

## Pharmacokinetics of Imipenem-Cilastatin in Neonates

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**Imipenem and its renal dehydropeptidase I inhibitor, cilastatin, were coadministered intravenously in a 1:1 ratio to 30 newborns. Five infants each received single doses of 10, 15, or 20 mg/kg of both drugs. Concentrations in plasma were proportional to the administered dose, and cilastatin achieved consistently higher concentrations than did equivalent doses of imipenem because of its smaller volume of distribution. The pharmacokinetics of both drugs were best described by a one-compartment model. The plasma half-lives of imipenem were 1.7 to 2.4 h, whereas those of cilastatin were 3.9 to 6.3 h. The plasma clearance of cilastatin was approximately one-quarter of that of imipenem in the dose range tested. The urinary concentrations of imipenem were 50% of those of cilastatin despite its higher clearance from plasma. Fifteen additional newborns received five to eight doses of imipenem-cilastatin at 20 mg/kg per dose every 12 h. There was no accumulation of either drug in plasma after repeated administrations, and the mean concentrations in plasma were similar when measured on the first and last days of the multiple-dose study. There was marked intersubject variability, more so for cilastatin. The pharmacokinetics of both drugs in neonates resembled those observed in adults with moderate to severe renal insufficiency. Because the effects of enzyme inhibition on neonates are unknown, additional studies with imipenem-cilastatin (primaxin) are recommended.**

Imipenem is a beta-lactam antibiotic with a carbapenem nucleus (5). It has excellent activity against aerobic and anaerobic gram-positive and gram-negative bacteria (1, 4, 8, 13). Cilastatin (MK0791) is an inhibitor of dehydropeptidase I, the renal tubular brush border enzyme that inactivates imipenem (9). The coadministration of imipenem and cilastatin increases the urinary recovery of imipenem and, to a lesser extent, its concentration in plasma (9). In experimental animals, the combination appears to prevent the nephrotoxicity associated with the administration of imipenem alone (3).

By virtue of its high in vitro potency against *Escherichia coli*, streptococci, *Staphylococcus aureus*, *Listeria monocytogenes*, *Pseudomonas aeruginosa*, and enterococci (1, 2, 4, 8), imipenem potentially might be the most useful single agent for initial, empirical treatment of neonatal infections. Imipenem provides broader coverage than the standard ampicillin-plus-aminoglycoside regimen while reducing the potential toxicities of antibiotic combinations to the newborn.

This study was undertaken to determine the pharmacokinetic properties of both imipenem and cilastatin (primaxin) in neonates.

### MATERIALS AND METHODS

**Study patients.** The study population consisted of 30 newborn infants born at Parkland Memorial Hospital, Dallas, Tex., who were being treated with ampicillin and gentamicin for suspected sepsis (Table 1). After informed, written consent was obtained from the parents, one to eight doses of imipenem-cilastatin (in a 1:1 ratio) were administered intravenously. Complete blood counts were obtained at the start of the study and again after the last dose of imipenem-cilastatin was infused. Serum creatinine, urinalysis, and other laboratory studies were performed as required by the condition of the patients.

The infusion solutions were prepared by mixing equal amounts (in milligrams) of imipenem (powder form) and

cilastatin (liquid form) and then diluting the resulting slurry in sufficient sterile saline to achieve a final concentration of 5 mg/ml for both drugs. The consistency of this preparation method was evaluated by measuring the concentrations of both imipenem and cilastatin in specimens from seven different infusion solutions.

A single dose of imipenem-cilastatin was infused intravenously over 60 min in 15 newborns; five each received doses of 10, 15, or 20 mg/kg. Blood specimens were obtained by heel punctures at 0, 0.5, 1, 2, 4, and 8 h after the end of the infusion. A dose of 20 mg of imipenem-cilastatin per kg was infused over 30 to 60 min every 12 h in 15 additional infants. Blood was collected at similar time intervals after one or two doses and again after five to eight doses. In addition, a single specimen was obtained at 0.5 h after dose 3 or 4 in these infants. The first voided urine specimen after the end of the intravenous infusion was collected and analyzed for imipenem and cilastatin concentrations.

