Adverse Reactions of Low Osmolality Contrast Media During Cardiac Angiography: A Prospective Randomized Multicenter Study

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A multicenter study was performed to determine the incidence of adverse reactions to two contrast media with similar low osmolality during cardiac angiography. The study was of a randomized double-blind design comparing ioxaglate (an ionic dimer) and iopamidol (a nonionic compound) and included 500 patients: 250 patients received ioxaglate and 250 iopamidol. There were 59 adverse reactions attributed to the contrast media in the ioxaglate group and 29 in the iopamidol group (p < 0.001). Chest pain occurred in 11 patients in the ioxaglate group compared with 5 in the iopamidol group (p = 0.133). Nausea or vomiting was present in 11 patients in the ioxaglate group compared with 5 in the iopamidol group (p < 0.001). Of 41 patients receiving ioxaglate who were premedicated with diphenhydramine, 4 had an allergic adverse event. In the iopamidol group 45 patients received similar premedication and none had an allergic adverse reaction (p < 0.03).

Thus, this multicenter study shows that adverse reactions occur more often with ioxaglate than with iopamidol and that patients with an allergic history have a greater risk with ioxaglate therapy compared with iopamidol.

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Many of the adverse reactions encountered during cardiac angiography are directly related to the contrast medium (1,2). Ideally, this medium should provide adequate radiographic opacity without any physiologic or pharmacologic side effects. It is well recognized that intracardiac injections of the contrast medium are often associated with electrophysiologic changes and a decrease in arterial pressure and in myocardial contractility (1-5). Chemotoxic effects, such as peripheral pain and warmth, and allergic reactions also occur (1,2). The factors that may be responsible for these adverse reactions include hyperosmolality, the sodium and calcium content and the union or molecular composition of the contrast medium (1-10). Although the osmolality of the contrast medium is not the only factor, it is a very important determinant of the cardiovascular and chemotoxic side effects (1,3,4,11,12) and may also play a role in allergic reactions (13-17).

During the past 2 decades there has been an active search for new radiographic contrast compounds to eliminate the cardiovascular side effects and chemotoxicity. To decrease the osmolality of the contrast medium, an effort has been made to increase the number of iodine atoms per osmotically active particle. In 1973 ioxaglate was synthesized (18). It is a structural dimer with six iodine atoms to one anionic functional group, as compared with the conventional diatrizoate molecule, which has only three iodine atoms to one anionic group. Other efforts to reduce osmolality have led to the development of nonionic contrast media. Conventional contrast media are ionic compounds with cation and anion particles in solution; nonionic compounds reduce their osmolality by having only one particle in solution for a given iodine content. The first nonionic contrast medium, metrizamide, was introduced in 1974 (19). Metrizamide has two major disadvantages: it is not heat stable and not stable in solution; therefore, it must be reconstituted from the lyophilized form immediately before intravascular injection. More recently the nonionic compounds iopamidol, iohexol and ioversol have been developed and released for clinical use. These compounds are very stable in aqueous solution.

Large multicenter studies (20-22) have shown that the

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incidence of severe and moderate adverse reactions is significantly less with the intravenous use of the low osmolality nonionic contrast media than of the conventional high osmolality ionic contrast media. The ionic dimer ioxaglate was not included in these multicenter trials because its intravenous use is associated with a high incidence of vomiting (20,22); however, ioxaglate is widely accepted for intraarterial procedures. Because the published studies (23-25) comparing the low osmolality ionic dimer with nonionic contrast medium were performed at single institutions and included only a small number of patients, the true incidence of the adverse reactions may be questioned. Therefore, this multicenter study was performed to evaluate the adverse reactions associated with the low osmolality ionic dimer ioxaglate and the nonionic monomer iopamidol during intravascular cineangiography and coronary injections.

Methods

Study design. The study was of a prospective randomized double-blind design for comparing the combination of ioxaglate meglumine, 39.3% and ioxaglate sodium, 19.6% (Hexabrix) with iopamidol, 76% (Iosuvel-370) as contrast media used for left ventriculography and selective coronary angiography. Twelve medical centers (nine in the U.S. and three in Canada) participated. Randomized lists for the two contrast media were generated by Squibb Diagnostics. The technicians or nurses in the laboratory selected the contrast medium from commercially available lots. The patients, the physicians (investigators) performing the study and the investigators analyzing the data did not know which contrast medium was used.

