Hexabrix—a new contrast medium in angiocardiology

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SUMMARY The hyperosmolality of current ionic angiographic media gives rise to several adverse effects. Use of the first low-osmolality medium, metrizamide (Amipaque), has been inhibited by expense and by the necessity for prior mixing into solution. Hexabrix is the first of such media to be available in stable solution, and its use in angiocardiology is reported, in direct comparison with Urografin, Triosil, Cardio-Conray, and metrizamide.

The low osmolality media cause significantly less discomfort than ionic media, and are better tolerated in paediatric angiocardiology. In coronary angiography Hexabrix causes comparable T wave change to Urografin and more than Triosil or metrizamide, but tends to have less effect on heart rate. The risk of exacerbating pulmonary arterial hypertension in right heart angiography appears to be reduced.

Angiographic contrast media are ionic solutions with an osmolality between five and eight times that of plasma. This hyperosmolality may have several effects:¹ vasodilatation, which may cause hypotension and is responsible for much of the subjective discomfort of angiography; a disproportionate increase in blood volume caused by osmotic fluid shift; erythrocyte deformity resulting from dehydration, which is probably the mechanism of exacerbation of pulmonary hypertension in right heart angiography,² and increased capillary permeability from endothelial damage.

Recently metrizamide (Amipaque, Nyegaard and Co.) was introduced for angiography. It is non-ionic, giving a solution with one-third of the osmolality of ionic media for a given iodine concentration (Fig. 1). It has been shown to cause less subjective discomfort than ionic media in left ventriculography, and less T wave change in coronary angiography.³ In children subjective discomfort is reduced,^{4 5} the heart rate falls less,^{4 6} and certain biochemical measurements such as plasma osmolality are less affected.⁵ Metrizamide, however, has not achieved widespread use in angiography because it is very expensive and requires time-consuming prior mixing, as it cannot be provided in stable solution.

Hexabrix is a more recent compound, stable in solution, and also of relatively low osmolality (Fig. 1). It has undergone clinical trials in the United

Kingdom and has been shown to cause less subjective discomfort in carotid angiography.⁷

The present paper describes the clinical experience with Hexabrix in angiocardiology.

Methods

A total of 49 patients being investigated for angina by left ventriculography and coronary angiography was randomly allocated to three groups, all receiving Hexabrix and one other medium. One group was given Urografin 370, one Triosil 370, and the other metrizamide in a concentration of 320 mg iodine/ml (Amipaque 320) which is also the iodine content of Hexabrix.

Fig. 1 Osmolalities of the five contrast media used in trial (with their iodine concentrations), compared with plasma and tissue fluid.

The method was similar to two previous trials of contrast media from this centre.^{3,8} The order in which the pairs of media were given was alternated, patients being randomly allocated which medium they would receive first. All patients had atropine 0.6 mg, and either diazepam or omnopon as pre-medication. Catheterisation was by the Judkins method, using 8F catheters.

After each left ventriculogram, always using 45 ml at 12 ml/second, the patient was asked about any subjective sensations experienced. In coronary angiography, the contrast media were given by hand at room temperature, and the volume and injection were recorded. The radiological equipment, the Philips Polydiagnost C with biplane, permitted multiple injections and projections without movement of the patient.

The electrocardiogram was recorded immediately before, during, and for 15 seconds after all angiograms. After each injection the next was delayed until the electrocardiogram had returned to its original state for at least one minute. The pressure at the catheter tip (measured by strain gauge) was recorded immediately before and, in the case of coronary angiography, immediately after the injection and for a further 15 seconds. Pressure was recorded after left ventriculography too, but there was always some delay in retrieving the pressure trace while the catheter was disconnected from the pump and flushed with saline.

If, during coronary catheterisation, the measured systolic pressure fell below 80 mmHg, the patients were excluded in order not to invalidate the electrocardiographic analysis.

Usual adherence to double blind methods was observed during the catheterisations and on analysis of the data. The electrocardiograms were analysed for maximum T wave deflection after each angiogram, and any rate change greater than five beats/minute and lasting for at least three cycles was recorded. All angiograms were reviewed for angiographic quality.

Another group of 10 patients undergoing left ventriculography was studied in the same way, using Hexabrix and Cardio-Conray as the contrast media. These two media were compared in a further group of 10 patients having ascending aortograms for the assessment of aortic valve disease.

Statistical analysis of the coronary angiographic data was carried out by the paired t test. In left ventriculography and aortography, the comparative discomfort with each medium was analysed by McNemar's test, and the incidence of severe discomfort by the exact probability test of Fisher, Irwin, and Yates (two-tailed).

Hexabrix was used as the sole angiocardigraphic

medium in 10 children under 3 years of age, most being randomly allocated within another contrast medium trial.

After completion of the formal trial in the adults, several patients were given Hexabrix in preference to other media and are referred to in the Discussion.

