Prospective Determination of Plasma Imipenem Concentrations in Critically Ill Children

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Plasma imipenem concentrations were measured in 19 critically ill children (median age, 0.8 year; range, 0.02 to 12.9 years). Wide interindividual variations (2 to 4× at peak and >10× at trough concentrations) resulted in unpredictable plasma levels in several children. To avoid subtherapeutic drug levels, we recommend treatment with at least 100 mg/kg of body weight/day of imipenem-cilastatin for critically ill children requiring such therapy.

Critically ill patients are particularly heterogeneous with regard to conditions that may alter drug levels in body fluids. Recently, we encountered problems in two critically ill children with *Enterobacter cloacae* septicemia who did not respond to treatment with imipenem-cilastatin, in spite of being infected with drug-susceptible pathogens (MIC of imipenem, 0.125 mg/liter). One patient developed hepatic microabscesses while under therapy. Concentrations of imipenem in the plasma were low (peak and trough levels, ≤ 20 mg/liter and undetectable, respectively), in spite of the use of doses within therapeutic recommendations (60 mg/kg of body weight/day) (4, 13). This prompted us to measure the concentrations of imipenem in the plasmas of children admitted to the intensive care unit and to determine whether individual variations could be predicted by bedside drug adjustment calculations, including age, size, weight, and renal function.

Methods and experimental design. Nineteen consecutive children requiring imipenem-cilastatin treatment were prospectively enrolled in an observational, noninterventional study between August 2000 and June 2001. Dosage and administration schedules were at the discretion of the physician in charge. The protocol was accepted by the local ethics committee, and written consent was obtained from the children's parents. Because of previous treatment failures with a total daily dose of 60 mg/kg, the physicians in charge prescribed 100 mg/kg/day of imipenem-cilastatin to all patients (Tienam; Merck Sharp and Dohme-Chibret AG, Switzerland). The drug was administered in either three (every 8 h [q8h]) or four (q6h) separate infusions (Fig. 1). Concentrations of imipenem were measured at the first dose and at steady state, i.e., between days 4 and 6 after treatment onset.

Blood samples (0.4 ml) were drawn from a central line

independent of the line used to infuse the drug, immediately chilled, centrifuged at 4°C, stabilized, and stored at -80°C as described previously (10). Imipenem concentrations were determined by high-performance liquid chromatography (10). Plasma was deproteinized by ultrafiltration (16), thus yielding the free fraction of the drug. Standard curves, quality controls, and validation complied with previously described methodologies (5). The limit of quantification was 0.5 mg/liter, linearity was up to 200 mg/liter, and interrun and intrarun coefficients of variation were $\leq 13.4\%$ (at 4, 40, and 120 mg/liter) and $< 6\%$, respectively (5).

Patient characteristics and imipenem concentrations in the plasma. Most children had high pediatric risk of mortality (PRISM) scores (Table 1) (19). Three patients were newborn (< 30 days old), seven were less than 1 year old, six were between 1 and 5 years old, and three were older (stratified following FDA recommendations [<http://www.fda.gov/cber/gdlns/ichclniped.htm#iia>]). All but two had harmonious weight-to-height ratios (20). Nine were mechanically ventilated, four were on continuous positive airway pressure, and all benefited from analgesia and sedation, including opiates and/or benzodiazepines. No cutaneous or neurological side effects were observed.

Sixteen (84%) patients had nosocomial infections, defined by onset ≥ 48 h after hospitalization. A presumed pathogen was cultured from 12/19 (63%) patients (Table 1). MICs of imipenem ranged from 0.125 to 4 mg/liter (susceptibility breakpoint, ≤ 4 mg/liter) (23), except that for a methicillin-resistant *Staphylococcus epidermidis* isolate (MIC of > 32).

Concentration-time profiles were obtained for 10/19 patients for the first dose and 16/19 patients for the steady-state dose (Table 1 and Fig. 1). Imipenem concentrations varied by 2 to 4× at peak levels and up to $> 10\times$ at trough levels (Fig. 1A). We sought whether pharmacokinetic (PK) values were associated with physiological variables (age, weight, body surface area, creatinine level, measured creatinine clearance, blood urea level, albumin level, blood lactate level, PRISM score,

