Contrast media for left ventricular angiography

A comparison between Cardio-Conray and iopamidol

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SUMMARY Forty consecutive patients with coronary artery disease undergoing left ventricular angiography took part in a randomised double blind trial comparing a conventional contrast medium sodium meglumine iothalamate (Cardio-Conray) with the low osmolar agent iopamidol. Iopamidol produced a smaller rise in heart rate and a smaller fall in left ventricular systolic pressure, but the changes in left ventricular end diastolic pressure and maximum rate of change of pressure (dP/dt max) were not different. The numbers of extrasystoles per minute for five minutes after ventriculography were similar in both groups except for the first 15 seconds, when the number of extrasystoles was increased in the iopamidol group. The frequency and magnitude of symptoms (heat, angina, headache, and nausea) were not significantly different in the two groups. Iopamidol causes less haemodynamic disturbance than Cardio-Conray, although the improvement is small and offers no advantage in reducing symptoms or extrasystoles.

Conventional contrast media affect patients with coronary artery disease undergoing left ventricular angiography in several ways. They produce haemodynamic deterioration by increasing preload,^{1,2} reducing contractility,^{1,3} reducing afterload,⁴ and increasing heart rate.⁵ Multiple extrasystoles may occur, making interpretation of the angiogram difficult and sometimes precipitating serious arrhythmias in these vulnerable patients. Lastly, these agents may produce serious symptoms^{4,6} (a sensation of severe heat, nausea, headache, or angina), making the examination unpleasant or even causing premature termination of the investigation.

It has been suggested that low osmolar agents may reduce the severity of these problems.^{4,6,7} We, therefore conducted a randomised double blind trial to compare one of these agents, iopamidol (Niopam, Merck), with a conventional agent sodium meglumine iothalamate (Cardio-Conray, May and Baker).

Patients and methods

Forty consecutive patients were studied, all of whom were suspected of having coronary artery disease with no evidence of valve pathology. They were given a premedication of 10 mg diazepam by mouth one hour

before catheterisation and were randomised to receive either Cardio-Conray (iodine content 400 mg/ml) or Niopam 370 (iodine content 370 mg/ml). The left ventricular angiogram always preceded the coronary angiograms and, as is the custom in this hospital, beta adrenergic blocking drugs were not withdrawn before angiography.

ANGIOGRAPHIC PROCEDURE

A pigtail angiographic catheter (Cordis, French gauge No 8) was placed in the left ventricle, and recordings were made of the electrocardiogram, heart rate, left ventricular systolic pressure, left ventricular end diastolic pressure (both before and after the "a" wave), maximum rate of change of pressure with time (dP/dt max), and the frequency per minute of extrasystoles (both atrial and ventricular). Control readings were made for two minutes (or longer if the haemodynamic status of the patient was unstable), after which 0.5 ml/kg of the contrast medium was injected using an Angiomat injector at 15 ml/s. Immediately after the injection the catheter was flushed with 3 ml of saline and further readings made at 40 s and 1, 2, 3, 4, and 5 minutes after injection. In addition the number of extrasystoles over the first 15 seconds was recorded.

The patient was then asked about four symptoms: heat, nausea, headache, and angina. If these were experienced he was then asked to grade severity on a scale from zero to 10, zero being defined as the absence of the symptom and 10 as an unbearably severe symptom.

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CALCULATIONS

For the haemodynamic results and the frequency of extrasystoles per minute, the two control values were averaged and subsequent results analysed as the change from the control mean value. The significance of this change was assessed by Student's paired *t* test. To compare the significance of the changes between the two groups, these differences at each time interval were compared using the unpaired *t* test.

The frequency of extrasystoles in the first 15 seconds was not distributed normally and the two groups were compared using Wilcoxon's non-parametric test making allowance for ties, the median and range being quoted rather than the mean and standard deviation.

Symptoms were analysed in two ways. Firstly, the incidence of the symptom was assessed using the χ^2 test with Yates's correction or Fisher's exact test where appropriate. The severity of the symptoms was analysed using Wilcoxon's non-parametric method as the frequency was not normally distributed being skewed towards zero.

Results

PATIENTS

Twenty patients in each group were studied (Table 1). They were comparable in terms of age, sex, history of myocardial infarction or bypass graft, and use of beta adrenergic blockers. The control haemodynamic values were also similar (Table 2). A mean volume of 41 ± 5 ml of iopamidol was used compared with 38 ± 5 ml of Cardio-Conray (difference not significant). The two groups may be considered to have been adequately randomised.

