UNIVERSITÉ DE LAUSANNE

FACULTÉ DE BIOLOGIE ET DE MÉDECINE

Département de Microbiologie Fondamentale

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"Prospective Determination of Imipenem Concentrations in the Plasma of Critically-ill Children"

THESE

Présentée à la Faculté de biologie et de médecine de

l'Université de Lausanne pour l'obtention du grade de

DOCTEUR EN MEDECINE

Par

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Originaire de Ormont-Dessous

Lausanne

2006

Détermination prospective des concentrations plasmatiques d'imipenem chez des patients de soins intensifs pédiatriques

Objectif: Les patients pris en charge en unité de soins intensifs représentent un collectif hétérogène atteint de pathologies pouvant altérer la distribution et l'élimination de médicaments. Dans notre institution, nous avons observé le cas de deux enfants atteints de sepsis sévère à *Enterobacter cloaque* traités sans succès par imipenem aux doses recommandées par la littérature (60 mg/kg/jour). Ces patients n'ont pas répondu au traitement malgré un germe sensible à l'imipenem. Leurs taux plasmatiques d'imipenem étaient nettement inférieurs aux concentrations efficaces prédites par les données de la littérature. Cette observation nous a incité à mesurer de façon prospective les concentrations d'imipenem chez les patients de soins intensifs pédiatriques traites par cet antibiotique.

Méthodes: Dix neuf enfants (âgés de 9 jours à 12.9 ans, médiane 0.8 an,) hospitalisés dans l'unité de soins intensifs pédiatriques du CHUV et traités par imipenem-cilastatine (100 mg/kg/jour) ont été inclus prospectivement après obtention d'un consentement éclairé. Le protocole a été préalablement approuvé par la commission d'éthique de la faculté de médecine de l'UNIL. Des échantillons sanguins on été prélevés au premier jour de traitement et à l'état d'équilibre (entre le 4^{è} et 6^{è} jour de traitement). Les concentrations plasmatiques d'imipenem ont été mesurées par chromatographie liquide à haute performance dans notre laboratoire.

Résultats: Les paramètres pharmacocinétiques obtenus à la première dose et à l'état d'équilibre sont les suivants : demi-vie 1.22 ± 0.47 et 1.35 ± 0.38 h ; clearance 0.27 ± 0.11 et 0.34 ± 0.14 l/h/kg ; volume de distribution (Vss) 0.30 ± 0.1 et 0.46 ± 0.25 l/kg. Ces valeurs sont comparables à celles observées lors d'études précédentes chez des patients pédiatriques. Toutefois ces concentrations plasmatiques présentent de larges variations interindividuelles. Ces variations ne peuvent être prédites de façon adéquate par les paramètres standard utilisés pour l'ajustement de posologie tels que l'age, le poids et la fonction rénale.

Conclusion: Cette étude révèle de larges variations interindividuelles des concentrations plasmatiques d'imipenem chez l'enfant pris en charge en unité de soins intensifs. Afin d'éviter des concentrations plasmatiques d'imipenem infra-thérapeuthiques, nous recommandons d'administrer une dose quotidienne d'imipenem d'au moins 100 mg/kg. Une mesure des concentrations plasmatiques d'imipenem peut être utile pour ajuster la posologie dans les cas complexes.

Prospective Determination of Imipenem Concentrations in the Plasma of Critically-ill Children

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Running title: Imipenem monitoring in critically ill children

Key Words: Monitoring; Pharmacokinetics; plasma concentration; imipenem-cilastatin; intensive care unit; children.

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ABSTRACT

Imipenem plasma-concentrations were measured in 19 critically-ill children (median 0.8 year, range 0.02-12.9 years). Wide inter-individual variations (2-4x at peak and >10x at through concentrations) resulted in unpredictable plasma-levels in several children. To avoid subtherapeutic drug levels we recommend at least 100 mg/kg/day of imipenem-cilastatin in critically-ill children requiring such therapy.