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FIG. 1. Imipenem concentrations in the plasmas of 19 critically ill children. All children received the same nominal dose of 100 mg/kg/day, given in either three separate infusions (q8h, open triangles) or four separate infusions (q6h, closed circles). The drug (50-mg vials) was dissolved in 100 ml of 0.9% NaCl, according to the manufacturer's recommendations, and infused over a period of 30 min via an infusion pump (BD Pilote C; Becton Dickinson). Five blood samples were collected for each series of dosages. For q8h regimens, samples were collected just before and 30, 120, 270, and 480 min after the infusion onset. For q6h regimens, samples were collected just before and 30, 90, 210, and 360 min after the infusion onset. Panel A presents the concentration profiles for all the children included in the study. The open diamonds (right panel) indicate the imipenem plasma concentrations for a child who received a dose of 60 mg/kg/day (q8h) and failed to respond to therapy. Wide interindividual variations were observed. Panel B presents the concentration-time profiles for children who were <1 year old. Arrows in the right panel indicate children who were <1 month old. In spite of a decreased rate of imipenem elimination in very young children (1, 4, 21, 22), the concentration-time profiles were not markedly different from those for other children. Panel C depicts the concentration profiles of imipenem in a subset of children with impaired renal function, defined by creatinine clearance ($\text{ml/min} \times 1.73 \text{ m}^2$) of <2 standard deviations for the age group (no cases requiring dialysis were included). Dotted lines represent approximations in a few cases where the last dosage was below the limit of quantification (i.e., 0.5 mg/liter). Note that since only a few points were taken during the first hour following administration, a precise distribution phase cannot be deduced from the figure.

mean blood pressure, heart rate, and central venous pressure). Individual PK values were determined by standard noncompartmental analysis and computed using published methodologies (11). Calculated parameters included the terminal slope (K_B), area under the curve (AUC; 0 to 6 h and 0 to 8 h for q6h and q8h regimens, respectively), area under the first moment curve (AUMC), terminal half-life ($T_{1/2\beta} = \log 2/K_B$), mean residence time ($\text{MRT} = \text{AUMC}/\text{AUC}$), systemic clearance

($\text{CLR} = \text{dose}/\text{AUC}$), and volumes of distribution ($V_B = \text{CLR}/K_B$ and $V_{ss} = \text{CLR} \times \text{MRT}$).

All parameters were within the ranges of reported values for children (shown in part in Table 2). High and low values did not cluster with particular children, such as those less than 1 year old (Fig. 1B) or those with altered renal function (defined as creatinine clearance of <2 standard deviations for the age group) (Fig. 1C), although no cases requiring dialysis were

TABLE 1. Characteristics of patients

Age/sex ^a	PRISM score	Underlying disease	Infection ^b	Pathogen	Imipenem MIC (mg/liter)	Dosing interval (h)	PK value (first dose/steady-state dose) ^{c,d}				
							$T_{1/2\beta}$ (h)	Clearance (liters/h · kg)	V (liters/kg)	V_{ss} (liters/kg)	$fT_{>MIC}$ (%)
9 D/F	10	Transposition of the great arteries	SIRS			8	NA/1.442	NA/0.361	NA/0.751	NA/0.539	
17 D/F	10	Double-outlet right ventricle	Necrotizing enterocolitis			6	1.813/NA	NA/0.514	NA/1.346	NA/1.016	
25 D/M	9	Tricuspid atresia	Pneumonia			6	NA/1.772	NA/0.339	NA/0.866	NA/0.697	
79 D/F	6	Congenital chylothorax	Urinary tract infection	<i>E. cloacae</i>	4	8	NA/2.057	NA/0.317	NA/0.942	NA/0.820	76
119 D/F	14	Congenital diaphragmatic hernia	Sepsis	<i>S. epidermidis</i>	>32	6	NA/1.056	NA/0.340	NA/0.518	NA/0.413	13
142 D/F*	5	Ventricular septal defect	SIRS			8	0.978/1.596	0.182/0.241	0.256/0.556	0.177/0.427	
143 D/M*	10	Truncus arteriosus	Pneumonia	<i>K. oxytoca</i>	0.125	8	1.484/1.132	0.202/0.266	0.433/0.435	0.392/0.283	100
148 D/M*	4	Transposition of the great arteries	Pneumonia	<i>P. aeruginosa</i>	1	8	1.244/1.678	0.378/0.416	0.679/1.008	0.442/0.625	100
260 D/F	11	Tricuspid atresia	SIRS			8	NA/1.267	NA/0.135	NA/0.247	NA/0.109	
292 D/M	8	Transposition of the great arteries	Pneumonia	<i>E. cloacae</i>	0.125	8	1.475/1.270	0.288/0.195	0.613/0.357	0.394/0.228	100
1 Y/F	8	Aspiration pneumonia	Pneumonia			6	2.149/NA	0.116/NA	0.360/NA	0.283/NA	
1 Y/M	0	Subdural hematoma	Urinary tract infection	<i>E. cloacae</i>	0.25	6	0.954/NA	0.303/NA	0.417/NA	0.274/NA	100
2 Y/M*	12	Transposition of the great arteries	Pneumonia	<i>K. pneumoniae</i>	0.19	8	1.472/1.621	0.166/0.182	0.353/0.427	0.170/0.218	100
3 Y/F*	23	Endocarditis	Pneumonia	<i>P. aeruginosa</i>	1	6	0.596/0.7153	0.480/0.338	0.289/0.349	0.350/0.259	71
3 Y/M	1	Extensive burn injury	Skin wound	<i>P. aeruginosa</i>	2	6	NA/1.068	NA/0.488	NA/0.752	NA/0.438	63
4 Y/M	10	Double-outlet right ventricle	Pneumonia	<i>H. influenzae</i>	0.5	6	1.278/NA	0.195/NA	0.360/NA	0.274/NA	100
11 Y/M	9	Truncus arteriosus	Sepsis	<i>K. pneumoniae</i>	0.125	6	0.567/NA	0.353/NA	0.289/NA	0.235/NA	89
12 Y/M	0	Subglottic stenosis	Sepsis	<i>E. cloacae</i>	0.25	6	NA/0.9801	NA/0.386	NA/0.545	NA/0.392	100
12 Y/M	7	Peritonitis	Sepsis			6	NA/1.276	NA/0.201	NA/0.371	NA/0.304	