Patient selection. Men or women ≥18 years of age who required coronary angiography and left ventriculography for clinical diagnostic evaluation were candidates for this study. Patients with the following conditions were excluded from the study: 1) pregnancy, childbearing potential or current breast feeding; 2) a history of a previous reaction to radiographic contrast medium or iodine compounds; 3) a bleeding disorder; 4) significant renal disease (serum creatinine >2 mg/dl); 5) phochromocytoma, sickle cell disease, multiple myeloma or paraproteinemias; 6) significant hepatic disease (bilirubin >2 mg/100 ml); 7) infection near the proposed site of catheter introduction; 8) acute myocardial infarction and scheduled streptokinase therapy or percutaneous transluminal coronary angioplasty; 9) known significant mitral or aortic valve disease; 10) significant primary cardiomyopathy; 11) a permanent pacemaker; 12) atrial fibrillation/flutter or frequent premature atrial or ventricular depolarizations (>5/min); 13) left bundle branch block; 14) electrocardiographic (ECG) evidence of left ventricular hypertrophy with strain pattern; 15) weight >160 kg; and 16) previous entry into this study or current participation in a clinical trial of an investigational drug.

Study protocol. The protocol was approved by the Human Research Committee at each of the 12 medical centers and informed written consent was obtained from each patient before the procedure.

Procedures. A brief cardiac history, a list of other concomitant illnesses and an allergic history were required for entry into the study. All medications received before or during the procedure were also recorded as part of the study. No dosage of any medications prescribed for the treatment of angina or other illnesses was withheld before the catheterization procedure. Sedation with diazepam and other agents administered for premedication were prescribed by the physicians performing the procedures. It was recommended that 5,000 U of heparin be given to all patients at the time of the arterial puncture.

The ECG and arterial pressure were monitored continuously during the entire procedure. All patients underwent left ventriculography and selective injections of the right and left coronary arteries and bypass grafts, if present. For the left ventriculogram, 0.5 ml/kg of contrast medium was used. The sequence of the injections was determined by the physicians performing the catheterization. The amount of contrast medium used and the time and the site of every injection were recorded. As part of the study protocol, the ECG was also recorded before, during and continuously for the last 2 min after the first right coronary artery injection, the first left coronary artery injection and the left ventriculogram.

At the end of the procedure, the patient was asked, "How did you feel during this study?" Questions concerning specific adverse reactions such as pain or nausea were not asked. All adverse reactions (such as symptoms or clinical manifestations of an embolic event, chest pain, dyspnea, arrhythmias, nausea, vomiting, bronchospasm or urticaria) noted by the investigators or reported by the patients and the treatment, if any, of these conditions were recorded. The investigators were asked to grade the adverse reactions as mild (resolving spontaneously without treatment), moderate (requiring medication or other treatment but not additional hospitalization) or severe (requiring additional hospitalization and treatment) and to state if the adverse reaction was secondary to the contrast medium. Adverse reactions that occurred during or after injections of contrast medium and were not related to procedural techniques or other medications were attributed to contrast medium.

Statistics. The unpaired t test was used to compare baseline values between the two patient groups, and the chi-square test was used to compare discrete variables (26). The data in the text and tables are presented as mean values ± 1 SD.

Results

Of the 500 patients included in this randomized multicenter study, 250 received ioxaglate and 250 received iopamidol. As shown in Table 1, patient characteristics of the two groups were similar except that the number of patients
with a history of allergy was significantly higher in the iopamidol group (p = 0.04).

Adverse reactions (Table 2). Sixty-seven patients in the ioxaglate group had 82 adverse events during the catheterization procedure, whereas 48 patients in the iopamidol group had 50 adverse events (p < 0.002). The adverse events attributed to the contrast medium were 58 in the ioxaglate group and 29 in the iopamidol group (p < 0.001) (Table 2). Except for the sensation of mild warmth associated with an injection, the incidence of all other adverse events listed in Table 2 was higher in the ioxaglate group than in the iopamidol group. All the adverse reactions attributed to contrast medium were classified as mild or moderate with the exception that one of the two cases of bronchospasm was graded as severe.

