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Pharmacokinetics and Transplacental Passage of Imipenem during Pregnancy

ANNE HEIKKILÄ,[1]* OLLI-VEIKKO RENKONEN,[2] AND RISTO ERKKOLA[1]

Department of Obstetrics and Gynecology, Turku University Central Hospital, Kiinamyllynkatu 4-8, 20520 Turku 52,[1] and Department of Serobacteriology, University of Helsinki, 00290 Helsinki,[2] Finland

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Imipenem pharmacokinetics were studied in early pregnancy (n = 7; length of gestation, 8.6 ± 1.5 weeks, mean ± standard deviation), in late pregnancy (n = 7; length of gestation, 38.7 ± 1.4 weeks), and in the nonpregnant state (n = 6). A single dose of 500 mg of imipenem-cilastatin (1:1) was administered as a 20-min infusion. Multiple plasma and urine samples, as well as specimens of umbilical plasma and amniotic fluid from the pregnant subjects, were collected at frequent intervals for 8 h. Imipenem concentrations were assayed by specific microbiologic assay. The mean peak concentrations in plasma were 14.7 ± 4.9, 14.9 ± 5.2, and 43 ± 28.3 μg/ml in early pregnancy, late pregnancy, and the nonpregnant state, respectively. The volumes of distribution were significantly larger during early pregnancy (0.98 ± 0.45 liter/kg of body weight, $P < 0.005$) and late pregnancy (0.59 ± 0.19 liter/kg, $P < 0.05$) than in the nonpregnant state (0.33 ± 0.10 liter/kg), and total clearances from plasma were faster in early pregnancy (12.7 ± 7.8 ml min^{-1} kg^{-1}, $P < 0.05$) and late pregnancy (10.7 ± 4.6 ml min^{-1} kg^{-1}, $P < 0.05$) than in the nonpregnant state (5.77 ± 1.19 ml min^{-1} kg^{-1}). The mean concentrations in amniotic fluid were 0.07 ± 0.01 and 0.72 ± 0.85 μg/ml in early and late pregnancy. The mean umbilical venous and arterial drug concentrations were 1.72 ± 1.22 and 1.64 ± 1.22 μg/ml. The feto-maternal ratio at the time of cesarean section was 0.33 ± 0.12. These results indicate that an adjustment of doses of imipenem may be required when treating pregnant women because of considerable changes in imipenem pharmacokinetics during pregnancy.

It has been confirmed that for many antibiotics, such as ampicillin and piperacillin, the pharmacokinetics alter and elimination is enhanced during pregnancy (10, 16). This applies especially for polar drugs, and in general, the higher the water solubility of a drug is, the more its half-life is shortened during pregnancy, while the reverse is true for lipid-soluble drugs (18). However, the pharmacokinetic behavior of a drug during pregnancy does not stick to the model predicted by the physicochemical properties only, as demonstrated in our previous study on the pharmacokinetics of mecillinam (11).

Imipenem is a fairly new carbapenem beta-lactam antibiotic which is clinically used in a 1:1 combination with cilastatin, a competitive inhibitor of dehydropeptidase, minimizing the renal metabolism of imipenem (2, 15). It is active against a broad spectrum of bacteria, including all the common members of the family *Enterobacteriaceae* (MIC < 1.3 μg/ml) and staphylococci (MIC < 2 μg/ml) (20), as well as *Listeria monocytogenes* (MIC for 90% of strains = 0.11 μg/ml [4]; MIC < 0.25 μg/ml [8]), *Neisseria gonorrhoeae* (MIC for 90% of strains < 0.30 μg/ml [4]; MIC = 0.01 to 0.1 μg/ml [3]), *Chlamydia trachomatis* (3), and *Bacteroides fragilis* (MIC for 90% of strains = 0.25 μg/ml) (5). There appear to be three previous studies on imipenem in the perinatal period. The transfer of the drug through placenta has been observed, and drug concentrations in the umbilical cord plasma and amniotic fluid were found to exceed MICs against main pathogenic organisms (6, 12, 14).