**Handling of specimens.** Concentrations of imipenem in plasma were measured immediately without storage in the majority of instances. When a specimen could not be promptly analyzed, an equal volume of plasma stabilizer was added, and the mixture was stored at  $-70^{\circ}\text{C}$  until it was analyzed 24 to 72 h later. This stabilization procedure was essential because imipenem undergoes rapid inactivation under conventional conditions of sample storage (MK0787/MK0791 Investigator's Brochure, Merck Sharp & Dohme, 1981). The plasma stabilizer consisted of a 1:1 mixture (vol/vol) of ethylene glycol and 1 M morpholinepropanesulfonate buffer (pH 6.8). Urine specimens were similarly mixed with morpholinepropanesulfonate and stored at  $-70^{\circ}\text{C}$  until they were analyzed 24 to 72 h later. Concentrations of cilastatin in plasma and urine were measured within a week of specimen collection.

**High-pressure liquid chromatography.** Imipenem and cilastatin concentrations were measured with a Waters liquid chromatograph equipped with an M450 UV absorption detector, a WISP automatic injector, and an M640 integrator (Waters Associates, Inc., Milford, Mass.).

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TABLE 1. Characteristics of the study group ( $n = 30$ )

Characteristic	Range	Median	Mean	SD
Wt (g)	1,180–3,810	2,085	2,395	761
Gestational age (wk)	31–42	35.5	36.1	3.4
Postnatal age (days)	0–10	2	2.3	2.5

Extraction of the two compounds from serum samples (0.3 ml) was accomplished simultaneously by using a two-phase procedure involving acetonitrile precipitation and methylene chloride concentration (12).

Imipenem was analyzed on a reverse-phase Hypersil-ODS column (particle size, 5  $\mu\text{m}$ ; 15 cm [length] by 4.6 mm [inside diameter]; Chromanetics Corp., Kensington, Md.) at a detector wavelength of 299 nm. A 2:98 mixture (vol/vol) of methanol and 0.01 M borate buffer (pH 7.2 with 1 N NaOH) at a flow rate of 2.0 ml/min was utilized as the mobile phase.

Cilastatin separation was achieved on a reverse-phase Spherisorb ODS-2 column (particle size, 5  $\mu\text{m}$ ; 25 cm [length] by 4.6 mm [inside diameter]; Chromanetics Corp.) at a detector wavelength of 230 nm. The mobile phase contained tetrabutyl ammonium phosphate, an ion-pairing reagent, in a 70% aqueous solution (pH 2.5) and 30% methanol pumped at 1.5 ml/min.

Serum standards were prepared by spiking pooled human sera with both drugs to achieve a wide range of concentrations. Linear regression equations were determined by generating standard curves with peak heights versus drug concentrations. Imipenem and cilastatin levels in the study patients were then calculated from the regression equations. The lowest detectable concentration for either drug was 1.0  $\mu\text{g/ml}$ .

Both imipenem and cilastatin were well separated from endogenous serum compounds with retention times of 2.5 and 5.3 min, respectively, for each high-pressure liquid chromatography separation mode.

The intra-assay precision of the methods was evaluated for both compounds by measuring a known standard extracted and analyzed 10 times in the course of a day. The coefficients of variation for both imipenem and cilastatin were 2.7 and 5.7%, respectively.

**Pharmacokinetic analysis.** The postinfusion concentrations of imipenem and cilastatin in serum for each infant were initially fitted to both one- and two-compartment models. When the two-compartment model did not provide a significantly better fit compared with the one-compartment model ( $F$ -statistic,  $P > 0.05$ ), the latter model was used to calculate the pharmacokinetic values.

For the one-compartment model, the equation for the nonlinear regression line was determined by the method of least mean squares (11). The half-life ( $t_{1/2}$ ) in hours was calculated by using the formula  $t_{1/2} = 0.693/K$ , where  $K$  is the slope of the natural logarithm concentration (in plasma)-time curve. The volume of distribution ( $V$ ) (milliliters per kilogram) was obtained by dividing the administered dose (micrograms per kilogram) by the product of  $K$  and AUC, where AUC is the area under the concentration (in plasma)-time curve expressed in microgram  $\cdot$  hours per milliliter and was obtained by successive trapezoidal approximations from postinfusion time zero to time infinity (11) and then corrected for the infusion time by the method of Loo and Riegelman (6). The plasma clearance ( $CL_P$ ) was calculated by using the formula  $CL_P = \text{dose}/\text{AUC}$  and was expressed in milliliters per kilogram per minute.

For the two-compartment model, the concentration in

plasma ( $C_P$ ) was fitted to the biexponential equation  $C_P = Ae^{-\alpha t} + Be^{-\beta t}$  by the NONLIN least-squares regression computer program (7) and then corrected for the infusion time (6).

