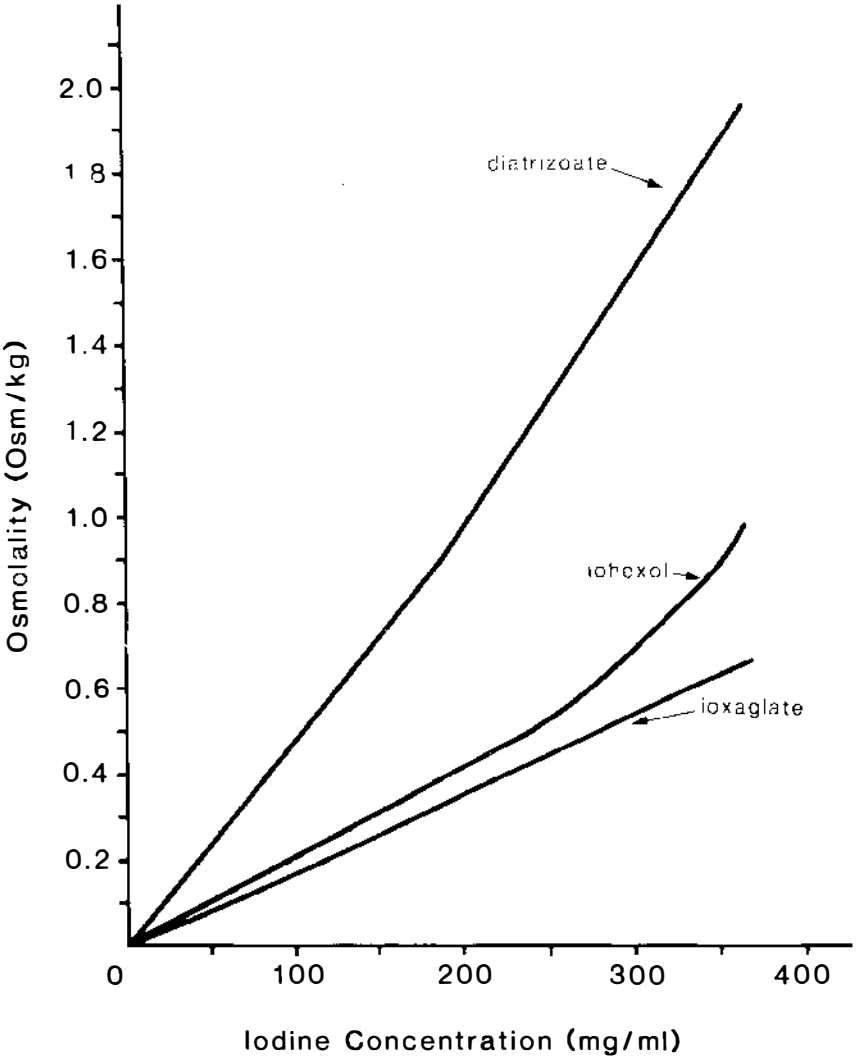

Figure 2 Osmolality in units of osmoles/kilogram (Osm/kg) water is shown as a function of iodine concentration for contrast media representing three types of media: ionic monomers (diatrizoate), monovalent ionic dimers (ioxaglate), and nonionic (iohexol). An iodine concentration of 190 mgI/ml would be 0.5 molar for diatrizoate or iohexol and 0.25 molar for ioxaglate. As the concentration increases, the solute volume of the solutions becomes substantial. For example, at 370 mgI/ml one ml of a diatrizoate solution contains 0.66 ml of H_2O and 0.34 ml of solute. This large solute volume is responsible for the upward curvature of these plots.