The current study describes the pharmacokinetics of imipenem during pregnancy compared with those in the nonpregnant state and the transplacental passage during pregnancy.

MATERIALS AND METHODS

Subjects. Twenty subjects participated in the study. Seven subjects had an early pregnancy and sought artificial termination of the pregnancy for social reasons (group A). Seven subjects were parturient women who delivered by cesarean section because of secondary arrest of labor or premature rupture of the membranes (group B). All of the mothers had an uncomplicated pregnancy. Six nonpregnant women of childbearing age who underwent a gynecological operation for benign disease served as controls (group C). None of the participants had any underlying disease, and none had taken antibiotics for at least 7 days. For the operative procedures (curettages, cesarean sections, and gynecologic operations) anesthesia and analgesics were given as normal. The study protocol was approved by the Joint Committee of Ethics of the University of Turku and the University Central Hospital of Turku, and all the participants gave informed consent before entering the study. The clinical characteristics of the 20 subjects who constituted the study population are summarized in Table 1. All participants received a single dose of 500 mg of intravenous imipenem-cilastatin (1:1) (Primaxin; Merck Sharp & Dohme) as an infusion over 20 min via an infusion pump.

Sampling. For all subjects blood was drawn through an indwelling intravenous catheter on the contralateral arm before the start of the drug infusion (zero sample), at the completion of the 20-min timed infusion, and at 5, 10, 15, 30, 45, 60, 120, 180, 300, and 480 min after the end of the infusion. The infusion was started 40 min before cesarean sections and gynecological operations and 200 min before

* Corresponding author.

TABLE 1. Clinical characteristics of the study population

Group	Length of gestation [wk (range)]	Age [yr (range)]	Wt (kg [mean ± SD])
A	8.6 (7–11)	30723 (16–36)	61.8 ± 6.4
B	38.7 (37–41)	30.3 (26–36)	78.3 ± 9.7
C	Nonpregnant	37.5 (27–42)	59.2 ± 10.7

the curettages. The urine specimens were collected in fractions at 0, 0 to 2, 2 to 5, and 5 to 8 h. At curettage, a sample of amniotic fluid was obtained from the intact amniotic sac through a puncture needle inserted transcervically. At cesarean section, samples of umbilical vein and artery as well as amniotic fluid were obtained at the time of birth. Initially, all the specimens were preserved on ice, the plasma was then separated from the blood samples, and they were stored at −70°C. The next day the samples were transported packed in carbon dioxide ice to the laboratory, where the assay was started immediately.

Sample analysis. The concentrations of imipenem were determined microbiologically by the standard agar well diffusion method (15). The medium used was antibiotic medium (Oxoid) at pH 7.2, and the test organism was *Bacillus subtilis* in spore form (ATCC 6051). At least seven standard concentrations were used on each plate. The standards and samples (80 μl) were placed in wells 7 mm in diameter.

The coefficients of variation (standard deviation [SD]/mean × 100) on the plates (n = 15) were 12.9, 6.0, and 3.0% at low (0.12-μg/ml), middle (1.0-μg/ml), and high (10-μg/ml) concentrations of imipenem, respectively. The corresponding mean diameters of the zones of inhibition were 16.3 mm (SD, 2.1 mm), 28.5 mm (SD, 1.7 mm), and 43.9 mm (SD, 1.3 mm), respectively. The regression lines (least-squares formula) were calculated with the values of seven to nine different standards. The mean deviations, in percentages of the standard concentrations measured from the respective points on the calculated regression lines, were +9.4% (SD, 4.7%) at the low concentration, −6.5% (SD, 7.2%) at the middle concentration and +9.6% (SD, 3.9%) at the high concentration.