^a D, days; Y, years; F, female; M, male.

^b SIRS, systemic inflammatory response syndrome.

^c $T_{1/2\beta}$, elimination half-life; V , volume of distribution at steady state; $fT_{>MIC}$, percentage of time above the MIC for the free fraction of the drug for the infecting organism; NA, not available.

^d Differences between the PK parameters at the first and steady-state doses were not statistically significant either for the whole population or for the five children tested at both time points (*) (Wilcoxon matched-pair test was not significant).

TABLE 2. Imipenem pharmacokinetics in children reported in various studies

Parameter and time of calculation	Mean reported value $\pm$ SD ^c				
	Present study	Engelhard et al. (9)	Jacobs et al. (14)	Begue et al. (1)	Claesson et al. (6)
First dose					
Age (yr)	3.1 $\pm$ 4.4	5.4 ^a	5.2 ^b $\pm$ 3.5		
$T_{1/2\beta}$ (h)	1.22 $\pm$ 0.47	1.12	1.08		
Clearance (liter/h $\cdot$ kg)	0.27 $\pm$ 0.11	0.27 $\pm$ 0.008	0.360 $\pm$ 0.035		
V (liter/kg)	0.42 $\pm$ 0.13	ND	ND		
V_{ss} (liter/kg)	0.30 $\pm$ 0.1	ND	0.66 $\pm$ 0.12		
Steady state					
Age (yr)	3.1 $\pm$ 4.4			7.3 ^c	ND ^d
$T_{1/2\beta}$ (h)	1.35 $\pm$ 0.38			0.87 $\pm$ 0.29	0.92
Clearance (liter/h $\cdot$ kg)	0.34 $\pm$ 0.14			ND	0.42
V (liter/kg)	0.64 $\pm$ 0.3			0.54 $\pm$ 0.58	ND
V_{ss} (liter/kg)	0.46 $\pm$ 0.25			ND	ND

^a Range, 2 to 11 years.^b Range, 2 to 12 years.^c Range, 3.5 to 14 years.^d Range, 3 to 12 years.^e ND, not determined.

included. Elimination parameters correlated with creatinine clearance ($R > 0.8$ by the Spearman correlation test). In addition, discrete positive and negative correlations were also found with several other factors, including blood pressure and acid/base equilibrium (Table 3). For instance, elimination was slower in the presence of high lactate and low bicarbonate levels. Lactic acidosis is a marker of poor perfusion. In patients with lactic acidosis, decreased blood flow to the kidneys could have resulted in decreased elimination of the imipenem. Moreover, although children who are <1 year old eliminate imipenem slower than older children (1, 4, 21, 22), the younger children did not demonstrate higher plasma levels of the drug (Fig. 1). This may reflect their larger volumes of distribution (3) (Fig. 2). While the correlations presented in Table 3 may have a direct or an indirect causal relation with renal elimination, the multiplicity of them could render drug adjustment notably difficult without the help of laboratory dosage and solid Bayesian-model predictions.

