Relative efficacy of haemoperfusion, haemodialysis and CAPD in the removal of procainamide and NAPA in a patient with severe procainamide toxicity

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Introduction

The pharmacokinetics of procainamide (PA) and its active metabolite, N-acetylprocainamide (NAPA) have been well characterized in normal subjects [1-4]. However, PA disposition in patients with renal failure can be highly variable and unpredictable [5-8]. The non-renal clearance of PA has been reported to be reduced in patients with renal failure [5-8]. NAPA, which is eliminated mainly by the kidneys, accumulates in patients with renal failure [7-9], although its non-renal clearance remains unaltered [7]. Elevated and sustained concentrations of both PA and NAPA are associated with an increased risk of adverse effects [10,11].

The small molecular size and low protein binding of PA and NAPA (14% for both) are desirable attributes for extracorporeal drug removal [11]. Indeed, PA toxicity has been treated, with varying degrees of efficiency, by several modalities, including peritoneal dialysis (PD) [12], haemodialysis (HD) and/or haemoperfusion (HP) [13,16] and continuous arteriovenous haemofiltration/haemodialfiltration (CAVH/CAVHD) [17]. We report a patient with procainamide toxicity managed by combined HP/HD and concurrent chronic continuous ambulatory peritoneal dialysis (CAPD).

Case report

A 66-year-old white male with end-stage renal disease secondary to diabetes mellitus had been treated with CAPD since 1992. This anuric patient was admitted to the hospital with complaints of progressive lethargy and mental confusion. His medications on admission included calcium acetate, colchicine, folic acid, vitamin B and C complex, and erythropoietin. Procainamide 500 mg Q8H had been started 2 months prior to admission for prophylaxis against recurrent atrial fibrillation. PA and NAPA levels drawn several hours after the last administered dose of PA were 17.4 µg/ml (therapeutic range: 4-10 µg/ml) and 31.2 µg/ml (therapeutic range: 6-20 µg/ml) respectively. PA and NAPA levels repeated 4 h later were 17.2 µg/ml and 36.4 µg/ml respectively. PA toxicity was diagnosed at this time and PA was immediately discontinued. Because of the severity of the PA and NAPA toxicity, combined HP/HD was initiated.

The patient’s neurological symptoms gradually improved with each of the four combined HP/HD treatments over 4 days. Levels of PA and NAPA were normalized by day 4 of dialysis, but the patient died shortly thereafter of an intestinal infarction secondary to mesenteric arterial insufficiency.

Methods

HP was performed using an Adsorba 300C haemoperfusion cartridge. This cartridge contained 300 g of activated carbon with a surface area of 300 000 m². Blood was also routed in series through an Althin MCA-180 hollow fibre haemodialysers with a surface area of 1.8 m² and an ultrafiltration coefficient of 5. The blood and dialysate flow rates were recorded for each session. A schematic of the setup is shown in Figure 1.

The first session of combined HP/HD was started about 2 h after the second levels of PA and NAPA were measured and lasted for 4 h. The patient underwent a total of four combined HP/HD, each 4 h in duration, over 4 consecutive days. Blood samples for the determination of PA and NAPA were obtained before, during, and about 3 h after HP/HD from the arterial port (Figure 1, site A, proximal to the haemoperfusion cartridge), the venous port (site C, distal to
the haemodialyser), and a port between the dialyser and the cartridge (site B).

The patient also continued his routine CAPD (four exchanges/day, 2-1 bag of dialysate, 1.5 or 2.5% dextrose). The volumes of spent peritoneal dialysate for each exchange (when the patient was off HP/HD) were measured and an aliquot of each was sent for the determination of PA and NAPA on days 2-4 of HP/HD. PA and NAPA concentrations were determined by an enzyme immunoassay method (Dupont Company, Wilmington, DE). Figure 2 demonstrates the concentration-time profiles of PA and NAPA over the four HP/HD sessions.

Using the data, a number of pharmacokinetic calculations were made:

1. The clearances of NAPA and PA were calculated using the formula:
   \[ \text{HP CL} = \frac{[A]-[B]}{[A]} \times 100\% \]
   \[ \text{HD CL} = \text{blood flow rate} \times \frac{[B]-[C]}{[B]} \times 100\% \]
   \[ \text{Combined HP/HDCL} = \text{blood flow rate} \times \frac{[A]-[C]}{[A]} \times 100\% \]

2. The amount of PA and NAPA removed in each 4-h HP/HD session was calculated using the following assumptions:
   (a) Combined HP/HD CL remained constant throughout the 4-h HP/HD session.
   (b) Average drug concentration throughout HP/HD was taken to be the level 3 h post dialysis.

