A Serial Application Study on Twice Daily Dose of Imipenem/Cilastatin in Patients Undergoing Slow Hemodialysis

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Table 1. Pharmacokinetic parameters of imipenem and cilastatin in patients undergoing slow HD.

HD. Blood was collected at 0, 0.5, 10 and 10.5 h after the start of slow HD. On the first day of the experiment, additional samples were collected at 0.25, 1, 1.5, 2.5, 4.5, 6.5, and 8.5 h after the start of the treatment. The concentrations of the drugs were determined by HPLC [2]. The hybrid parameters and microscopic constants were computed after fitting individual concentration-time data to a two-compartment open model and pharmacokinetic parameters were calculated.

Values are expressed as mean $\pm$ SE.

Dear Sir,

Infection and renal failure are the major problems of the critically ill. In patients with both complications, antibiotic therapy should be modified according to residual renal function and efficacy of renal replacement therapy used. Slow hemodialysis (HD) has recently been introduced in managing such complicated cases, because it can correct the uremic state without adversely affecting cardiovascular stability [1]. Previously, we demonstrated that this approach has profound effects on single-dose kinetics of imipenem/cilastatin, broad-spectrum antibiotics useful for compromised cases with infections [2]. In the present study, we attempted to determine the kinetics of serially applied imipenem/cilastatin during slow HD, the objective being to establish an optimal dosage schedule.

Five critically ill patients with renal failure, 4 males and 1 female, were entered into the study after informed consent was obtained from each patient or a responsible relative. Mean age was 68 years, range between 61 and 76. Slow HD was performed as described previously [1]. In brief, vascular access was via femoral vein catheters and veno-venous circulation was driven by the blood pump at a flow rate of 80 ml/min. A bicarbonate-containing dialysate was passed into the dialyzer (FB-70U, cellulose triacetate membrane, 0.7 m², Nipro, Japan) at a flow rate of 30

ml/min. The treatment was conducted for 10 h during the day. Imipenem/cilastatin (0.5/0.5 g, i.v.) was administered over 30 min at the start and the end of each session of slow

$T_{1/2\beta}$, elimination phase half-life; V_c , volume of distribution of central compartment; V_{ss} , volume of distribution at steady state; A_e , the amount of the drug eliminated by slow HD (% of drug administered); AUC, area under the curve (0-10 h); CL_{tr} , total body clearance; CL_{shd} , extracorporeal clearance by slow HD. Values are expressed as mean $\pm$ SE from 5 patients. Table 1 shows pharmacokinetic parameters during slow HD. The elimination half-life ranged from 2.45 to 3.35 h for imipenem and from 5.29 to 8.15 h for cilastatin. The total body clearance of imipenem ranged between 68.17 and 90.33 ml/min and that of cilastatin between 37.10 and 44.80 ml/min. Slow HD clearance for imipenem and cilastatin represented 37.32 ± 2.02 and $63.48 \pm 6.06\%$, respectively, of the total body clearance. Following repeated doses of imipenem/cilastatin, the peak and trough serum levels were

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Imipenem
[?] [?]
B5B3
12 24 36 48 60 72 84

0 12 24 36 48 60 72 84 Time (h)

Fig. 1. Peak and trough concentrations of imipenem and cilastatin in patients undergoing slow HD during the day (shaded bars). The drugs (0.5 g) were administered twice a day over 30 min at the start and the end of a 10-hour session of slow HD. Values are the mean $\pm$ SE. obtained as shown in figure 1. The maximum peak concentration of imipenem was 48.70 ± 4.29 mg/l. All trough concentrations of this drug were less than 3 mg/l. On the other hand, the peak and trough concentrations of cilastatin increased with successive doses. They reached steady levels within 4 days after initiating slow HD. The maximum peak concentration of cilastatin was 89.67 ± 7.32 mg/l. The trough concentrations of cilastatin were affected by slow HD; the maximum trough concentration before slow HD was 46.22 ± 11.66 mg/l whereas that after slow HD 21.63 ± 4.30 mg/l.

In patients with severe renal failure, imipenem and cilastatin considerably accumulate. When creatinine clearance has decreased to less than 5 ml/min, the elimination half-life of imipenem is prolonged to 4 h and that of cilastatin to more than 15 h [3]. Various forms of renal replacement therapy differently affect the pharmacokinetics of these drugs in patients with renal failure. The present study demonstrated that the elimination half-lives of imipenem and cilastatin during slow HD were 2.89 and 6.45 h, respectively. On the other hand, continuous hemofiltration minimally affects the kinetics [4, 5]. In contrast, conventional HD eliminates these drugs more rapidly; the elimination half-lives were 1.5-2.5 h for imipenem and 3-7 h for cilastatin during the treatment [6].