Pharmacokinetic analysis. The SIPHAR computer program (version 4.0; SIMED Centre d'Etudes et de Recherches en Statistiques et Informatique Medicales, Poitiers, France) was used to obtain pharmacokinetic parameter estimates. Determination of the optimal structural model was based on visual inspection of the concentration-time curves and the model selection criterion obtained from SIPHAR. The concentration-time data for all subjects were fit to two- and three-exponential models by using the least-squares algorithm. The following parameters were estimated from the model: the half-life and volume of distribution associated with the β phase. The following parameters were estimated by noncompartmental methods (log trapezoidal rule): the area under the concentration-time curve and the total clearance from plasma. Imipenem renal clearance was calculated by Ae_{0-8}/AUC_{0-8}, where Ae_{0-8} was the amount of imipenem excreted unchanged in the urine from 0 to 8 h and AUC_{0-8} was the area under the concentration-time curve from 0 to 8 h.

Statistical analysis. A two-tailed, unpaired Mann-Whitney test was used to determine the statistical significance. A P value of <0.05 was considered to be statistically significant.

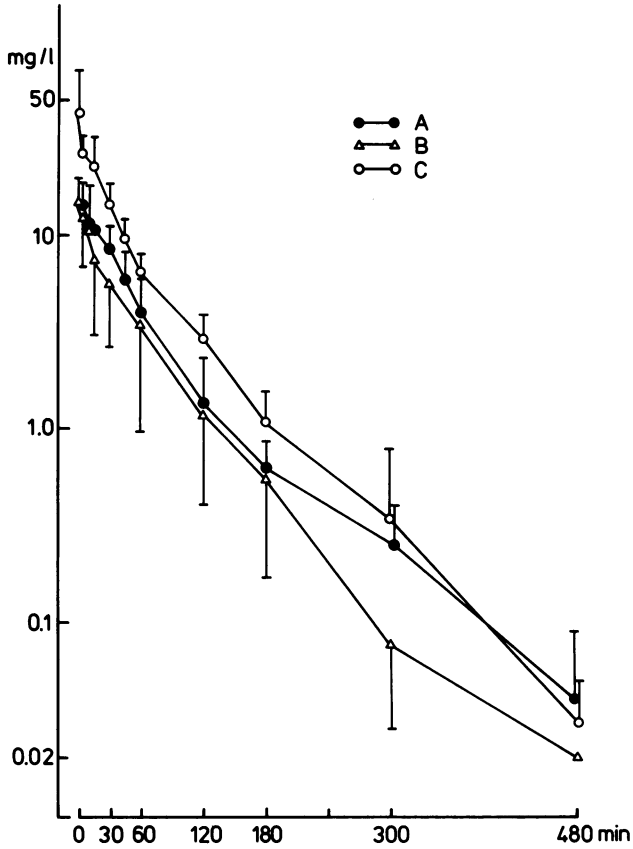

FIG. 1. Semilogarithmic time-concentration curves for women in early pregnancy (A), women in late pregnancy (B), and nonpregnant women (C). The concentrations ≤0.02 μg/ml (the lowest measurable level) are shown as 0.02 μg/ml.

RESULTS

Figure 1 shows a semilogarithmic plot of mean plasma imipenem concentrations versus time of women in early pregnancy, women in late pregnancy, and nonpregnant women. The peak level in plasma achieved immediately after the infusion was significantly lower during pregnancy (mean ± SD, 14.7 ± 4.9 and 14.9 ± 5.2 μg/ml in early and late pregnancy, respectively) than in the nonpregnant state (43 ± 28 μg/ml; $P < 0.05$). At 2 h, the concentrations in plasma during pregnancy were still significantly lower than in the nonpregnant state (1.3 ± 0.9, 1.3 ± 0.8, and 2.9 ± 0.9 μg/ml; $P < 0.05$). At 8 h after the dose, levels were unmeasurable (<0.02 μg/ml) in most subjects and the highest levels observed were 0.15 μg/ml in early pregnancy and 0.08 μg/ml in the nonpregnant state.

