Clinical Radiology (1991) **43,** 331–336

Plasma Osmolality, Iodine Concentration and Urographic Images Following High and Low Osmolar Contrast Media

A. W. TODD*, G. P. NAISBY*, J. P. OWEN†, P. A. SMITH‡, T. J. BUTLER§, P. J. KELLY§, L. N. S. MURTHY*, J. Y. ROBSON‡ and M. F. LAKER‡

**Department of Radiology, Freeman Hospital, Newcastle upon Tyne, The University Departments of ‡Clinical Biochemistry and Metabolic Medicine and †Radiology, Royal Victoria Infirmary, Newcastle upon Tyne, §The University Division of Medical Statistics, The Medical School, Newcastle upon Tyne*

Three contrast media (sodium iothalamate, iopamidol and sodium/methylglucamine ioxaglate) in a dose of 240 mg iodine per kilogram of body weight were compared in clinical urography. The ionic monomer sodium iothalamate was the only medium to significantly elevate the plasma osmolality though it returned to normal values within 4 min. All three media exhibited first order linear kinetics. When corrected for the effects of diuresis, sodium iothalamate was shown to give the highest urinary iodine concentrations. On visual scoring sodium iothalamate produced better nephrograms and overall urograms than either of the low osmolar agents. Todd, A.W., Naisby, G.P., Owen, J.P., Smith, P.A., Butler, T.J., Kelly, P.J., Murthy, L.N.S., Robson, J.Y. & Laker M.F. (1991). *Clinical Radiology* **43,** 331–336. Plasma Osmolality, Iodine Concentration and Urographic Images Following High and Low Osmolar Contrast Media

It is widely believed that the nephrographic phase of the excretion urogram results from contrast medium within the vascular spaces and proximal convoluted tubules (PCT) of the kidney. The optimal nephrographic image is achieved with peak plasma iodine concentration, a high glomerular filtration rate and rapid tubular absorption of water and sodium ions. More osmotically active ionic contrast agents are expected to cause dilution of contrast in the PCT and therefore a reduced nephrographic 'density' compared with low osmolar agents.

A study by Dawson *et al.* (1984) suggested that low osmolar agents produced denser pyelograms and delayed maximal nephrographic images than high osmolar media. Also it is said that sodium salts achieve higher urinary concentrations because of active tubular reabsorption of sodium ions with passive water diffusion.

In addition to potential benefits in urographic quality there is a growing body of evidence which indicates that low osmolality contrast agents have fewer unpleasant and serious side-effects than conventional urographic media (Grainger, 1980; Dawson *et al.*, 1983). The reduction in complications has been in part attributed to the low osmolality but other factors such as a reduction in cholinesterase inhibition may also be important (Dawson and Edgerton, 1983).

The present study was designed to compare an ionic, high osmolar agent, a non-ionic, low osmolar medium and an ionic, low osmolar contrast agent in clinical urography. We were particularly interested in the effects on plasma osmolality, their plasma kinetics, urinary concentrations and the quality of the resulting urograms.

MATERIALS

Contrast media chosen were:

Correspondence to: Dr J. P. Owen, Imaging Laboratory, Royal Victoria Infirmary, Newcastle upon Tyne NE1 4LP.

In Memoriam. Percy Smith died suddenly and unexpectedly before he was able to complete the biochemical analyses in this project. We have lost a dedicated and talented professional colleague who will be greatly missed.

1 *Conray 420* (sodium iothalamate [May and Baker Ltd]; ionic, high osmolar, monomer; 420 g I/litre; osmolality 2227.5 mmol/kg).
2 *Niopam 370* (iopamidol [Bracco/E. Merck Ltd]; non-ionic, low osmolar, monomer; 370 g I/litre; osmolality 796 mmol/kg).
3 *Hexabrix 320* (sodium/methylglucamine ioxaglate [Guerbert/May and Baker Ltd]; ionic, low osmolar, dimer; 320 g I/litre; osmolality 580 mmol/kg).

PATIENTS AND METHODS

Approval for the study was granted by the local Joint Ethical Committee and informed consent obtained from the patients.