There were no deaths, serious ventricular arrhythmias, pulmonary edema or embolic events in either patient group. Heparin was given to all patients in this study: 452 patients received 5,000 U of heparin at the beginning of the procedure, 38 patients received heparin doses of 2,000 to 10,000 U through the angiographic procedure. The dosage used to maintain therapeutic partial thromboplastin levels was continued throughout the angiographic procedure.

No patient in this study required cardiac pacing and there were no reports of heart block or significant bradyarrhythmias attributed to contrast medium. Only 6 of the 590 patients (2 in the ioxaglate group and 4 in the iopamidol group) received atropine, which was given as premedication or for a vagal episode that occurred during the arterial puncture.

Twenty patients in the ioxaglate group had nausea or vomiting, whereas only 2 patients in the iopamidol group had nausea. In the ioxaglate group, 7 of the 96 patients who received the initial injection of contrast medium during left ventriculography developed nausea or vomiting compared with 13 of 153 patients who had the ventriculogram at the end of the procedure (p = 0.73). Thus, timing of the left ventriculogram, which requires a relatively large bolus injection, at the beginning or at the end of the procedure did not affect the incidence of this adverse reaction in ioxaglate-treated patients.

In this report allergic-type adverse reactions included itching, rash, urticaria, bronchospasm or anaphylactoid shock. No patient in this study developed anaphylactoid shock. There were 16 allergic adverse reactions in the 250 patients receiving ioxaglate compared with 4 such responses in the 250 patients receiving iopamidol (p < 0.01). Of these allergic adverse reactions, 15 of the 16 in the ioxaglate group were attributed to the contrast medium compared with only 1 of the 4 in the iopamidol group (p < 0.007) (Table 2). The remaining four allergic adverse reactions were attributed to protamine; all four such reactions involved a rash or urticaria and occurred within 5 to 15 min after intravenous administration of protamine. These events were attributed to the medication administered by the patient's physician.

History of allergy (Table 3). Patients with a previous history of a reaction to radiographic contrast medium or iodine compounds were excluded from this study. However, in the iopamidol group 77 patients reported a history of other allergic responses: 3 had asthma, 72 had drug allergies, 2 had food allergies, 2 had pollinosis and 2 had allergies to insect bites or stings. In the ioxaglate group 52 patients had a
similar history: 5 with asthma, 44 with drug allergies, 1 with food allergy, 1 with poliomyelitis and 2 with allergies to insect bites/ stings.

None of the 77 patients in the iopamidol group with a history of allergy had an allergic-type adverse event attributed to the contrast medium, compared with 7 of the 52 patients in the ioxaglate group with such a history (p = 0.001) (Table 3). Thus, the incidence of an allergic adverse event in the patients receiving ioxaglate was significantly higher in those with a history of allergy (13.5%) than in the total group (6%) (p = 0.001). Despite a significantly greater number of patients with a history of allergy in the iopamidol group, the incidence of allergic-type adverse events remained very low (0.4%) in the total group and 0% in the group with a history of allergy.

Premedication (Table 4). The pharmacologic agents commonly used for premedication, as well as the adverse events in each group, are listed in Table 4. There was no difference between the two patient groups in the number of patients who received any of the specific agents used for premedication. The number of patients taking each of these agents is too small to permit definite conclusions about the efficacy of premedication. However, the data suggest that pretreatment with diphenhydramine or sedation with diazepam will not prevent an allergic adverse reaction with ioxaglate.