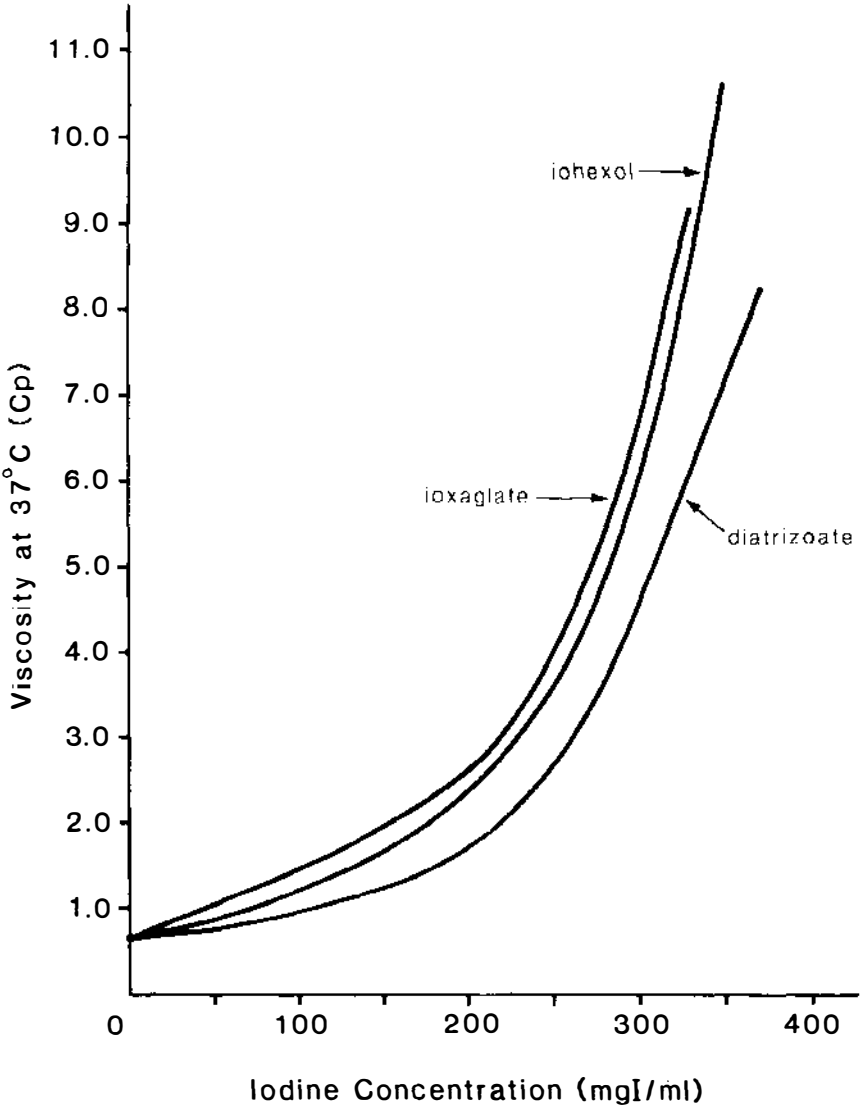

Figure 3 Viscosity in units of centipoise (Cp) is shown as a function of iodine concentration for the same three contrast media. At the higher concentrations solute-solute interactions and viscosity increase rapidly. The most commonly used radiocontrast media concentrations of 370 and 300 mgI/ml have viscosities several times greater than the viscosity of plasma.

contrast agents can enhance the difference in the absorbance of soft tissue because of the difference in the distribution of the contrast media molecules (9, 10). For example, some brain tumors lack a blood-brain barrier and contrast media will diffuse into them while they will not diffuse into areas retaining a normal blood-brain barrier (16). The distribution volume of contrast media is often used to quantify these studies. The distribution volume is calculated as 100 times the ratio of tissue concentration divided by plasma concentration and can be obtained directly from CT data and the blood hematocrit ratio.

