Use of Nonionic or Low Osmolar Contrast Agents in Cardiovascular Procedures

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Background

Iodinated radiopaque contrast agents are utilized in many of the approximately 1 million or more cardiovascular imaging procedures performed each year in the United States. Until recently, the primary agents employed for cardiovascular imaging consisted of diatrizoate sodium or a combination of diatrizoate sodium and various meglumine salts. These agents are referred to as "ionic" or "high osmolar" agents and have osmolalities exceeding 1,500 mOsm/kg. The cardiovascular effects of the conventional high osmolar iodinated contrast agents are well investigated (1-6).

In recent years (1986 to the present), several "nonionic" or "low osmolar" agents have been introduced and widely marketed in the U.S. These include iohexol (Omnipaque, Winthrop), iopamidol (Isovue, Squibb) and ioversol (Optiray, Mallinckrodt). An additional agent, ioxaglate (Hexabrix, Mallinckrodt) is best described as an ionic, but low osmolar contrast agent. We will subsequently refer to this group of agents interchangeably as either nonionic or low osmolar, unless specified otherwise. This policy statement does not apply to other classes of contrast agents that may become available in the future. All four of these newer agents have osmolalities in the range of approximately 600 to 700 mOsm/kg. The cardiovascular effects of the newer low osmolar agents have been thoroughly investigated during premarketing surveillance and subsequent clinical use (7-14). These data suggest that the low osmolar agents are better tolerated than the high osmolar agents and are possibly safer in hemodynamically compromised patients, but that the low osmolar agents are much more expensive.

The low osmolar agents cost hospital pharmacies approximately $100/100 ml. This represents approximately 10 times the cost of conventional ionic agents. Despite the high cost, use of these agents is increasing and is now estimated to represent approximately 60% to 70% of current practice in cardiac catheterization. The conversion to the newer low osmolar agents for cardiac catheterization represents a substantial cost to hospitals, insurers and patients. Total replacement of ionic contrast usage by nonionic agents for cardiovascular procedures will add approximately $100 to $200 million to the annual U.S. health care budget. Replacement of ionic agents by nonionic or low osmolar contrast media for all radiographic procedures is estimated to add $1.1 to 1.3 billion to health care costs. Controversy exists over whether the possible safety benefits of low osmolar agents outweigh their substantial increase in costs.

Electrophysiologic Effects of Contrast Media

Intracardiac or intracoronary administration of conventional high osmolar contrast agents results in major electrophysiologic effects. The ionic contrast agents reduce the rate of depolarization of the sinoatrial node and prolong the PR interval by slowing the atrioventricular node conduction. These effects produce transient bradycardia in many patients and occasionally high grade heart block or sinus arrest. High osmolar agents also produce marked transient alterations in T wave configuration of unknown significance.

The constellation of electrophysiologic effects occurring during contrast injection is associated with ventricular fibrillation in approximately 1 in 200 cardiac angiography procedures (1). Ventricular fibrillation is probably produced by transient hypocalcemia mediated by the binding of calcium ions by the radiopaque anion and the presence of calcium sequestering agents (15-17). Improvements in formulations of all contrast agents (ionic and nonionic) have reduced the incidence of ventricular fibrillation during coronary angiography. However, available evidence indicates a greater reduction in the frequency of adverse electrophysiologic phenomena when the newer low osmolar agents are employed. The nonionic agents produce less bradycardia, fewer alterations in T wave configuration and less ventricular fibrillation (18,19). However, there exist no published, con-
trolled trials demonstrating that the reduced incidence of adverse electrophysiologic effects results in improved patient outcome or reduced hospital costs.

Hemodynamic Effects of Contrast Media

The hemodynamic effects of intracardiac or intracoronary administration of iodinated contrast agents are also well established (4-7,9). Intracoronary injection of conventional high osmolar agents produces depression in myocardial contractile performance. This results in a decrease in blood pressure and first derivative of left ventricular pressure (dP/dt) followed by an increase in left ventricular end-diastolic pressure. A rebound compensatory increase in blood pressure, probably mediated by baroreceptor reflexes, occurs within 8 to 10 s after administration of high osmolar contrast agents. The decrease in blood pressure or the occurrence of rebound hypertension, or both, may provoke or exacerbate myocardial ischemia, an effect that is usually transient but may be sustained in patients with severe coronary artery obstruction or unstable ischemic syndromes as well as in those with severe aortic valve stenosis or severe heart failure. The newer low osmolar contrast agents produce little or no depression of myocardial contractility and only a minimal decrease in blood pressure (7-10). Accordingly, the nonionic agents are reported as less likely to provoke myocardial ischemia.