TEXT

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* septicaemia who did not respond to treatment with imipenem-cilastatin, in spite of drug-susceptible pathogens (MIC of imipenem: 0.125 mg/l). One patient developed hepatic micro-abscesses while under therapy. Concentrations of imipenem in the plasma were low (peak and trough levels $\leq$20 mg/l and undetectable, Figure 1A) in spite of doses within therapeutic recommendations (60 mg/kg/day)(4, 13). This prompted us to measure the concentration of imipenem in the plasma of children admitted to the intensive care unit, and determine whether individual variations were 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, non-interventional 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 ethic 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, physicians in charge prescribed 100 mg/kg/day of imipenem-clistatin to all the patients (Tienam^{R}, Merck Sharp and Dohme-Chibret AG, Switzerland). The drug was administered either in 3 (q8h) or 4 (q6h) separate infusions (Figure 1). Concentrations of imipenem were measured at the first dose and at steady state, i.e. between day 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 (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 were complied with described methodologies (5). The limit of quantification was 0.5 mg/l, linearity was up to 200 mg/l, and inter-run and intra-run coefficients of variation were $\leq$13.4% (at 4, 40, and 120 mg/l) 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 one year old, six were between 1 and 5 years old, and 3 were older (stratified following FDA recommendations; http://www.fda.gov/cber/gdlns/ichclinped.htm#iia). All but 2 had harmonious weight to height ratios (20). Nine were mechanically ventilated, 4 were on continuous positive airway pressure and all benefited from analgesia and sedation, including opiates and/or benzodiazepines. No cutaneous of neurological side effects were observed.

Sixteen (84%) had nosocomial infections, defined by onset $\geq$48h after hospitalization. A presumed pathogen was cultured in 12/19 (63%)(Table 1). Minimal inhibitory concentrations (MIC) of imipenem ranged from 0.125 to 4 mg/l (susceptibility breakpoint $\leq$ 4 mg/l)(23), except for the methicillin-resistant *S. epidermidis* (MIC > 32).

Concentration-time profiles were obtained in 10/19 patients for the first dose and in 16/19 patients for steady state dose (Table 1 and Figure 1). Imipenem concentrations varied by 2-4 times at peak levels and up to >10 times at trough levels (Figure 1A). We sought whether pharmacokinetic (PK) values were associated with physiological variables (age, weight, body surface area, creatinine, measured creatinine clearance, blood urea, albumin, blood lactate, PRISM score, mean blood pressure, heart rate, central venous pressure). Individual PK values were determined by standard non-compartmental analysis and

computed using published methodologies (11). Calculated parameters included terminal slope (K_β), area under the curve (AUC; 0-6h and 0-8h for q6h and q8h regimens, respectively), AUC under the first moment curve (AUMC), terminal half-life ($T_{1/2\beta}$ = Log 2 / K_β), Mean Residence Time (MRT = AUMC/AUC), systemic clearance (CLR = Dose / AUC) and volumes of distribution (V_β = CLR / K_β and Vss = CLR x MRT).