For the patients undergoing slowly performing renal replacement therapies, recommended dosage schedules of imipenem/cilastatin have been based solely on data from single-dose kinetic studies [2, 4]. The present study demonstrated that safe and effective serum concentrations of imipenem may be obtained when 0.5 g is applied twice a day at the start and

the end of each session of slow HD. After repeated doses, the steady-state trough level of imipenem was about 2 mg/l, suggesting no accumulation of imipenem. Because the minimum inhibitory concentrations of this drug are usually less than 1 mg/l [7], our dosage schedule may be adequate for most cases with bacterial infection.

With progressive decrease in renal function, the pharmacokinetics of imipenem and cilastatin profoundly dissociate. In patients with severe renal dysfunction, the total body clearance of imipenem decreases to 60 ml/min whereas that of cilastatin decreases to 10-15 ml/min [3, 6]. This large difference is due to the presence of significant plasma clearance of imipenem. As a result, a dosage schedule for maintaining a therapeutic level of imipenem produces unexpectedly high concentrations of cilastatin. It has been suggested that patients with glomerular filtration rate less than 10 ml/min should not receive more than 0.5 g of imipenem/cilastatin every 12 h [3]. In a case presentation on continuous hemofiltration, a maximum cumulation level of cilastatin of 114.6 mg/l was noted without accumulation of imipenem, when 0.5 g of the drugs was administered every 12 h [5]. Using a similar dosing schedule, trough levels of cilastatin occasionally exceed 100 mg/l in patients undergoing conventional HD [6].

In contrast, the present study demonstrated that trough levels of cilastatin did not exceed 50 mg/l, while serum concentrations of imipenem were adequate to inhibit most bacteria. This small kinetic dissociation of the drugs can be explained by the relatively high efficacy for solute removal by slow HD. Imipenem is eliminated by both plasma and extracorporeal clearance whereas cilastatin elimination entirely depends on extracorporeal clearance [3]. Thus, large extracorporeal clearance decreases the difference in the total body clearance of these drugs. A 10-hour session of slow HD gave a daily clearance of 15.2 l/day for imipenem and 18.6 l/day for cilastatin. This efficacy was higher than that of conventional HD applied every other day [6]. In conclusion, when 0.5/0.5 g of imipenem/cilastatin was applied twice a day at the start and the end of each 10-hour session of slow HD, a therapeutic concentration of imipenem was maintained without producing considerable accumulation of cilastatin.

References

Kihara M, Ikeda Y, Shibata K, Masumori S, Fujita H, Ebira H, Toya Y, Takagi N, Shionoiri H, Umemura S, Ishii M: Slow hemodialysis performed during the day in managing renal failure in critically ill patients. *Nephron*, in press.

Kihara M, Ikeda Y, Shibata K, Masumori S, Ebira H, Ueda S, Takagi N, Umemura S, Shionoiri H, Ishii M: Pharmacokinetics of intravenous imipenem/cilastatin during slow hemodialysis in critically ill patients. *Clin Nephrol*, in press.

Gibson TS, Demetriades JL, Bland JA: Imipenem/cilastatin: pharmacokinetic profile in renal insufficiency. *Am J Med* 1985;78:54-61.

Keller E, Fecht H, Böhler J, Schollmeyer P: Single-dose kinetics of imipenem/cilastatin during continuous arteriovenous haemofiltration in intensive care patients. *Nephrol Dial Transplant* 1989;4:640-645.

Przechera M, Bengel D, Risler T: Pharmacokinetics of imipenem/cilastatin during continuous arteriovenous hemofiltration. *Contrib Nephrol* 1991;93:131-134.

Berman SJ, Sugihara JG, Nakamura JM, Kawahara KK, Wong EGC, Musgrave JE, Wong LMF, Siemsen AM: Multiple-dose study of imipenem/cilastatin in patients with end-stage renal disease undergoing long-term hemodialysis. *Am J Med* 1985;78: 113-116.

Jones RN: Review of the in vitro spectrum of activity of imipenem. Am J Med 1985;78:22-32.
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