Patients were excluded if under 18 years of age or had thyrotoxicosis, known iodine sensitivity, diabetes mellitus or an abnormality of renal structure or function. Patient preparation and radiographic techique were identical to those outlined in earlier studies from this centre (Owen *et al.*, 1981; Owen *et al.*, 1983).

Renal function was measured by a 24 h creatinine clearance commencing on the day before IVU and venous blood samples taken on admission to the radiology department for electrolytes, urea, creatinine and osmolality.

Patients were weighed and a 19 gauge butterfly needle inserted into an available (usually ante-cubital fossa) vein. Contrast agents were allocated by random number selection, the volume administered calculated to achieve a dose of 240 mg I/kg of body weight. They were administered by rapid i.v. bolus injection over 30 s via the butterfly needle.

Seven millilitre blood samples were taken from the indwelling butterfly needle, the first 2 ml of each sample being discarded. Samples were taken immediately after injection and at 1 min intervals for the first 5 min and then at 10, 15 and 20 min.

Radiographs were scored by all four participating

radiologists working independently by a modified version of the method of Kelsey Fry *et al.* (1967), film identification having been removed.

Biochemical Methods

Plasma concentrations of contrast media were determined by spectrophotometry following deproteinization with barium hydroxide, zinc sulphate and magnesium sulphate. The wavelengths were 241 nm for Conray, 243 nm for Hexabrix and 242 nm for Niopam. Recoveries of contrast media were 97.6–101% and between batch imprecision (CV) varied between 0.65 and 3.04%.

Contrast media concentrations in urine were determined using high performance liquid chromatography (HPLC). The method of Thomayant *et al.* (1984) was used for Conray and this was modified for Niopam and Hexabrix. The HPLC system was supplied by Pye Unicam (Cambridge, UK) and included an isocratic pump, a variable wavelength UV detector set at 243 nm, a video control centre, a Rheodyne syringe loading sample injector and a 25 cm Apex octadecyl column (particle size 10 μm, ID 4.6 mm; Jones Chromatography, Hengoed, Mid-Glomorgan). The mobile phase was 3.5%, 5% and 8% acetonitrile in 0.04% phosphoric acid pH 2.5 ± 0.05 for Conray, Niopam and Hexabrix, respectively. Flow rates were 1.8 ml/min at ambient temperature for Conray and Niopam and 1.7 ml/min for Hexabrix. Each mobile phase was filtered through a 0.2 μm nylon filter before use and degassed under helium during chromatography. Standards were constituted in a urine base with p-aminobenzoic acid as internal standard in the analysis of Conray and Niopam and iodohippuric acid as internal standard for the analysis of Hexabrix. Between batch imprecision was 1.3–8.8% and recoveries for Hexabrix were 92.4–108%.

Osmolalities were determined by freezing point depression and other biochemical variables by standard techniques using an Astra 9 analyser (Beckman RIIC, High Wycombe, Bucks).

RESULTS

The sex-distribution, age and weights of the patients are recorded in Table 1. Variation between sex was ruled out on physiological grounds. Hence randomization was not stratified by sex resulting in a predominance of male patients allocated Hexabrix contrast medium. A one-way analysis of variance on the age of the patients established no significant difference in the mean age between the treatment groups ($P = 0.5$).

Results for one-way analysis of variance on control plasma data (not presented in the interest of brevity), showed no significant differences between contrast media groups. Analysis considered Na, K, Cl, CO_2, urea and creatinine concentrations. The characteristics for patient number 14 are considered separately since this patient exhibited results greater than two standard deviations away from the mean of the same contrast agent group on all variables analysed.

Analysis on control plasma osmolality showed no significant difference between the groups ($P = 0{\cdot}97$). Analysis of Covariance was carried out on plasma osmolality over time and although Conray was initially significantly higher ($P = 0{\cdot}03$) than Hexabrix and Niopam the slopes (Fig. 1) were not significantly different ($P = 0{\cdot}28$). The fitted lines recorded in Fig. 1 show that the ionic high osmolar medium Conray caused the largest changes in plasma osmolality and Hexabrix, an ionic low osmolar agent the least disturbance. As expected, only Conray, the ionic agent, exceeded the physiological value of 300 mmol/kg.

