A comparison of the clearance of urographic contrast medium (sodium diatrizoate) by peritoneal and haemodialysis

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Summary

1. The clearance of isotopically labelled sodium diatrizoate by haemodialysis was measured in vitro, with simulated extracellular fluid, and in vivo in eleven patients, at varying rates of fluid or plasma flow. Clearance was also measured in five patients undergoing peritoneal dialysis. In all instances simultaneous measurements of urea clearance were made and the diatrizoate/urea clearance ratio was calculated.

2. In haemodialysis studies, diatrizoate and urea clearances showed a linear increase with increasing 'extracellular fluid' or plasma flow through the dialyser while the diatrizoate/urea clearance ratio fell.

3. The clearance of diatrizoate in vivo was slightly less than clearance in vitro at corresponding flow rates, but the diatrizoate/urea clearance ratio showed no significant difference.

4. Diatrizoate and urea clearances during peritoneal dialysis were very much lower than during haemodialysis but the diatrizoate/urea clearance ratios were within the same range.

5. The rapid removal of diatrizoate in patients with renal failure requires haemodialysis.

Key words: diatrizoate, haemodialysis, kidney (artificial), peritoneal dialysis, urography.

Introduction

The availability of non-toxic radiographic contrast media has led to the widespread use of high-dose excretion urography for the investigation of patients with severe oliguric and non-oliguric renal failure (Schwartz, Hurwitt & Ettinger, 1963; Fry & Cattell, 1971, 1972). The safety of this investigation and the valuable information provided fully justify its increasing use (Grainger, 1972). Because the contrast media in common use are primarily excreted by the kidneys (Denneberg, 1965; Donaldson, 1968; Cattell, 1970) and because there always remains the possibility of adverse systemic reactions to the drug (Berlyne & Berlyne, 1962; Ansell, 1970; McClennan, Kassner & Becker, 1972; Davies, Roberts & Roylance, 1975), it has been recommended that high-dose excretion urography should only be carried out on patients with severe renal failure where facilities are available for treatment by dialysis (Saxton, 1969; Brown, Glancy, Fry & Cattell, 1970; Fry & Cattell, 1971; Grainger, 1972). Because the diffusibility of contrast media has been little investigated we have examined the effectiveness of dialysis in the elimination of a commonly used contrast medium, sodium diatrizoate, both by peritoneal and haemodialysis.

Materials and methods

'Haemodialysis' study in vitro

Sodium diatrizoate is distributed throughout the extracellular fluid space (Denneberg, 1965) and exhibits little, if any, protein binding (Lasser, Farr, Fujimagari & Tripp, 1962). Extracellular fluid was simulated by the use of a reservoir containing 15 l of dialysis fluid (composition: sodium 130 mmol/l, potassium 1-34 mmol/l, calcium 1-65 mmol/l, magnesium 0-5 mmol/l, chloride 101 mmol/l,
acetate 35 mmol/l, lactate 1.3 mmol/l, glucose 10 mmol/l) maintained at body temperature (37°C). Urea was added to this solution to a concentration of 84 mmol/l (500 mg/100 ml). To measure diatrizoate clearance, 30 μCi of 125I-labelled sodium diatrizoate was added to the reservoir, and the contents were adequately mixed. Clearance was studied by using a two layer, single-pass standard Kiil dialyser, with an 11.5 μm cross-grain wet-stretched cuprophone membrane of area 1.0 m². The simulated extracellular fluid was dialysed against dialysing fluid of the same electrolyte composition to which no urea or diatrizoate had been added. Dialysate flow rate was maintained at 500 ml/min; "extracellular fluid" flow rate through the kidney was varied between 60 and 170 ml/min. The net transmembrae ultrafiltration pressure was maintained constant at 30 mmHg.

"Haemodialysis" study in vivo

Eleven oliguric patients were studied. All had end-stage renal failure and were undergoing regular dialysis treatment in hospital. The patients were told of the nature and purpose of the investigation and all gave their informed consent. All studies were carried out during the course of routine dialysis with two-layer single-pass flat-plate dialysers, with 11.5 μm cross-grain wet-stretched cuprophone membranes of area 1.0 m². Six patients used standard Kiil dialysers and five patients used Meltec multipoint pyramid dialysers. Dialysate flow rate was maintained at 500 ml/min and net transmembrae ultrafiltration pressure was maintained constant at 100 mmHg. Blood flow through the dialyser was controlled by a Watson–Marlow MHRE blood pump, thus allowing deliberate variation in the flow rate. Each patient was given an intravenous injection of 30 μCi of sodium [125I]-diatrizoate, and after a 2 h equilibration period, blood samples were taken from the inlet and outlet lines of the dialyser, and the blood flow rate was measured by the bubble flow method (Jameson, 1968). Three further pairs of samples were obtained from each patient at different rates of blood flow.