Results

LEFT VENTRICULOGRAPHY

In the *Urografin/Hexabrix* group there were 20 patients. Eleven experienced less sensation of heat with Hexabrix, while one patient preferred Urografin ($p=0.002$); eight noted no difference. Severe discomfort (described as "very" or "extremely" hot or painful) was experienced with Urografin by 12 patients, with Hexabrix by five, the difference being on the verge of significance ($p=0.053$). Two patients had severe nausea and vomiting (with accompanying heart rate and systolic pressure rises) with Hexabrix. Three patients had some nausea with Hexabrix only, and three with Urografin only.

In the *Triosil/Hexabrix* group there were 10 patients. Eight experienced less sensation of heat with Hexabrix, and two patients felt no difference ($p=0.004$). Severe discomfort occurred on eight occasions with Triosil, and on two with Hexabrix ($p=0.023$). No nausea or vomiting occurred.

In the *metrizamide (Amipaque 320)/Hexabrix* group there were 10 patients. Metrizamide was preferred by two patients, and Hexabrix by one. Seven noted no difference. Severe discomfort occurred on three occasions and slight nausea once with both media. None of these differences was statistically significant.

In the *Cardio-Conray/Hexabrix* group there were 10 patients. Nine preferred Hexabrix, one describing no difference ($p=0.002$). Six had severe discomfort with Cardio-Conray, one with Hexabrix ($p=0.057$). One patient had severe nausea and vomiting with Cardio-Conray, with accompanying heart rate and systolic pressure rises. An additional two patients had some nausea alone, one with each medium.

If the ionic media as a whole are compared with Hexabrix (therefore excluding the Amipaque group), the number of patients preferring Hexabrix was 28, against only one preferring an ionic medium, clearly a highly significant difference. In addition, the eight instances of severe discomfort with Hexabrix is significantly different from the 26 with ionic media ($p=0.00009$). The incidence of nausea and vomiting is not significantly different between the media, either in separate groups or studied as a whole.

Fig. 2 depicts the degrees of discomfort produced by each medium in all four patient groups under-

Fig. 2 Proportion of injections producing each degree of sensation of heat in the five patient groups.

going left ventriculography. There were no changes on the electrocardiogram during or after ventriculography which could be attributed to the contrast media.

CORONARY ANGIOGRAPHY

Injection times and volumes were examined and only minimal and variable differences were seen between the media, thus confirming that the changes on the electrocardiogram had not been affected by these factors.

Most patients received six injections in the left coronary artery, thus allowing three comparisons, and two in the right. It was found that the T wave changes tended to be consistent with each medium in a given patient, that is, if one of the media caused a certain amount of change in one coronary injection, it could be expected to do the same no matter how many injections were given. In order not to give undue statistical significance to the results, therefore, the mean T wave change produced by each medium in each patient was taken as a single observation, and it is on this basis that the results are calculated.

In the 10 patients in whom a satisfactory com-

parison could be made between *Urografin* and *Hexabrix*, the mean T wave changes were 13.7 mm with *Urografin* and 12.7 mm with *Hexabrix*. The difference is not statistically significant. Corresponding figures in the *Triosil/Hexabrix* group of nine patients are 9.7 mm for *Triosil* and 13.4 mm for *Hexabrix* ($p < 0.02$); and in the *metrizamide/Hexabrix* group of 10 patients, 3.8 mm for *metrizamide* and 7.4 mm for *Hexabrix* ($p < 0.01$).

No arrhythmias occurred. Adequate information on heart rate changes was available in 11 patients in the *Urografin/Hexabrix* group. *Urografin* produced a mean fall of 20 beats/minute after each coronary injection in one patient, whereas *Hexabrix* produced none. Ten patients had no rate change greater than the methodological limits set out above. In 10 patients receiving *Triosil* and *Hexabrix*, there were mean falls of 22 and 17 beats/minute in two patients with *Triosil*, and six and four, respectively, with *Hexabrix*. Two further patients showed rate reductions of 19 and 15 beats/minute with *Triosil*, *Hexabrix* producing no change. In the *metrizamide/Hexabrix* group, there were no rate changes. These differences between *Hexabrix* and either *Triosil* or *Urografin* are not statistically significant (significance of *Triosil/Hexabrix* figures: $0.1 > p > 0.05$).

No significant pressure changes were seen in coronary angiography, but the pressure was always somewhat damped by contrast medium in the catheter, which then had to be filled with blood by aspiration to avoid the possibility of the next injection including some of the previous medium. Similarly, no significant pressure changes were seen in aortography or left ventriculography (except accompanying severe vomiting), but there was always a few seconds delay before obtaining a pressure trace after the injections. Thus it cannot be said that good pressure traces capable of detecting small changes were obtained, but certainly changes of clinical significance did not occur. A further trial is now being conducted using separate transducer-tipped catheters.

No significant difference in angiographic quality between the media was observed.