All parameters were within the range of reported values in children (shown in part in Table 2). High and low values did not cluster in particular children such as those <1 year old (Figure 1B) or those with altered renal function (defined as a creatinine clearance <2 standard deviations for the age group)(Figure 2C), although no cases requiring dialysis were 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 <1 year eliminate imipenem slower than older children (1, 4, 21, 22), they did not demonstrate higher plasma levels (Figure 1). This may reflect their larger volume of distribution (3) (Figure 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 of all children at first-dose and steady state were not significantly different [Wilcoxon matched paired test not significant](Table 1). The PK parameters of the five children that were studied at both 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 (Mean ± SD) 9.6 ± 3.4 days. Most patients received additional antibiotics including vancomycin in 13, amikacin in 2, and metronidazole in 3 patients. Pharmacodynamic recommendations for maximal bacterial killing by beta-lactams advocate a time-above-MIC of the free fraction of the drug ($fT_{<MIC}$)(18) of $\geq$ 40% for carbapenems, $\geq$ 50% for penicillins, and $\geq$ 60-70% for cephpalosporins (7, 8, 12, 25). In the present study, the high-dose regimen (100 mg/kg/day) used by the physicians in charge ensured $fT_{<MIC}$ of 70%-100% for all the recovered pathogens except for the methicillin-resistant *S. epidermidis* ($fT_{<MI}$ = 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 10-20% $fT_{<MIC}$ for its 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 *P. aeruginosa* (MIC = 1-2 mg/l) became resistant (MICs 6-32 mg/l) in spite of a time-above-MIC around 60%. This reminds us 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 conclusion. First, the lower range dosage of 60 mg/kg/day of imipenem-cilastatin carries a non-negligible risk of subtherapeutic drug levels in the plasma. Thus it may be insufficient in critically-ill children. Second, the higher range dosage 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 dosage was also appropriate in the three neonates (below 1 month of age), a category for which recommendations advocate 75 mg/kg/day in the USA and 60 mg/kg/day in Europe. Third, inter-individual variations of imipenem plasma-concentrations

exist and are difficult to predict in critically ill children, as recently reported in 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 measurement of drug concentrations should be considered in complex and uncertain situations (17).

ACKNOWLEDGEMENTS

This work was supported by the Foundation for Advances in Medical Microbiology and Infectious Diseases and by an unrestricted grant from Merck Sharp and Dohme-Chibret.

We thank Saskia Bolay for outstanding technical assistance.

REFERENCES

1. **Begue, P. C., S. Baron, P. Challier, J. L. Fontaine, and G. Lasfargues.** 1987. Pharmacokinetic and clinical evaluation of imipenem/cilastatin in children and neonates. Scand J Infect Dis Suppl **52:**40-5.

2. **Belzberg, H., J. Zhu, E. E. Cornwell, 3rd, J. A. Murray, J. Sava, A. Salim, G. C. Velmahos, and M. A. Gill.** 2004. Imipenem levels are not predictable in the critically ill patient. J Trauma **56:**111-7.

3. **Besunder, J. B., M. D. Reed, and J. L. Blumer.** 1988. Principles of drug biodisposition in the neonate. A critical evaluation of the pharmacokinetic-pharmacodynamic interface (Part I). Clin Pharmacokinet **14:**189-216.

4. **Blumer, J. L.** 1996. Pharmacokinetic determinants of carbapenem therapy in neonates and children. Pediatr Infect Dis J **15:**733-7.

5. **Bugnon, D., E. Giannoni, P. Majcherczyk, M. P. Glauser, and P. Moreillon.** 2002. Pitfalls in cefepime titration from human plasma: plasma- and temperature-related drug degradation in vitro. Antimicrob Agents Chemother **46:**3654-6.

6. **Claesson, G., M. Eriksson, and J. D. Rogers.** 1992. Pharmacokinetics of imipenem/cilastatin sodium in children with peritonitis. Pharmacol Toxicol **71:**103-6.

7. **Craig, W. A.** 1995. Interrelationship between pharmacokinetics and pharmacodynamics in determining dosage regimens for broad-spectrum cephalosporins. Diagn Microbiol Infect Dis **22:**89-96.

8. **Drusano, G. L.** 2003. Prevention of resistance: a goal for dose selection for antimicrobial agents. Clin Infect Dis **36:**S42-50.

9. **Engelhard, D., I. Shalit, H. R. Stutman, R. Greenwood, J. Griffis, and M. I. Marks.** 1986. Single-dose pharmacokinetics of imipenem-cilastatin in pediatric patients. Pediatr Pharmacol (New York) **5:**273-9.