Plasma concentrations of the contrast media expressed as a g I/litre are recorded in Fig. 2*a–c*. Patient number 14 (in the Conray group) showed results which were significantly different from others in the same group and has been excluded from group analysis. In order to summarize this data into a manageable form it was assumed that the contrast media exhibited first order linear kinetics, an assumption that seemed reasonable following an inspection of these plots on a log scale. Log linear regressions, ignoring time points zero and one minute, were carried out and the fitted lines are shown in Fig. 2*d*.

A striking feature of the graphs of iodine concentration against time is the temporary rise in plasma iodine between 2 and 9 min in five of the Hexabrix patients. The Hexabrix patients showing this rise were compared with those without it but no statistical difference was found between them. These results have been attributed to observational error in the absence of a rational explanation. In this analysis Conray and Niopam were not significantly different from each other although Hexabrix was significantly higher than both Conray and Niopam ($P = 0.009$).

Table 1 – Sex, age and weight of patients

	Conray	*Niopam*	*Hexabrix*
Number of patients	11	10	11
males	6	7	10
females	5	3	1
Age (years) mean (SEM)	48.6 (4.78)	56.3 (5.01)	49.7 (4.78)
Weight (kg) mean (SEM)	72.9 (4.08)	66.8 (4.28)	77.2 (4.08)

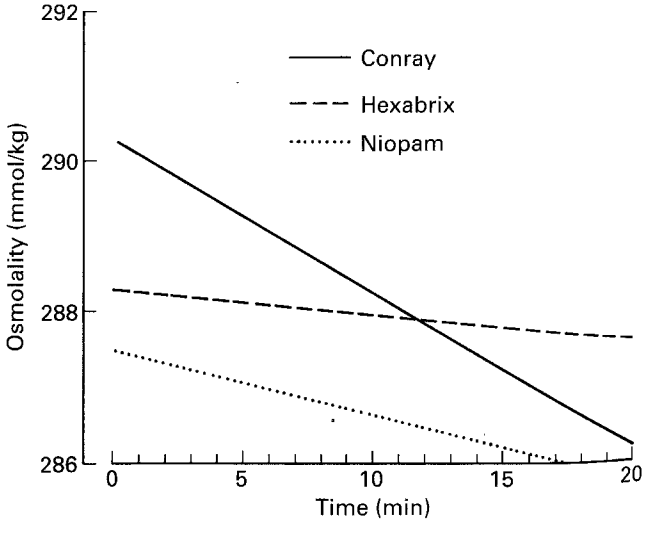

Fig. 1 – Lines fitted to plasma osmolality for each group (with standard errors of estimates). Conray (mmol/kg) $= 290.2\ (0.82) - 0.193\ (0.075)$ min. Hexabrix (mmol/kg) $= 288.2\ (0.78) - 0.03\ (0.072)$ min. Niopam (mmol/kg) $= 287.4\ (0.77) - 0.825\ (0.064)$ min.

Results from one-way analysis of variance on spot urine data are recorded in Table 2. Niopam had the highest iodine concentration and Hexabrix the lowest. Hexabrix recorded the lowest iodine/creatinine ratio but the highest creatinine concentration.

Analysis of inter-observer variation in scoring the radiographs was undertaken by non-parametric methods due to the ordinal scale of the scored data. The tests used were Cohen's Kappa (K) and Kendall's Coefficient of

