The Choice of Contrast Media In the Cardiac Catheterisation Laboratory
THE CHOICE OF CONTRAST MEDIA IN THE CARDIAC CATHETERISATION LABORATORY

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ABSTRACT

Contrast media (CM) in cardiology is used in vessel visualisation, stenosis identification, localisation and identification of vessel ramifications and cardiovascular malformations. The identification of a CM that has the optimum visual properties and a safe profile was investigated in this study, along with other significant parameters. Quantitative assessment in choosing appropriate CM was investigated in the following properties: concentration, osmolality and viscosity, presence of ethylene-diamine tetraacetic acid (EDTA), cardiac tolerability, nephrotoxicity, delayed adverse reactions, thyrotoxicity, and cytotoxicity. Comparisons of possible candidates of CM include: iopamidol, iobitridol, iodixanol, iopromide, iohexol and ioversol, under study of the aforementioned parameters.

Keywords: Contrast media, optimal visualisation, osmolality, contrast-induced nephropathy, thyrotoxicity, cytotoxicity, iomeprol.

INTRODUCTION

The purpose of contrast media (CM) is to assist the cardiologist in vessel visualisation (localisation, dimensions), stenosis identification and localisation (how many, where, size), and identification of main vessel ramifications and cardiovascular malformations. Numerous different CM have been used in the past. It is essential that the most effective CM (one that combines a superior quality of images and has minimal complications) is identified.

The properties of CM have altered over time. The first-generation CM had significantly greater osmolality than plasma. Non-ionic CM have reduced osmolality and include non-ionic monomers and non-ionic dimers that have osmolality as low as that of plasma (iso-molar CM), however this low osmolality increases viscosity! Though there are significant differences in the chemical and physical characteristics of iodinated CM (Table 1) that are currently available, there have been considerable improvements in angiographic image quality. However, the importance of the CM in obtaining optimal visualisation is frequently forgotten. Harrison (2001), following a review of literature, suggests that image quality enhancement improves diagnostic accuracy in cardiac angiographic procedures.

The elements essential to a successful cardiac catheterisation laboratory (cath lab) procedure are; catheter (length and lumen diameter), investigator (pressure difference), contrast medium (viscosity, iodine content), and iodine delivery rate (flow, iodine content).

Vascular enhancement is dependent on the iodine delivery rate and persistency. Higher concentration improves visualisation, reduces volume and cost, and enables a shorter procedural time. Good contrast tolerability provides improved patient outcomes and compliance and a lower cost for overall patient management.

It is important that efficacy and safety are evaluated when choosing a contrast medium. Therefore, the
following should be considered in order to select the most suitable contrast medium; concentration, osmolality and viscosity, presence of ethylene-diamine tetraacetic acid (EDTA), cardiac tolerability, nephrotoxicity, delayed adverse reactions, thyrotoxicity, and cytotoxicity.

Arterial enhancement is critically dependent on the iodine delivery rate (IDR). This is due to arterial enhancement being proportional to iodine concentration (higher iodine concentration results in higher IDRs). Therefore, higher concentration provides stronger enhancement and consequently improved visualisation of small peripheral arteries. To enable stronger enhancement, high concentration iodine contrast material is required to provide the desired stronger enhancement. Iomeron® (iomeprol) is a non-ionic CM and has one formulation with the highest iodine concentration (400 mgI/mL) available on the market. A CM with a high concentration of iodine is particularly advantageous in patients with poor peripheral venous access who are unable to tolerate high injection rates. Stronger enhancement allows the flow rate and/or the CM volume to be reduced. This results in improved patient compliance with the same level of enhancement.2-5

The persistency of CM is important when performing angiographic and arteriographic procedures. CM can be classified by their physiochemical characteristics (iodine content, osmolality, level of ionisation, and degree of polymerisation); non-ionic, low or iso-osmolar CM have a good tolerability and safety profile and are the most frequently used in clinical practice.5

Molecular viscosity is significant in renal tolerability (less viscosity results in improved glomerular filtration). The molecular weight is directly proportional to viscosity therefore viscosity is dependent on molecular features and not concentration.6,7

Osmolality plays a role in renal concentration but not contrast induced nephropathy; osmolality between 290 and 800 mgI/mL is not nephrotoxic. Compared with all other monomeric CM, Iomeron possesses the lowest osmolality at given concentrations and, compared with all other non-ionic CM, it shows the lowest viscosity at all concentrations.5,8