Table 2 shows the pharmacokinetic parameters calculated for imipenem. The apparent volume of distribution in β phase was significantly larger ($P < 0.05$) during pregnancy than in the nonpregnant state. Imipenem was also cleared from the plasma significantly faster during pregnancy, at average rates of 0.7 ± 0.4 liter/min or 13 ± 8 ml min^{-1} kg of body $weight^{-1}$ ($P < 0.05$) in early pregnancy and of 1.0 ± 0.5 ml min^{-1} ($P < 0.005$) or 11 ± 5 ml min^{-1} kg^{-1} ($P < 0.05$) in late pregnancy, than in the nonpregnant state, 0.3 ± 0.1 liter/min or 6 ± 1 ml min^{-1} kg^{-1}. The renal clearance of the drug accounted for 39% of the total clearance from plasma in early pregnancy, 35% in late pregnancy, and 33% in the nonpregnant state. The mean area under the concentration-

TABLE 2. Pharmacokinetic parameters[a] in women in early pregnancy, women in late pregnancy, and nonpregnant women

Group (n)	V		CL		$t_{1/2\beta}$ (min)	AUC (mg · min/liter)	CL_R		C_{max} (μg/ml)
	Liters	Liter/kg	ml/min	ml/min/kg			ml/min	ml/min/kg	
A (7)	54.7 ± 23.7*	1.0 ± 0.4*	703 ± 365*	13 ± 8*	48 ± 21	862 ± 346*	270 ± 187*	5.1 ± 3.7	14.7 ± 4.9*
B (7)	47.1 ± 14.8†	0.6 ± 0.2†	973 ± 47†	11 ± 5†	36 ± 8	643 ± 326†	301 ± 69†	3.8 ± 1.8	14.9 ± 5.2†
C (6)	18.9 ± 5.8*†	0.3 ± 0.1*†	338 ± 85*†	6 ± 1*†	41 ± 16	1,548 ± 339*†	110 ± 43*†	2.0 ± 0.4	43.0 ± 28.3*†

[a] Abbreviations: V, volume of distribution associated with β phase; CL, total clearance from plasma; $t_{1/2\beta}$, half-life at β phase; AUC, area under the concentration-time curve; CL_R, renal clearance; C_{max}, maximum concentration of drug in serum. Significant differences ($P < 0.05$) between the groups are marked (* and †).

time curve was significantly smaller ($P < 0.05$) during pregnancy than in the nonpregnant state. The mean half-life at β phase in plasma did not differ significantly among the pregnant and nonpregnant women.

Imipenem passes the placenta in considerable quantity. The concentration in amniotic fluid varied greatly and was approximately (mean ± SD) 47% ± 39% of the simultaneous maternal concentration in plasma when sampled 3 h after the infusion in early pregnancy and 16% ± 25% when sampled 30 min after the infusion in late pregnancy. The imipenem mean concentration in umbilical venous and arterial blood was (mean ± SD) 33% ± 12% and 31% ± 13% of that in the maternal blood (Table 3).

DISCUSSION

Imipenem has an extended spectrum of antimicrobial activity, excellent pharmacokinetic properties in nonpregnant subjects, and low toxicity (1). No accumulation of imipenem has been noted in treatment of full-term infants (15). Imipenem is considered effective and safe in treating perinatal infections (6), and it has also been used for premature infants (17).

In pregnancy, the MICs of imipenem for the most common pathogens prevail only for 2 h, while in the nonpregnant state the mean concentration in plasma remains above or at the MIC for 3 h after the infusion.

Most strains of *L. monocytogenes* are susceptible to as little as 0.25 μg of imipenem per ml (9), and concentrations at or above this value are observed for as long as 5 h after the infusion as well as in early pregnancy (mean ± SD, 0.3 ± 0.2 μg/ml) as in the nonpregnant state (0.4 ± 0.3 μg/ml) but in late pregnancy are observed only for 3 h (0.5 ± 0.4 μg/ml).