10. **Garcia-Capdevila, L., C. Lopez-Calull, C. Arroyo, M. A. Moral, M. A. Mangues, and J. Bonal.** 1997. Determination of imipenem in plasma by high-performance liquid chromatography for pharmacokinetic studies in patients. J Chromatogr B Biomed Sci Appl **692:**127-32.

11. **Gibaldi, M., Perrier, D.** 1982. Noncompartmental analysis based on statistical moment theory. Marcel Dekker, New York.

12. **Gunderson, B. W., G. H. Ross, K. H. Ibrahim, and J. C. Rotschafer.** 2001. What do we really know about antibiotic pharmacodynamics? Pharmacotherapy **21:**302S-318S.

13. **Henry, N. K., J. L. Hoecker, and K. H. Rhodes.** 2000. Antimicrobial therapy for infants and children: guidelines for the inpatient and outpatient practice of pediatriac infectious diseases. Mayo Clin Proc **75:**86-97.

14. **Jacobs, R. F., G. L. Kearns, J. M. Trang, A. L. Brown, B. Marmer, J. C. McIntosh, F. L. Underwood, and R. B. Kluza.** 1984. Single-dose pharmacokinetics of imipenem in children. J Pediatr **105:**996-1001.

15. **Livermore, D. M.** 1995. Bacterial resistance to carbapenems. Adv Exp Med Biol **390:**25-47.

16. **Majcherczyk, P. A., P. Moreillon, L. A. Decosterd, D. Sanglard, J. Bille, M. P. Glauser, and O. Marchetti.** 2002. Single-step extraction of fluconazole from plasma by ultra-filtration for the measurement of its free concentration by high performance liquid chromatography. J Pharm Biomed Anal **28:**645-51.

17. **Mohr, J. F., A. Wanger, and J. H. Rex.** 2004. Pharmacokinetic/pharmacodynamic modeling can help guide targeted antimicrobial therapy for nosocomial gram-negative infections in critically ill patients. Diagn Microbiol Infect Dis **48:**125-30.

18. **Mouton, J. W., M. N. Dudley, O. Cars, H. Derendorf, and G. L. Drusano.** 2005. Standardization of pharmacokinetic/pharmacodynamic (PK/PD) terminology for anti-infective drugs: an update. J Antimicrob Chemother **55:**601-7.

19. **Pollack, M. M., K. M. Patel, and U. E. Ruttimann.** 1996. PRISM III: an updated Pediatric Risk of Mortality score. Crit Care Med **24:**743-52.

20. **Prader, A., R. H. Largo, L. Molinari, and C. Issler.** 1989. Physical growth of Swiss children from birth to 20 years of age. First Zurich longitudinal study of growth and development. Helv Paediatr Acta Suppl **52:**1-125.

21. **Reed, M. D., R. M. Kliegman, T. S. Yamashita, C. M. Myers, and J. L. Blumer.** 1990. Clinical pharmacology of imipenem and cilastatin in premature infants during the first week of life. Antimicrob Agents Chemother **34:**1172-7.

22. **Routledge, P. A.** 1994. Pharmacokinetics in children. J Antimicrob Chemother **34 Suppl A:**19-24.

23. **Steward, C. D., J. M. Mohammed, J. M. Swenson, S. A. Stocker, P. P. Williams, R. P. Gaynes, J. E. McGowan, Jr., and F. C. Tenover.** 2003. Antimicrobial susceptibility testing of carbapenems: multicenter validity testing and accuracy levels of five antimicrobial test methods for detecting resistance in Enterobacteriaceae and Pseudomonas aeruginosa isolates. J Clin Microbiol **41:**351-8.

24. **Tegeder, I., A. Schmidtko, L. Brautigam, A. Kirschbaum, G. Geisslinger, and J. Lotsch.** 2002. Tissue distribution of imipenem in critically ill patients. Clin Pharmacol Ther **71:**325-33.

