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The pharmacokinetics of mecillinam and pivmecillinam in pregnant and non-pregnant women

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1 The pharmacokinetics of parenteral mecillinam ($n = 27$) and oral pivmecillinam ($n = 12$) were studied in pregnant ($n = 27$) and non-pregnant ($n = 12$) subjects.

2 In early pregnancy (9–14 weeks of gestation) the mean peak plasma drug concentration ($C_{max} = 19 \pm 9$ μg ml^{-1}) after an intravenous injection of 200 mg mecillinam was significantly lower ($P < 0.05$) and the volume of distribution ($V = 49 \pm 20$ 1) significantly larger ($P < 0.05$) than in non-pregnent subjects ($C_{max} = 35 \pm 18$ μg ml^{-1}, $V = 29 \pm 12$ 1). In late pregnancy (39–40 weeks of gestation) the plasma mean peak concentration ($C_{max} = (29 \pm 14$ μg ml^{-1}) after parenteral administration of 200 mg mecillinam was slightly lower and the volume of distribution ($V = 65 \pm 29$ 1, $V = 0.9 \pm 0.4$ l kg^{-1}) significantly larger than that in non-pregnant subjects ($V = 0.4 \pm 0.3$ l kg^{-1}). Also after oral administration of 200 mg pivmecillinam, equimolar to 136.5 mg mecillinam, the mean peak plasma concentration in pregnant subjects ($C_{max} = 1.8 \pm 1.2$ μg ml^{-1}) was slightly lower than that in non-pregnant subjects ($C_{max} = 1.7 \pm 1.2$ μg ml^{-1}).

3 The mean half-life of elimination after parenteral administration of mecillinam was significantly longer during both early ($t_{½,z} = 133 \pm 38$ min, $P < 0.05$) and late pregnancy ($t_{½,z} = 107 \pm 41$ min, $P < 0.05$) as compared with the non-pregnant state ($t_{½,z} = 75 \pm 21$ min). After oral administration of pivmecillinam the elimination half-life was similar in pregnant ($t_{½,z} = 57 \pm 34$ min) and non-pregnant women ($t_{½,z} = 61 \pm 32$ min).

4 The transfer of mecillinam across the placenta was fast and it was detected in umbilical venous and arterial plasma, and in amniotic fluid. The ratio of umbilical venous plasma concentration to maternal plasma concentration in late pregnancy was 0.85. The ratios of amniotic fluid to maternal plasma drug concentration were 0.18 and 0.21 during early and late pregnancy after parenteral administration.

6 After parenteral administration of mecillinam its urinary recoveries in the first 8 h were 66% in early pregnancy, 72% in late pregnancy and 81% in the non-pregnant state. After oral administration 8 h urine recoveries were 28% and 39% in pregnant and non-pregnant states, respectively.

7 It is concluded that there is no need to increase the dosage of mecillinam or pivmecillinam during pregnancy.

Keywords mecillinam pivmecillinam pharmacokinetics pregnancy placental transfer

Introduction

Mecillinam is a β-lactam antibiotic with a broad spectrum of activity against most gram-negative bacteria, including the Enterobacteriaceae (Reeves, 1977). Moreover, when administered in combination with other β-lactam antibiotics, the effect of mecillinam is synergistic (Cleeland & Squires, 1983; Gambertoglio *et*

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al., 1980). The toxicity of mecillinam is low, as is the case with other penicillins. Thus the drug can be regarded as a safe and effective alternative to the aminoglycosides when combination therapy is required and aminoglycosides are contraindicated, as is the case for serious infections during pregnancy (Demos & Green, 1983).

Mecillinam is effective for the treatment of infections of the urinary tract (Cox, 1983). The oral formulation of this drug, pivmecillinam, is widely used for both symptomatic and asymptomatic infections of this kind during pregnancy (Brumfitt *et al.*, 1979; Sanderson & Menday, 1984). Pivmecillinam is the pivaloyloxymethylester of mecillinam and lacks antibacterial activity *per se*. Unlike mecillinam it is absorbed from the gastrointestinal tract after which it is hydrolysed in the blood and intestinal wall to mecillinam (Godtfredsen, 1977).