A third mode of using contrast media is to visualize their route of excretion from the body. Most of the current molecules for intravascular use are excreted primarily by the kidney (17). As these molecules are cleared by the kidney they will opacify the renal parenchyma, then the tubular structures, the renal calyces and pelvis, and finally the ureter and bladder. These agents are concentrated by the kidney and thus provide excellent visualization of the entire renal system. In patients with renal failure there is a much slower vicarious excretion of contrast media through the biliary system and bowel. There is an additional class of intravascular contrast media that are excreted primarily into the biliary system by the hepatocytes (18). These media, such as iodipamide, are not frequently used today because of their higher toxicity and because of the increased use of CT and ultrasound to examine the liver and biliary system.

The dose of contrast media used varies considerably depending on the procedures to be performed. For example, peripheral intra-arterial DSA procedures may require less than 0.15 gI/kg while a complete conventional cardiac study can require as much as 1.5 gI/kg. The procedures requiring the highest doses usually involve multiple injections, often at different vascular sites.

DISTRIBUTION

All of the contrast media molecules available have molecular weights ranging from 600 to 1700 and have low lipid solubility (this is excluding the biliary agents). These molecules distribute in body fluids in much the same way as extracellular markers such as sucrose, Cr-EDTA, Tc^{99m} DTPA, or inulin. The molecules do not enter normal cells in significant amounts although very small intracellular concentrations have been reported (19). The molecules enter the interstitial space quickly in most tissue (20, 21) but they do not appear to cross the blood-brain barrier. The molecules do enter cerebrospinal fluid through fenestrated areas such as the choroid plexus (16).

Diagnostic procedures take advantage of the differential distribution space and kinetics of normal and abnormal tissue. Figure 4 illustrates the CT attenuation of blood and different tissues in a series of patients (22). The CT attenuation at equilibrium depends on the dose given and the extracellular space or distribution volume of tissue, which does vary with tissue type. The kinetics of

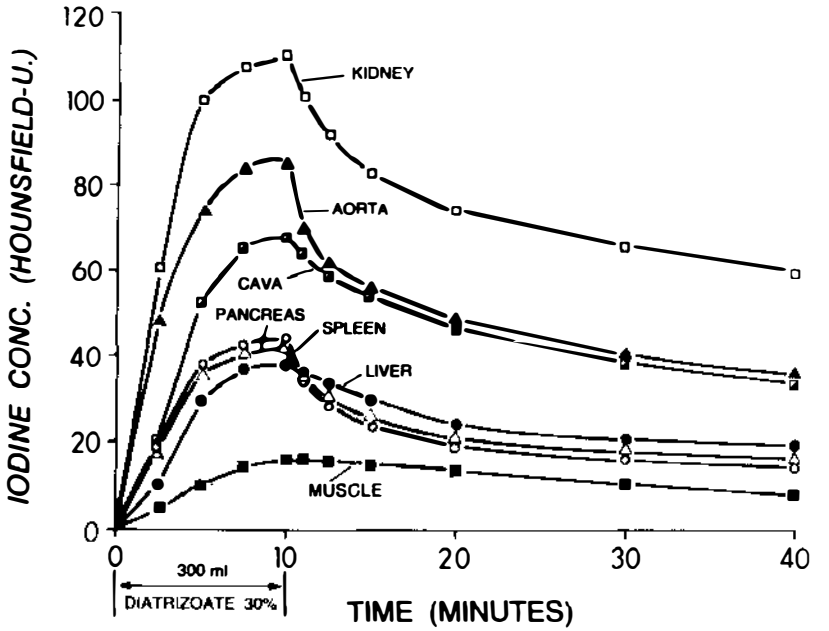

Figure 4 Iodine concentrations derived from CT measurements and presented as Hounsfield units are shown as a function of time in patient blood and tissues. (25 Hounsfield units are equivalent to 1 mgI/ml.) The greatest differences in iodine concentrations among the tissues occur during the infusion of contrast media and are related to distribution kinetics (22). (Reprinted with permission from the authors and *Am. J. Roentgenol.*)

contrast media distribution vary considerably more than the extracellular space and depend on blood flow, capillary density, capillary permeability, interstitial diffusion distances, and the diffusivity of the interstitial matrix. All of these factors can be altered in different types of abnormal tissue. By obtaining CT images at different times after intravascular injection, one can take advantage of the differences in tissue contrast media accumulation. As illustrated in Figure 4, this is most effective during or immediately after the contrast media infusion. The distribution kinetics of the new low osmolality contrast media appear to be very similar to the distribution kinetics of the conventional ionic monomers (23).