   Amount of PA and NAPA removed (mg)
   \[ = \text{concentration of PA or NAPA 3 h post} \]
   \[ \times \text{HP/HD CL} \times 4 \times 60 \]

3. Clearance by peritoneal dialysis was calculated by the formula:
   \[ \text{Cl}_{PD} (\text{ml/min})
   = \frac{\text{dialysate concentration} \times \text{volume of dialysate}}{\text{mid-point serum concentration} \times \text{dwell time}} \]

4. Total amount removed by CAPD per day
   \[ = \frac{\text{total amount of NAPA/PA measured in dialysate}}{24} \]

5. Clearance by HP/HD (ml/min)
   \[ = \frac{\text{dialysate concentration} \times \text{volume of dialysate}}{\text{mid-point serum concentration} \times \text{dwell time}} \]

6. % of PA removed from body by day 4
   \[ = \frac{\text{Total amount of PA removed by HP/HD and CAPD}}{\text{Total body burden of PA before dialysis}} \times 100\% \]

7. Half life of PA off dialysis
   \[ = 0.693 \times \text{time interval between the peak and trough } \]
   \[ = \frac{(\ln [PA]_{\text{peak}}/[PA]_{\text{trough}})}{\text{time interval between the peak and trough } \}

where \( [A] \), \( [B] \) and \( [C] \) are serum concentrations of NAPA/PA at sites A, B and C as shown in Figure 1.

Results

Table 1 summarizes the clearances of the different treatment modalities and the total amounts of PA and NAPA removed by HP, HD, and CAPD.

HD was found to be more efficient than HP for removing NAPA. Nevertheless, the combination of HD and HP increased substantially the clearance of PA and NAPA achievable by using either modality alone. A rebound in serum PA and NAPA concentrations were observed 3 h after HP/HD.
Table 1. Clearance (Cl) of PA and NAPA by HP/HD and peritoneal dialysis and the total amount of PA and NAPA removed by each treatment modality

<table>
<thead>
<tr>
<th>Day</th>
<th>Cl procainamide (ml/min)</th>
<th>Cl NAPA (ml/min)</th>
<th>Amount of procainamide removed (mg)</th>
<th>Amount of NAPA removed (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Start of HP/HD</td>
<td>HP&amp;HD: 135</td>
<td>136.7</td>
<td>304</td>
<td>938</td>
</tr>
<tr>
<td></td>
<td>PD: NM</td>
<td>NM</td>
<td>61#</td>
<td>235#</td>
</tr>
<tr>
<td>2</td>
<td>HP: 61.2</td>
<td>46.9</td>
<td>207</td>
<td>565</td>
</tr>
<tr>
<td></td>
<td>HD: 87.8</td>
<td>76.9</td>
<td>61</td>
<td>235</td>
</tr>
<tr>
<td>Total: 127</td>
<td></td>
<td>109</td>
<td>207</td>
<td>565</td>
</tr>
<tr>
<td>PD: 4.9 (18 h)</td>
<td></td>
<td>5.5</td>
<td>61</td>
<td>235</td>
</tr>
<tr>
<td>HP: 88</td>
<td></td>
<td>53.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HD: 57</td>
<td></td>
<td>99.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total: 120</td>
<td></td>
<td>132</td>
<td>66</td>
<td>501</td>
</tr>
<tr>
<td>PD: 5.3 (9.5 h * 1.5%D)</td>
<td></td>
<td>5.1</td>
<td>12</td>
<td>92</td>
</tr>
<tr>
<td>PD: 3.1 (8 h * 2.5%D)</td>
<td></td>
<td>3.2</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>HP: ~</td>
<td></td>
<td>92.6</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>HD: ~</td>
<td></td>
<td>99.3</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Total: ~</td>
<td></td>
<td>155</td>
<td>-</td>
<td>40</td>
</tr>
<tr>
<td>PD: ~ (9.4 h *1.5%D)</td>
<td></td>
<td>5.7</td>
<td>-</td>
<td>72.7</td>
</tr>
<tr>
<td>PD: ~ (8 h * 2.5%D)</td>
<td></td>
<td>5.9</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Total amount removed by HD/HP</td>
<td></td>
<td></td>
<td>577</td>
<td>2044</td>
</tr>
<tr>
<td>Total amount removed by PD</td>
<td></td>
<td></td>
<td>134</td>
<td>635</td>
</tr>
<tr>
<td>(19% of total amount)</td>
<td></td>
<td></td>
<td>(24% of total amount)</td>
<td></td>
</tr>
</tbody>
</table>

NM, not measured.
~ levels undetectable.
*Amount of PA and NAPA removed by CAPD was calculated for 24 h.
#Minimal estimate of amount removed based on day 2 calculations.