During pregnancy the plasma concentrations of some β-lactam antibiotics tend to be lower and their elimination is enhanced (Heikkilä & Erkkola, 1991; Philipson, 1982). Nevertheless, dosage regimens are based on pharmacokinetic data from healthy non-pregnant volunteers (Meyers *et al.*, 1983).

In the present study the pharmacokinetics and placental transfer of mecillinam were studied after parenteral dosage of mecillinam and oral dosage of pivmecillinam.

Methods

Drugs and chemicals

The drugs used were mecillinam (Selexidin®, Lövens Kemiske Fabrik, Ballerup, Denmark) and pivmecillinam hydrochloride (Selexidin®, Lederle, Copenhagen, Denmark). Mecillinam was administered as a single intravenous injection of 200 mg over 5 s and pivmecillinam hydrochloride as tablets of 200 mg, equimolar to 136.5 mg mecillinam, by mouth.

Subjects

Thirty-nine subjects participated in the study. They were divided into five groups: Group A (n = 11) comprised subjects in early pregnancy (9–14 gestational weeks), group B (n = 10) were women at term pregnancy, group D (n = 6) were pregnant women (10–32 gestational weeks) and groups C (n = 6) and E (n = 6) were non-pregnant female volunteers of child-bearing age (Table 1). The subjects in groups A and D attended the hospital for termination of pregnancy for social reasons except for one subject in group A, who had the termination because of established fetal chromosomal anomaly and one subject in group D, who had an asymptomatic bacteriuria at 32 gestational weeks when participating in the study and who later delivered a normal infant.

The mothers in group B had uncomplicated pregnancies, and they were admitted for Caesarean section because of feto-pelvic disproportion (n = 9) or for vaginal delivery (n = 1). None had taken antibiotics for at least 1 week before the study and none used regular medication.

The study protocol was approved by the Conjoint Ethics Committee of Turku University and Turku University Central Hospital. All of the subjects gave informed consent.

Table 1 Demographic data of the study population (mean ± s.d.)

Route of administration	n	*Age (years)*	*Weight (kg)*	*Duration of gestation (weeks) [range]*
Group A parenteral	11	27 ± 8	61 ± 12	10.7 [9–14]
Group B parenteral	10	32 ± 5	73 ± 12	39 [39–40]
Group C parenteral	6	32 ± 6	61 ± 10	non-pregnant
Group D oral	6	26 ± 6	62 ± 10	18.8 [10–32]
Group E oral	6	32 ± 6	61 ± 10	non-pregnant

Study design

Subjects in groups A, B and C received 200 mg of mecillinam as an intravenous injection over 5 s in groups A + B 30 min before the operative procedure, and in group C on the morning of the study after an overnight fast. Distal veins were cannulated in both arms and a blood sample was obtained before injection of the drug. Serial samples were taken from the cannula contralateral to the one through which the drug was administered, at 2, 5, 10, 15, 30, 45, 60, 120, 180, 300 and 480 min after the injection. The subjects voided urine before the injection (zero-sample) and urine was collected in fractions from 0–2 h, 2–5 h and 5–8 h. Amniotic fluid samples were obtained at curettage (n = 10, group A) or at the time of birth (n = 10, group B). In group B samples of umbilical arterial and venous blood were collected at the time of birth.

After an overnight fast subjects in groups D and E each received orally 200 mg pivmecillinam hydrochloride on the morning of the study and serial blood samples were taken from a cannulated distal arm vein before and at 15, 30, 60, 120, 180, 300 and 480 min after ingestion of the drug. Urine was collected as in groups A, B and C.

Mecillinam assay

Bond Elut PH tubes (Analythicem International, Harbor City, CA, U.S.A.), were conditioned by adding in succession 1 ml methanol, 1 ml water and 1 ml 1M potassium phosphate buffer, pH 7.0. Then 50–500 μl of the sample (plasma or amniotic fluid) and 100–200 μl azidocillin (10 μg ml^{-1} in water) as internal standard were added and the tubes were washed with 2 ml diethyl ether and 1 ml hexane. Mecillinam was eluted with 250–500 μl 20% v/v acetonitrile in water. Urine samples were diluted with distilled water and centrifuged prior to extraction.

