Influence of Plasma Exchange Pheresis on Plasma Elimination of Ceftriaxone

JOHAN S. BAKKEN,1,* STEPHEN J. CAVALIERI,2 AND DAVID GANGENESS3

Department of Infectious Diseases, Duluth Clinic,1 and Pharmacy Services, St. Mary’s Medical Center,2 Duluth, Minnesota 55805, and Department of Medical Microbiology, Creighton University School of Medicine, Omaha, Nebraska 681782

Received 17 October 1989/Accepted 7 March 1990

The plasma elimination rates of serial 2-g intravenous injections of ceftriaxone were studied in a patient who also was treated with therapeutic plasma exchange pheresis. Plasmapheresis had negligible influence on the total clearance of ceftriaxone.

Therapeutic plasma exchange pheresis (plasmapheresis) has become a widely accepted therapeutic modality for a number of autoimmune illnesses as well as certain illnesses of presumed or proven infectious etiology (4, 5). The influence of plasmapheresis on the elimination of antibiotics is largely unknown. Prince et al. (6) noted more than 30% reduction in ampicillin and gentamicin concentrations in serum from septic neonates treated with exchange transfusions. The elimination kinetics of a single 2-g intravenous dose of ceftazidime were recently studied in 11 patients with various autoimmune diseases and who were treated with plasmapheresis (2). Only 2 to 9% of the administered dose was removed by plasmapheresis, suggesting that the dosage of ceftazidime should be determined solely by monitoring renal function (2).

We recently cared for a young man who was treated with intravenous ceftriaxone and plasmapheresis for presumed neurological Lyme disease. This report describes the influence of plasmapheresis on the elimination kinetics of maintenance ceftriaxone therapy.

A 25-year-old homosexual male presented with urinary retention and paresthesias of the lower extremities 7 days after an influenzalike illness. Past medical history was pertinent for migraine headaches over the past 4 years and nephrolithiasis 2 years previously. There was no past or recent history of tick bites. His temperature at admission was normal. The general and neurological examination revealed a dilated urinary bladder (residual volume, 900 ml), mild nuchal rigidity, and paresthesias of both lower extremities. Admission urinalysis, complete blood cell count, and multianalyzer chemistry profile were all normal. The erythrocyte sedimentation rate was 10 mm/h, and C-reactive protein was 1.3 mg/dl (normal is <0.8 mg/dl). Lumbar puncture demonstrated mild mononuclear pleocytosis in the cerebrospinal fluid as well as mild protein elevation in the cerebrospinal fluid. The cerebrospinal fluid/serum glucose ratio was normal. The basic myelin protein in cerebrospinal fluid was elevated at 19 ng/ml (normal is <4.0 ng/ml). Venereal Disease Research Laboratory, fluorescent antinuclear antibody, and mycoplasma immunoglobulin M tests as well as acute and convalescent viral serology (including human immunodeficiency virus, enzyme immunoassay, human T-lymphotropic virus, herpes simplex virus, Epstein-Barr virus, and enterovirus) were all negative or nonreactive. An initial Lyme enzyme immunoassay titer was mildly elevated, and the patient began treatment with intravenous ceftriaxone 2 g every 24 h (30-min infusions) for suspected Borrelia burgdorferi-associated transverse myelitis.

Over the next week the patient’s headaches intensified. He developed paraparesis, and the dermatomal level of his paresthesias progressed cephalad to T7. It was therefore decided to institute daily plasmapheresis over a 3-day period and during ongoing ceftriaxone therapy. The plasma exchanges began on day 6 of ceftriaxone therapy, employing a Senwal PS 400 plasma exchange machine (continuous flow). Each plasmapheresis began circa 12 h after the ceftriaxone infusion and lasted for 150 min. Equal volumes of human albumin replaced his daily 3-liter plasma volume loss. Blood samples for ceftriaxone plasma concentrations were collected in heparinized test tubes at 30 min before and 60 min after the start of the ceftriaxone infusion as well as immediately before and after plasmapheresis. Ceftriaxone concentrations in plasma were analyzed in triplicate by using a microbiological assay with human plasma as the control diluent and Escherichia coli ATCC 25922 as the indicator organism. The results of the actual (measured) concentrations in plasma and the projected trough values for days 2 and 3 of plasmapheresis are shown in Fig. 1. Assuming a first-order ceftriaxone elimination process, pharmacokinetic parameters (elimination constants and elimination half-lives) were determined as described by Sawchuk et al. (7) (Table 1).

The clinical recovery in our patient was slow and was not influenced by ceftriaxone or plasmapheresis. The sensory deficits had resolved after 6 weeks, and he was discharged to his home with mild paraparesis.

Some variation was registered between the plasma elimination curves from each day (Fig. 1, Table 1). However, both curves demonstrated a significant and parallel increase in the rate of elimination of ceftriaxone during plasmapheresis. This was quite expected, since ceftriaxone is 95% protein bound (3). The ceftriaxone concentration of the plasma volume that was removed was unfortunately not determined. Thus, the dialytic clearance of ceftriaxone by plasmapheresis could not accurately be determined from this study. A maximum of 107.7 mg (5.4% of the 2-g ceftriaxone dose given may have been removed by the pheresis [3 liters of plasma removed × 35.9 ng/ml (mean concentration in plasma before plasmapheresis)]. The estimated amount removed appeared to be less than 30 mg (plasma volume removed divided by plasma AUC for each day [data not

* Corresponding author.
plasmapheresis. The arrow indicates the intravenous infusion starting point for 2 g of ceftriaxone. The bar indicates the period of plasmapheresis. Curves show data for day 2 (●) and day 3 (○) of plasmapheresis.

It is likely that the majority of the ceftriaxone load was to be found in the interstitial compartment at the time when plasmapheresis started (3). Since ceftriaxone is highly protein bound, drug mobilization from the interstitium to the vascular compartment would presumably be slow. A reverse distribution of ceftriaxone (rebound effect) from interstitium to plasma could theoretically take place in the first hour after plasmapheresis. If so, this would tend to overestimate the elimination constant during the procedure in this case study. No late plasma sample was obtained to evaluate this possibility.

Even though up to 67% of a ceftriaxone dose may be eliminated via biliary excretion (1), it is unlikely that significant drug concentrations could be returned to the vascular space through the enterohepatic circulation. A study by Stoeckel et al. (8) showed that ceftriaxone excreted in bile becomes microbiologically inactivated, and virtually no ceftriaxone is reabsorbed from the intestinal tract (Stoeckel, personal communication). The impact of the daily removal of 3 liters of plasma had little influence on the total ceftriaxone clearance; only 3.7 and 10.6% deficits were registered when actual trough levels in plasma were compared with expected levels. Thus, no drug dosage adjustments appear necessary when plasmapheresis is performed within 12 h of redosing. Further research is currently being conducted to determine the dialytic clearance of ceftriaxone in patients treated with plasmapheresis, the extent of a possible post-pheresis rebound effect, and whether plasmapheresis adversely affects the early elimination curve of ceftriaxone, necessitating redosing shortly after the plasma exchange. Special thanks to Barb Jablonski for typing the manuscript.

LITERATURE CITED