PAEDIATRIC ANGIOCARDIOGRAPHY

A trial comparing *metrizamide* and *Cardio-Conray* in separate patients under 3 years of age has been recently completed.⁵ Within the period of this trial seven patients were randomly allocated to receive *Hexabrix* as the sole contrast medium, and it has been the medium used in three more patients since then. These 10 patients are well matched in terms of both patient and procedure details with those receiving one of the other media. Comparison of the results is therefore relevant. The following measure-

Table Paediatric angiocardiology; comparison of Hexabrix data with results of previous Cardio-Conray/metrizamide trial

	Hexabrix	Cardio-Conray	Metrizamide (Amipaque 370)
<i>Mean change in blood values (%)</i>			
Osmolality increase	1.5	7.5	3
Haemoglobin decrease	9	14	7
White cell count decrease	11	19	12
Chloride decrease	4	8.5	4
<i>Degree of subjective reaction to angiograms</i>			
None	15	10	19
"Slight"	2	3	2
"Moderate"	0	6	0
<i>Reduction in heart rate > 5 per cent</i>			
Incidence (%)	32	40	21
Mean (beats/min)	14	21	12
Maximum (beats/min)	40	80	20
<i>Angiographic quality</i>			
"Fair"	3	5	3
"Good"	15	16	18
"Very good"	4	6	7

Only those blood values in which there was a significant difference between Cardio-Conray and metrizamide are included.

ments were made: changes in plasma osmolality, haemoglobin, white cell count, and some electrolytes measured from vena cava samples taken at the beginning and end of the procedures; observable patient reaction to angiograms in those patients not under general anaesthetic; reduction in heart rate of more than 5 per cent occurring within 20 seconds of injection; and angiographic quality. The results, which include the corresponding figures of the other two media from the previous trial, are shown in the Table.

Discussion

The most striking feature of Hexabrix (as with metrizamide) in angiocardiology is that subjective patient discomfort is significantly less than with ionic media. Since completion of the formal trial, Hexabrix has been used in several patients in whom it was regarded as particularly indicated. Two mentally subnormal adolescent girls, one undergoing left ventriculography and the other subclavian angiography, had local anaesthesia with modest premedication, and reported only a minor sensation of heat during the angiograms. A 70-year-old man had a vaso-vagal reaction associated with severe pain when a test hand injection of Cardio-Conray was made in his thoracic aortic aneurysm: on recovery, at the same session, full angiography with Hexabrix, using a total of 90 ml, was performed without adverse effect. Clearly, description of these cases is anecdotal, but I am confident that this experience will be confirmed elsewhere.

Hexabrix caused approximately the same degree of T wave change during coronary angiography as Urografin, but more than Triosil and, notably,

metrizamide. The significance of T wave changes in coronary angiography, however, is uncertain, and though they are a ready means of observing the effect of a contrast medium on an aspect of the heart's electrical activity, they do not seem related to more immediately important effects, such as changes in rate or pressure. Hexabrix appeared to be well tolerated from these aspects. There was no significant pressure change and, though it was not statistically significant, a trend in favour of Hexabrix compared with the ionic media in the effect on heart rate. All the patients had been given atropine, which, of course, masks much of the tendency to bradycardia. Whether there is any difference in effect on human cardiac function measured by other means, such as indices of left ventricular contractility, between the ionic and low-osmolality media, or between the low-osmolality media themselves, remains to be seen.

In paediatric angiocardiology, Hexabrix is also clearly well tolerated, being approximately comparable to metrizamide and producing less adverse effects than Cardio-Conray.

Two other patients are of interest. One with a ventricular septal defect and a pulmonary artery pressure of 65/20 mmHg had a pulmonary angiogram with 45 ml Cardio-Conray, causing a rise in pulmonary artery pressure to 110/30 mmHg for five minutes. A further projection was needed, and a repeat angiogram with the same volume of Hexabrix had no effect. The second patient, with a pulmonary artery pressure of 110/60 mmHg associated with a ventricular septal defect, had a pulmonary angiogram using 40 ml Hexabrix, with no effect on the pulmonary artery pressure, nor other adverse effect. These cases appear to confirm that it is the hyperosmolality of contrast media which may exacerbate

pulmonary hypertension by its effect on the erythrocytes.²

Thus the new relatively low osmolality contrast media have significant advantages compared with ionic media which are not offset by reduction in image quality or other adverse effects. They are currently expensive, possibly making their routine use in adult cardiology difficult to justify, but they are likely to be of particular value in the following situations: (a) in paediatric angiocardiology; (b) when the increase in blood volume caused by hyperosmolar medium may be particularly significant; (c) when the subjective discomfort of angiography may be predicted to be such that undue distress would be caused, or the efficacy of the examination compromised; (d) in right heart angiography in the presence of pulmonary arterial hypertension; (e) when significant reduction in heart rate occurs during coronary angiography with ionic media despite atropine, as bradycardia may be less likely to occur.

Hexabrix is the first of such media to be available ready made in solution.

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