CLEARANCE

The contrast media molecules are excreted primarily by filtration at the renal glomerulus. They are not significantly secreted or reabsorbed in the tubules at clinical doses and are essentially equivalent to the standard marker for glomerular filtration, inulin (17, 24). The half times for excretion calculated from two

compartment models are given in Table 1 for several different contrast media molecules.

During renal artery injections, small differences in clearance rates for different molecules have been observed and may relate to their osmolality. During intra-arterial injections the higher osmolality ionic monomer contrast media cause greater shrinkage of glomerular endothelial cells that may lead to increased filtration. In isolated perfused canine kidneys we observed that the renal vein concentration of ioxaglate was highest, nonionic monomers were intermediate, and and the ionic monomers were the lowest (25).

Although the total excretion is similar for all contrast media following i.v. injections, the urine concentration depends on the type of molecule. The low osmolality nonionic and mono-acidic dimer contrast media are more highly concentrated in the urine than the more hypertonic ionic monomer contrast media (26–28). The ionic monomer contrast media cause higher water flux into the tubules and a greater diuresis. The larger fluid volume causes greater distention of the pelvic structures. The higher urine concentrations of the low osmolality contrast media produce greater visualization of small structures and boundaries. A smaller difference in urine concentration has been noted between meglumine and sodium salts of the ionic monomers (29). The sodium salts are believed to reach higher concentrations because of sodium reabsorption.

LOCAL EFFECTS

The direct injection of radiopaque contrast media into arteries causes alterations in fluid and electrolyte balance, hemodynamics, and vascular resistance. These changes are caused primarily by the high osmolality and viscosity of the media. During and immediately following an intra-arterial injection, the contrast media viscosity raises the vascular resistance in the downstream vascular bed (30). This effect is apparent only for the brief period during which the media is located in the resistance vessels or arterioles (30). The high osmolality of the contrast media causes a rapid loss in water by red cells, endothelium, and tissue extravascular space (25, 31, 32). Figure 5 illustrates the relationship between red cell volume and solution osmolality that we have observed with contrast media. A similar loss of water by endothelial cells can result in shrinkage of the endothelial cells and the opening of tight junctions such as those in the blood-brain barrier (16). Recent studies of the endothelium have demonstrated that the molecular structure of the contrast media also plays a role in producing endothelial damage (33).

The shift of water from tissue parenchyma is biphasic with an initial loss followed by a later gain (25). This response appears to result because the bolus of blood and contrast media first passing through the tissue capillaries removes tissue water and raises tissue osmolality. As this mixture is washed through the