HAEMODYNAMIC INDICES

The heart rate in both groups increased after injection of the contrast medium and then returned to baseline values (Figure a). The peak increase in heart rate for Cardio-Conray was 9.4 beats/min ($p < 0.001$) and for iopamidol 3.9 beats/min ($p < 0.05$). The increase in heart rate was significantly greater for Cardio-Conray than iopamidol ($p < 0.05$) at 40 s, but thereafter a difference was not seen.

Left ventricular systolic pressure (Figure b) fell with Cardio-Conray to 12 mm Hg less than the control ($p < 0.001$) but rose with iopamidol by 4.5 mm Hg ($p < 0.05$), the difference between the two groups being significant for the first two minutes (for 40 s and one minute $p < 0.01$ and at two minutes $p < 0.05$).

Left ventricular end diastolic pressure, whether measured before or after the "a" wave, showed a similar pattern for both groups: a rise (to a maximum of 2.2 mm Hg ($p < 0.001$) before the "a" wave and 3.3 mm Hg ($p < 0.001$) after the "a" wave for iopamidol;

Table 1 Clinical characteristics of patients undergoing angiography using either Cardio-Conray or iopamidol

	Cardio-Conray	Iopamidol	Significance
No of men	16	19	NS
Mean ($\pm$ SD) age (y)	47 ± 9	49 ± 10	NS
Previous infarct	11	11	NS
Previous coronary grafts	0	2	NS
Taking beta blockers	10	13	NS
Total No of patients	20	20	

Table 2 Haemodynamic values (mean $\pm$ ISD) before injection of the contrast medium in the two groups of patients

	Cardio-Conray	Iopamidol	Significance
Heart rate (beats/min)	74 ± 14	67 ± 11	NS
Left ventricular pressures (mm Hg)			
Systolic	134 ± 19	133 ± 29	NS
End diastolic (before "a" wave)	11 ± 4	13 ± 5	NS
End diastolic (after "a" wave)	19 ± 8	19 ± 8	NS
dP-dt max (mm Hg/s)	1804 ± 684	1866 ± 527	NS
Extrasystoles (per min)*	1	1	NS

*Median value.

and to a maximum of 2.3 mm Hg ($p < 0.001$) and 3.2 mm Hg ($p < 0.01$) respectively for Cardio-Conray). The difference between the two groups was not, however, statistically significant. Only the changes in pressure after the "a" wave are shown in Figure c, but the values before the "a" wave were similar.

For both agents dP/dt max showed a small but non-significant rise before reverting to the baseline, there being no difference between these groups.

EXTRASYSTOLES

The frequency of extrasystoles in the first minute after injection increased for both groups (5.7/min ($p < 0.01$) for iopamidol and 2.7/min ($p < 0.05$) for Cardio-Conray) there being no difference in the increase for these groups. After the first minute the frequency of extrasystoles in both groups was no different from the control. But in the first 15 seconds the absolute number of extrasystoles after iopamidol (median value 4) was significantly greater than after Cardio-Conray (median value 1, $p < 0.05$ using Wilcoxon's non-parametric test).

SYMPTOMS

A sensation of heat was felt by all patients (Table 3), and the severity of the heat was similar (mean value 6.4 for Cardio-Conray and 6.7 for iopamidol). The incidence of angina was identical for both groups (3/20), and the severity of the symptoms was similar (0.5

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Figure Effect of iopamidol and Cardio-Conray on (a) heart rate, (b) left ventricular systolic pressure, and (c) left ventricular end diastolic pressure (LVEDP) after the "a" wave.

for Cardio-Conray and 0.6 for iopamidol). Three patients in the Cardio-Conray group complained of headache but none in the iopamidol group (not significant), and the severity of the headache was not

Table 3 Number of patients experiencing symptoms (and their magnitude*) during angiography using the two different contrast media

Symptom	Cardio-Conray (n=20)	Iopamidol (n=20)	Significance
Heat	20 (6.4)	20 (6.7)	NS (NS)
Angina	3 (0.5)	3 (0.6)	NS (NS)
Headache	3 (0.7)	0 (0)	NS (NS)
Nausea	8 (2.2)	3 (0.6)	NS (NS)

*Scores (mean) reported by patients (maximum range 0–10).

different (a score of 0.7 for Cardio-Conray and 0 for iopamidol). Three patients in the iopamidol group and eight in the Cardio-Conray group experienced nausea (the difference not being significant); the difference in severity was also not significant (a mean score of 2.2 for Cardio-Conray and 0.6 for iopamidol). No patient in either group retched or vomited.

