Contrast media in radiology - a practical guide

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Curriculum vitae

Dr L Bester graduated MB ChB from the University of Pretoria in 1972. He completed his Housemanship and Senior Housemanship in Port Elizabeth and then spent from 1974–1983 as a general practitioner in the Johannesburg area. He was a Registrar in Radiology from 1984–1987. Dr Bester also received his BSc (Hons) in Pharmacy from the University of Potchefstroom in 1980, and the MFGP (SA) in 1982. He has published 6 papers, 3 of which were in overseas journals. He has also been a member of the executive of the National Academy of General Practitioners.

S Afr Fam Pract 1987; 8: 221–7

Summary

Intravascular radiographic contrast media are well tolerated by patients and their value in radiological procedures is enormous. New low osmolar contrast agents have been developed in an attempt to decrease the severity and incidence of side effects. The number of major risk factors and the severity of any predisposing conditions that a patient may suffer from, correlate well with the likelihood of developing radiographic contrast induced reactions. The role of the new low osmolar radiographic contrast media in acute renal failure, cardiac failure, dehydration, multiple myeloma, sickle cell anaemia and diabetes melitus is discussed.

KEYWORDS: Contrast media; Radiography; Hypersensitivity; Drug toxicity

Intravascular radiographic contrast media (IRCM) are used extensively in radiology. Their use is sometimes associated with a significant incidence of side effects. Of all IRCM examinations 5–8% are complicated by adverse reactions. Fortunately, only a third are severe and call for immediate treatment[1]. In the ill or allergic patient, the injudicious use of intraveneous contrast media can either make the existing disease worse or cause important new disease.

The risks and side effects associated with the use of intravenous radiographic contrast media are well described. Briefly, these side effects can be categorised into two main groups: idiosyncratic (anaphylactoid) and non-idiosyncratic (osmolar and chemotoxic)[2]. The major risk to an otherwise healthy patient is mainly from idiosyncratic reactions. In a

compromised patient with renal failure, cardiac failure or other conditions as described below, the risk is mainly from the non-idiosyncratic effects of the contrast media.

New intravenous radiographic contrast media have been developed in the past few years in an attempt to decrease the incidence and severity of side effects[3]. These contrast media have been shown to decrease the incidence and severity of non-idiosyncratic side effects, both by objective and subjective measurements[4]. There is as yet no conclusive proof that the incidence of idiosyncratic reactions has been reduced by the new contrast media, but early experiences by different investigators suggest that the incidence and severity of severe and fatal complications are reduced[3,4,5].

The aim of this article is to provide a practical guide to the use of intravascular contrast media in the healthy patient, the ill patient and the allergic patient, and to discuss some of the relevant pharmacokinetic properties of radiographic contrast media.

Of all IRCM examinations, 5–8% have adverse reactions

Iodine concentrations

There are two methods used for expressing the iodine concentrations in contrast media and this is indicated as a number after its trade name eg Conray 420 or Urografin 76%. If there is no percentage (%) sign, the number refers to the concentration of iodine in mg/ml. A % sign refers to the concentration of the whole contrast molecule in solution (weight/volume %). Table 1 outlines the iodine concentrations of commonly used contrast media.

Table 1: *Iodine concentrations in contrast media*

Contrast	Iodine Concentration
Conray 420	420 mg iodine/ml
Conray 325	325 mg iodine/ml
Conray 280	280 mg iodine/ml
Hexabrix	320 mg iodine/ml
Urografin 76%	370 mg iodine/ml
Urografin 60%	292 mg iodine/ml
Urografin 30%	146 mg iodine/ml
Jopamiron 370	370 mg iodine/ml
Jopamiron 300	300 mg iodine/ml
Jopamiron 200	200 mg iodine/ml

During most contrast examinations, high doses of the contrast medium are used. It is important to know the maximum dose that may be used. These maximum dosages are outlined in Table 2.

Table 2: *Maximum dosages of contrast that may be used*

Contrast	Maximum dose of iodine
Conray and Urografin	600– 800 mg iodine/kg BW
Hexabrix	800–1000 mg iodine/kg BW
Jopamiron	800–1100 mg iodine/kg BW

Pharmacokinetics

The connection between pharmacokinetics and tolerance becomes particularly obvious in the case of Radiographic Contrast Media (RCM). There is no evidence that Ionic and Non-Ionic, monomeric or dimeric aromatic benzene rings can penetrate into intact cells, except hepatocytes. The RCM cations such as the sodium, penetrate into cells to a large extent while cations such as meglumine penetrate only very slightly. Thus, intravascular administered RCM themselves are distributed in the body exclusively via the blood stream and are practically not metabolized. This fact enables us to almost completely predict and explain the pharmacokinetic behaviour of contrast media[5,6].