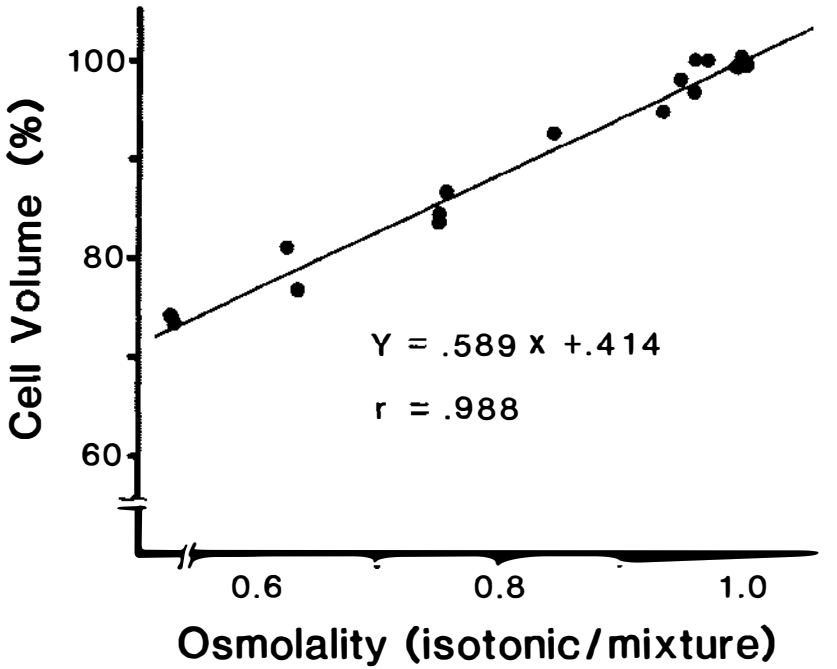

Figure 5 Red blood cell volume, presented as a percentage of the isotonic volume, is shown as a function of the ratio of isotonic and test solution osmolalities. The test solutions were made hypertonic by adding sodium diatrizoate. Red cell volumes were measured using both isotope and microcapillary hematocrit techniques and are corrected for dilutions.

capillaries it is replaced by blood of normal osmolality and water is then lost to the tissue. The return of fluid to tissues is enhanced by the increased solute concentration caused by the movement of contrast media molecules from capillaries to the interstitial space. The loss of tissue water and increase in tissue osmolality are the most likely causes of the vasodilation observed in most vascular beds following intra-arterial contrast media injections (34, 35). Figure 6 illustrates the changes we have observed in femoral blood flow with 5-sec injections of different contrast media solutions (36). When the solutions were isotonic there was no difference between the maximum flow observed for contrast media and blood, while hypertonic solutions caused large increases in flow.

The high osmolality of contrast media has also been associated with pain during selective arteriography in many sites (37). It has been shown in several clinical studies that the new low osmolality contrast media produce significantly less pain (38–42).

The injection of contrast media into coronary arteries can cause effects on myocardial electrical and mechanical function (43, 44). The hypertonic ionic

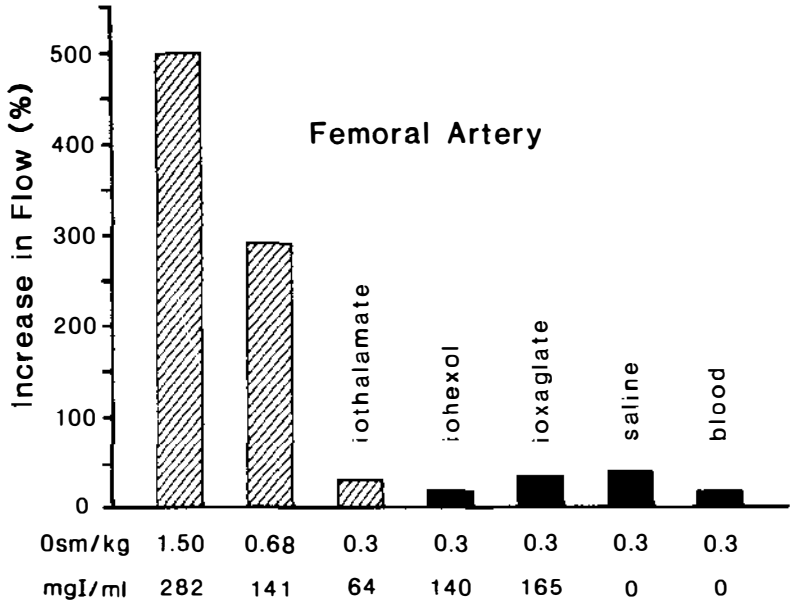

Figure 6 The maximum increase in femoral artery flow (at constant arterial pressure) is shown from a single canine experiment. The injection was for 5 seconds at 0.5 ml/second and maximum flow occurred between 5 and 60 seconds after the start of the injection. The isotonic solutions produce similar maximum flows that are much smaller than those for hypertonic iothalamate solutions.