25. **Vogelman, B., S. Gudmundsson, J. Leggett, J. Turnidge, S. Ebert, and W. A. Craig.** 1988. Correlation of antimicrobial pharmacokinetic parameters with therapeutic efficacy in an animal model. J Infect Dis **158:**831-47.

Table 1. Characteristics of the patients

Age/sex	PRISM score	Underlying disease	Infection	Pathogen	Imipenem MIC (mg/l)	Dosing interval	PK values (1st dose/steady state dose) T ½β (h)	Clearance (l/h.kg)	V (l/kg)	Vss (l/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	*E. cloacae*	4	8	NA/ 2.057	NA/ 0.317	NA/ 0.942	NA/ 0.820	76
119 D/F	14	Congenital diaphragmatic hernia	Sepsis	*S. epidermidis*	> 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	*K. ocytoca*	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	*P. aeruginosa*	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	*E. cloacae*	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	*E. cloacae*	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	*K. pneumoniae*	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	*P. aeruginosa*	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	*P. aeruginosa*	2	6	NA/ 1.068	NA/ 0.488	NA/ 0.752	NA/ 0.438	63
4 Y/M	10	Double outlet right ventricle	Pneumonia	*H. influenzae*	0.5	6	1.278/ NA	0.195/ NA	0.360/ NA	0.274/ NA	100
11 Y/M	9	Truncus arteriosus	Sepsis	*K. pneumoniae*	0.125	6	0.567/ NA	0.353/ NA	0.289/ NA	0.235/ NA	89
12 Y/M	0	Subglottic stenosis	Sepsis	*E. cloacae*	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	

D, days; Y, years; F, female; M, male; SIRS, sepsis inflammatory response syndrome; *E. cloacae*, *Enterobacter cloacae*; *S. epidermidis*, *Staphylococcus epidermidis*; *K. ocytoca*, *Klebsiella ocytoca*;.*P. aeruginosa*, *Pseudomonas aeruginosa*; *H. influenzae*, *Haemphilus. Influenzae.* $T_{1/2\beta}$, elimination half life; V, volume of distribution; V_{SS}, volume of distribution at steady state; $fT_{>MIC}$, % time-above MIC of the free fraction of the drug for the infecting organism; NA, not available. Differences between the PK parameters at first-dose and steady state were not statistically significant either for the whole population or for the five children tested at both time points(*)(Wilcoxon matched paired test not significant).

Table 2. Comparison with other studies of imipenem pharmacokinetics in children.

	Present study		Engelhard et al (9)		Jacobs et al (14)	
1st dose	Mean	SD	Mean	SD	Mean	SD
Age (years)	3.1	4.4	5.4[a]	ND	5.2[b]	3.5
$T_{1/2\beta}$ (h)	1.22	0.47	1.12	ND	1.08	ND
Clearance (l/h.kg)	0.27	0.11	0.27	0.008	0.360	0.035
V (l/kg)	0.42	0.13	ND	ND	ND	ND
V_{SS} (l/kg)	0.30	0.1	ND	ND	0.66	0.12
Steady state	Present study		Begue et al (1)		Claesson et al (6)	
Age (years)	3.1	4.4	7.3[c]	ND	ND[d]	ND
$T_{1/2\beta}$ (h)	1.35	0.38	0.87	0.29	0.92	ND
Clearance (l/h.kg)	0.34	0.14	ND	ND	0.42	ND
V (l/kg)	0.64	0.3	0.54	0.58	ND	ND
V_{SS} (l/kg)	0.46	0.25	ND	ND	ND	ND

[a]Range 2-11 years; [b]Range 2-12 years; [c]Range 3.5-14 years; [d]Range 3-12 years.

$T_{1/2\beta}$, elimination half life; V, volume of distribution; V_{SS}, volume of distribution at steady state.

SD, standard deviation.

Table 3. *R* values for significant correlations between physiological and pharmacokinetic parameters. Heart rate, blood urea, albumin, creatinine, pH, pCO2, and PRISM score did not correlate significantly with pharmacokinetic parameters.