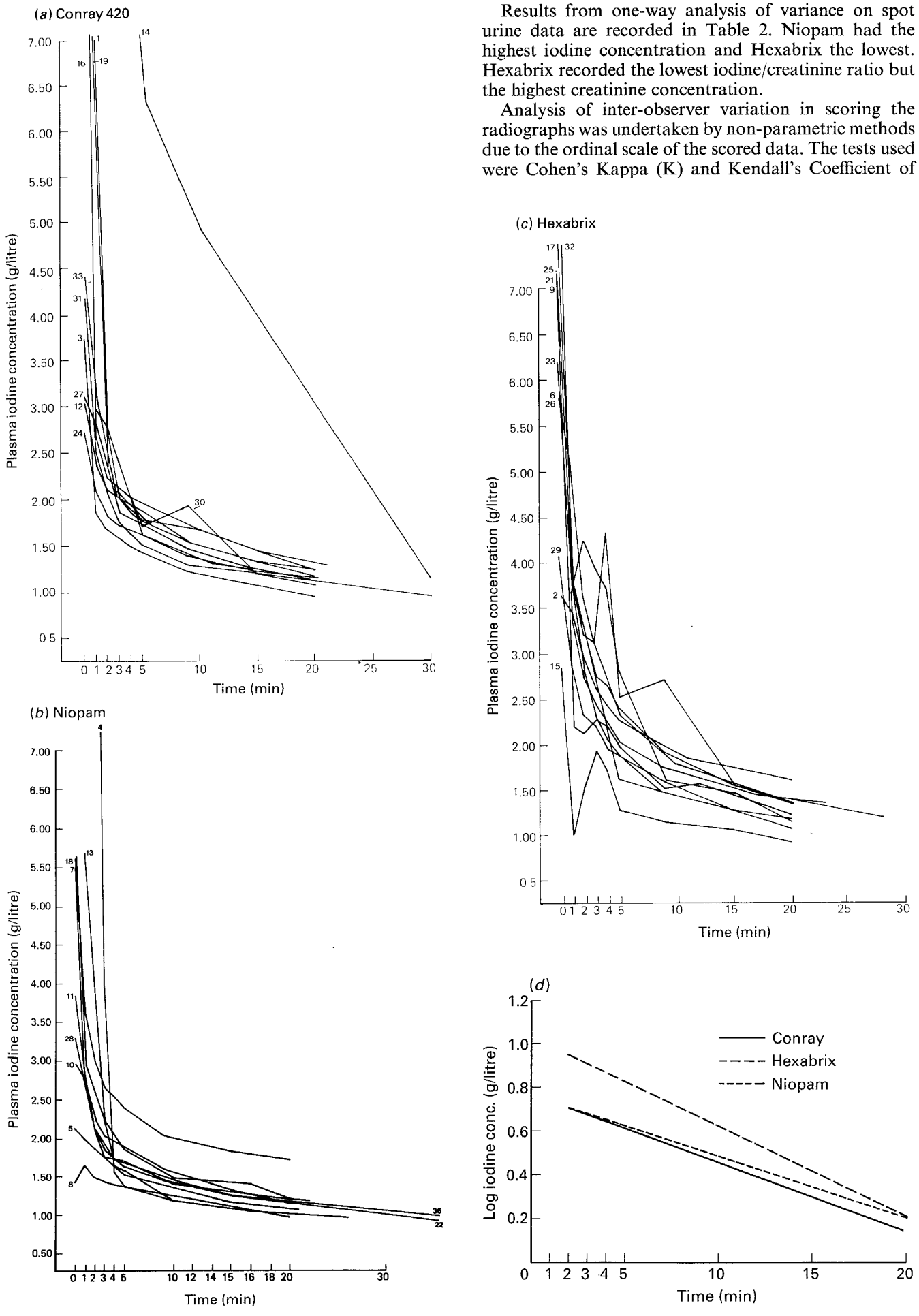

Fig 2 – Plasma iodine concentration vs time. (*a*) Conray. (*b*) Niopam. (*c*) Hexabrix. (*d*) Lines fitted to log plasma iodine concentration.

Table 2 – Results from one-way analysis of variance on spot urine data

	Iodine concentration (g/litre)	*Creatinine concentration (mmol/litre)*	*Iodine/creatinine ratio (g/mmol)*
P value	0.43	0.012	0.02
General mean	59.04	8.85	7.92
Conray (SEM)	58.3 (5.72)	6.65 (0.99)	10.9 (1.39)
Hexabrix (SEM)	54.5 (5.72)	11.2 (0.99)	5.06 (1.39)
Niopam (SEM)	65.6 (6.32)	8.7 (1.09)	7.70 (1.53)

Note: *P* values are testing the hypothesis that the three groups, namely Conray, Hexabrix and Niopam, come from the same population.

Table 3 – Analysis of inter-observer variation in scoring the radiographs using Kendall's Coefficient of Concordance [with chi square approximations on 30 degrees of freedom ( )]

Time after injection (min)	*Overall scores*	*Nephrogram density*	*Pyelogram density*	*Pyelogram distension*
0	0.74 (88.7)	0.75 (95.3)	0.98 (117.9)	1.00 (120)
5	0.61 (74.2)	0.58 (70.1)	0.69 (83.6)	0.79 (94.3)
10	0.83 (99.8)	0.64 (77.1)	0.76 (91.3)	0.81 (98.3)
15	0.80 (96.2)	0.57 (68.6)	0.77 (93.2)	0.77 (93.2)

Concordance (W) (Siegel and Castellan, 1988). Scores from left and right kidneys were added and all analyses of scored data consider that total.

