Comparison between a low-osmolar ionic (ioxaglate) and a low-osmolar non-ionic (iopamidol) contrast agent in cardiac imaging

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Summary

The aim of this study was to compare the subjective, haemodynamic and electrocardiographic changes associated with a low-osmolar ionic (ioxaglate) and a low-osmolar non-ionic (iopamidol) injection during routine ventriculography and coronary angiography. The double-blind study was terminated when 120 patients had been randomised to either ioxaglate or iopamidol. More patients (9) experienced nausea with ioxaglate than with iopamidol (2). One patient in each group developed urticaria during and immediately after the procedure. No patient in any group developed serious arrhythmias during dye injection. After left ventriculography the mean left ventricular end-diastolic pressure (LVEDP) increased significantly in the iopamidol group (P < 0.001). In all parameters no significant differences could be demonstrated in the effects caused by the two contrast agents in any of the groups. In the ioxaglate group with both right and left coronary artery injection, the mean QRS duration, mean Q-T interval and T-wave amplitude changed significantly (P < 0.001). In the iopamidol group the QRS duration and Q-T interval were prolonged significantly only with left coronary artery injection (P < 0.001). In all parameters no significant differences were noted in the two groups; only minor differences in heart rate with either left ventricular or selective right and left coronary artery injections in any of the groups.

Conventional high-osmolar contrast media (CM), such as sodium meglumine diatrizoate, are still the most commonly used agents in coronary angiography.1,2 Although rare, death directly attributable to the use of CM does occur and is often preceded by a sudden and persistent fall in blood pressure.3-5 There is abundant evidence that hyperosmolality and the induced hypocalcaemia play a major role in this precipitous fall in blood pressure. The deleterious effects are the result of a direct depressant effect on cardiac contractility in combination with peripheral vasodilatation.4-5

Conventional high-osmolar CM are ionic salts of tri-iodinated benzoic acid derivatives. The cation is either methylmeglucone or sodium, or a mixture of both. When these CM dissolve in water, each of their molecules dissociates into two particles: a cation and an anion containing the three iodine atoms. Thus, in order to obtain high-contrast density, strongly

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hypertonic or hyperosmolar solutions have to be synthesised. Recently, significant lowering of osmolality has been achieved in two different ways: either by the synthesis of non-ionic CM or by the synthesis of so-called 'dimers'.

The introduction of these low-osmolar CM into cardiac imaging was a welcome development and it is now evident that they are better tolerated and safer than the conventional high-osmolar agents. However, several studies suggested that not only hyperosmolarity of CM, but also the constituents themselves, could be implicated as a cause of altered haemodynamics and changes in cardiac electrophysiology. In this regard, the ionic composition and more specifically the cations sodium, calcium and methylglucamine, as well as the toxicity of the anion used, appear to be of importance.

In vivo studies demonstrated an inverse relationship between extracellular sodium concentration and myocardial contractility: hypotraemic solutions augment and hypertraemic solutions depress contractility. Since the non-ionic CM contain no sodium, an increased myocardial contractile force might be expected. This would lead to increases in myocardial oxygen consumption and angina might be precipitated. Kozeny et al. thus recommended that further studies with different amounts of sodium added to the non-ionic contrast agents would be necessary to determine optimal formulations. Limited clinical data on non-ionic CM have thus far failed to support such an assumption.

No comparative clinical data between low-osmolar ionic agents, i.e. with ionising constituents, and low-osmolar non-ionic agents, i.e. without ionising constituents, were available, and such a study therefore seemed justified. Sodium meglumine ioxaglate (iodine content of 320 mg/ml) is a new low-osmolar contrast agent, a mono-acid dimer which dissociates in solution and is thus ionic. Iopamidol (iodine content of 370 mg/ml), another new osmolar contrast agent, is an amide which does not dissociate in solution and is thus non-ionic. The purpose of this randomised, double-blind study was to compare the subjective, haemodynamic and electrocardiographic changes associated with ioxaglate and iopamidol injection during routine ventriculography and coronary angiography.