The pharmacokinetic characteristics for the nonpregnant women correspond well to those reported previously (13). During pregnancy, however, many of the observed parameters differ significantly from those in the nonpregnant state. The enlarged apparent volume of distribution is only partially explained by the increased body weight associated with late pregnancy (Table 1). Imipenem is likely to be distributed efficiently into the feto-maternal compartment, since the degree of protein binding in plasma is low, 13 to 21% (7, 18). The clearance of imipenem from plasma is accelerated, while the renal clearance is not consistently changed, suggesting accelerated nonrenal clearance of imipenem during pregnancy. The half-life of imipenem, being dependent on both volume of distribution and clearance from plasma, does not vary considerably among the pregnant and nonpregnant subjects.

The transplacental passage of imipenem is noted, and even therapeutic concentrations are achieved in umbilical blood and amniotic fluid during late pregnancy. At 30 min after the infusion the ratio of the umbilical venous and arterial drug concentrations is 1.05, almost a state of equilibrium. The elimination of imipenem from the amniotic fluid seems to be slow, since as late as 3 h after the infusion the feto-maternal ratio is approximately 47% (in early pregnancy). The ratio of umbilical venous blood drug concentration to simultaneous maternal concentration in plasma was 33% 30 min after the start of the infusion. The same ratio has been reported by Hirabayashi and Okada to be 30% at the end of a 30-min infusion of 500 mg of imipenem (12).

In conclusion, the pharmacokinetics of imipenem change considerably during pregnancy. An adjustment of the dose should be considered when treating pregnant women with serious infections.

TABLE 3. Maternal and fetal imipenem concentrations in early pregnancy and in late pregnancy[a]

Subject	Concn (μg/ml)[b] in:				Ratio	
	mp	uv	ua	af	uv/mp	af/mp
1	0.17			0.07		0.41
2	0.08			0.07		0.88
3	—			—		
4	0.69			<0.02		
5	0.81			<0.02		
6	0.81			<0.02		
7	0.57			0.06		0.11
Mean	0.52			0.07		0.47
SD	0.32			0.01		0.39
8	7.6	3.2	3.2	0.68	0.42	0.09
9	9.2	3.4	3.4	1.2	0.37	0.13
10	7.2	2.3	1.9	0.18	0.32	0.03
11	3.4	0.96	0.80	2.2	0.28	0.65
12	3.0	0.72	0.79	0.06	0.24	0.02
13	3.6	0.50	0.42	0.02	0.14	0.01
14	1.9	0.98	0.98	—	0.52	
Mean	5.13	1.72	1.64	0.72	0.33	0.16
SD	2.81	1.22	1.22	0.85	0.12	0.25

[a] Early pregnancy, subjects 1 to 7, with sampling 3 h after the infusion; late pregnancy, subjects 8 to 14, with sampling 30 min after the infusion.

[b] The lowest measurable level of imipenem was 0.02 μg/ml. —, no sample; mp, maternal plasma; uv, umbilical vein; ua, umbilical artery; af, amniotic fluid.

REFERENCES

1. **Amin, N. M.** 1988. New antibiotics: carbapenems, monobactams and quinolones. Am. Fam. Physician 4:125–134.
2. **Begue, P., B. Quinet, S. Baron, P. Challier, J. L. Fontaine, and G. Lasfargues.** 1989. Clinical and pharmacokinetic study of imipenem/cilastatin in children and newborn infants. Pathol. Biol. (Paris) 5:485–490.
3. **Berkeley, A. S., K. Freedman, J. Hirsch, and W. J. Ledger.** 1985. Imipenem/cilastatin in the treatment of obstetric and gynecologic infections. Am. J. Med. 78(Suppl. 6A):79–84.