The properties of contrast media are of fundamental importance during long and complicated angiographic procedures as one may easily reach the limits of contrast doses as specified in Table 3. Considering the pharmacokinetics of the radiographic contrast medium, and taking into account that the half-life of most contrast media is between 30-60 minutes, one may in certain circumstances be able to safely exceed the maximum dose of contrast medium[6]. This may allow an examination to be completed, rather than requiring the patient to return for a second sitting.

Injudicious use of IRCM can make an existing disease worse or cause important new diseases

The rate of excretion will change in compromised patients, especially those with renal decompensation, cardiac failure and the aged, as the excretion of a contrast medium depends on cardiac output, blood pressure, blood rheology, hematocrit and blood flow[7].

Special conditions

There are certain conditions in which contrast media should be used with caution. Some guidelines

Pharmacokinetics

Table 3: *Showing the half life and rates of excretion of some contrast media*

Contrast	Half life (50% excretion)	At 3 hrs (% excreted)	At 24 hrs (% excreted)
Conray	30-60 mins	75-85	90-95
Urografin	30-60 mins	75-85	90-95
Hexabrix	30-60 mins	70-75	90-95
Jopamiron	30-60 mins	75-85	90-95

for the use of contrast media in these conditions are given below:

- *Renal failure*

Acute renal failure is a common condition which occurs in a variety of clinical circumstances. In a recent worldwide review of 2200 cases of acute renal failure, 43% were related to surgery, 26% to medical illness, 13% to pregnancy, 9% to trauma, and 9% to nephrotoxins. In past years, poisons and industrial chemicals were the most common nephrotoxic agents encountered; today, however, antibiotics (specifically aminoglycosides), radiographic contrast media and anaesthetic gasses have become the prime offenders[8]. In a prospective study involving 2216 patients, Hou found 129 episodes of hospital-acquired renal insufficiency - an incidence of 4,9%[9].

Clinical experience and retrospective surveys have taught us, however, that certain groups are more

Ionic contrast material appears to have a direct toxic effect on the kidney

likely than others to develop contrast-induced renal failure. Significant risk factors include advanced age, current or prior renal insufficiency, dehydration, diabetes mellitus, multiple doses of contrast medium within a short time span, and multiple myeloma. Other, less significant, factors proposed include hypertension, peripheral vascular or renal vascular disease, congestive heart failure, hypoalbuminaemia, hyperuricaemia and cirrhosis.

Acute renal failure classically has been divided into three groups depending on the location of the cause. Pre-renal azotemia is caused by either volume depletion states such as haemorrhage, severe diarrhoea and burns, by reduced cardiac output states such as congestive heart failure, cardiac tamponade or acute pulmonary embolism, or by vascular obstruction such as bilateral renal artery occlusion or thrombosis. Post-renal azotemia can be caused by ureteral or bladder neck obstruction, or bilateral ureteral obstruction. Causes of renal azotemia include the glomerular lesion such as glomerulonephritis and the many vasculites, and tubular lesions. Tubular lesions leading to acute renal failure are also referred to as acute tubular necrosis. Causes of acute tubular necrosis (ATN) include ischemia, obstetric accidents, pigment releases (such as in myoglobulinuria or hemoglobulinuria), tubular obstruction (as seen in urate nephropathy and hypercalcaemia), nephrotoxins and radiocontrast media.

Contrast-induced acute tubular necrosis, like other forms of acute tubular necrosis, is comprised of three distinct clinical phases. The first, or oliguric,

One may easily reach the limits of contrast doses in long term procedures

phase begins hours to a few days after the administration of contrast and has a typical duration of 1 to 4 days. Daily urine output averages about 150 millilitres, and there is a characteristic rise of the urea and creatinine. One also frequently observes a hyperkalaemic acidosis with its attendant physiologic consequences. During the second, or diuretic, phase, urine output is markedly increased, even up to one to two litres per day. In spite of increased urine output, the glomerular filtration rate is still reduced and abnormal serum and urine chemistries persist. The diuresis can lead to significant dehydration, hypokalemia and hyponatremia. The final recovery phase lasts between three and twelve months, during which time renal function returns towards normal. The rapidity and extent of the recovery depend on the length of oliguria, the age of the patient, and the severity of any intrinsic renal disease. The renal failure caused by contrast is almost always reversible except in patients with additional and severe failure caused by diabetes mellitus or by early-onset diabetes mellitus.