Calculation of clearance

For "haemodialysis" studies both in vitro and in vivo, clearance of diatrizoate and urea was calculated from the formula

\[ F = \frac{A - V}{A} \]

where \( A \) and \( V \) are the urea or diatrizoate plasma concentrations in the samples obtained simultaneously from the inlet and outlet lines respectively. In studies in vitro \( F \) is the measured 'extracellular fluid' flow rate through the dialyser. In studies in vivo, to allow comparison with the studies in vitro, plasma clearance was measured, where \( F \) is the calculated plasma flow rate derived from the formula

\[ \text{Plasma flow rate} = \left( \frac{1 - \text{packed cell volume}}{100} \right) \times \text{measured blood flow rate} \]

The packed cell volume value used was the mean for each pair of samples.

Peritoneal dialysis

Studies were carried out on five patients, who presented with acute oliguric renal failure and who required peritoneal dialysis for their management. The nature and purpose of the study having been explained, their consent was freely obtained. Each patient was given 30 μCi of sodium [125I]-diatrizoate intravenously at least 12 h before measurement of peritoneal clearance. Clearance was measured with the patient fully established on dialysis, and 2 litre exchanges of dialysis fluid (Dialaflex 61) were made. The cycle time, measured from the start of inflow to completion of outflow, was recorded on each of three consecutive cycles. The fluid recovered from each cycle was collected separately, its volume measured, and an aliquot removed for urea and diatrizoate estimation. A blood sample was taken for urea and diatrizoate estimation at the midpoint of each cycle. In each patient the sequence was repeated on a separate occasion about 24 h later. Peritoneal clearance of urea and diatrizoate was calculated from the formula

\[ \text{Peritoneal clearance (ml/min)} = \frac{UV}{Pt} \]

where \( U \) is the concentration of urea or diatrizoate (mmol/l) and \( V \) is the volume (ml) of the outflow fluid, \( P \) is the plasma concentration of urea or diatrizoate (mmol/l) and \( t \) is the cycle time (min). The rate of peritoneal dialysis was expressed as the dialysed volume (l/h) calculated by multiplying the inflow volume in litres (2) by 60 and dividing by the cycle time (\( t \)) in minutes.
The radioactivity of all samples was measured in a well-type scintillation counter, pulse-height analysis being used to detect the photopeak of \(^{125}\)I, and urea was measured by Technicon AutoAnalyzer.

Results

Haemodialysis in vitro

The relationship between urea and diatrizoate clearances and 'extracellular fluid' flow rate is shown in Fig. 1. Both show a positive correlation with flow rate (urea, \(r = 0.986, P < 0.001\); diatrizoate, \(r = 0.940, P < 0.001\)). From the regression lines (method of least squares), at an 'extracellular fluid' flow rate of 100 ml/min, the diatrizoate clearance is 34.7 ml/min, and the urea clearance 68.2 ml/min.

\[
\text{urea clearance} = 27.6 + 0.41E, \quad r = 0.986, \quad P < 0.001;
\]
\[
\text{diatrizoate clearance} = 22.9 + 0.120E, \quad r = 0.940, \quad P < 0.001.
\]

In vitro, at a plasma flow rate of 100 ml/min, the diatrizoate/urea clearance ratio for the Kiil dialyser is 51.5% and for the Meltec multipoint dialyser 54%.

Haemodialysis in vivo

Urea and diatrizoate clearances again showed a linear increase with increasing plasma flow both with the Kiil dialyser (urea, \(r = 0.938, P < 0.001\); diatrizoate, \(r = 0.746, P < 0.001\)) and the Meltec multipoint dialyser (urea, \(r = 0.945, P < 0.001\); diatrizoate, \(r = 0.953, P < 0.001\)). The urea and diatrizoate clearances obtained with the Kiil dialyser were slightly less than those obtained in the study in vitro. Thus, at a plasma flow rate of 100 ml/min, the diatrizoate clearance was 31.8 ml/min and the urea clearance 61.6 ml/min. Considerably greater clearances were obtained with the Meltec multipoint dialyser and at a plasma flow rate of 100 ml/min the diatrizoate clearance was 43.2 ml/min and the urea clearance 81.7 ml/min. Regression equations for the above data are presented at the end of this section.

