Pharmacokinetics of epsilon-aminocaproic acid during peritoneal dialysis

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Two patients requiring peritoneal dialysis were treated with epsilon-aminocaproic acid (EACA), an anti-fibrinolytic agent. Samples of serum and dialysate were assayed for EACA concentrations. Total body clearance, dialysis clearance, EACA half-life, and volume of distribution of EACA were calculated. Total body clearance of EACA was 26 ml/min, which is 25% of the drug clearance in patients with normal renal function. Our results suggest that patients undergoing peritoneal dialysis should receive 25% of the usual recommended dose of EACA. Dialysis clearance accounted for only 58% of total body clearance, suggesting an alternative route of elimination of EACA.

KEY WORDS • epsilon-aminocaproic acid • pharmacokinetics • peritoneal dialysis • cerebral aneurysm • polycystic kidney

Epsilon-aminocaproic acid (EACA), an antifibrinolytic agent, has been used successfully in the treatment of subarachnoid hemorrhage (SAH) for protection against early clot lysis prior to surgery. Subarachnoid hemorrhage from a ruptured intracranial aneurysm has been associated with a marked increase in fibrinolytic activity in cerebrospinal fluid (CSF) due to a rapid increase in fibrinogen. Administration of EACA prevents lysis of formed clots by inhibiting the activation of plasminogen to plasmin, and by inhibiting plasmin itself.

The kidney is the major, if not only, organ of EACA elimination. Its plasma half-life is about 1 to 2 hours in patients with normal renal function; however, decreased renal function leads to accumulation of EACA. Case studies of this accumulation have been reported, but as yet it is not possible to predict the amount of accumulation of drug based on the degree of renal failure. This paucity of information regarding the dialyzability of EACA has prompted this report.

Case Reports

Case 1

This 60-year-old man had chronic renal failure secondary to polycystic kidney disease, and a history of poorly controlled hypertension. He had been on chronic hemodialysis for 8 years. He was transferred from another hospital for treatment of a presumed intracranial hemorrhage. Ten days before his present admission, the patient had noted the gradual onset of a right supraorbital headache associated with a stiff neck, diplopia, and photophobia.

Course. The patient was alert and oriented, and had a fixed right pupil. A computerized tomographic (CT) scan performed on admission revealed a right hemispheric intracerebral hemorrhage. Four-vessel cranial angiography showed a small aneurysm at the origin of the right posterior communicating artery.

The patient was treated with peritoneal dialysis to avoid the heparinization required by hemodialysis. Epsilon-aminocaproic acid therapy was administered until just prior to surgery 12 days later. At surgery, the ruptured aneurysm was successfully clipped.

EACA Administration. Aminocaproic acid was administered by continuous intravenous infusion using an IVAC infusion pump. Initially, 36 gm of EACA per day was administered in D5W (dextrose in water)

*IVAC infusion pump manufactured by IVAC Corp., 11353 Sorrento Valley Road, San Diego, California.
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for 3 days. The dose was then decreased to 24 gm per day for 9 days, and discontinued 3 hours prior to surgery. Intermittent peritoneal dialysis was performed daily for durations as indicated in Fig. 1. The Drake-Willock automated peritoneal dialyzer† was set to cycle at 3-minute inflow times, 10-minute dwell times, and 10-minute outflow times, delivering 1500 ml of a 50% dextrose solution of Dianeal 134.5 (a peritoneal dialysis solution) per cycle.

Blood samples for EACA determinations were obtained before and after each dialysis and intermittently at mid-dialysis. A final blood sample was collected 48 hours after discontinuation of the constant infusion. Blood was collected in Vacutainer tubes‡ containing no additives and was centrifuged. The plasma was separated and frozen. Samples were sent to Lederle Laboratories in Pearl River, New York, where they were assayed using a modification of the gas chromatographic method reported by Solow.15

Case 2

This 54-year-old woman with chronic renal failure secondary to polycystic kidney disease presented with gross hematuria. She had been maintained with chronic hemodialysis for 7½ years, but, because of access problems, was changed to peritoneal dialysis 1 month prior to admission.

Course. On admission, prothrombin time, partial thromboplastin time, and thrombin time were all within normal limits. The platelet count was 257,000/cc, hemoglobin was 5.4 gm%, and bleeding time was greater than 10 minutes. Blood urea nitrogen was 102 mg/dl. Blood transfusions were refused for religious reasons. Epsilon-aminocaproic acid therapy was begun to prevent any clots that might form from lysing. The drug was administered for 8 consecutive days. Gross hematuria persisted, and EACA therapy was considered a failure and was discontinued.

EACA Administration. Epsilon-aminocaproic acid was administered orally, beginning with 1 gram every 4 hours for 24 hours, then 1 gram every 2 hours for the next 8 days. The patient underwent peritoneal dialysis daily. On the day of sampling, the Drake-Willock automated peritoneal dialyzer delivered 2000 ml of a 30% dextrose solution of Dianeal 134.5 per cycle, with an inflow of 4 minutes, dwell time of 6 minutes, and outflow of 10 minutes.

A blood sample for steady-state EACA determination was drawn in Vacutainer tubes containing no additives on the morning of the 8th day of therapy prior to initiation of dialysis. A second blood sample was collected 2 hours later at the end of that dosing interval. Samples of peritoneal dialysate fluid were collected for dialysis clearance determination and were handled as in Case 1.