A dehydrated patient should be rehydrated before a contrast examination

Ionic contrast material appears to have a direct toxic effect on the kidney. Moreau reviewed 211 renal biopsies performed on patients following an excretory urogram of renal arteriogram within the preceding ten days. In 47 specimens, an intense

vacuolization of the cytoplasm in proximal tubular cells was observed, which was not felt to be a part of any intrinsic renal disease. Similar changes were noted in the kidneys of infants who died after cardiac catheterization and in pigs given contrast material[10].

There is evidence that the newer nonionic agents may differ significantly from the ionic agents in their nephrotoxicity. These, like the ionic agents, are fully substituted benzene rings with three iodine atoms per molecule. The nonionic agents, however, do not dissociate into cationic and anionic moieties when placed in solution. Dimeric compounds consist of two bonded benzene rings with a total of six iodine atoms per molecule that, when in solution, dissociate into a cation and an anion. Therefore, with dimeric compounds, one gets twice the iodine concentration for any given number of dissolved ions[11].

Since intravenous water soluble contrast media are excreted primarily by the kidney, their use in patients with compromised kidneys should be carefully considered. Some guidelines for their use are provided in Table 4.

Patients with poor renal function

Table 4: *Giving some guidelines to the choice of contrast media in renal disease*

Normal values:	Urea Creatinine	2,5 - 7,5 mmol/l 60 - 130 mmol/l
Urea (mmol/l)	**Creatinine (umol/l)**	**Contrast medium to be used**
2,5 - 7,0	20 - 240	Conray, Urografin
7,0 - 9	240 - 600	Hexabrix
9,0 - 12	600 - 800	Jopamiron
>12	>800	No contrast should be used as further renal damage will occur. Do dialysis prior to examination.

- *Cardiac disease*

The introduction of a bolus of hyperosmolar RCM into the intravascular space, results in osmotically driven expansion of circulating plasma volume as the homeostatic mechanisms of the body attempt to dilute the contrast. There is an initial brief hypertensive response, as the peak plasma expansion is reached in approximately the first two minutes. The plasma volume increase is of the order of 10-15%, when a typical urography dose is used[12]. There is also an increase in the central venous pressure, right ventricular pressure, pulmonary artery pressure and cardiac output.

The increase in osmolality also causes a diuresis, and equilibrium is reached with the extracellular compartment in 10-15 minutes[13]. Further, there may be a reversal of the initial increase in blood volume and this may lead to hypovolaemia. This rapid increase in blood volume and subsequent decrease, may lead to hypovolaemic cardiovascular compromise, and is particularly important in patients with a history of congestive cardiac failure.

Patients with cardiac disease are 4 to 5 times more likely to have systemic reactions, and these tend to be more severe

For these reasons, contrast examinations are contraindicated in cardiac failure or in patients with a compromised cardiovascular system. However, if a contrast examination must be done, low osmolar contrast media are recommended.

- *Dehydration*

In a dehydrated patient with a depleted intravascular and extravascular volume, the fluid shifts will be relatively more marked. Further, sufficient body fluid may not be available to provide adequate dilution of the contrast. This will allow the irritant effect of a hyperosmolar solution to damage vessel endothelium[14]. Specifically, the kidneys are most susceptible to damage, and the use of contrast media in dehydrated patients may precipitate renal failure[6,11]. For this reason, a dehydrated patient should be rehydrated before a contrast examination but if the examination is a matter of urgency, low osmolar radiographic contrast media should be used.

- *Myeloma*

The use of contrast media in patients with myeloma will result in precipitation of Bence-Jones protein in the renal tubules. This may cause renal failure. Therefore, contrast examinations are relatively contraindicated in patients with myeloma, but where that must be done, low osmolar contrast together with adequate hydration must be used[11].

- *Diabetes*

Diabetes is often associated with some underlying damage. Further, poorly controlled diabetics may be dehydrated. Diabetes is also associated with small vessel disease. Since the use of high osmolar contrast media should be avoided in both renal failure and dehydrated patients, and since high osmolar contrast media may damage small vessels, as well as precipitation of complexes of contrast with normal tubular glycoprotein causing an obstructive uropathy[11,15], the use of such contrast

media should be avoided in diabetics. Therefore, in diabetics low osmolar contrast media should be used, especially if diabetic nephropathy is suspected.