**Statistical analysis.** For the single-dose study, the concentrations in plasma at the various postinfusion times and the calculated pharmacokinetic parameters for the different dosage regimens were compared by using the Kruskal-Wallis test. Differences between imipenem and cilastatin concentrations and pharmacokinetic parameters for individual patients within each group were analyzed with the paired-sample Student  $t$  test. For the multiple-dose study, the concentrations at various postinfusion times and pharmacokinetic parameters of both imipenem and cilastatin for individual patients determined after one or two doses and again after five to eight doses were compared by using the paired-sample Student  $t$  test. Correlation coefficients between the plasma half-life and both weight and gestational age were determined for imipenem and cilastatin, and the significance of the correlations was analyzed with the Student  $t$  test (15).

## RESULTS

**Reproducibility of reconstitution technique.** Consistent concentrations for both drugs were obtained from seven infusion solution specimens, with coefficients of variation of 3.4 and 6.7% for imipenem and cilastatin, respectively. There was no added benefit to vortexing the infusion solution for 1 min, as compared with manual mixing.

**Single-dose pharmacokinetics.** Of 15 newborns receiving a single dose of imipenem-cilastatin, one infant was eliminated from analysis because of erratic concentrations in plasma. Concentrations of both imipenem and cilastatin in plasma were directly proportional to the administered dose (Fig. 1). The peak concentrations of imipenem in plasma were achieved at the end of the 60-min infusion in 12 of 14 neonates and at 0.5 h in the remaining two neonates. Cilastatin peak concentrations occurred at 0, 0.5, and 1 h in seven, six, and one infants, respectively.

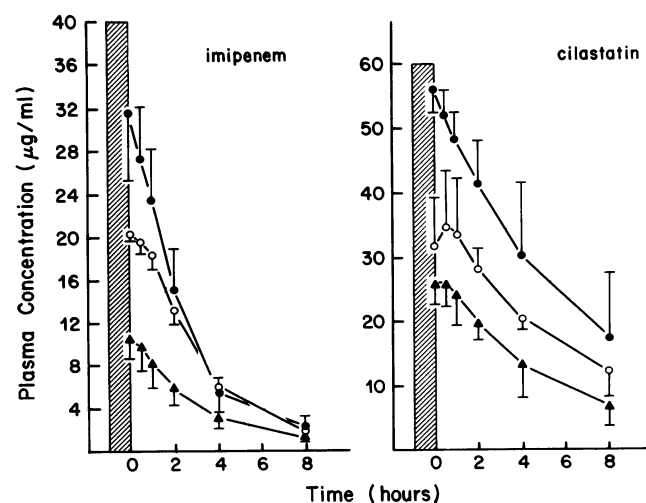


FIG. 1. Mean concentrations of imipenem and cilastatin in plasma when drugs were administered intravenously in doses of 10 ( $\blacktriangle$ ), 15 ( $\circ$ ), and 20 ( $\bullet$ ) mg/kg. The cross-hatched vertical columns represent the infusion time of 60 min, and the vertical bars represent the standard deviations.

TABLE 2. Single-dose pharmacokinetic parameters of imipenem and cilastatin<sup>a</sup>

Drug	Dose (mg/kg)	No. of infants	C <sub>max</sub> <sup>b</sup> (μg/ml)	t <sub>1/2</sub> <sup>c</sup> (h)	V (ml/kg)	CL <sub>P</sub> (ml/kg per min)	AUC (μg · h/ml)
Imipenem	10	5	11.1 ± 2.1	2.4 ± 0.2	873 ± 204	4.2 ± 0.9	41.1 ± 9.6
	15	4	20.7 ± 0.4	2.2 ± 0.2	566 ± 29	3.0 ± 0.2	82.6 ± 6.3
	20	5	31.6 ± 6.2	1.7 ± 0.4	528 ± 85	3.6 ± 0.8	96.5 ± 20.5
Cilastatin	10	5	27.5 ± 3.8	3.9 ± 1.1	334 ± 47	1.1 ± 0.4	172 ± 59
	15	4	36.6 ± 7.1	6.3 ± 3.4	416 ± 92	0.9 ± 0.3	315 ± 112
	20	5	56.5 ± 3.5	5.2 ± 2.8	329 ± 20	0.9 ± 0.4	452 ± 230

<sup>a</sup> All values are mean ± standard deviation.