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Clearance Calculations

Total body clearance (TBC) during intermittent peritoneal dialysis was calculated as follows:

\[
TBC = \frac{F \cdot \text{dose}}{C_{pss}}
\]

†Drake-Willock automated peritoneal dialysis machine manufactured by Drake-Willock, 500 N.E. Multnomah, Portland, Oregon.
‡Vacutainer tubes manufactured by Becton-Dickinson and Co., P. O. Box 310, Rutherford, New Jersey.
where $F = \text{bioavailability}$, dose = administered EACA dose, and $C_{p_{ss}}$ = serum concentration at steady state.

Half-life of EACA was calculated from the blood level determinations obtained after termination of the constant-rate infusion. The volume of distribution ($V_D$) was then determined using the following equation:

$$V_D = \frac{TBC \times t^{1/2}}{0.693},$$

where $t^{1/2} = \text{half-life}$.

Dialysis clearance during intermittent peritoneal dialysis was calculated using the following equation:

$$Cl_D = \frac{(X_D | T_{10} \times t_{10}^{1/2})}{16.7}{C_{p_{ss}}}$$

where $Cl_D = \text{dialysis clearance (ml/min)}$, $X_D | T_{10} = \text{amount in the dialysate from time 0 to T (mg)}$, $t_{10} = \text{time from time 0 to T (hrs)}$, $C_{p_{ss}} = \text{serum concentration at steady state (mg/liter)}$, and 16.7 is the factor for converting liters per hour to milliliters per minute.

Results

Figure 1 shows serum EACA concentrations for Case 1. While this patient was receiving 36 gm/day of EACA, the average steady-state serum concentration achieved was 972 µg/ml. Total body clearance calculated on this dose was 25.7 ml/min. When the EACA dose was decreased to 24 gm/day, the average steady-state concentration was 582 µg/ml and total body clearance was 28.6 ml/min.

Table 1 summarizes serum and dialysate concentration data for Case 2. Total body clearance calculated from the steady-state concentration measured after 69 hours of therapy was 23.9 ml/min. Dialysis clearance calculated from dialysate concentration was 13.8 ml/min.

The half-life of EACA during intermittent peritoneal dialysis was calculated to be 30.7 hours and the volume of distribution was 65.2 liters or 0.9 liters/kg.

Discussion

Both patients presented here had polycystic kidney disease. One of these patients suffered SAH from a ruptured intracranial aneurysm. Intracranial aneurysms occur more commonly in patients with polycystic kidney disease than in the normal population. Renal excretion is the primary route of elimination for EACA. McNicol, et al., recovered 86% of the administered dose in the urine 24 hours later. They found EACA clearance to be about 75% of the creatinine clearance in healthy individuals. This figure suggests that the drug is primarily filtered and possibly reabsorbed by the kidney. It is also consistent with excretion by an alternative route.

% It is thought that EACA is somewhat dialyzable, based on its chemical and pharmacokinetic characteristics. The drug is a small molecule, having a molecular weight of 131 daltons, which will allow diffusion through most dialysis membranes. It does not appear that EACA is protein bound, which leaves the drug free in the plasma, accessible to dialysis. The drug moves in and out of cells in relation to its extracellular concentration. It is therefore theorized that removal of the drug from the central compartment will cause a reequilibration between compartments and a decreased concentration in the peripheral compartment.

Dialysis has been used in vitro as a means of removing antifibrinolytic activity, and presumably EACA, from plasma. After dialysis the plasma had substantially greater fibrinolytic activity when compared to the undialyzed plasma. However, the amount of drug removed, as estimated from the remaining fibrinolytic activity, was variable and unpredictable.

The half-life of EACA in Case 1 was found to be 30.7 hours. It must be noted that this half-life determination is based on two data points and that between the times of the first and second points the patient underwent surgery, postoperative fluid imbalance, and dialysis. For this reason, we consider that the volume of distribution for EACA as calculated from the half-life may be an underestimation of the true value.

There is also some question as to whether steady-state concentrations were achieved in Case 1 after the initial dosing regimen, since usually four to five half-lives must elapse before reaching steady state. How-

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**TABLE 1**

<table>
<thead>
<tr>
<th>EACA Dose (gm)</th>
<th>Time After Initiation of Therapy (hrs)</th>
<th>EACA Concentrations (µg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Serum</td>
<td>Dialysate</td>
</tr>
<tr>
<td>1</td>
<td>69.0</td>
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</tr>
<tr>
<td></td>
<td>69.8</td>
<td>76</td>
</tr>
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<td>70.5</td>
<td>27</td>
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<tr>
<td></td>
<td>70.8</td>
<td>24</td>
</tr>
<tr>
<td>1</td>
<td>71.2</td>
<td>267</td>
</tr>
</tbody>
</table>
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however, our calculations of total body clearance at both dosing regimens were remarkably close, and compare well with the results reported for Case 2.

Total body clearance indicates the rate of removal for drugs from the body and is the summation of all clearances, including renal, hepatic, biliary, and dialysis. In Case 2, total body clearance was found to be 23.9 ml/min, but dialysis clearance was only 13.8 mg/min. This is consistent with one or more alternative routes of elimination of EACA from the body.

Our results show that EACA is removed by peritoneal dialysis. Clearance of EACA in patients with normal renal function is 98 ml/min or approximately 75% of creatinine clearance. In our patients, EACA clearance was 26 ml/min. These results indicate that the clearance of EACA in patients undergoing peritoneal dialysis is approximately 25% of normal, and suggests that these patients should receive approximately 25% of the dose of EACA recommended for patients with normal renal function.

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References


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