Administration of high osmolar contrast agents produces a systemic arterial vasodilation. This phenomenon results in characteristic flushing or sensation of warmth experienced by the patient. These effects are dose dependent and are generally much more evident after contrast ventriculography than after intracoronary contrast injection. The sensation is described as unpleasant by most patients undergoing cardiac catheterization, particularly when the internal mammary artery is injected. This sensation is clearly reduced by low osmolar agents.

Anticoagulant Effects of Contrast Media

Conventional high osmolar ionic contrast agents have anticoagulant and antiplatelet aggregating properties that may contribute to the safety of coronary arteriography. The newer nonionic agents exert much less anticoagulant effect. Some workers have suggested a higher potential for thrombogenicity with the nonionic contrast media (20-27). The low osmolar ionic agent ioxaglate is reported to have anticoagulant properties similar to those of conventional ionic contrast media. Thrombi formed during contact between blood and low osmolar contrast media may be resistant to thrombolysis (22). Clinically significant thromboembolic phenomena have been described and may be more common with nonionic agents (26). These differences have resulted in warnings by the manufacturers of the nonionic agents to avoid prolonged contact between blood and contrast media.

Whether the lesser anticoagulant effects of low osmolar contrast media are clinically important is an area of controversy. Proponents of low osmolar agents have argued that minimizing blood–contrast medium contact is prudent catheterization and angiographic practice regardless of the agent utilized. They propose that meticulous angiographic technique can reduce or eliminate any theoretic thromboembolic risk and that the reduced hemodynamic and electrophysiologic effects of nonionic agents outweigh any theoretic increase in thromboembolic risk. An alternative point of view is that prolonged contact between blood and contrast media cannot always be avoided, particularly in circumstances such as balloon angioplasty, where blood flow may be relatively stagnant. Some have suggested that the requirement for meticulous avoidance of prolonged blood–contrast medium contact makes nonionic agents less forgiving in the clinical setting.

There are no carefully controlled prospective trials examining the clinical impact of the relative anticoagulant effects of high and low osmolar agents in coronary angiography or angioplasty. In view of the controversy concerning the anticoagulant properties of nonionic or low osmolar contrast media, it may be prudent to consider administration of systemic heparin when these agents are used.

Renal Toxicity

Administration of iodinated contrast medium may produce acute renal insufficiency. This is frequently manifested as an alteration in the laboratory measures of renal function, but less commonly requires treatment with dialysis or results in permanent injury. A number of risk factors have been identified in predicting this complication including diabetes mellitus, multiple myeloma and volume depletion (28). Data from studies performed in experimental animals suggest that low osmolar agents may exhibit reduced renal toxicity (29). Some prospective clinical trials have not demonstrated any reduction in the risk of contrast-induced nephropathy when the newer nonionic agents are employed during cardiac catheterization (30-33). However, a recent randomized comparison in patients with renal impairment (e.g., serum creatinine ≥1.5 mg/dl) found that a low osmolar, nonionic agent was less nephrotoxic than a high osmolar, ionic agent, but the difference in nephrotoxicity was small (34). These findings were confirmed in another study of more than 1,100 patients (35). In the latter trial all patients received standard hydration in addition to either a nonionic, low osmolar agent or a high osmolar agent. The relative risk of nephrotoxicity doubled comparing the high osmolar to the low osmolar agent. The possible clinical value of these findings remains uncertain.

Allergic Manifestations

Anaphylactoid reactions occur in 1% to 2% of patients undergoing procedures utilizing iodinated contrast media. The incidence of severe reactions is approximately 0.1% and
the incidence of mortality <1 in 10,000 cases. In one recent cardiac catheterization trial, urticaria was more frequent in the ionic, high osmolar group than in the nonionic, low osmolar group (32). Another study comparing two low osmolar agents showed more allergic reactions in the group with the ionic formulation (ioxaglate) than in the group with the nonionic formulation (iopamidol) (36). Thus, mild allergic reactions may be reduced when the nonionic agents are used, although the effect on the incidence of anaphylactoid reactions is not known.

**Morbidity and Mortality**

Fatal reactions to contrast media are very uncommon. Several very large scale radiologic studies (37-39) have compared complications (including mortality) in patients who receive contrast agents, usually intravenously, for procedures such as pyelography or computed tomography. However, these large studies were not randomized and the choice of contrast agent was determined by the radiologist. The low incidence of contrast agent-related mortality in general radiography (1 in 40,000) has precluded definitive conclusions from the published studies regarding the relative mortality risk of the available agents.

The prospective studies (37-39) of contrast reactions in general radiographic applications have documented a reduction in the risk of major and minor complications when low osmolar agents are utilized. However, most of the reactions experienced are minor and neither prolong hospital stay nor result in an adverse outcome.