### Table 4. Types of Premedication and Adverse Events in 500 Patients

<table>
<thead>
<tr>
<th>Premedication</th>
<th>Iopamidol</th>
<th>Ioxaglate</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diazepam</td>
<td>192</td>
<td>192</td>
<td>NS</td>
</tr>
<tr>
<td>Allergic type adverse reaction</td>
<td>1</td>
<td>13</td>
<td>0.001</td>
</tr>
<tr>
<td>Nausea/Vomiting</td>
<td>1</td>
<td>13</td>
<td>0.001</td>
</tr>
<tr>
<td>Diphenhydramine</td>
<td>45</td>
<td>41</td>
<td>NS</td>
</tr>
<tr>
<td>Allergic type adverse reaction</td>
<td>0</td>
<td>4</td>
<td>0.68</td>
</tr>
<tr>
<td>Nausea/Vomiting</td>
<td>0</td>
<td>1</td>
<td>NS</td>
</tr>
<tr>
<td>H2-receptor antagonist</td>
<td>32</td>
<td>37</td>
<td>NS</td>
</tr>
<tr>
<td>Allergic type adverse reaction</td>
<td>0</td>
<td>1</td>
<td>NS</td>
</tr>
<tr>
<td>Nausea/Vomiting</td>
<td>3</td>
<td>2</td>
<td>NS</td>
</tr>
<tr>
<td>Steroids</td>
<td>2</td>
<td>2</td>
<td>NS</td>
</tr>
<tr>
<td>Allergic type adverse reaction</td>
<td>0</td>
<td>0</td>
<td>NS</td>
</tr>
<tr>
<td>Nausea/Vomiting</td>
<td>0</td>
<td>0</td>
<td>NS</td>
</tr>
<tr>
<td>Diazepam and diphenhydramine</td>
<td>25</td>
<td>19</td>
<td>NS</td>
</tr>
<tr>
<td>Allergic type adverse reaction</td>
<td>0</td>
<td>3</td>
<td>0.04</td>
</tr>
<tr>
<td>Nausea/Vomiting</td>
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<td>1</td>
<td>NS</td>
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<tr>
<td>Diazepam and H2-receptor antagonist</td>
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<td>27</td>
<td>NS</td>
</tr>
<tr>
<td>Allergic type adverse reaction</td>
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<td>1</td>
<td>NS</td>
</tr>
<tr>
<td>Nausea/Vomiting</td>
<td>0</td>
<td>2</td>
<td>NS</td>
</tr>
<tr>
<td>Diphenhydramine and H2-receptor blocker</td>
<td>10</td>
<td>16</td>
<td>NS</td>
</tr>
<tr>
<td>Allergic type adverse reaction</td>
<td>0</td>
<td>0</td>
<td>NS</td>
</tr>
<tr>
<td>Nausea/Vomiting</td>
<td>0</td>
<td>1</td>
<td>NS</td>
</tr>
<tr>
<td>Diazepam, diphenhydramine and H2 receptor antagonist</td>
<td>7</td>
<td>10</td>
<td>NS</td>
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<tr>
<td>Allergic type adverse reaction</td>
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<td>NS</td>
</tr>
<tr>
<td>Nausea/Vomiting</td>
<td>0</td>
<td>1</td>
<td>NS</td>
</tr>
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</table>

Discussion

Adverse reactions during angiography. This was the first multicenter study to compare in a prospective, randomized and blinded fashion the adverse reactions to ionic and nonionic contrast media with similar relatively low osmolality administered during cardiac angiography. The incidence of mild to moderate adverse reactions was significantly higher with the ionic diem (ioxaglate) than with the nonionic compound (iopamidol). Among the 500 patients studied, there were no deaths, serious ventricular arrhythmias or cardiac events. Two patients in the ioxaglate group developed bronchospasm; one of these adverse events was classified as severe and the other as moderate. No severe adverse reactions were reported in the iopamidol-treated patients.

Multicenter trials for intravenous procedures. Large multicenter studies (20-22) have compared the adverse reactions associated with the intravenous administration of nonionic with ionic contrast media. Palmer (20) performed a prospective survey of reactions to intravenous contrast medium injections in multiple hospitals and private practices in Australia and New Zealand; 109,546 cases were included. The incidence of adverse reactions in high risk patients receiving ionic contrast medium was 1.3% compared with 1.5% in the high risk patients receiving a nonionic medium (p < 0.001); severe reactions were 0.36% and 0.03%, respectively (p < 0.001). In a similar intravenous study conducted in Japan, Katayama et al. (22) reported on 337,647 cases. In that study the overall incidence of adverse reactions was 12.7% for ionic contrast medium and 3.1% for nonionic medium, whereas that of severe adverse reactions was 0.26% and 0.04% in the respective groups. These studies were not randomized or blinded and the number of patients receiving nonionic contrast medium was significantly greater in the high risk groups. Despite the limitations, these studies clearly show that the incidence of adverse reactions associated with the intravenous use of nonionic contrast medium is significantly less than with the ionic contrast medium. The ionic contrast media in these studies were all ionic monomers with high osmolality compared with that of the
In addition, several reports (27,28) have stated that the incidence of adverse reactions related to the ionic nature of the compounds. In the present study we observed that the QT interval prolongation immediately after the coronary injection was more significant in the ioxaglate than in the iopamidol group. ST segment and T wave changes were also observed in the ioxaglate-treated patients; however, because placement of the ECG leads was not uniform in this multicenter study, it was not possible to quantitate changes in these variables. Other studies (23-25) have also reported that the ST segment and T wave changes and QT interval prolongation are significantly greater with ioxaglate than with nonionic contrast medium. The origin of these ECG alterations remains uncertain. The results of several laboratory studies (5-7,29) suggest that the calcium-chelating properties of the contrast medium may be an important factor associated with these ECG changes. The significance of these changes is also not known. Studies in animals (5,30,31) have shown that the ventricular fibrillatory threshold is inversely related to the QT interval prolongation after contrast medium injections. However, no patient in our study had ventricular tachycardia or fibrillation. With the conventional ionic contrast media, the incidence of this adverse event varies from 0.6% to 1.3% (32,33). Thus, these data suggest that the incidence of serious ventricular arrhythmias may even be lower for both iopamidol and ioxaglate.