<sup>b</sup> C<sub>max</sub>, Peak concentration in plasma.

<sup>c</sup> t<sub>1/2</sub>, Half-life.

The pharmacokinetics of imipenem were equally well described by one- and two-compartment models in 13 of 14 newborns and by only a one-compartment model in one infant. While the concentrations of imipenem in plasma increased with larger infused doses, only those measured at 0, 0.5, 1, and 2 h for the 10- and 20-mg/kg regimens were significantly different ( $P < 0.05$ ). The AUC increased and the  $V$  decreased at larger doses, but significant differences were detected only between the 10- and 20-mg/kg regimens ( $P < 0.05$ ). The plasma half-life gradually decreased from 2.4 to 1.7 h ( $P > 0.05$ ) (Table 2). There was considerable intersubject variability within each dosage group.

The concentrations of cilastatin in plasma increased with increasing dosage, but statistically significant differences in concentration ( $P < 0.05$ ) were detected only between the 10- and 20-mg/kg groups except for the concentrations measured 8 h postinfusion ( $P > 0.05$ ). Cilastatin pharmacokinetics could be described only by a one-compartment model in 6 of 14 (43%) infants, whereas the parameters derived from either model were not statistically different in the remaining eight. The AUC was larger with larger doses, but significant increases were noted only between the 10- and 20-mg/kg groups ( $P < 0.05$ ). The half-life,  $V$ , and CL<sub>P</sub> for the three dosage groups were not significantly different ( $P > 0.05$ ).

Cilastatin achieved higher concentrations in plasma than did equivalent doses of imipenem (one-tailed Student  $t$  test,  $P < 0.05$ ). Cilastatin also had a longer half-life ( $P < 0.05$ ), larger AUC ( $P < 0.025$ ), smaller  $V$  ( $P < 0.025$ ), and smaller CL<sub>P</sub> ( $P < 0.0025$ ) than equivalent doses of imipenem (Table 2). The clearance of cilastatin from plasma was only 25 to 30% of that of imipenem for each of the three dosage groups. As for imipenem, there was considerable intersubject variability within each dosage group.

**Multiple-dose pharmacokinetics.** The mean concentrations of imipenem in plasma were similar when measured after one or two intravenous doses (day 1) or on day 3 or 4 after five to eight doses were infused ( $P = 0.14$  to  $0.98$  for all sampling times) (Fig. 2). Peak concentrations in plasma were achieved at the end of the intravenous infusion in most infants. The predose (trough) concentrations were undetected in all but three infants, the highest measured concentration being 2.7 μg/ml.

At 0 h on day 3 or 4, the mean concentrations of cilastatin in plasma were significantly higher than the values on day 1 (one-tailed Student  $t$  test,  $P < 0.01$ ). The concentrations measured at later times were similar ( $P = 0.59$  to  $0.85$  for the various sampling times) (Fig. 2). Predose concentrations of cilastatin were detected in two-thirds of the infants on day 1 (maximum, 26.1 μg/ml) and in 92% of the infants on day 3 or 4 (maximum, 39.1 μg/ml).

The concentrations of imipenem and cilastatin measured

at 0.5 h after dose 3 or 4 (day 2) were  $29.4 \pm 10.2$  μg/ml and  $72.1 \pm 18$  μg/ml, respectively. These values were comparable to the 0.5-h concentrations of both drugs on day 3 or 4.

Imipenem pharmacokinetics after multiple doses could be described only by a one-compartment model in two-thirds of the study patients and were described equally well by either the one- or two-compartment models in the remaining infants. After multiple administrations, the peak concentrations of imipenem in plasma slightly increased, whereas the plasma half-life ( $P = 0.08$ ), AUC ( $P = 0.63$ ),  $V$  ( $P = 0.21$ ), and CL<sub>P</sub> ( $P = 0.25$ ) remained unchanged (Table 3). The intersubject variability was large for all parameters. There was an inverse correlation between plasma half-life and both weight ( $r = -0.69$ ,  $P = 0.009$ ) and gestational age ( $r = -0.77$ ,  $P = 0.002$ ) (Fig. 3).