In a randomized trial of 443 patients undergoing elective cardiac catheterization, Hlatky et al. (33) found no significant increase in the incidence of major adverse events but did find an increase in adverse events overall in patients receiving an ionic versus a nonionic agent. These investigators estimated the overall costs of the two agents, including costs of treating adverse reactions. The only significant difference between the two groups was the increased cost of the nonionic agent, which averaged $186/case. Only 11 patients undergoing emergency cardiac catheterization for acute myocardial infarction were excluded from this study (33). Two additional randomized trials of nonionic and ionic contrast agents in patients undergoing cardiac catheterization (31,32) were recently reported. In a 505-patient study from Johns Hopkins (31), there were no differences in severe reactions between groups receiving either an ionic or a nonionic contrast medium. There was a threefold increase in moderate reactions in the group receiving the ionic contrast agent. Eighty-five percent of the patients with moderate or severe reactions were >60 years of age or had unstable angina. A 1,490-patient randomized Canadian study (32) found an increased incidence of both mild and severe adverse reactions among patients in the group receiving the ionic contrast agent. Most of the reactions occurred in patients with severe coronary disease or unstable angina. There were no deaths or permanent sequelae from any reaction in either group in this study. These two studies excluded 21% and 10% of patients, respectively, who were believed to represent too high a risk for ionic agents by their attending physicians and thus do not represent all patients presenting for catheterization. A study from Emory University (40) randomized 913 patients undergoing 1,035 percutaneous transluminal coronary angioplasty procedures and showed a reduced incidence of various arrhythmias in the group receiving a nonionic agent but no reduction in death, myocardial infarction or need for surgery.

The Johns Hopkins (31) and Canadian (32) studies estimated net costs per case to prevent a moderate or severe reaction, citing figures of $1,698 and $2,363, respectively, for a strategy employing low osmolar, nonionic agents in high risk cases only, versus about twofold to threefold higher costs per case if such agents were given to all patients. In the nephrotoxicity study from the Mayo Clinic (34), an estimated additional cost of about $900,000 would be required if a low osmolar contrast medium was used in the approximately 5,000 cases studied yearly.

**Economic Issues**

The estimated incremental cost per patient for universal use of low osmolar contrast agents in cardiac catheterization is $100 to $200. Because there are annually approximately 1 million catheterizations performed, the cost of conversion to nonionic agents is estimated at $100-$200 million. These health care costs are distributed in a variety of ways. Many, but not all, third-party insurers provide additional payments for the costs associated with low osmolar contrast agent administration.

Controversy exists regarding the reasons for the relatively high costs of low osmolar nonionic agents. Suppliers of these agents cite high development and manufacturing costs as the primary explanation for these costs. Critics of the cost of low osmolar agents point out that the same low osmolar agents are sold for as little as 30% of the U.S. price in overseas markets.

**Risk/Benefit Strategies**

Some authorities (41,42) recommend use of nonionic contrast agents for patients at high risk for complications. Proponents of this approach cite the potential for cost savings in comparison to universal employment of the more expensive agents. Opponents of selective use of nonionic agents cite the difficulty in predicting which patients will suffer adverse complications before undertaking the procedure.

**Summary**

Low osmolar contrast agents produce less adverse electrophysiologic and hemodynamic alterations during cardiac catheterization. The nonionic agents probably reduce the
risk of provoking myocardial ischemia during coronary arteriography or ventriculography. Patients also report less subjective sensation of discomfort during administration of low osmolar agents for cardiovascular procedures.

However, nonionic agents have not been proved to reduce the incidence of several serious complications of cardiac catheterization, including acute renal failure and anaphylactoid reaction. Although evidence is inconclusive, there may be an increased risk of thromboembolic complications during cardiac catheterization when certain low osmolar nonionic agents are administered. Nonionic contrast agents have not been definitely proved to reduce the risk of death after cardiac catheterization.

Conclusion and Recommendations

On the basis of the available data, nonionic contrast agents may be of value in selected patients at high risk for hemodynamic complications during cardiac catheterization and in patients with a history of allergic reaction to contrast medium. These include patients with congestive heart failure, severe aortic stenosis, cardiogenic shock and left main coronary artery disease. Whether low osmolar agents reduce the risk of catheterization in patients with unstable angina or evolving myocardial infarction, or during balloon angioplasty remains uncertain. Several of the low osmolar agents exert a lesser anticoagulant effect than that of conventional ionic agents and may increase the risk of thromboembolic complications during catheterization.

There are no conclusive data to support the universal use of nonionic contrast agents in routine cardiac catheterization, in view of the increased cost. In the absence of definitive data, the decision to use low osmolar contrast agents is a matter of individual preference. The American College of Cardiology supports the concept of a large scale prospective clinical trial to evaluate the relative benefits and cost-effectiveness of the available radiopaque iodinated contrast agents in cardiac catheterization. The ACC supports the principle that cardiovascular practitioners, in consultation with their patients, should determine the choice of contrast agent for cardiovascular procedures.

References