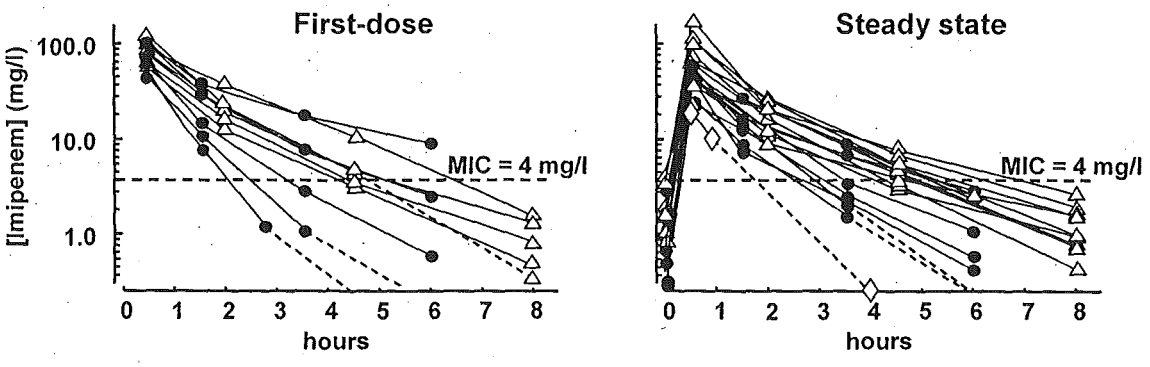
	Kβ	$T_{1/2\beta}$	MRTiv	Clearance	V	Vss
Staturo-ponderal parameters						
Age[a]	NS	NS	-0.47	NS	-0.52	-0.55
Weight[a]	+0.40	-0.40	-0.48	NS	-0.56	-0.58
Height[a]	+0.44	-0.44	-0.50	NS	-0.53	-0.56
Body surface area[a]	+0.41	-0.41	-0.49	NS	-0.56	-0.58
Hemodynamic and metabolic parameters						
Mean blood pressure[a]	+0.60	-0.65	-0.58	NS	NS	NS
Central venous pressure[a]	NS	NS	NS	-0.49	NS	NS
Creatinine clearance[a]	+0.83	-0.74	-0.70	NS	NS	NS
HCO3[a]	+0.56	-0.49	-0.50	NS	NS	NS
Blood lactate[b]	-0.45	+0.45	NS	-0.40	NS	NS

[a] Analyzed by the Spearman by correlation test; [b] Analyzed by the Pearson correlation test.

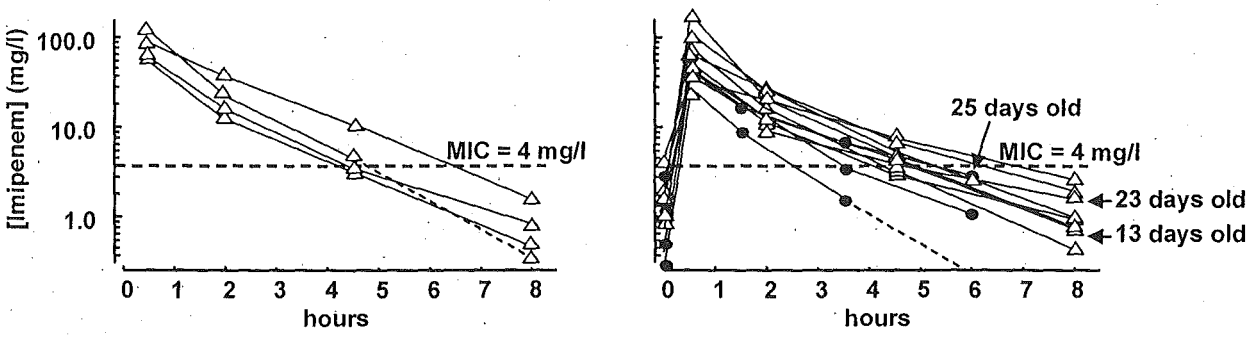
K_β, elimination rate; $T_{1/2\beta}$, elimination half life; MRT_{iv} mean residence time after intravenous bolus; V, volume of distribution; V_{SS}, volume of distribution at steady state; NS, not statistically significant