One of the complications of angiography is a sudden fall in blood pressure, which can be persistent. This problem may be due to calcium chelating agents within the CM. The use of chelation therapy, e.g. EDTA, is the administration of chelating agents to remove heavy metals from the body. There is continued debate surrounding its clinical benefit; Caulfield et al. (1975) reported that ‘addition of contrast material with its attendant calcium chelating agents has a negative inotropic effect on isolated cat papillary muscle’9 and the American College of Cardiology Foundation/ American Heart Association (ACCF/AHA) guidelines (November 2011);10 state that chelation (e.g. EDTA) is not indicated for the treatment of intermittent claudication and may have harmful adverse effects (Level of Evidence: A). EDTA has a calcium subtraction effect and is present in CM (iopamidol, iobitridol, iodixanol, iopromide, iohexol and ioversol). Iomeron (iomeprol) is EDTA-free thus reducing the possibility of the complications of plummeting blood pressure in patients undergoing angiography.

**Cardiovascular Effects**

Studies evaluating the cardiac tolerability of CM compared iomeprol with iopamidol and iodixanol; no significant differences were shown in cardiac tolerability between these contrast media.11-13 Vijayalakshmi et al. (2004)14 found electrocardiogram (ECG) changes in 0.7% of patients who received iopamidol and 2.6% of patients who received iobitridol (p=<0.01). Dunket et al. (1995)15 found that the peak rate of isovolumetric contraction (LV dP/dt(max)) was slightly decreased by iodixanol and slightly more decreased by iopromide. Schmid et al. (2004)13 observed that iomeprol has a negligible effect on heart rate (HR). In two double-blind randomised studies, 216 patients who underwent cardiac angiography (CA) or peripheral intra-arterial digital subtraction angiography (IA-DSA), received iomeprol or iodixanol. No significant differences were noted between iomeprol and iodixanol in mean changes of HR during left coronary arteriography (p=0.8), right coronary arteriography (p=0.9), and left ventriculography (p=0.8). In patients undergoing IA-DSA, no differences between CA were noted in effects on mean HR after the first injection (p=0.6). The study concluded that iomeprol and iodixanol have equally negligible effects on HR and left ventricular pressures or arterial blood pressure during and after selective intra-cardiac injection and peripheral IA-DSA. This shows a good tolerability profile for iomeprol and iodixanol with regard to cardiac rhythm, and clinical preference should be based on diagnostic image quality alone.
Contrast-induced nephropathy (CIN) is an acute decrease in renal function following the intravascular administration of a contrast agent in the absence of other causes. The definition of CIN includes three components; an acute deterioration of renal function, a temporal relationship with the administration of CM, the absence of other causes (e.g. atheromatous embolic disease, ischaemia, and other nephrotoxins). In particular, CIN is generally defined as a rise in creatinine level of either at least 0.5 mg/dL or 25% above baseline after the exposure to contrast medium. The majority of trials consider 48 hours as the time point for the definition of CIN however, other studies prolong this time point to 72 hours or even 7 days. In patients undergoing coronary angiography, the incidence of CIN varies widely (2-50%).

Pre-existent renal insufficiency is the most important factor for the development of CIN (moderate to severe renal insufficiency: glomerular filtration rate [GFR] stably <60 mL/min/1.73 m²). The potentially high incidence of chronic renal insufficiency in patients undergoing