Cilastatin pharmacokinetics after multiple doses could be described only by a one-compartment model in 44% of the instances. In contrast to the data for imipenem, there was a significant decrease in plasma half-life ( $P < 0.005$ ) and  $V$  ( $P < 0.01$ ) after repeated administrations of cilastatin (one-tailed Student's  $t$  test). Using individual patient data, we found that the plasma clearance and AUC of cilastatin also changed significantly after multiple administrations ( $P = 0.05$  and  $P = 0.002$ , respectively; two-tailed Student  $t$  test). The peak concentration in plasma, plasma half-life, and the AUC for cilastatin were 2.4, 2.9, and 6.3 times larger, respectively, than those for imipenem when measured on

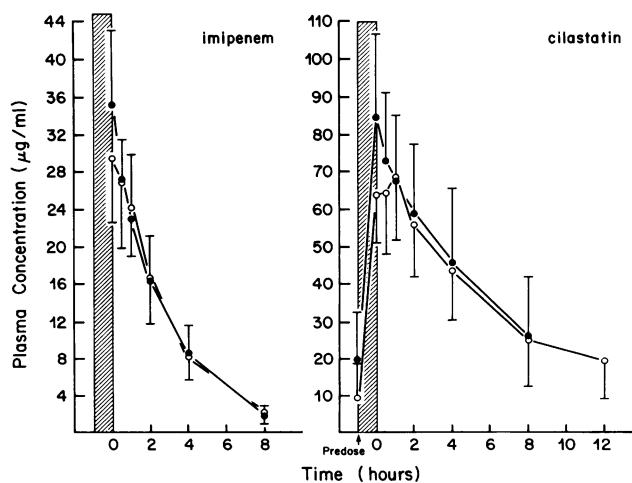


FIG. 2. Mean concentrations of imipenem and cilastatin in plasma after one or two doses (○) and after five to eight doses (●). The cross-hatched vertical columns represent the infusion time of 30 to 60 min, and the vertical bars represent the standard deviations.

TABLE 3. Multiple-dose pharmacokinetic parameters of imipenem and cilastatin<sup>a</sup>

Drug	Day	No. of infants <sup>b</sup>	C <sub>max</sub> <sup>c</sup> (μg/ml)	t <sub>1/2</sub> <sup>d</sup> (h)	V (ml/kg)	CL <sub>P</sub> (ml/kg per min)	AUC (μg · h/ml)
Imipenem	1	13	30.4 ± 6.5	2.1 ± 0.4	600 ± 117	3.4 ± 0.6	101.6 ± 21.1
	3 or 4	13	35.3 ± 7.8	1.9 ± 0.4	538 ± 105	3.5 ± 1.0	103.3 ± 23.0
Cilastatin	1	12 (1) <sup>e</sup>	71.9 ± 16	6.4 ± 3.1	292 ± 64	0.7 ± 0.5	637 ± 306
	3 or 4	13 (1) <sup>e</sup>	86.4 ± 20.9	5.3 ± 2.5	246 ± 50	0.7 ± 0.6	657 ± 352

<sup>a</sup> All values represent the mean ± standard deviation.

<sup>b</sup> Number of infants in whom adequate data were obtained for analysis.

<sup>c</sup> C<sub>max</sub>, Peak concentration in plasma.

<sup>d</sup> t<sub>1/2</sub>, Half-life.

<sup>e</sup> Numbers in parentheses indicate the number of patients whose pharmacokinetic parameters were best described by a two-compartment model.

both day 1 and day 3 or 4 (Table 3). The plasma clearance of cilastatin was only 20% of that of imipenem. The inter-subject variability was larger for cilastatin than for imipenem. There was an inverse correlation between plasma half-life and both weight ( $r = -0.72$ ,  $P = 0.006$ ) and gestational age ( $r = -0.80$ ,  $P = 0.001$ ) (Fig. 3).

**Urinary concentrations.** The first spontaneously voided urine specimens were collected between 0 and 8 h after the end of the intravenous infusions. The urinary concentrations of imipenem ranged between 49 and 894 μg/ml, with a mean ± standard deviation of 339 ± 218 μg/ml and a median of 307 μg/ml. The urinary recovery during the 0- to 8-h postinfusion period ranged between 1 and 24% of the administered dose. For cilastatin, the urinary concentrations ranged between 72 to 2,570 μg/ml, with a mean ± standard deviation of 690 ± 549 μg/ml and a median of 536 μg/ml. The urinary recovery for the 0- to 8-h postinfusion period ranged between 3 and 61% of the administered dose.