Figure 1

A. All age groups



B. Children below 365 days of life



C. Children with impaired renal function

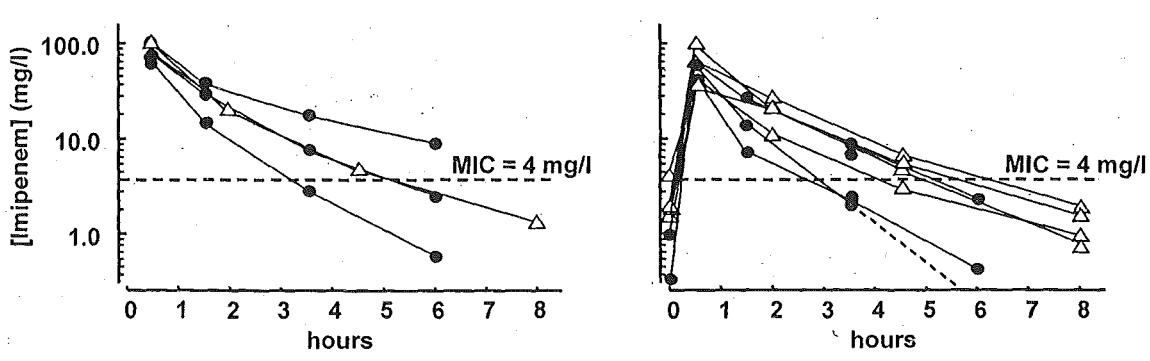
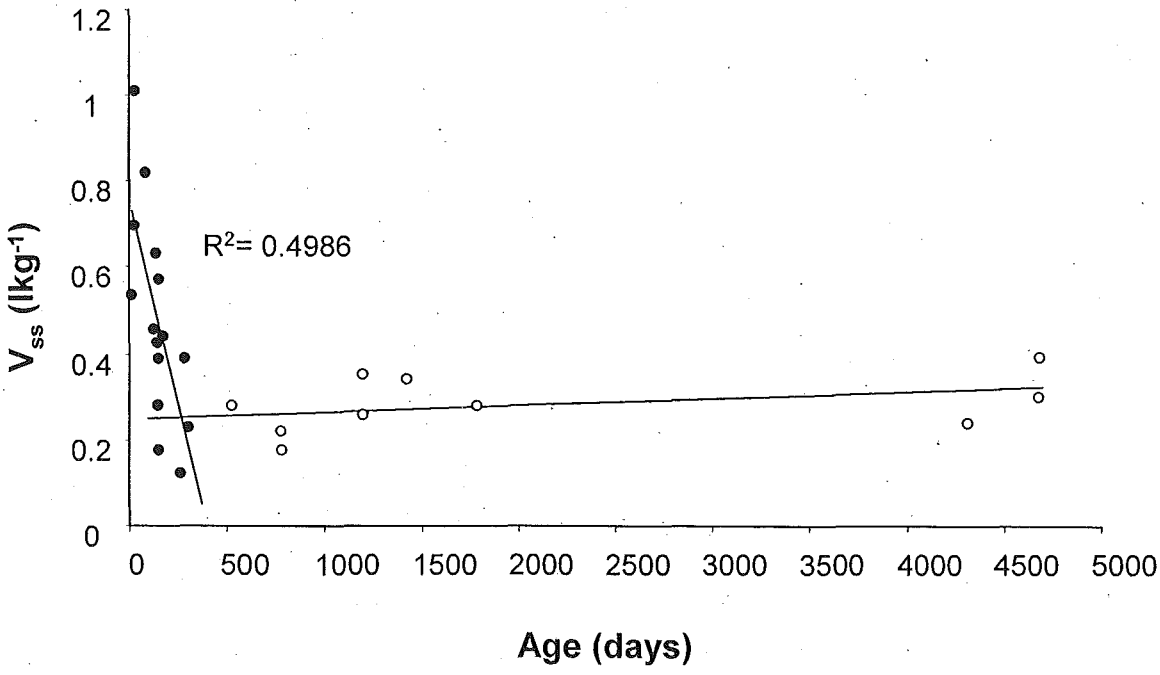