solutions have been shown to cause both bradycardia and significant decreases in contractile function, while hypertonic nonionic solutions have been shown to cause an increase in contractile force (43, 45, 46). During prolonged exposures of the myocardium to contrast media the importance of electrolyte composition is also apparent. In dog experiments it has been shown that both calcium chelators and the lack of sodium increase the risk of ventricular arrhythmias and fibrillation (47–50). These electrolyte effects appear to be related to decreases caused in conduction velocities and cell repolarization (51). The importance of electrolyte composition in clinical practice is less well established, but there is some agreement with animal studies (52–54).

Renal artery injections of contrast media produce hemodynamic changes different from those observed in other vascular beds. In the kidney there is an initial vasodilation followed by a later, more prolonged increase in vascular resistance (55). This increase in vascular resistance coincides with the period during which the kidney tissue is regaining water from blood (25). There has been much debate over the mechanism for this increase in resistance (56–58). The bulk of the existing evidence seems to indicate that the increased resistance can be explained by an increase in tubular pressure and a subsequent decrease in

filtration fraction, and glomerular filtration plus compression of glomerular capillaries (57). The increased tubular pressure might also tend to cause compression of post-glomerular vessels. Many vasoconstrictor substances have also been suggested and may play some role. The injection of contrast media into the renal artery has also been shown to cause a transient proteinuria (59), presumably from osmotic disruption of the glomerular endothelial cells. Both the hemodynamic effects and the proteinuria are significantly reduced with the use of the new low osmolality contrast media (60, 61).

Since the kidney is the primary organ for excretion of contrast media all arterial and venous injections of contrast media result in high renal concentrations of contrast media. Thus the hemodynamic alterations observed with renal artery injections can also be observed with all contrast media injections, but they are delayed and of lesser magnitude (62).

Rapid intravenous injections such as those used in angiocardiography, dynamic CT scanning, and i.v. DSA produce effects in the lungs very similar to the effects of intra-arterial injections in other tissues. The large bolus (typically 20 to 40 ml) is delivered in less than two seconds and results in a high osmolality mixture of blood and contrast media entering the pulmonary vascular system. Thus the same fluid shifts that occur in other tissues occur in the lungs (63). A large increase in pulmonary water content has been documented using a combination of thermal and dye tracers with an indicator dilution analysis (64). The mechanism is believed to be a leakage of serum proteins as well as contrast media into the pulmonary interstitium following the osmotic shrinkage of endothelial cells. As would be expected, there is less of an increase in lung water with the new low osmolality contrast media (65).

In a clinical study it was observed that all patients receiving intravenous contrast media had a mild but measurable bronchospasm (66). The bronchospasm could be related to water shifts or to the release of a substance such as histamine. The intravenous injection of contrast also causes an increase in pulmonary artery pressure that may be related to the shrinkage and decreased deformability of red blood cells (67). This increase in pulmonary artery pressure has been shown to be reduced with the new low osmolality contrast media (68).

A recent study has demonstrated a local effect of intravenous contrast media on the production of cerebrospinal fluid (69). This decrease was significant even at clinical doses and did not appear to be related to hypertonicity. The mechanism may be related to the specific structure of the contrast media molecules.

SYSTEMIC EFFECTS

Both intravenous and selective intra-arterial injections can cause systemic responses and reactions. Selective intra-arterial injections in the carotid and

vertebral arteries are known to produce bradycardia and systemic vasodilation that are mediated by the autonomic nervous system (70–72). The mechanism is believed to be initiated by carotid chemoreceptors and other receptors in the cerebral vasculature (71). Coronary artery injections of contrast media cause changes in cardiac output because of their effects on both heart electrophysiologic and contractile function (44).