Selective coronary angiography with the conventional ionic contrast medium is often associated with bradycardia and heart block (1,11,34,35). No significant bradycardia or heart block attributable to contrast medium or heart block were reported in this study. This finding agrees with those of previously published reports (11,23-25,34) from relatively small trials at single institutions; that is, coronary injections of nonionic contrast medium or ioxaglate are not associated with significant increases in RR intervals.

Ioxaglate is widely used for arterial angiography. In addition, several reports (27,28) have stated that the incidence of adverse reactions differs between intravenous and intraarterial angiography. Thus, the present study was performed to compare ioxaglate and iopamidol during cardiac angiography. Our findings agree with those of the large multicenter intravenous studies: that is, the incidence of the adverse reactions is significantly higher with ionic than with nonionic contrast media. Because both contrast media in our study had similar osmolality, our data suggest that the molecular structure may play an important role in determining the side effects of the contrast media.

Adverse cardiac effects. The side effects of contrast media during cardiac angiography can be classified as cardiac, hemodynamic or systemic. In the present study we observed that the QT interval prolongation immediately after the coronary injection was more significant in the ioxaglate than in the iopamidol group. ST segment and T wave changes were also observed in the ioxaglate-treated patients; however, because placement of the ECG leads was not uniform in this multicenter study, it was not possible to quantitate changes in these variables. Other studies (23-25) have also reported that the ST segment and T wave changes and QT interval prolongation are significantly greater with ioxaglate than with nonionic contrast medium. The origin of these ECG alterations remains uncertain. The results of several laboratory studies (5-7,29) suggest that the calcium-chelating properties of the contrast medium may be an important factor associated with these ECG changes. The significance of these changes is also not known. Studies in animals (5,30,31) have shown that the ventricular fibrillatory threshold is inversely related to the QT interval prolongation after contrast medium injections. However, no patient in our study had ventricular tachycardia or fibrillation. With the conventional ionic contrast media, the incidence of this adverse event varies from 0.6% to 1.3% (32,33). Thus, these data suggest that the incidence of serious ventricular arrhythmias may even be lower for both iopamidol and ioxaglate.

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Hemodynamic variables and myocardial contractility were not measured in this study. However, there were no reports of pulmonary edema or significant hypotension during or immediately after the procedure. The osmolality of the contrast medium appears to play a major role in the hemodynamic alterations, such as transient hypotension and elevation of the left ventricular end-diastolic pressure that occur after intraarterial injections of contrast medium (1,3,4,11,18,23,25,34-36). Previous studies that have measured these hemodynamic indexes have shown that the changes produced during bolus left ventricular injections are similar for the nonionic monomers and the ionic dimer ioxaglate and that these changes are minimal compared with those induced by similar injections of the conventional ionic monomer agents (11,18,23,25,34,36-38). Animal studies (39,40) assessing myocardial contractility have demonstrated that the negative inotropic effects associated with injections of the conventional ionic contrast media are significantly less with ioxaglate and that the nonionic contrast media have a small positive inotropic effect.

Nausea and vomiting. Nausea and vomiting represent a systemic chemotoxic effect of contrast media. A possible explanation for this side effect is that the contrast molecules bind to protein and results in enzyme inhibition of cholinesterase (2,41,42). In vitro experiments (41) have shown that nonionic contrast media such as iopamidol and iohexol produce less inhibition of cholinesterase than does ioxaglate. Intravenous injections of ioxaglate are often associated with a high incidence (25% to 37%) of nausea and vomiting (42-44). In this intraarterial randomized study, nausea or vomiting, or both, occurred in 8% of the patients receiving ioxaglate. In the iopamidol group, nausea only occurred in 0.9% (p < 0.0003). Other studies (23,25,41) that used ioxaglate for intraarterial procedures have also reported a higher incidence of this adverse reaction.