**Safety and tolerance.** The intravenous infusion of both drugs was well tolerated without any apparent clinical or laboratory adverse effects. None of the study patients developed thrombophlebitis related to imipenem-cilastatin administration.

## DISCUSSION

The one-compartment pharmacokinetic model best described the plasma concentration-time curves for both imipenem and cilastatin. Both drugs achieved higher concen-

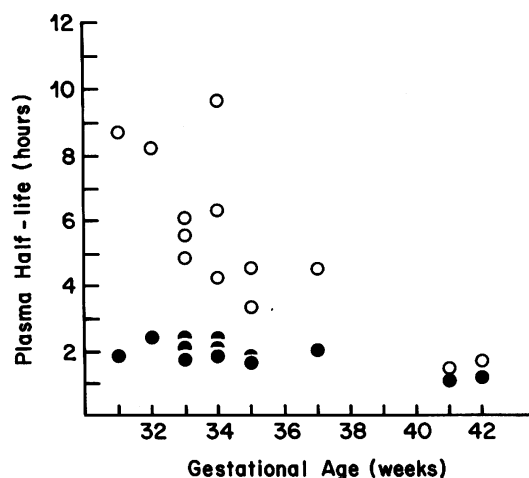


FIG. 3. Scatter diagram depicting the relationship of plasma half-lives of imipenem (●) and cilastatin (○) to gestational age.

trations after larger infused doses, and cilastatin consistently achieved higher concentrations than those observed with equivalent doses of imipenem because of its smaller apparent volume of distribution.

Nonparametric analysis of variance was used for comparing the different groups in this report because of the small number of patients and the large variability within each group. This more conservative approach led to the dismissal of several apparent differences in concentrations in plasma and pharmacokinetic parameters between the various groups as not significant statistically. Repeated trials with larger numbers of patients will probably permit the detection of additional significant differences between the different dosage regimens.

Imipenem did not accumulate in plasma after repeated administrations, as evidenced by undetectable trough concentrations in the majority of infants and similar mean concentrations in plasma at different postinfusion times after one or two doses and after five to eight doses.

The mean trough concentrations of cilastatin after the infusion of one or two doses was 19.7 μg/ml, but there was no evidence of further accumulation in plasma. The mean concentrations in plasma at various times were similar on the first and last days of the study.

Studies in healthy adult volunteers indicate that the plasma half-lives of both drugs are approximately one h (9, 10; G. A. Verpooten, L. Verbist, and M. E. DeBroe, Proc. Int. Congr. Chemother. 13th, Vienna, Austria, p. 95/38-95/45, 1983), which is considerably shorter than those observed in neonates. The half-life was more prolonged in premature infants than in full-term infants and was longer for cilastatin than for imipenem. The half-lives of both drugs are increased in adults with different degrees of renal failure, but cilastatin has a more prolonged half-life than imipenem (Verpooten et al., 13th ICC, 1983). Neonates in general, and premature infants in particular, are characterized by low glomerular filtration rates comparable to those in adults with moderate or severe renal insufficiency (Verpooten et al., 13th ICC, 1983). This may account for the observed discrepancies in the half-lives of both drugs in newborns.

The urinary concentrations of imipenem were lower than those of cilastatin in our study patients, despite more rapid clearance of imipenem from plasma. This may be explained by an extrarenal pathway of imipenem metabolism that is not inhibited by cilastatin administration (3, 9).

Maximal urinary recovery of imipenem in adults can be achieved by an imipenem-to-cilastatin ratio of 1:0.25 (9). Increasing the amount of cilastatin relative to that of imipenem does not affect the total urinary recovery of imipenem but only prolongs the inhibition of its metabolism. The plasma clearance of cilastatin in neonates is only 20 to 30%

of that for imipenem. Thus, an imipenem-to-cilastatin ratio of 1:0.25 might achieve maximal urinary recovery of the antibiotic and prolonged inhibition of its metabolism comparable to that observed with the 1:1-ratio formulation used in our patients.

The physiologic role of dehydropeptidase I is unclear. Welch and Campbell (14) suggested that the enzyme might play a role in retaining essential amino acids by hydrolyzing filtered dipeptides that would otherwise be excreted in the urine. The effects of enzyme inhibition by cilastatin on neonatal homeostasis are unknown.

Further studies with imipenem-cilastatin in its current formulation or in a different ratio of imipenem to cilastatin are necessary before this antibiotic can be routinely used for the treatment of neonatal infections.

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