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Short communication

Maternal and fetal blood levels of moxifloxacin, levofloxacin, cefepime and cefoperazone

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ABSTRACT

Wide-spectrum quinolones such as moxifloxacin and levofloxacin as well as high-order cephalosporins such as cefoperazone and cefepime have increased antimicrobial activity. However, little is known about their distribution in fetal blood. Therefore, the aim of this study was to measure and compare maternal and fetal blood levels of these agents. For the measurement of blood levels, 9 pregnant women received cefepime hydrochloride, 10 received cefoperazone, 10 received moxifloxacin and 12 received levofloxacin intravenously. Maternal and umbilical cord blood samples were drawn during delivery. Antibiotic levels were analysed by high-performance liquid chromatography. Mean transplacental passage rates of moxifloxacin, levofloxacin, cefepime and cefoperazone were 74.84%, 66.53%, 23.21% and 12.68%, respectively, and mean transfetal passage rates were 90.78%, 84.22%, 79.17% and 79.78%, respectively. The transplacental passage rate for either quinolone was significantly higher than that of either cephalosporin, and the transplacental passage rate of cefoperazone was lower than that of cefepime. In conclusion, both quinolones have high transplacental passage rates. Cefepime and cefoperazone have a lower transplacental passage rate and thus may be used as prophylaxis in situations where transplacental passage is undesirable.

1. Introduction

Caesarean section is known to be the most important risk factor for postpartum infections [1]. Women undergoing Caesarean delivery have a 20-fold greater risk of postpartum infection compared with those undergoing vaginal delivery. Caesarean also increases the length of hospitalisation, which is also a risk factor for infectious morbidities. Major infectious morbidities following Caesarean delivery are fever, wound infection, endometritis, bacteraemia, urinary tract infections and other rarer and more serious infectious conditions such as pelvic abscess and septic shock [1,2]. When the high level of Caesarean rates is considered, morbidity and even mortality resulting from these infections may reach significant levels.

Use of antibiotic prophylaxis has been observed to decrease these infectious morbidities. In a recent meta-analysis of randomised trials [2] it was reported that both in elective and non-elective situations, use of prophylactic antibiotics prior to Caesarean section significantly reduced the incidence of postpartum infectious morbidities. In another meta-analysis of 51 antibiotic trials [3] it was confirmed that use of first-generation cephalosporins and ampicillin had similar efficacy compared with wider-spectrum second- or third-generation cephalosporins. Based on these findings and the increased incidence of ampicillin-resistant *Escherichia coli* isolates, the American College of Obstetricians and Gynecologists (ACOG) recommended the use of narrow-spectrum antibiotics such as first-generation cephalosporins for prophylaxis in Caesarean deliveries [4].

However, in some newer studies it has been observed that throughout the years, with the use of wider-spectrum antibiotics, postpartum infectious morbidities have decreased [5]. With these findings and the rising resistance to commonly used antimicrobials, there is a need for new and wider-spectrum antibiotics for use in obstetrics.

Moxifloxacin and levofloxacin are quinolones with a wide spectrum of antibiotic activity including Gram-positive and Gram-negative bacteria [6]. Cefoperazone, a third-generation cephalosporin, and cefepime, which is accepted as a fourth-generation cephalosporin, also have increased activity against Gram-negative and Gram-positive bacteria [7]. Regarding teratogenicity, both levofloxacin and moxifloxacin have been classified as category C and the cephalosporins as category B by the American Food and Drug Administration Pregnancy Category [8].

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Table 1
Characteristics of patients and drug administration.

	Cefepime	Cefoperazone	Moxifloxacin	Levofloxacin
No. of patients	9	10	10	12
Route of administration	i.v.	i.v.	i.v.	i.v.
Dosage (mg)	1000	1000	400	500
Maternal age (years)[a]	28.67 (±4.53)	27.63 (±5.46)	27.60 (±5.42)	31.08 (±4.94)
Maternal weight (kg)[a]	70.89 (±6.85)	71.30 (±9.71)	75.30 (±8.81)	70.70 (±8.93)
Gestational age at time of procedure (days)[a]	269.11 (±2.62)	269.00 (±4.24)	270.20 (±2.49)	268.5 (±1.83)
Interval between end of i.v. dosing and sampling (min)[a]	26.11 (±3.33)	25.5 (±3.69)	27.00 (±6.75)	26.67 (±4.44)

i.v., intravenous.
[a] Mean ± standard deviation.