No prognostic test is as yet available to identify patients at high risk

- *Sickle cell anaemia*

High osmolar RCM cause shrinkage and clumping of the normal erythrocytes due to intracellular fluid loss from the red blood cells. The deformed and changed RBCs undergo internal viscosity increases to such an extent, that they cannot distort themselves sufficiently to negotiate the capillaries, resulting in considerable increase in peripheral resistance to blood flow, with local tissue anoxia, resembling an agglutination-thrombosis effect[13].

Haemoglobin SS containing erythrocytes on the other hand may become deformed permanently when exposed to hypertonic solutions, causing a sickle cell crisis. Therefore patients with sickle cell disease, must be well hydrated before an IV RCM injection and low osmolar contrast media should be used[16].

Allergic reactions

Patients who have had previous allergic reactions or who have a strong allergic history must be given contrast cautiously[13]. Some data about allergic patients is provided in Table 5.

Allergic patients

Table 5: *Giving some details about patients with a history of allergy*

Condition	Percentage reaction
Previous reaction	17 - 35
Asthma, hay fever, atopic	11 - 15
Slow injection	5 - 7

Note: The intra-arterial route is four times safer than the intravenous route

Anaphylactoid reactions have been reported in all age groups, including infants. A disproportionately

high number of IV RCM reactions occur in the 3rd and 4th decades of life[17]. Patients with cardiac disease are 4—5 times more likely to have systemic reactions, and these reactions also tend to be more severe[17].

In diabetics, low osmolar contrast media should be used especially if diabetic nephropathy is suspected

It has been suggested that distinctly fewer reactions occur at a dose of less than 20 g iodine[16] but this has not been confirmed by other workers. There is also a difference in incidence between ethnic groups, with an 8-fold increase in Indians living in England, as compared to native Britons[17].

No prognostic test or procedure is currently available to identify patients at high risk. Pretesting by the administration of an intravenous test dose as a universal screening procedure leaves much to be desired, as a few patients have suffered severe reactions and/or died from the test dose[18].

Skin testing has also been used, but false positive and negative cutaneous reactions occurred. These tests are considered useless by most authorities since there is no correlation between test reactions and subsequent reactions with IV RCM. The reason for this is that skin testing only tests for IgE mediated anaphylactic reactions[19].

A repeat reaction rate of 35%–60% is expected in patients who have had previous reactions[20]. However, it may be essential in certain cases to repeat IV RCM examination in a patient who has had a previous reaction. If this is to be done, the risks should be fully explained to the patient. If consent is obtained then a pretreatment regime should be initiated.

A pretreatment regime was suggested by Greenberger; it has been shown to reduce the incidence of repeat reactions to as low as 3,1%[20]. The regime is

It is mandatory that the necessary emergency equipment be available whenever IV RCM examination is done

summarised in Table 6. However, it has been modified to meet the availability of drugs in South Africa.

Pretreatment regime for allergic patients

Table 6: *Pretreatment regime for patients who have had a previous contrast reaction (modified from Greenberger)*

1. Prednisone, 50 mg, 13, 7 and 1 hour before procedure.
2. Diphenhydramine, 50 mg by mouth or intramuscularly, 1 hour before procedure.
3. Adrenaline 0,3 ml of 1:1000 solution 10 minutes before procedure.

The use of the H_2 blockers (eg cimetidine) has been suggested to supplement the blocking of histamine. However, the benefits of this have not been conclusively demonstrated[21].

It is mandatory that the necessary emergency equipment be available whenever an IV RCM examination is done on a patient who has had a previous reaction.

Intra-arterial versus Intravenous route

An intravenous injection is four times more risky than an intra-arterial injection. Since the contrast is more concentrated due to slower flow in the veins, more endothelial damage takes place with the release of allergic and inflammatory mediators, eg histamine, complement, bradykinin and prostacycline A_2. During an intravenous injection of RCM, histamine is also liberated from the pulmonary mast cells and may lead to an allergic-like reaction which is not IgE mediated[13, 18].

Conclusion

It appears that the incidence of radiograph contrast medium-induced side effects is between 5–8% in the general population. Major risk factor include advanced age, current or prior renal insufficiency, cardiac failure, dehydration, diabetes, multiple myeloma and multiple contrast medium exposures within a short time span.

The number and severity of predisposing conditions correlate well with the likelihood of developing serious side effects. The current literature suggests that the new low osmolar radiographic contrast media are considerably safer than the conventional high osmolar radiographic contrast media. With their use, it is thought that there will be a reduction in incidence of severe or fatal reactions in the already compromised patients.

The new low osmolar contrast media are considerably more expensive than the high osmolar media and should be used with discretion.

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