Allergic-type adverse reactions. Allergic-type or "anaphylactoid" adverse reactions can be the most severe or life-threatening adverse reactions that result from intravascular injections of contrast medium. In this study two patients developed bronchospasm, classified as severe in one and as moderate in the other; both patients were in the ioxaglate group. No patient developed anaphylactoid shock or circulatory collapse. In addition to the two cases of bronchospasm, there were 13 other mild to moderate allergic-type adverse reactions in the ioxaglate group compared with only 1 in the iopamidol group (Table 2).

The exact mechanism for these allergic-type adverse reactions is unclear (46). The classic antigen-antibody immune reaction has been postulated (47,48) but not proved. Anticontrast medium antibodies have not been detected in patients with adverse reactions (12). Similarly, a high percentage of these patients do not experience recurrence of the adverse reaction during subsequent angiographic procedures (49). Contrast media can induce histamine and serotonin...
release (38,51) and can also activate the complement and coagulation systems (17). Contact-system activators are present in vascular endothelium and mast cells; release of these activators by contrast media as well as other hyperosmolar agents can result in a series of proteolytic events leading to the production of bradykinins (15-52). Lalli and Greenstreet (16) hypothesized that many of the adverse reactions are secondary to anxiety and are controlled by the central nervous system. Whether one or several of these mechanisms are responsible for the allergic-type adverse reactions remains to be determined. However, the understanding of the pathophysiology of these events may become very important in the selection of or the future development of contrast media.

Several clinical studies (22,27,53-57) have shown that the incidence of adverse reactions to contrast medium is two to four times greater in patients with asthma or a history of any allergy than in patients without these conditions. Among the ioxaglate-treated patients in our study, 13.5% of those with asthma or a known allergy had an allergic-type adverse event compared with 4% of those without these conditions. However, although more patients with a history of asthma or allergy were receiving iopamidol, only one allergic-type adverse reaction occurred in this group and the affected patient had no known allergy. These data strongly suggest that patients with asthma or a history of an allergy are at an increased risk for an adverse event during angiography with ioxaglate and that the use of a nonionic contrast medium may reduce the risk in such patients. Several previous studies (13-17) have implied that the high osmolality of the contrast medium may be responsible for many of these adverse events. However, the similar osmolality of the two contrast media in our study suggests that the incidence of allergic-type adverse reactions is significantly lower with nonionic contrast medium iopamidol. The allergic-type adverse reactions were also higher in the ioxaglate-treated patients (6%) than in the iopamidol group (0.0%) (p < 0.0007). Among patients treated with ioxaglate, those with asthma or a history of a known allergy had a 3.4 times greater incidence of an allergic-type adverse event than did patients without a known allergy. None of the patients with asthma or a known allergy receiving iopamidol had an allergic-type adverse event. Thus, these data suggest that a nonionic contrast medium should be used for cardiac angiography to avoid allergic-type adverse reactions, especially in patients with a known allergy.

Premedication with various pharmacologic agents has been advocated to reduce the risk of these adverse events. These agents include steroids (58,39), diphenhydramine or H1-receptor antagonist (60), diazepam (16,61) and, most recently, H2-receptor antagonist (62,63). Controversy exists as to the efficacy of these medications in reducing the incidence and the severity of the adverse events induced by contrast medium (49,60,63-66). In our study the number of patients receiving premedication did not differ significantly between the ioxaglate and iopamidol groups (Table 4). Although our study was not designed to assess the effects of the various medications used for pretreatment, the data suggest that pretreatment with diphenhydramine or sedation with diazepam does not completely protect against an allergic-type adverse reaction to ioxaglate. In addition, cases have been reported (60,65,67,68) of severe anaphylaxis with circulatory collapse occurring with the use of conventional ionic contrast media and ioxaglate after premedication with diphenhydramine and steroids. Rapoport et al. (64) described six patients who developed a severe anaphylactoid reaction to conventional high osmolality ionic contrast me-

References