Discussion

The effects of contrast media on haemodynamic indices are complex. Preload rises^{1,2} owing to the volume injected and the increase in intravenous volume from the osmotic load; contractility initially falls^{1,3} owing to a direct depressant action of the medium on the myocardium; afterload decreases⁴ with the vasodilatation induced by the contrast medium, and the heart rate rises⁵ reflexly in response to the hypotension. The new low osmolar agents such as iopamidol have the potential for reducing haemodynamic disturbance^{4,6,7} because the rise in preload is reduced owing to the reduced osmotic load; the fall in contractility is less and vasodilatation which is dependent on the osmolality of the contrast medium is also reduced. This study confirms that iopamidol induces less change in heart rate and left ventricular systolic pressure than Cardio-Conray, and in patients with severely compromised left ventricular function this may be important. Nevertheless, the improvement produced by iopamidol is small and short lived, and the two contrast agents produce almost identical changes in left ventricular end diastolic pressure and dP/dt max. It seems unlikely, therefore, that iopamidol offers a clinically significant haemodynamic advantage to patients with normal or near normal left ventricular function.

Animal studies also show that iopamidol causes less haemodynamic change than conventional agents when used in left ventricular angiography⁸ or coronary arteriography.⁹ In man, Partridge *et al* showed that iopamidol caused less hypotension than ionic agents when used for coronary angiography but was unable to show a haemodynamic benefit when using it for left ventricular angiography.⁵ Other non-ionic agents such as metrizamide,^{9,10} iohexol,^{10–12} and ioxaglic acid salts¹¹ show the same trend, causing less circulatory upset when used for cardiac angiography.

It is probable that extrasystoles during left ventricular angiography are caused mainly by the recoil and movement of the catheter and the direct effect of the jet of contrast on the myocardium. The low osmolality of iopamidol may be of less benefit here, and the increase in extrasystoles in the iopamidol group may be due to the greater viscosity of iopamidol (9.4 cp at 37°C) compared with Cardio-Conray (8.6 cp at 37°C) causing more movement in the catheter system.

Low osmolar agents would be expected to be better

tolerated than conventional agents.^{4 6 13} Vasodilatation is responsible for the sensation of heat, and this depends on the osmolality of the agent used. Nausea—possibly produced by the agent crossing the blood-brain barrier or by the reflex response to hypotension—will be less, and headache, caused perhaps by vasodilatation or by direct central effects of the agent, should be reduced. Angina, provoked perhaps by increased myocardial oxygen demand as heart rate and left ventricular end diastolic pressure rise, would also be less. This study failed, however, to show that either the frequency or the severity of any of the symptoms was reduced by iopamidol. One reason for this is that the incidence and severity of symptoms (apart from the transient symptom of heat) were low in both groups, and consequently it was difficult to show a statistical advantage. The major factor reducing the incidence of symptoms has been the improvement in radiological equipment, which allows good angiograms to be taken with low volumes of contrast agents. Another reason for the lack of improvement with iopamidol may be the rapid dilution of the agent as it is injected into the left ventricle. This differs from the technique used in peripheral arteriography, in which large volumes are injected into single arteries, producing much higher local concentrations, and in which low osmolar agents are more likely to show clear advantage.^{14 15} A crossover study—that is, two angiograms using two contrast agents—in the same patient might possibly be a more sensitive method of detecting differences in unfamiliar symptoms such as transient vasodilatation. In view of the considerable changes in fluid distribution and haemodynamic variables it is, however, doubtful whether the haemodynamic response to the first agent could be compared legitimately with that of the second without the patient having to wait an intolerable time, and this experimental design was rejected.

The experience of other workers has been variable. Cumberland also reported that low osmolar agents do not reduce nausea but they do cause less pain after left ventricular angiography.¹³ Partridge *et al* found fewer adverse reactions with iopamidol but did use a compound scoring system combining both discomfort and nausea into one scale.⁵

Our findings show that (a) for left ventriculography iopamidol produces less haemodynamic disturbance than Cardio-Conray, although the difference is not great, (b) the increase in frequency of extrasystoles after angiography is not changed apart from an increase in absolute number over the first 15 s after iopamidol, and (c) iopamidol does not reduce the incidence or severity of side effects. It seems reasonable, therefore, to use iopamidol in high risk patients (particularly those with severely depressed left ventricular function) or those needing multiple angiograms,

but the case for routine use of this agent in all adults undergoing left ventricular angiography remains unproved.

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