### Table 1. Chemical and physical characteristics of some iodinated contrast media.

<table>
<thead>
<tr>
<th>COMPOUND</th>
<th>Osmolality mOsm/Kg H₂O</th>
<th>Viscosity mPa.s/37°</th>
<th>Iodine Content mg/ml</th>
<th>Molecular Weight Daltons</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ionic</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Monomer</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diatrizoate</td>
<td>1515</td>
<td>2.3</td>
<td>300</td>
<td>809 Meglumine 635 Sodium</td>
</tr>
<tr>
<td>Iothalamate</td>
<td>1843</td>
<td>2.75</td>
<td>325</td>
<td>809 Meglumine 635 Sodium</td>
</tr>
<tr>
<td>Ioxitalamate</td>
<td>2130</td>
<td>2.5</td>
<td>350</td>
<td>839 Meglumine 646 Sodium</td>
</tr>
<tr>
<td><strong>Dimer</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ioxaglate</td>
<td>600</td>
<td>7.5</td>
<td>320</td>
<td>1270</td>
</tr>
<tr>
<td><strong>Non-Ionic</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Monomer</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Iohexol</td>
<td>672</td>
<td>6.3</td>
<td>300</td>
<td>821</td>
</tr>
<tr>
<td>Iopentol</td>
<td>810</td>
<td>12</td>
<td>350</td>
<td>835</td>
</tr>
<tr>
<td>Iopamidol</td>
<td>630 796</td>
<td>4.7 9.4</td>
<td>300 370</td>
<td>777</td>
</tr>
<tr>
<td>Ioversol</td>
<td>645 792</td>
<td>5.5 9</td>
<td>300 350</td>
<td>807</td>
</tr>
<tr>
<td>Iopromide</td>
<td>610 770</td>
<td>4.6 9.5</td>
<td>300 370</td>
<td>791</td>
</tr>
<tr>
<td>Iomeprol</td>
<td>520 620 726</td>
<td>4.5 7.5 12.6</td>
<td>300 350 400</td>
<td>778</td>
</tr>
<tr>
<td>Iobitridol</td>
<td>695 915</td>
<td>6 11.4</td>
<td>300 350</td>
<td>835</td>
</tr>
<tr>
<td>Ioxilan</td>
<td>585 695</td>
<td>5.1 8.1</td>
<td>300 350</td>
<td>791</td>
</tr>
<tr>
<td><strong>Dimer</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Iotrolan</td>
<td>320</td>
<td>8.1</td>
<td>320</td>
<td>1626</td>
</tr>
<tr>
<td>Iodixanol</td>
<td>290 290</td>
<td>11.8 6.3</td>
<td>320 270</td>
<td>1550</td>
</tr>
</tbody>
</table>

Contrast-Induced Nephropathy (CIN)
coronary angiography highlights the importance of CIN prevention. The scientific evidence surrounding CIN prevention does not give a definitive solution to the problem, consequently a judicious choice of the contrast medium is essential. Usually, the more severe the degree is of renal impairment, the greater the risk of developing CIN and the risk is highest in patients with stage 4 or 5 chronic kidney disease (CKD), i.e. patients with GFR <30 mL/min/1.73 m².

Many studies have been performed on CIN and the role of contrast media.29-37 Most studies have compared iodixanol with other low-osmolar contrast agents (Table 2).

The studies suggest that iodixanol may be less nephrotoxic than iohexol, iopromide, and ioxaglate. No significant difference between iopamidol, iomeron/imeron, and iodixanol has been seen in any study or meta-analysis, however there were higher mean serum creatinine (Scr) changes following the iso-osmolar CM. The studies did not show a difference in CIN rates between iodixanol and ioversol, although there were higher mean Scr changes following ioversol. Moreover, the CARE follow-up study24 indicated that the use of iodixanol is associated with a higher rate of long term adverse events compared with iopamidol. Following analysis of the results of CIN studies, the ACC guidelines (2009) recommended the use of either low-osmolar (Level of Evidence: A) or iso-osmolar (Level of Evidence: B) CM for patients with renal impairment. More recently, the ACC (2011) has revised the guidelines with respect to the administration of CM for percutaneous coronary intervention in patients with CKD. In particular the ACC guidelines state that ‘trends in CIN favouring iodixanol are no longer significant…subanalyses showed variations in relative renal safety by specific low-osmolar contrast media…no difference was noted in the comparisons of iodixanol with iopamidol…and a single trial favoured iomeprol’.

This recommendation is supported by the ACTIVE study,30 which concluded that the incidence of CIN was significantly higher after the IV administration of iodixanol-320 than iomeprol-400 in patients with moderate-to-severe CKD. The mean increase in Scr from baseline was also higher in patients receiving iodixanol. It is possible that the individual characteristics of contrast agents, other than osmolality, may be important in causing nephrotoxicity. A pooled analysis of the ACTIVE and IMPACT studies showed that a significantly higher proportion of CIN cases were observed after iodixanol administration in higher risk patients with GFR <40 mL/min. In cardiac catheterisation procedures, the CONTRAST study concluded that the routine use of iso-osmolar CM is not associated with a significant reduction of nephrotoxicity compared with low-osmolar CM in patients with chronic renal failure undergoing percutaneous coronary intervention.

Delayed Adverse Reactions

A late adverse reaction to iodine-based CM is defined as a reaction that occurs 1 hour to 1 week after the CM injection. Iodine-based CM present a different rate of delayed adverse reactions (Figure 1). Iomeprol shows an overall reduced incidence of delayed adverse reactions compared with iodixanol.

Thyrotoxicity

Some iodine-based compounds can release iodine with toxic effects on the thyroid. Rhee et al. found, in a nested case-control study of patients treated between 1990 and 2010, that iodinated CM exposure is associated with subsequent development of incident hyperthyroidism and incident overt hypothyroidism. In order to avoid this, many CM use chelants such as EDTA however, some of them (particularly iodixanol and iohexol) remain contraindicated in patients at risk of thyrotoxicosis.