4. **Birnbaum, J., F. M. Kahan, and H. Kropp.** 1985. Carbapenems, a new class of beta-lactam antibiotics. Am. J. Med. **78**(Suppl. 6A):3–21.
5. **Brown, J. E., V. E. Del Bene, and C. D. Collins.** 1981. In vitro activity of *N*-formimidoyl thienamycin, moxalactam, and other new beta-lactam agents against *Bacteroides fragilis*: contribution of beta-lactamase to resistance. Antimicrob. Agents Chemother. **19**:248–252.
6. **Cho, N., K. Fukunaga, K. Kunii, I. Kobayashi, and K. Tezuka.** 1988. Studies on imipenem/cilastatin sodium in the perinatal period. Jpn. J. Antibiot. **11**:1758–1773.
7. **Drusano, G. L., and H. C. Standiford.** 1985. Pharmacokinetic profile of imipenem/cilastatin in normal volunteers. Am. J. Med. **78**(Suppl. 6A):47–53.
8. **Edberg, S. C.** 1986. The measurement of antibiotics in the human body fluids: techniques and significance, p. 381–395. *In* V. Lorian (ed.), Antibiotics in laboratory medicine. The William & Wilkins Co., Baltimore.
9. **Eliopoulos, G. M., and R. C. Moellering, Jr.** 1981. Susceptibility of enterococci and *Listeria monocytogenes* to *N*-formimidoyl thienamycin alone and in combination with an aminoglycoside. Antimicrob. Agents Chemother. **19**:789–793.
10. **Heikkilä, A., and R. Erkkola.** 1991. Pharmacokinetics of piperacillin during pregnancy. J. Antimicrob. Chemother. **28**:419–423.
11. **Heikkilä, A., K. Pyykkö, R. Erkkola, and E. Iisalo.** 1992. The pharmacokinetics of mecillinam in pregnant and non-pregnant women. Br. J. Clin. Pharmacol. **33**:629–633.
12. **Hirabayashi, K., and E. Okada.** 1988. Pharmacokinetic and clinical studies of imipenem/cilastatin sodium in the perinatal period. Jpn. J. Antibiot. **11**:1797–1804.
13. **MacGregor, R. R., G. A. Gibson, and J. A. Bland.** 1986. Imipenem pharmacokinetics and body fluid concentrations in patients receiving high-dose treatment for serious infections. Antimicrob. Agents Chemother. **29**:188–192.
14. **Matsuda, S., M. Suzuki, K. Oh, M. Ishikawa, A. Soma, H. Takada, T. Shimizu, S. Makinoda, S. Fujimoto, and T. Chimura.** 1988. Pharmacokinetic and clinical studies on imipenem/cilastatin sodium in the perinatal period. A study of imipenem/cilastatin sodium in the perinatal co-research group. Jpn. J. Antibiot. **11**:1731–1741.
15. **Musson, D. G., R. Hajdu, W. F. Bayne, and J. D. Rogers.** 1991. Quantification of imipenem's primary metabolite in plasma by postcolumn chemical rearrangement and UV detection. Pharm. Res. **1**:33–39.
16. **Philipson, A. E. L.** 1982. Pharmacokinetics of antibiotics in the pregnant woman, p. 37–60. *In* W. J. Ledger (ed.), Antibiotics in obstetrics and gynecology. Martinus Nijhoff, The Hague, The Netherlands.
17. **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**:1172–1177.
18. **Reeves, D. S., S. T. Chapman, A. J. Davies, F. Ferber, and J. D. Rogers.** 1983. Human pharmacokinetics of N-formimidoyl thienamycin alone and in combination with a dehydropeptidase inhibitor (MK-791) and probenecid, p. 30–33. *In* K. H. Spitzy and K. Karrer (ed.), Proceedings of the Thirteenth International Congress of Chemotherapy, vol. 95.
19. **Reynolds, F., and C. Knott.** 1989. Pharmacokinetics in pregnancy and placental drug transfer, p. 389–449. *In* S. R. Milligan (ed.), Oxford reviews of reproductive biology. Oxford University Press, New York.
20. **Verbist, L., and J. Verhaegen.** 1981. In vitro activity of *N*-formimidoyl thienamycin in comparison with cefotaxime, moxalactam, and ceftazidime. Antimicrob. Agents Chemother. **19**:402–406.