Figure 2


1.2
1
0.8
0.6
0.4
0.2
0
V_{ss} (lkg^{-1})
R^2= 0.4986
0
500
1000
1500
2000
2500
3000
3500
4000
4500
5000
Age (days)

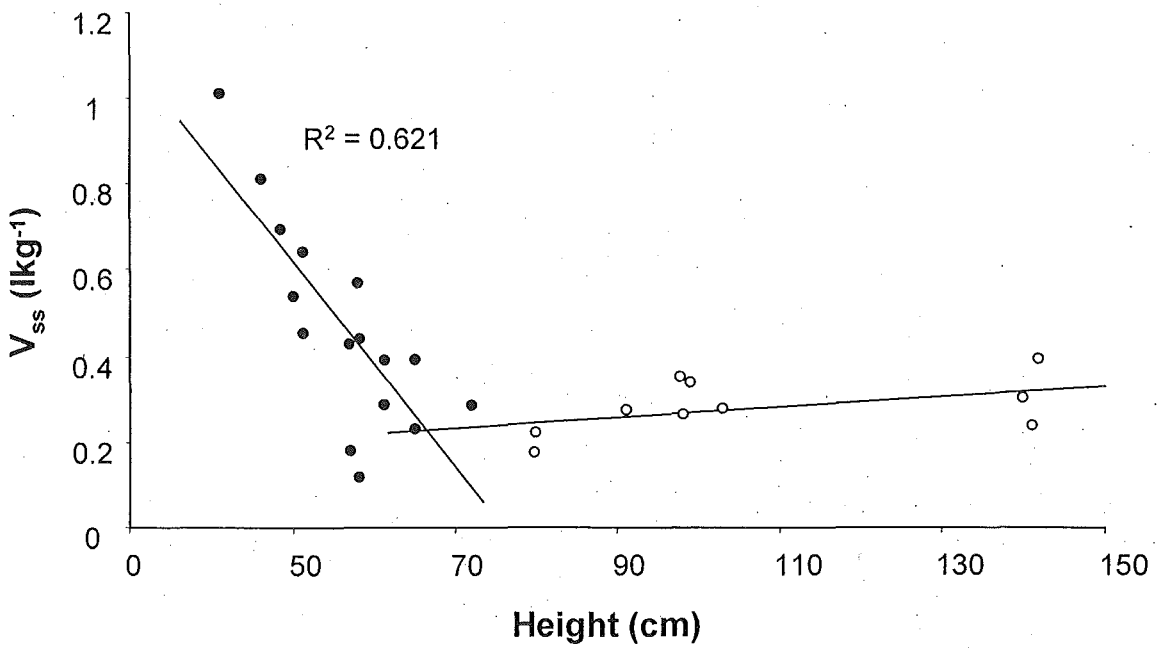

1.2
1
0.8
0.6
0.4
0.2
0
V_{ss} (lkg^{-1})
R^2 = 0.621
0
50
70
90
110
130
150
Height (cm)

FIGURE LEGENDS

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

Figure 2. Correlation between the children's age and 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 below < 1 year old and/or 70 cm of height. Open circles represent children above these respective values. There was a fracture between the two correlation curves at one year and/or 70 cm. Caution is warranted below these values, because both age and size are inversely correlated with V.