Mecillinam was assayed by h.p.l.c. using the method of Lee & Brooks (1982). The limit of quantitation of mecillinam in plasma and amniotic fluid was 50 ng ml^{-1} and in urine it was 1 μg ml^{-1}. The inter-assay coefficients of variation were 1.7% for plasma and 1.5% for urine and amiotic fluid.

Data analysis

The SIPHAR program was used to calculate pharmacokinetic parameters from the parenteral data assuming bi-exponential decay. The peak drug concentration in plasma (C_{max}) and the time to peak (t_{max}) were obtained directly from the data. Differences between subject groups were compared using the Mann-Whitney U-test.

After oral administration of pivmecillinam $t_{½,z}$ values were estimated by log linear regression of the termal data points (n = 3). Plasma clearance was calculated from dose/AUC. Renal clearance was calculated from urine recoveries divided by corresponding AUC values. Comparisons were made using the Mann-Whitney U-test for unpaired data. The results are reported as mean ± s.d.

Results

The mean peak plasma mecillinam concentration after parenteral administration was significantly lower during early pregnancy (19 ± 9 μg ml^{-1}) than in non-pregnant women (35 ± 18 μg ml^{-1}, $P < 0.05$). In late pregnancy the mean peak plasma drug concentration was 29 ± 14 μg ml^{-1} and this value did not differ significantly from that in the non-pregnant subjects (Figure 1a). After oral administration mean peak concentrations of mecillinam were similar in pregnant and non-pregnant subjects, but the peak was reached later in the pregnant women (Figure 1b). The volumes of distribution (V) after parenteral drug administration were significantly larger during both early and late pregnancy as compared with the non-pregnant state ($P < 0.05$). Also the weight-corrected volumes of distribution were significantly larger in early pregnancy compared with the non-pregnant state or late pregnancy ($P < 0.05$). Values of weight corrected plasma clearance after parenteral administration were significantly higher during early pregnancy compared with late pregnancy ($P < 0.05$), but neither value differed significantly from that in the non-pregnant state (Table 2).

The elimination half-life ($t_{½,z}$) of the drug estimated from limited data, was significantly longer during early ($P < 0.05$) and late pregnancy ($P < 0.05$) compared with the non-pregnant state after parenteral administration. After oral administration the $t_{½,z}$ of pregnant subjects did not differ significantly from that of non-pregnant subjects (Table 2).

After parenteral administration 66% of the mecillinam was excreted unchanged in subjects 9–14 weeks pregnant, 72% in subjects 39–40 weeks pregnant and 81% in non-pregnant women in the urine within 8 h. The fractions of urine collected 0–2 h, 2–5 h and 5–8 h after drug administration contained 56 ± 17%, 8 ± 6% and 2 ±