Cytotoxicity

Cytotoxicity is a significant issue in the use of CM. First-generation ionic CM have greater osmolality than plasma. Iso-osmolar CM achieved osmolality as low as that of plasma (using non-ionic monomers and non-ionic dimers) however, viscosity is considerably increased. The capillary lumen and the slackness of the capillary mesh of the intrarenal microcirculation in the outer medulla present a risk for regular blood flow. Heinrich et al. (2005) compared the effects of dimeric and monomeric iodinated CM on renal tubular cells. The results of the study indicated that dimeric CM molecules have a greater potential for cytotoxic effects on renal tubular cells in vitro than monomeric CM molecules. Molecular weight is directly related to the size of the molecule, therefore the lower the molecular weight, the smaller the molecule will be. Glomerular filtration is easier with small molecules accordingly low-osmolar and iso-osmolar CM are generally recommended. Lomeron® (iomeprol) has a lower molecular weight than a non-ionic dimmer, thus decreasing the likelihood of alteration of glomerular filtration and cytotoxicity.
<table>
<thead>
<tr>
<th>Publication</th>
<th>Patient Population</th>
<th>CIN Endpoint</th>
<th>Contrast Agents</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspelin P et al. New Engl J Med. 2003;348:491-499.</td>
<td>Patients with diabetes mellitus and CKD (N=129)</td>
<td>SCr≥0.5 mg/dL at 72 hrs post-dose</td>
<td>Iodixanol 320 (N=64)</td>
<td>No significant difference (iodixanol 10%, p=n.s.)</td>
</tr>
<tr>
<td>Chalmers N et al. Br J Radiol. 1999;72:701-703.</td>
<td>Patients with CKD (N=102)</td>
<td>SCr≥0.5 mg/dL at 48 hrs post-dose</td>
<td>Iodixanol 270 or 320 (N=54)</td>
<td>Iohexol&gt;rate than iodixanol (26% vs 3%, p&lt;0.05)</td>
</tr>
<tr>
<td>Briguori C et al. Kidney Int. 2005;68:2250-2255.</td>
<td>Patients with CKD (N=225)</td>
<td>SCr≥0.5 mg/dL and/or SCr≥72 hrs post-dose</td>
<td>Iodixanol 320 (N=110)</td>
<td>No significant difference (iodixanol 4%, p=n.s.)</td>
</tr>
<tr>
<td>Jo SH et al. JACC. 2006;48:924-930.</td>
<td>Patients with CKD (N=275)</td>
<td>SCr≥0.5 mg/dL at 48 hrs post-dose</td>
<td>Iodixanol 320 (N=156)</td>
<td>No significant difference (iodixanol 4%, p=n.s.)</td>
</tr>
<tr>
<td>Rudnick MR et al. Am Heart J. 2008;156:1-7.</td>
<td>Patients with CKD (N=299)</td>
<td>SCr≥0.5 mg/dL at 24, 48 and 72 hrs post-dose</td>
<td>Iodixanol 320 (N=140)</td>
<td>No significant difference (iodixanol 17% vs 8%, p&lt;0.05)</td>
</tr>
<tr>
<td>Nie B et al. Catheterization and Cardiovascular Interventions. 2008;72:958-965.</td>
<td>Patients with CKD (N=324)</td>
<td>SCr≥0.5 mg/dL within 72 hours</td>
<td>Iodixanol 320 (N=162)</td>
<td>No significant difference (iodixanol 16.7% vs 5.7%, p&lt;0.01)</td>
</tr>
</tbody>
</table>

Table 2: Studies performed on CIN and the role of different contrast media.

‘>’ means significantly higher risk; ‘−’ means no significant difference.
CONCLUSION

In conclusion, all iodine-based CM are different. The choice of CM should be based on the properties of each molecule, the chemical features (osmolality, viscosity, concentration, and excipients), efficacy and tolerability (renal, cardiac, thyrotoxicity, and hypersensitivity). In addition, potential adverse events should be evaluated. An effective CM requires a high iodine concentration to provide maximum opacification in angiography and arteriography. It should maintain good persistence causing a negligible effect on cardiac rhythm; have a good renal tolerability and minimal cytotoxic effects. The optimal properties of CM to provide the best possible visualisation are low viscosity, low osmolality and low molecular weight. Iomeprol incorporates all of these properties and has an encouraging efficacy and safety profile.

REFERENCES

10. www.cardiosource.org

Figure 1: Delayed adverse reactions of iodine based contrast media.