The total amount of procainamide removed by the four sessions of combined HP/HD was about 577 mg. The total body burden of procainamide just prior to HP/HD, estimated as described above, was found to be 1.7 g. Hence, at the end of the four sessions of HP/HD, about 34% of the initial total body load of procainamide was removed. Thirty-one percent of the initial NAPA burden was removed by the first 4 h of combined HP/HD.

The amount of PA and NAPA removed by CAPD contributed about 19 and 24% respectively of the total amount removed by all treatment modalities.

The half-life of PA was 38 h, and that of NAPA was 39 h.

**Discussion**

The half-life of PA and NAPA in ESRD patients has been reported to be about 14 h and 42 h respectively (normal, 3 h and 6.6 h). The Vd of PA has been calculated to be about 1.4 l/kg in ESRD patients in the same studies [1,7]. The half-life of PA and NAPA in our patient was found to be 38 h and 39 h. This prolonged PA half-life may be due to the unpredictable reduced non-renal clearance of PA in renal failure [7]. The exact mechanisms of non-renal elimination of PA and NAPA are unclear. The half-life of NAPA in this patient was in agreement with that reported by other studies [1,7].

There is controversy in the literature regarding the efficacy of HD, HP, and PD for the management of procainamide and NAPA toxicity. Rosansky and Brady [5] reported that HP increased the total clearance of NAPA by approximately 36%, and combined HP/HD was about three times as effective as HD alone in the removal of NAPA. About 1.4 g of NAPA was removed by HP/HD over 5 h in this study. Braden et al. [15] demonstrated that HD clearance of NAPA (36 ml/min) was inferior to HP clearance of NAPA (127 ml/min). Other authors [16] reported that 0.5 g of NAPA was recovered in the dialysate after 4 h of HD at a clearance of 47.7 ml/min. A study similar to ours showed that 4 h of combined HP/HD cleared a total of 1.22 g of NAPA, equivalent to 24% of the total body burden of NAPA [13].

Our results showed that the degree to which HD clearance of NAPA was greater than that of HP varied from 7 to 85%. This discrepancy in findings compared to other studies may be due to the differences in dialysers and haemoperfusion cartridges used. The rate of removal of both PA and NAPA by HP/HD far exceeded the rate of their re-distribution from tissue stores. CAVH/CAVHD would have promoted steady drug removal and stable serum concentrations, but at a lower clearance. Domoto et al. [17] reported substantial removal of 4.7 g of NAPA over 3 days of CAVH, though the clearance was small (23.1 ml/min).

Many investigators have calculated the amount of NAPA and PA removed by multiplying the blood flow by the average arteriovenous concentration difference [13,15]. This method may over or underestimate the actual amount removed as the arteriovenous concentration difference varies with time. As we had determined the concentrations of PA and NAPA at sites A, B, and C only once during each HP/HD session, we...
used the average steady-state concentrations of PA and NAPA, multiplied by their respective clearances, to calculate the amount of PA and NAPA removed.

To the best of our knowledge, there is only one reported case in which peritoneal dialysis was used to remove NAPA and PA [12]. A patient with normal renal function acutely ingested 19 g of procainamide. Peritoneal dialysis with sorbitol solution (1.5% alternating with 4.5%) was performed for 24 h. The peritoneal clearance of NAPA was found to be about 6 ml/min, a value which was insignificant compared to non-renal and renal clearances. In our patient, who lacked functioning kidneys, a similar clearance of NAPA by CAPD, 5 ml/min, accounted for 24% of all NAPA removed.

In summary, the use of combined HP/HD and CAPD is effective in the plasma clearance of PA and NAPA. However, because of the large volume of distribution (1.4 kg/l), PA and NAPA equilibrate more slowly between blood and extravascular stores than they are eliminated by HP and HD. As a result, a rebound in serum concentration can be seen a few hours after dialysis. In cases of severe PA toxicity, a combination of CAVH and HD/HP may be best for rapid and sustained removal of PA and NAPA. CAPD can also make a significant contribution to the total amount of drug removal in patients who lack intrinsic renal function.

References


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