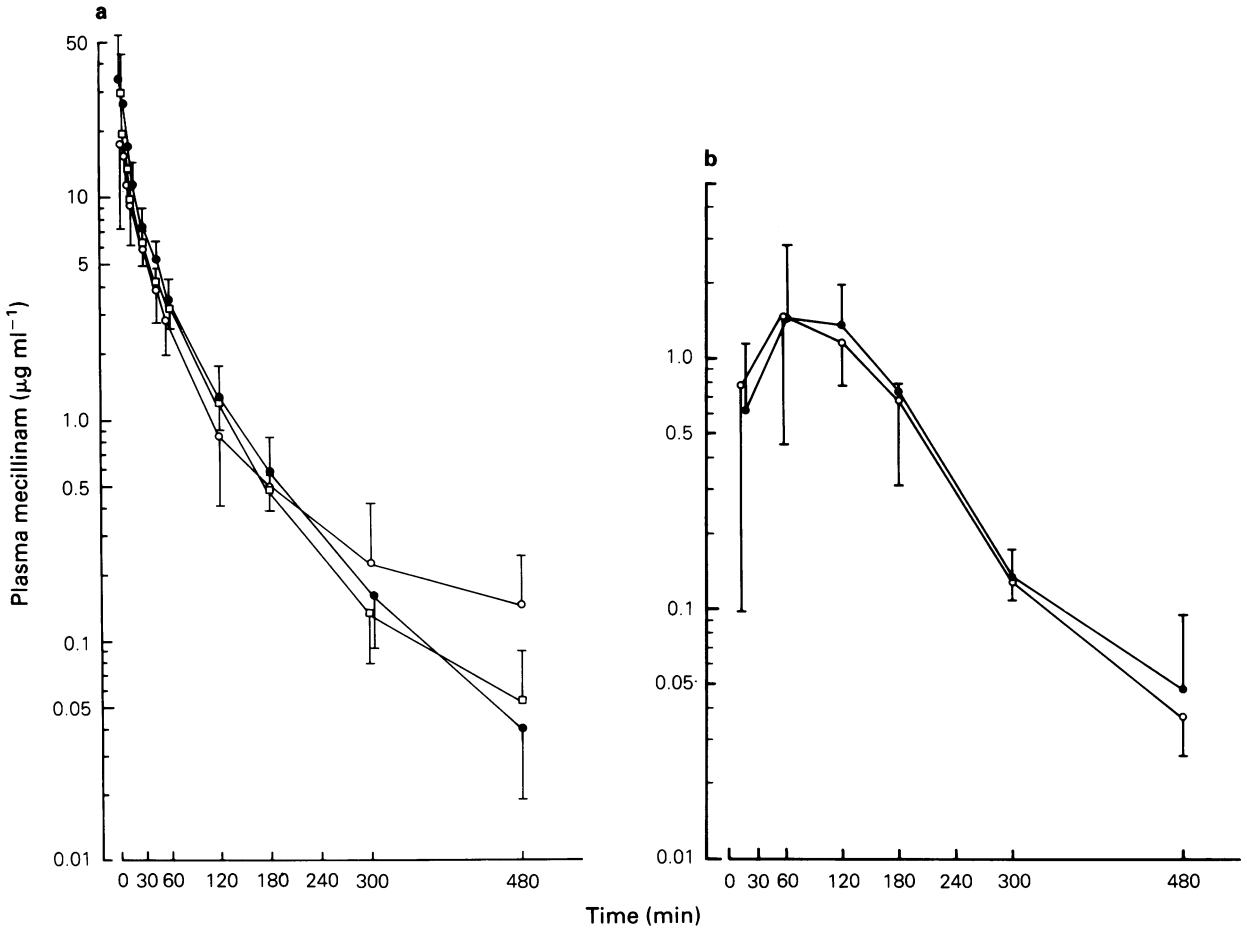

Figure 1 (a) Mean (± s.d.) plasma mecillinam concentrations after a single intravenous dose of 200 mg mecillinam to women in early pregnancy (A, ○), women in late pregnancy (B, □) and non-pregnant women (C, ●). (b) Mean (± s.d.) plasma mecillinam concentrations after a single oral dose of 200 mg of pivmecillinam to pregnant women (○) and to non-pregnant women (●).

Table 2 Pharmacokinetic parameters of mecillinam during pregnancy (A, B and D) and in the non-pregnant state (C and E) after a single parenteral dose of 200 mg mecillinam and an oral dose of 200 mg pivmecillinam (corresponding to 136.3 mg of mecillinam). Mean (± s.d.). * and # indicate statistical difference ($P < 0.05$) between the respective groups

	i.v.			*oral*	
	Group A n = 11	*Group B* n = 10	*Group C* n = 6	*Group D* n = 6	*Group E* n = 6
Clearance (ml min^{-1})	260 ± 70	260 ± 60	240 ± 70	620 ± 230*	580 ± 100*
Clearance (ml min^{-1} kg^{-1})	4.3 ± 0.3*	3.6 ± 0.5*	4.0 ± 0.1	10 ± 5	10 ± 3
Renal clearance (ml min^{-1})	167 ± 57	192 ± 14	186 ± 41	210 ± 85	230 ± 60
Renal clearance (ml min^{-1} kg^{-1})	2.8 ± 0.9	2.6 ± 0.5	3.1 ± 0.9	3 ± 1	4 ± 1
$t_{½,\ initial}$ (min)	22 ± 5.2	28 ± 8.8	20 ± 3.5		
$t_{½,\ z}$ (min)	133 ± 38*	107 ± 41#	75 ± 21*#	57 ± 34	61 ± 32
V (l)	49 ± 20*	65 ± 29#	29 ± 12*#		
V (l kg^{-1})	0.7 ± 0.3	0.9 ± 0.4*	0.4 ± 0.3*		
AUC (μg ml^{-1} min)	816 ± 191	786 ± 126	918 ± 292	253 ± 108	214 ± 44
t_{max} (min)	3 ± 1.5	2.3 ± 1.0	2 ± 0	100 ± 31	90 ± 33
C_{max} (μg ml^{-1})	19 ± 9*	29 ± 14	34 ± 18*	1.8 ± 1.1	1.7 ± 1.1

2% of the unchanged drug in the early pregnancy group. The corresponding recoveries in the late pregnancy group were 63 ± 6%, 8 ± 3% and 2 ± 2%; and in the non-pregnant group 62 ± 8%, 18 ± 17% and 1 ± 1%.