Intravenous contrast media injections have been shown to cause hypotension and bradycardia in both animal and patient studies (73–75). Based on the animal studies these effects seem to be dose dependent (73) and to be reduced with the new low osmolality contrast media (74). In a study of 97 patients, 51 were observed to respond with a measurable decrease in arterial pressure and 6 had mean arterial pressures drop below 60 mm Hg (75). In animal studies this effect has been shown to be markedly potentiated by a preexisting dehydration (76).

ADVERSE REACTIONS

Adverse reactions to contrast media are classified as minor, intermediate, or severe (77). Minor reactions include all reactions such as nausea, vomiting, mild rash or urticaria, and mild dyspnea that require no treatment. Intermediate reactions are those that require treatment (but not hospitalization) and include bronchospasm, mild laryngeal and facial edema, dyspnea, hypotension, extensive urticaria, and mild chest pain. Severe reactions that are life threatening and require hospitalization include laryngeal and pulmonary edema, circulatory collapse with refractory hypotension, angina, cardiac arrhythmias, and cardiac or respiratory arrest. The incidence of these 3 types of reactions is not precisely known (77–79) but they are relatively infrequent. Conservative estimates for the ionic monomer contrast media are that minor reactions occur in 1 out of 20 patients, intermediate reactions in 1 out of 100, and severe reactions in 1 out of 2000 (80). The mortality rate reported in the literature is quite variable, ranging from 1 in 14,000 to 1 in 117,000 patients (81). Sample size limitations and patient population characteristics make it difficult to assess this rate more precisely; however, the figure most generally quoted is 1 in 40,000 patients. The risk of having a severe reaction to contrast media appears to increase with some predisposing risk factors (80). These factors include a previous reaction, a history of allergy, asthma, dehydration, cardiac disease, and advanced age. The incidence of these reactions seems to be lower with the new low osmolality contrast media (82–84), but the number of patients studied is too small for a statistical assessment.

The development of CT and DSA technology has led to a general increase in the total number of contrast media studies and to an increase in the number of contrast media studies performed in elderly patients and in patients with renal impairment. Coincident with this, there has been an increase in the number of

reported cases of acute renal failure (85–87). Many renal specialists believe that it is the presence of preexisting risk factors and acute stresses that potentiate these renal responses to contrast media (85, 88). The new lower osmolality media will substantially reduce the osmotic load on the kidneys and should reduce the incidence of acute renal failure.

Several hypotheses have been developed to explain the occurrence of adverse reactions to radiopaque contrast media (89–93). Many of the reactions appear similar to anaphylactic reactions and some researchers believe there is an antigen-antibody response (91). Other researchers in the field, however, believe that the reactions are more properly termed anaphylactoid and that they are induced by other mechanisms that may involve some of the same reaction "pathways" (93). These hypotheses are based on the premise that the hypertonic contrast media cause endothelial disruptions and the release of active chemical substances or transmitters. It has also been suggested that the contrast media enter areas of the CNS having fenestrated capillaries and then cause autonomic responses that produce the reactions (93). All of these mechanisms are possible but it is difficult for one hypothesis to explain all the observed reactions. The literature appears to indicate that the mechanisms for adverse reactions are multifaceted and complex. We do know, however, that preexisting factors play a role (80). The accumulation of clinical data for the new low osmolality contrast media should test the hypothesis that the initiating mechanism is related to hypertonicity.

CONCLUDING REMARKS

Radiopaque contrast media are an extremely important diagnostic tool. They are among the least toxic of intravascular agents but they commonly must be used in high concentrations and doses to achieve their X-ray absorbing function. These high concentrations and doses will always produce transient physiologic and pharmacologic alterations. These responses are generally small and of little clinical concern. Adverse reactions requiring medical treatment are infrequent with conventional ionic monomer molecules, but they are still of medical concern. New low osmolality contrast media molecules will soon be available in the United States that have been shown to produce significantly smaller physiologic and pharmacologic responses. It is believed that these new molecules will also reduce the incidence of adverse reactions significantly, but the patient data available is still incomplete.

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