Results of Cohen's Kappa are omitted in the interests of brevity but showed that there was substantial agreement among the four observers. Results for Kendall's Coefficient of Concordance are given in Table 3. Overall score was obtained by taking the total of the three separate scores. Due to the very high chi-square statistics (*P* value for all of them <0.0001) again it is concluded that there was very good agreement among the four radiologists in all respects.

Consequently scores were then averaged over the four observers. There was too much serial correlation between time points to consider the measurements at each time point as independent replications. Thus for each set of scores three summary measures were considered. These were:

1 *Maximal score achieved.* A measure of peak iodine concentrations in the proximal convoluted tubules (nephrogram) and collecting system (pyelogram) respectively.
2 *Time to maximum score.* A measure of glomerular filtration rate (nephrogram) and glomerular filtration rate with urine flow rate (pyelogram) respectively.
3 *Area under the score curve.* A measure of the glomerular clearance of the contrast (nephrogram) and glomerular clearance with tubular clearance (pyelogram), respectively.

Analysis of the data scored in this was largely non-parametric, although parametric analysis was used in 3 (above) where normality assumptions seemed reasonable. Kruskal-Wallis statistics were used in items 1 and 2 to investigate differences between the average score for each contrast agent. Analysis was carried out upon the overall score and the nephrogram density, pyelogram density and pyelogram distension scores. Due to the problems associated with repeated significance testing, only results with *P* values less than 0.01 were considered to be significant.

The maximum score is a measure of the highest quality urogram attainable. Results did not show any significant

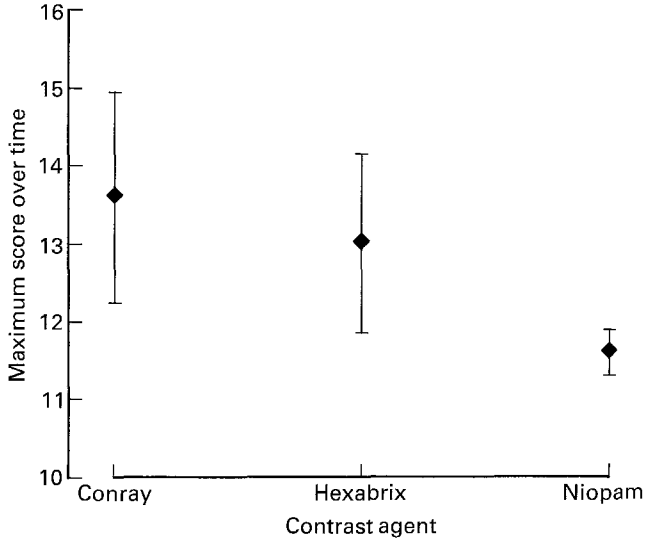

Fig. 3 – Plot of maximum scores achieved with 95% confidence intervals.

difference between contrast agents on nephrogram density, pyelogram density and pyelogram distension scores. Niopam was significantly poorer than both Conray and Hexabrix on the overall score (*P* value $=0.003$) (Fig. 3).

The time to maximum density records the optimum time after injection to take the urogram. The results are recorded in Table 4. It is noted that Hexabrix generally peaked earlier than either Conray or Niopam although this was not statistically significant. All patients receiving Hexabrix recorded maximum density nephrograms immediately after injection of the contrast agent. The fact that this was not significant was felt to be due to the small sample size rather than no effect being present.