The diatrizoate/urea clearance ratio shows a negative correlation with flow rate in vitro \((r = 0.882, P < 0.001, \text{Fig. 2})\) and in vivo with both the Kiil dialyser \((r = 0.812, P < 0.001)\) and the Meltec multipoint dialyser \((r = 0.733, P < 0.001)\). Regression lines for the experiments in vitro and in vivo with the Kiil dialyser are almost identical. The regression line for the experiments in vivo with the Meltec dialyser differs slightly (see 'Regression equations', below) but the difference is not statistically significant.

In vivo, at a plasma flow rate of 100 ml/min, the diatrizoate/urea clearance ratio for the Kiil dialyser is 51.5% and for the Meltec multipoint dialyser 54%.

Peritoneal dialysis

Table 1 shows the mean diatrizoate and urea peritoneal clearances and the diatrizoate/urea clearance ratio for each patient. Four patients gave very similar results whereas one patient (J.H.) gave much higher values. The latter also differed in that he had undergone intermittent peritoneal dialysis 6 weeks before these measurements and had been treated for peritoneal infection on a number of occasions. The others were all studied during their initial dialysis. The mean diatrizoate clearance of all patients studied was 7.1 ml/min (SD 2.8), the urea clearance 13.8 ml/min (SD 3.3) and the diatrizoate/urea clearance ratio 49.8% (SD 9.0). If the patient J.H. is excluded the mean diatrizoate and urea clearances are 5.8 ml/min (SD
1.0) and 12.5 ml/min (SD 2.1) respectively, and the diatrizoate/urea clearance ratio 45.6% (SD 4.5). The peritoneal dialysis rate varied from 1.8 to 2.8 l/h. There was no correlation between dialysis rate and diatrizoate/urea clearance ratio.

Regression equations

**Kii1 dialyser in vitro.** Urea clearance = 27.6 + 0.41E (E is flow rate of 'extracellular fluid'). Diatrizoate clearance = 22.9 + 0.120E. Diatrizoate/urea clearance ratio = 63.1 - 0.117E.

**Kiil dialyser in vivo.** Plasma urea clearance = 26.4 + 0.35P (P is plasma flow rate). Plasma diatrizoate clearance = 20.6 + 0.11P. Diatrizoate/urea clearance ratio = 63.5 - 0.117P.

**Meltec multipoint dialyser.** Plasma urea clearance = 23.8 + 0.58P. Plasma diatrizoate clearance = 24.5 + 0.19P. Diatrizoate/urea clearance ratio = 66.6 - 0.128P.

Discussion

The only published data on diatrizoate clearance by haemodialysis in vivo are those of Bahlmann & Kruskemper (1973). Studying the decrease in total plasma iodine after the injection of meglumine sodium diatrizoate in eight patients undergoing haemodialysis on modified Kiil dialysers, they reported a whole blood clearance value of 52.9 ± 8 ml/min at a mean blood flow rate of 172 ml/min. Exact comparison with our studies of plasma clearance is not possible in the absence of values for packed cell volume in their patients. Increasing the packed cell volume will reduce the plasma flow for the same blood flow through the dialyser and as diatrizoate clearance decreases with decreasing plasma flow, variation in the packed cell volume will influence the results obtained. In our studies, the mean packed cell volume was 21.3% (range 15-25%) and from this value and the regression line for diatrizoate and urea clearance and diatrizoate/urea clearance ratio during peritoneal dialysis

Results for individual patients are mean values (± SD) for six cycles.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Dialysis rate (l/h)</th>
<th>Diatrizoate clearance (ml/min)</th>
<th>Urea clearance (ml/min)</th>
<th>Diatrizoate/urea clearance ratio (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>J.H.</td>
<td>1.8</td>
<td>11.8 ± 1.2</td>
<td>18.4 ± 2.5</td>
<td>63.7 ± 3.5</td>
</tr>
<tr>
<td>L.K.</td>
<td>2.2</td>
<td>5.1 ± 0.7</td>
<td>12.8 ± 2.2</td>
<td>40.0 ± 1.7</td>
</tr>
<tr>
<td>S.T.</td>
<td>2.8</td>
<td>6.5 ± 1.3</td>
<td>14.6 ± 2.0</td>
<td>44.2 ± 3.1</td>
</tr>
<tr>
<td>O.H.</td>
<td>2.5</td>
<td>5.6 ± 0.5</td>
<td>11.2 ± 0.9</td>
<td>50.2 ± 2.5</td>
</tr>
<tr>
<td>W.W.</td>
<td>2.2</td>
<td>5.1 ± 1.0</td>
<td>11.6 ± 1.6</td>
<td>45.0 ± 1.4</td>
</tr>
<tr>
<td>Mean</td>
<td>2.3</td>
<td>7.1 ± 2.8</td>
<td>13.8 ± 3.3</td>
<td>49.8 ± 8.8</td>
</tr>
<tr>
<td>Mean</td>
<td>2.4</td>
<td>5.8 ± 1.0</td>
<td>12.5 ± 2.1</td>
<td>45.6 ± 4.5</td>
</tr>
</tbody>
</table>
Clearance of diatrizoate by dialysis