The PK parameters for all children at the first dose and steady state were not significantly different (a Wilcoxon matched-pair test was not significant)(Table 1). The PK parameters for the five children studied at both the first dose and steady state were not significantly different either, indicating individual stability (Table 1).

All children were clinically cured. The total duration of imipenem treatment was 9.6 $\pm$ 3.4 days (mean $\pm$ standard deviation). Most patients received additional antibiotics, including vancomycin for 13, amikacin for 2, and metronidazole for 3 patients. Pharmacodynamic recommendations for maximal bacterial killing by beta-lactams advocate a time above the MIC for the free fraction of the drug ($fT_{>MIC}$) (18) of >40% for carbapenems, >50% for penicillins, and >60 to 70% for cephalosporins (7, 8, 12, 25). In the present study, the high-dose regimen (100 mg/kg/day) used by the physicians in charge ensured an $fT_{>MIC}$ of 70% to 100% for all recovered pathogens except the methicillin-resistant *S. epidermidis* isolate

TABLE 3. R values for significant correlations between physiological and pharmacokinetic parameters^a

Physiological parameter	R value for correlation with indicated PK parameter ^d					
	K_{β}	$T_{1/2\beta}$	MRT_{iv}	Clearance	V	V_{ss}
Staturoponderal parameters						
Age ^b	NS	NS	-0.47	NS	-0.52	-0.55
Weight ^b	+0.40	-0.40	-0.48	NS	-0.56	-0.58
Height ^b	+0.44	-0.44	-0.50	NS	-0.53	-0.56
Body surface area ^b	+0.41	-0.41	-0.49	NS	-0.56	-0.58
Hemodynamic and metabolic parameters						
Mean blood pressure ^b	+0.60	-0.65	-0.58	NS	NS	NS
Central venous pressure ^b	NS	NS	NS	-0.49	NS	NS
Creatinine clearance ^b	+0.83	-0.74	-0.70	NS	NS	NS
HCO ₃ level ^b	+0.56	-0.49	-0.50	NS	NS	NS
Blood lactate level ^c	-0.45	+0.45	NS	-0.40	NS	NS

^a Heart rate, levels of blood urea, albumin, and creatinine, pH, pCO₂, and the PRISM score did not correlate significantly with pharmacokinetic parameters.^b Analyzed by the Spearman correlation test.^c Analyzed by the Pearson correlation test.^d K_{β} , elimination rate; MRT_{iv} , mean residence time after intravenous bolus; NS, not statistically significant.

FIG. 2. Correlation between age or height and the volume of distribution at steady state (V_{ss}) in the study population. Each data point represents a single patient. Closed circles indicate patients who were <1 year old or had <70 cm in height. Open circles represent children with values above these respective cutoffs. There was a fracture between the two correlation curves at 1 year and/or 70 cm. Caution is warranted for data below these values, because both age and size are inversely correlated with V .

($fT_{>MIC} = 13\%$) (Table 1). This is on the safe side of the recommended 40% $fT_{>MIC}$ mentioned above. In contrast, post hoc evaluation of the patient who failed treatment with the 60-mg/kg/day dosage gives an estimate of 10 to 20% $fT_{>MIC}$ for the pathogen, which is insufficient.

Although the high-dosage regimen appeared optimal, one should keep in mind that imipenem concentrations are lower in tissues than in the plasma and that this may also affect the therapeutic outcome (24). Three initially susceptible *Pseudomonas aeruginosa* isolates (MIC = 1 to 2 mg/liter) became resistant (MICs of 6 to 32 mg/liter), in spite of having a time above the MIC value of about 60%. This reminds us of the capacity of this organism to develop imipenem resistance (15) and that low drug concentrations in specific compartments may promote resistance (8).

Taken together, these data convey the following conclusions. First, the lower-range dose of 60 mg/kg/day of imipenem-cilastatin carries a nonnegligible risk of subtherapeutic drug levels in the plasma. Thus, it may be insufficient for critically ill children. Second, the higher-range dose of 100 mg/kg/day was uniformly appropriate over the whole pediatric population tested, irrespective of the q6h or q8h administration schedule (premature children were not included). This dose was also appropriate for the three neonates (<1 month of age), a category for which recommendations advocate 75 mg/kg/day in

the United States and 60 mg/kg/day in Europe. Third, interindividual variations in imipenem plasma concentrations exist and are difficult to predict in critically ill children, as recently reported for critically ill adults (2). We propose that critically ill children requiring imipenem-cilastatin therapy should receive a dose of 100 mg/kg/day and that recourse to measurements of drug concentrations should be considered in complex and uncertain situations (17).

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