**Methods**

The study was conducted in accordance with a protocol slightly modified from that of Gertz et al., who compared a high- and a low-osmolar agent. Consecutive patients undergoing routine left ventriculography and coronary angiography were eligible for the study. The study was double-blind and was terminated when 120 patients had received either ioxaglate or iopamidol. On the day of study all patients continued taking their current medication and in addition received 2.5 mg lorcazepam orally 1 hour before the procedure. No patient received atropine. Electrocardiographic standard lead I was monitored continuously during the procedure. Patients were studied by the Judkins technique. A 7F Cordis sheath was introduced into the femoral artery for continuous monitoring of the systemic arterial pressure. All patients received 5000 IU heparin intra-arterially before the ventriculogram. The ventriculogram was performed with a 7F Cordis high-flow pig-tail catheter into which 0.5 ml/kg body weight of contrast medium was injected at a rate of 12 ml/s. The electrocardiogram (ECG), left ventricular pressure and femoral artery pressures were recorded continuously for 10 seconds before and for the first 2 minutes after the ventriculogram. During the injection and for the first 30 seconds after it the left ventricular pressure could not be recorded. During this time the pig-tail catheter was reconnectected to the pressure transducer and flushed. The left ventriculogram always preceded the selective right and left coronary angiograms. The ECG and aortic pressure were continuously recorded before and for 1 minute after the last selective injection of the right and left coronary arteries. Routinely, two injections in the right coronary artery and four injections in the left coronary artery were made in rapid succession. The time between the first and last coronary artery injections was noted. All recordings were made at a strip-chart speed of 25 mm/s. Immediately after the procedure all patients were given 50 mg protamine sulphate.

The total volume of injected contrast agent was noted in each patient. Blood for determination of levels of urea, serum creatinine and electrolytes was obtained the day before and the day after the study. Informed written consent was obtained from all the patients.

The significance of difference in parameters before and after CM injection was determined by the paired Student's t-test. Comparison between changes induced by the CM was made by one-way analysis of variance.

**Results**

Of the 120 patients evaluated, 61 (mean age 49.5 ± 11.8 years) received ioxaglate and 59 (mean age 50.2 ± 12.7 years) received iopamidol. The times between the first and second right coronary artery injections were 33 seconds and 35 seconds respectively in the ioxaglate and iopamidol groups and 105 seconds between the first and fourth left coronary artery injections in both the ioxaglate and iopamidol groups.

Twenty-seven patients in the ioxaglate group and 31 in the iopamidol group were on calcium channel-blocking agents. There was no significant difference in the other drugs prescribed for patients studied in the two groups. No patient in any group complained of angina pectoris and no patient developed serious arrhythmias during dye injection. There was no significant difference in the baseline blood urea and serum creatinine levels. The mean volumes of dye injected were 123 ml and 117 ml respectively in the ioxaglate and iopamidol groups. There was no significant difference in the blood urea and creatinine levels on the day after the study in all patients. Nine patients in the ioxaglate group and 2 in the iopamidol group experienced nausea. One patient in each group developed urticaria during and immediately after the procedure.

There were no significant differences between baseline mean left ventricular end-diastolic pressure (LVEDP) and baseline mean systolic pressure in the two groups. After left ventriculography the mean LVEDP increased transiently in both groups (Fig. 1). The
rise in mean LVEDP was significant in the iopamidol group \( (P < 0.001) \). The difference in the rise of LVEDP in the two groups was not significant. In both groups the systolic arterial pressure fell transiently after left ventriculography (Fig. 1). The mean fall in systolic pressure was significant in both groups \( (P < 0.001) \) but the difference between the two groups was not significant.

After selective injections of the left coronary artery an insignificant drop in blood pressure was observed in both the ioxaglate and iopamidol groups. There was no change in systolic and diastolic pressure after selective injection of the right coronary artery.

There was no significant change in the R-R and P-R intervals with either left ventricular or selective right and left coronary artery injections in either of the groups (Fig. 2).

**Discussion**

Subjective changes associated with injection of CM include pain, flushing, nausea and vomiting. The pain and flushing are the result of peripheral vasodilatation and seem to be closely related to the degree of osmolality of the CM. The many comparative studies between high- and low-osmolar CM have shown that the magnitude of changes is much less with the low-osmolar agents. Peck et al. found no significant differences between low-osmolar ionic and low-osmolar non-ionic CM in 225 patients evaluated for nausea, vomiting, heat, pain, voiding sensation and urticaria. In our study, 9 patients in the ioxaglate group and only 2 in the iopamidol group experienced nausea. One patient in each group developed urticaria during the procedure.