Diatrizoate clearance we calculated an expected whole blood diatrizoate clearance value of 51 ml/min at a blood flow of 172 ml/min.

The diatrizoate clearance we obtained with the Meltec dialyser was greater than that obtained with the Kiiil dialyser. However, there was also an increase in the urea clearance and comparison of the diatrizoate/urea clearance ratios between the two dialysers revealed no significant difference. Thus although the pyramid support system considerably improved the overall clearances, relative clearance was unaltered.

Studies of diatrizoate clearance in vitro with a few dialysers at a single flow rate of 200 ml/min have been reported previously (von Hartitzsch, Hoenich, Peterson, Buselmeier, Kerr & Kjellstrand, 1973). For the Kiiil dialyser they obtained a mean value of 44.0 ± 2.4 ml/min and extrapolation of our data yields a similar value, 45.6 ml/min.

The diatrizoate/urea clearance ratio for the Kiiil dialyser in vivo was identical with that obtained in vitro, which supports the findings of Lasser et al. (1962) that significant protein binding of diatrizoate does not occur. Demonstration of identical results in vivo and in vitro for the diatrizoate/urea clearance ratio allows studies to be undertaken in vitro for the evaluation of other dialysers. This is of some special interest as sodium diatrizoate has a molecular weight of 639 and hence lies within the range of 'middle molecules', which have been held to be responsible for uraemic toxicity in dialysed patients (Babb, Popovich, Christopher & Scribner, 1971).

The diatrizoate clearance observed during peritoneal dialysis was considerably lower than during haemodialysis. This was not unexpected for the urea clearance was also much lower. The diatrizoate/urea clearance ratio for peritoneal dialysis (49 ± 9%) was very similar to that obtained during haemodialysis in the range of plasma flow from 100 to 150 ml/min. There are only two previous reports of peritoneal clearance measurements in a total of six patients (Brooks & Barry, 1974; Milman & Christensen, 1974). In the latter study of five patients a mean diatrizoate clearance of 10.7 ml/min was achieved but in two patients with the highest values hypertonic dialysis solutions were used, and in neither study was urea clearance measured.

Although the safety of high-dose excretion urography in renal failure is well established, provided that the patient is not dehydrated and conventional doses of contrast media are not exceeded (Grainger, 1972; Doyle, Sherwood, Steiner, Breckenridge & Dollery, 1967), severe, sometimes fatal, systemic reactions have been reported commonly due to excessively large doses (Ansell, 1970; McClennan et al., 1972; Davies et al., 1975). Our studies have confirmed that, in the event of adverse reactions diatrizoate can be removed by both haemodialysis and peritoneal dialysis, the clearance in each case being approximately half that of urea. However, because of the relatively low clearance which can be obtained by peritoneal dialysis, rapid removal of diatrizoate requires haemodialysis.

In clinical practice the effectiveness of removal of a non-protein-bound substance is commonly expressed in terms of the plasma half-life (t1/2). In patients with severe renal failure, the t1/2 for diatrizoate can be as long as 140 h, despite some extrarenal excretion (Van Waes, 1971). If we assume an extracellular volume, and hence distribution volume for sodium diatrizoate, of 15 l in our patients we estimate that, at a plasma flow rate of 100 ml/min, the t1/2 with the Kiiil dialyser would be 5 ½ h, with the Meltec multipoint dialyser 4 h, and by peritoneal dialysis between 24 and 30 h, exclusive of any extrarenal excretion.

It should also be noted that if dialysis becomes necessary during the course of excretion urography, e.g. before a final 24 h film (Fry & Cattell, 1971), haemodialysis will markedly affect the blood concentration of contrast and possibly the evolution of a delayed nephrogram or pyelogram.

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References