Area under the score curve is an overall measurement of urographic quality over the four time points. Results are recorded in Fig. 4. Conray recorded a significantly higher nephrogram score than either Hexabrix or Niopam ($P=0.005$). On the overall score, Niopam produces a poorer urogram than Conray ($P=0.005$) but not Hexa-

Table 4 – Results for 'time to maximum density'

Overall scores
Kruskal-Wallis statistic = 4.99 ~ χ^2 (2)
P value = 0.08

	Mean	(SEM)	Median
Conray	11.25	(1.25)	11.25
Hexabrix	7.72	(1.03)	5.00
Niopam	11.25	(1.45)	13.75

Nephrogram density
Kruskal-Wallis statistic = 6.79 ~ χ^2 (2)
P value = 0.03

	Mean	(SEM)	Median
Conray	3.75	(1.6)	1.25
Hexabrix	0.0	(0)	0
Niopam	2.5	(1.11)	0

Pyelogram density
Kruskal-Wallis statistic = 4.51 ~ χ^2 (2)
P value = 0.1

	Mean	(SEM)	Median
Conray	12.0	(1.10)	12.5
Hexabrix	8.4	(1.02)	7.5
Niopam	10.75	(1.39)	11.25

Pyelogram distension
Kruskal-Wallis statistic = 3.25 ~ χ^2 (2)
P value = 0.2

	Mean	(SEM)	Median
Conray	12.5	(1.1)	15.0
Hexabrix	9.54	(1.2)	10.0
Niopam	12.0	(1.333)	15.0

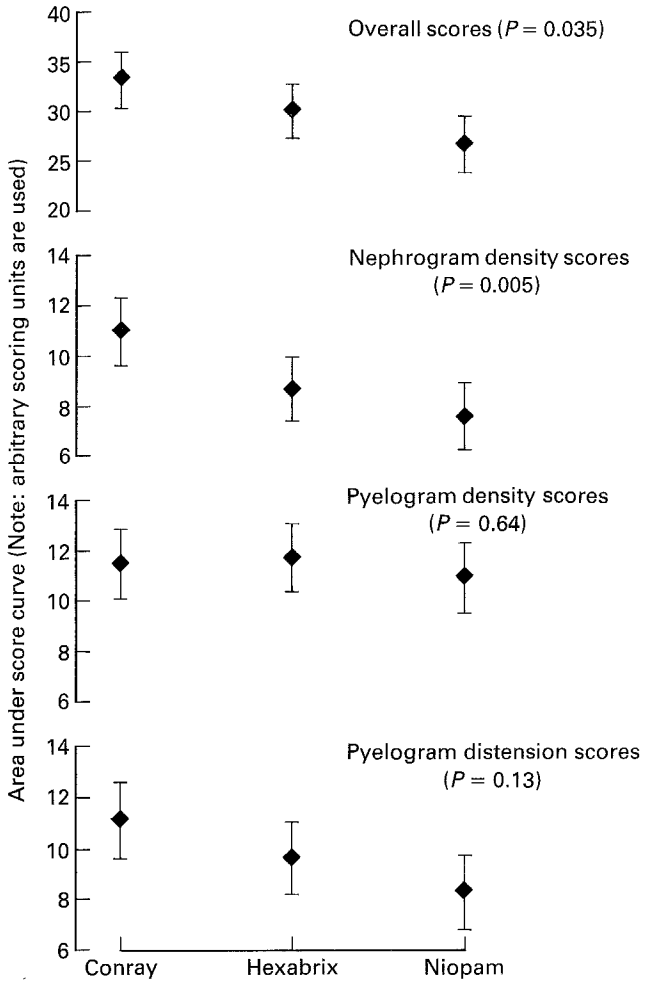

Fig. 4 – Plots of area scores with 95% confidence intervals.

brix ($P=0.08$). There was no statistical difference between the three contrast agents for pyelogram density and pyelogram distension scores.

The relationship between plasma iodine concentrations, plasma osmolality and the quality of the urographic images was investigated. The intercepts and slopes (slope is related to GFR) of the fitted lines for the log plasma iodine concentrations and osmolalities were each plotted and then tested for correlation against the area scores and times of maximum density scores. No significant observations were made.

The relationship between spot urine concentrations of iodine and the radiographic image was also investigated. It was felt that final urine concentration was most likely to be related to pyelogram density and distension so tests for correlations were not carried out on the nephrogram density and the overall scores. Pyelogram density was negatively correlated with iodine/creatinine ratio $r=-0.38$ ($P=0.03$) for the 'area' score whilst 'time to maximum density' was positively correlated with the iodine/creatinine ratio $r=0.40$ ($P=0.03$). There were no other significant correlations.

