Resin Hemoperfusion as Treatment for Theophylline-induced Seizures*

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Hemoperfusion with resin was used to treat a 63-year-old man with seizures secondary to theophylline intoxication. The patient illustrates the efficacy of treatment by resin hemoperfusion in this situation, emphasizes the risk of fixed theophylline dosage regimens and the necessity of monitoring plasma theophylline concentrations in acutely ill patients.

Theophylline has a narrow but well-defined therapeutic range (10-20 μg/ml) and as drug concentrations exceed this range, dangerous side-effects occur in the form of cardiac arrhythmias and seizure activity. These side-effects may be refractory to conventional therapy and carry a high mortality. Optimal administration of theophylline is complicated by large intersubject and intrasubject variability in theophylline clearance. Liver disease, heart failure, age, and high carbohydrate-low protein diet may all prolong theophylline clearance and predispose to toxicity. Hemodialysis, and more recently resin hemoperfusion, have been utilized in the aggressive management of theophylline toxicity.

CASE REPORT

A 63-year-old white man weighing 69 kg was hospitalized because of progressive dyspnea and ankle swelling. He was a heavy smoker, and had smoked 25 cigarettes a day for the previous 50 years; he gave a history of episodic wheezing and productive cough for many years. There was no history of previous seizures, liver disease or excessive alcohol intake and he was taking no medication. Physical findings on admission included marked expiratory wheezing, signs of right heart failure, but no hepatomegaly or other signs of hepatic dysfunction. Routine liver function studies were all within the normal range.

Treatment was instituted with controlled oxygen therapy and intravenous aminophylline, 0 mg/kg as a loading dose over 30 minutes and then 0.9 mg/kg/hour as an intravenous maintenance infusion. Despite these measures, the patient continued to deteriorate and required mechanical ventilation on his third day in the hospital. Seven days after admission, he developed ventricular premature beats and, after two grand mal seizures, went into status epilepticus which was refractory to large doses of intravenous diazepam and phenytoin. The aminophylline infusion was discontinued immediately and a plasma theophylline concentration obtained two hours later was 40.5 μg/ml. Because of the risk of continuing seizure activity and malignant cardiac arrhythmia, renal hemoperfusion was instituted.

Hemoperfusion was accomplished by placing a Sheldon catheter in the left femoral vein to provide input to the Amberlite column at 300 ml/min, and return was through the left subclavian vein. Blood was drawn half-hourly from the input line for the 2% hour duration of hemoperfusion and then at regular intervals during the 36 hours following the hemoperfusion. No adverse effects were noted from the period of hemoperfusion and the seizure activity abated during this period. Phenytoin plasma concentrations were determined using an enzyme immunoassay (EMIT), and theophylline plasma concentrations were measured using a high pressure liquid chromatographic assay. Protein binding of 14C theophylline was assessed at a pH of 7.4 at a theophylline concentration of 15 μg/ml by equilibrium dialysis.

The theophylline and phenytoin plasma concentrations are shown in Figure 1. During the 2% hour hemoperfusion, theophylline concentrations fell from 36.6 μg/ml to 14.1 μg/ml and phenytoin concentrations from 18.5 μg/ml to 10.2 μg/ml. Theophylline plasma concentrations before and after hemoperfusion are plotted logarithmically against time and the plasma half-life (t%) derived from the slope of the elimination phase which was assessed by the method of least squares. The t% prior to hemoperfusion was 19.6 hours and after hemoperfusion 13.3 hours. In our patient, 33 percent of theophylline was protein bound compared to that of six age-matched normal subjects 46 percent ± 2.5 (mean ± SD).

DISCUSSION

The dosage of theophylline our patient received was in line with standard recommendations for the use of intravenous theophylline. These dosage guidelines more recently have been felt to be too rigid and not to take account of the effects of age and associated illnesses on theophylline metabolism. The theophylline disposition in our patient was difficult to predict as smoking increases theophylline clearance, whereas heart failure decreases it. This report emphasizes the necessity for monitoring theophylline plasma concentrations for safe and effective therapy. It is important that this monitoring be continued for the total duration of therapy, as a large intrasubject variability of theophylline clearance has been observed over a four-day period in acutely ill patients. It should also be noted that our patient was...

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receiving aminophylline for seven days prior to developing neurotoxicity and that patients with low clearances may take a prolonged time to equilibrate, with toxic plasma concentrations of theophylline occurring only after several days of therapy. Although many variables existed during the 36 hours we assessed theophylline concentrations, and only three values were obtained before hemoperfusion, the observation that the plasma theophylline t½ was 6.3 hours longer before hemoperfusion compared to after hemoperfusion tends to support the conclusion of Weinberger et al. that theophylline may follow dose-dependent rather than first order kinetics at high concentrations of theophylline.

Much of the emphasis in discussions on theophylline toxicity have centered around variations in clearance, but it appears that theophylline protein binding is also subject to significant variations. The theophylline protein binding of our patient was significantly lower than in our group of normal subjects, which would allow larger amounts of free drug to be available at the same total plasma concentration and predispose to toxicity.

Prior to the introduction of dialysis for theophylline toxicity, the only treatment was that of discontinuation of the drug and supportive therapy. This would have led to our patient being in the toxic range for approximately 19 hours. Resin hemoperfusion would appear to be the treatment of choice for any life-threatening episode of theophylline toxicity when this has been documented by plasma theophylline concentrations. It is safe and effective, periods of 2-2½ hours hemoperfusion appear adequate, and it is faster than conventional hemodialysis. It should also be noted that hemoperfusion reduces the plasma concentrations of anticonvulsants and these should be supplemented if seizure activity continues during the period of hemoperfusion.

REFERENCES