After oral administration of pivmecillinam the recovery of unchanged mecillinam in 8 h in the urine was 28% during pregnancy and 39% in non-pregnant state. When divided into fractions of 0–2 h, 2–5 h and 5–8 h the recoveries were 17 ± 8%, 8 ± 4% and 3 ± 2% for the pregnant group and 23 ± 8%, 15 ± 8% and 2 ± 0.4% for the non-pregnant control group.

In the parturient group B ($n = 10$) the mean umbilical vein mecillinam concentration at the time of birth 1 h after the injection of the drug was 2.9 ± 0.9 μg ml^{-1} and the mean umbilical arterial concentration was 2.7 ± 0.9 μg ml^{-1}. The ratio of umbilical vein concentration to mecillinam concentration in the maternal plasma one hour after drug injection was 0.85.

The mean amniotic fluid drug concentration was 0.7 ± 0.3 μg ml^{-1} at 1 h after parenteral administration of mecillinam in the parturient group, 0.45 ± 0.6 μg ml^{-1} in early pregnancy and 0.06 ± 0.06 ml^{-1} after oral dosage during pregnancy. The ratios of amniotic fluid drug concentration to simultaneous maternal plasma drug concentration were 0.21, 0.18 and 0.04 for the three groups, respectively.

Discussion

Lowered maternal plasma drug concentrations of antibiotics have often been associated with pregnancy (Philipson, 1982; Kjer & Ottesen, 1986). Since mecillinam in its esterified form, pivmecillinam, is one of the most popular antibiotics for the treatment of both symptomatic and asymptomatic bacteriuria during pregnancy, it is important to assess the pharmacokinetics of mecillinam to avoid subtherapeutic dosage and toxicity. Our results indicate that the pharmacokinetics of mecillinam change during pregnancy, but these changes are apparently not of clinical importance. The maternal plasma volume expands at 30–34 weeks of pregnancy by nearly 50% (Parker, 1984), which probably affects the volume of distribution of polar drugs (Reynolds & Knott, 1989). The weight corrected plasma clearance was significantly faster during early than late pregnancy, which may also reflect the pooling of blood in the feto-maternal unit. Mecillinam is only about 5–25% bound to plasma proteins (Reeves *et al.* 1975; Tybring, 1975). Hence, any decrease in serum protein-binding during pregnancy (Reynolds & Knott, 1989) should not influence the pharmacokinetics of mecillinam.

Mean peak plasma drug concentrations were lower during early and late pregnancy as compared to the non-pregnant state, and this was more pronounced in early pregnancy. This difference disappears within the first 30 min after parenteral administration and is probably of no clinical importance.

The half-life of parenteral mecillinam is longer during pregnancy as compared to the non-pregnant state (Table 2). This is probably caused by the expansion of the volume of distribution combined with an unchanged clearance. The somewhat lower rate of urinary excretion of mecillinam during pregnancy is explained by the lower drug concentrations in the blood. Mecillinam crosses the placenta readily, since the ratio of umbilical to maternal plasma concentration is high, and the concentration in umbilical plasma exceeds the MIC-values (1–6 μg ml^{-1}) for susceptible organisms (Neu, 1977). On the other hand, diffusion through the amniotic membranes and excretion of the drug by the foetus

seems to be minimal. Passage of the drug across the placenta is fast, and the umbilical venous and arterial concentrations are already near to equilibrium at one hour after administration.

These results suggest that no increase in the dosage of mecillinam/pivmecillinam is necessary during pregnancy in spite of some change in pharmacokinetics. Because, like other penicillins, mecillinam has a low toxicity, overdosage is not a significant problem and normal doses of mecillinam/pivmecillinam are appropriate during pregnancy.

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