DISCUSSION

Niopam showed a high initial plasma iodine concentration between 1 and 2 min after injection, which may be a result of its lower volume of distribution (Kormano, 1981; Wilcox *et al.*, 1983). At 2 min the average plasma iodine concentration for Niopam is 3.19 g I/l and Conray is 2.26 g I/l. This suggests that, for a plasma volume of 2.75 l, 48% of Niopam and 63% of Conray has been transferred from the intravascular space. Dawson *et al.* (1984) cite a figure of 75% which is very similar to our calculation if dilution is allowed for. We know that the high osmolar agents cause a rapid influx of fluid into the intravascular space which itself will cause a dilution effect of up to 10% (Olutola *et al.*, 1986).

Interpretation of the log plasma iodine concentrations (Fig. 2*d*) would suggest that excretion of Hexabrix was initially slower than the other contrast agents and that as the examination progresssed it gradually caught up. It is felt, however, that this difference was due to five of the Hexabrix patients showing an initial, temporary rise in their plasma iodine concentrations.

Plots of the osmolality data (not included) showed, as expected, a huge variation in the first minute which settled down shortly afterwards. It was anticipated that Conray, being highly ionized, would dilute more rapidly than other agents. However, although Conray had the most negative slope (Fig. 1) it was not statistically different from the others.

Consideration of the timing of the maximum scores for nephrograms achieved by the patients showed that Hexabrix nephrograms are all maximally dense immediately after injection. This finding did not reach statistical significance, probably due to the small sample size rather than no effect being present.

We have confirmed the findings of other workers that the low osmolar monomer, Niopam, produces significantly poorer nephrograms than ionic monomers (Dawson *et al.*, 1984; Davies *et al.*, 1985). Dawson *et al.* (1984) attributed this to differences in iodine concentration. However, our study shows that this is also true after equal doses of iodine, but is equally true for the low osmolar ionic dimer Hexabrix.

No convincing explanation for the better nephrogram with ionic media has yet been given. It is known that the high osmolar load of Conray will cause a fall in GFR (Webb, 1984), and a reduction in systolic BP. The bolus of contrast is known to pass along the renal arteries within 20 s of injection. The concentration of contrast is higher at this point in time than at any subsequent time due to diffusion and distribution within plasma and extracellular fluid. The fall in renal blood flow and in GFR will now cause a temporary reduction in flow along the tubules. The high concentration of contrast in the first pass 'bolus' is now effectively stationary in the tubules giving rise to a dense nephrogram. Tubular flow will resume as the contrast is distributed and its concentration and osmolality reduce.

Our study suggests that Niopam not only produces poorer nephrograms but poorer overall urograms than both Conray and Hexabrix. Because of the low sample size we were unable to differentiate between Conray and Hexabrix in this respect.

The lower urinary creatinine concentration after Conray than Niopam suggests a greater diuresis after Conray, decreasing the concentration of contrast in the urine. However, the contrast/creatinine ratios, which correct for diuretic effects, confirm the findings of other workers that sodium containing ionic monomers achieve higher urinary concentrations of contrast than low osmolar media.

Hexabrix produced the most concentrated urine and yet appeared to excrete the least amount of contrast. This suggests a minimal diuretic effect and a low rate of urinary excretion. Weinmann *et al.* (1981), showed that only 70% of Hexabrix is excreted by the kidneys and that extrarenal excretion may account for this finding.

No correlation was found between the pyelogram density and urinary iodine concentration alone. However, pyelogram density showed a negative correlation with the iodine/creatinine ratio in the urine. In other words the low urinary iodine and relatively concentrated urine produced by Hexabrix correlated with the high pyelogram density scores.

Our study suggests that, in terms of image quality, the ionic monomer Conray is superior to the low osmolar agents Hexabrix and Niopam for urography.

Clinical choice of contrast agent, however, must rest upon a finely judged balance between cost, safety and efficacy. We are drawn to the conclusion that sodium containing ionic monomers should be the first-line choice for urography and that low osmolar agents should be reserved for patients at high-risk of contrast medium reactions.

Acknowledgements. We thank our radiographic colleagues in the Department of Radiology, Freeman Hospital for their radiographic skills and Mrs J. T. Stoddart for typing the manuscript.

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