The myocardial depressant effect of CM results in a rise in LVEDP and a fall in systemic arterial pressures. It has been conclusively shown that these haemodynamic changes are brought about mainly by the drastic fall in calcium ions in the myocardial blood supply, with a resultant imbalance in the ratio of calcium to sodium ions. Calcium ions are necessary for normal ventricular function and normal vascular tone. The fall in calcium ions with high-osmolar CM, such as sodium meglumine diatrizoate, was attributed to two mechanisms. Firstly, a dilutional effect was demonstrated in dogs, in which the haematocrit declined from 0.44 to 0.23, indicating that nearly half of the blood in the coronary circulation was transiently displaced by the injectate. Secondly, the number of calcium ions may fall as a result of sodium citrate and disodium edetate, which are added as a buffer and to absorb any free metals, but also bind calcium so that free ionised calcium is reduced. A dilutional fall in calcium ion concentration is thus to be anticipated with both ioxaglate and iopamidol infusion. Furthermore, both ioxaglate and iopamidol contain sodium edetate as a chelating agent and stabiliser.

Another important factor seems to be the ionic composition of the CM which would transiently influence the ratio of calcium to sodium ions. Diatrizoate with high osmolality and physiological levels of sodium caused the same fall in serum sodium as iopamidol which contained no sodium. The sodium content of the ioxaglate used in this study was 150 mEq/l. On theoretical grounds, therefore, no difference in haemodynamic parameters can be expected. In our study iopamidol, surprisingly, caused slightly more haemodynamic effects than ioxaglate. The differences between changes caused by the two drugs were, however, not significant (Fig. 1).

The electrophysiological changes due to conventional CM infusion include sinus bradycardia, slowing of atrioventricular conduction, widening of the QRS complex, Q-T prolongation, ST segment displacement and changes in T-wave polarity. The sinus slowing and atrioventricular conduction dysfunction seem to be the result of two mechanisms: firstly, a direct effect on the pacemaker cells and conduction tissue which is related to the osmolality of the agent — the higher the osmolality, the more pronounced the effect; and secondly, sinoatrial and atrioventricular nodal suppression occur as a result of reflex-mediated parasympathetic stimulation, triggered by a high osmolar injectate and partly blocked by atropine administration. Owing to the markedly lower osmolality of the two agents used in this study, lesser effects are to be anticipated. Slight sinus slowing did occur in a few patients, but the mean heart rate did not change in any of the two groups of patients (Fig. 2). No change in the P-R interval was observed in any patient.

Infusion of hyperosmolar CM into the left coronary artery caused the mean frontal plane QRS vector to shift transiently to the left and the ST- and T-wave vector to shift to the right. With right coronary artery injection the opposite occurred.
The observed electrocardiographic changes are the result of differences in potential between areas of myocardium perfused with CM and areas containing no CM. The changes in the magnitude and the spatial mean T vector are much more pronounced than the changes in the QRS complex. The T-wave changes closely resemble those observed with certain electrolyte disturbances. In patients with hypocalcaemia and hypopotassiumemia the ECG shows a prolonged ST segment and prominent 'repolarisation' wave which consists of T and U waves. The Q-T interval is therefore prolonged because of a GT.


In conclusion, ioxaglate tended to cause more nausea and more electrocardiographic changes than iopamidol, and iopamidol caused more haemodynamic disturbance than ioxaglate. All the changes were slight and the differences between the effects caused by the two agents were not significant. The selection of an appropriate contrast medium is thus solely dependent upon the relative cost of the two agents, which are presently markedly different.

Addendum

Since completion of the study, ioxaglate has been used in all patients undergoing cardiac imaging. In the first 180 patients the left ventriculogram always preceded the coronary angiogram and in this group 25 (14%) patients experienced nausea. In the subsequent 156 patients the selective coronary angiogram always preceded the left ventriculogram and in this group 9 (5%) patients experienced nausea. The difference in the incidence of nausea among the groups was significant (P < 0.05) (chi-square analysis with Yates's correction).

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