Although other quinolones and cephalosporins are widely studied in the literature, the abovementioned antibiotics have not been studied elsewhere with respect to maternal and fetal levels. Therefore, the aim of this study was to measure and compare maternal and fetal blood levels of these new, wider-spectrum cephalosporins (cefoperazone and cefepime) and quinolones (levofloxacin and moxifloxacin).

2. Materials and methods

For maternal and fetal blood level measurements, 41 pregnant women who were scheduled to undergo Caesarean section for obstetric indications were selected. Written informed consent was obtained from all patients. For prophylaxis prior to Caesarean, 9 women received 1 g of cefepime hydrochloride (Maxipime® 1 g IV; Bristol-Myers Squibb, New York, NY), 10 received 1 g of cefoperazone sodium (Cefobid® 1 g IV; Pfizer, New York, NY), 10 received moxifloxacin 400 mg (Avelox® 400 mg IV; Bayer, Leverkusen, Germany) and 12 received levofloxacin 500 mg (Tavanic® 500 mg IV; Sanofi-aventis, Paris, France) intravenously. Quinolones were administered as a 60-min intravenous (i.v.) infusion and cephalosporins were administered in a 30-min i.v. infusion. Dosing of agents was completed 20–25 min before the first incision. After clamping the umbilical cord, 2 mL samples of umbilical arterial and venous blood were drawn from the placental site and 2 mL of maternal blood was drawn at the same time. Plasma was obtained from blood centrifuged at 4500 rpm for 25 min. Plasma and amniotic fluid samples were protected from light and stored at −25 °C until analysis. The amount of antibiotic in the samples was measured by two different high-performance liquid chromatography (HPLC) methods, one for analysing cefoperazone and cefepime [9] and the other for moxifloxacin and levofloxacin [10]. Briefly, analyses were performed with reversed-phase columns. Standards and samples were prepared using solid-phase extraction technique. Elutes were transferred into a vial and 20 μL of the extraction solution was injected into the system and chromatograms were obtained. The details of the methods can be obtained from the relevant literature [9,10].

General characteristics of the pregnant women, such as maternal age, weight, gestational age at the time of sampling, and time interval between use of the drug and sampling, were also recorded. The transplacental passage rate was calculated as the percentage of fetal venous concentration to maternal blood concentration, and the transfetal passage rate was calculated as the percentage of fetal arterial concentration of drug to fetal venous concentration in percent.

For analysis of the data, Statistical Package for Social Sciences version 11.5 (SPSS Inc., Chicago, IL) was used. For comparison of the demographic characteristics of the patients and blood levels of drugs, non-parametric Kruskal–Wallis analysis of variance was used. A *P*-value of <0.005 was considered significant.

3. Results

A total of 41 pregnant women were included in the study. The mean age of the pregnant women, mean gestational age and maternal weight at the time of sampling and the mean time interval between drug use and sampling within groups are summarised in Table 1. When these variables were compared, no statistically significant differences were found between groups regarding maternal age, maternal weight, gestational age at time of delivery and time interval ($P = 0.362$, $P = 0.566$, $P = 0.337$ and $P = 0.954$, respectively).

Maternal and fetal blood levels of the antibiotics are given in Table 2. The mean ± standard deviation (S.D.) maternal blood level of moxifloxacin was 4.96 ± 1.36 μg/mL and the fetal venous and arterial blood levels were 3.57 ± 0.53 μg/mL and 3.23 ± 0.49 μg/mL, respectively. The transplacental passage rate was calculated as 74.84% and the transfetal passage rate as 90.78% (Table 2).

For levofloxacin, the mean ± S.D. maternal blood level was 8.18 ± 1.68 μg/mL and the fetal venous and arterial blood levels were 5.44 ± 1.23 μg/mL and 4.54 ± 0.93 μg/mL, respectively. The transplacental passage rate was calculated as 66.53% and the transfetal passage rate as 84.22% (Table 2).

The mean ± S.D. maternal blood level of cefepime was 37.33 ± 7.13 μg/mL and the fetal venous and arterial blood levels were 8.63 ± 3.17 μg/mL and 6.72 ± 2.76 μg/mL, respectively. The transplacental passage rate was calculated as 23.21% and the transfetal passage rate as 79.17% (Table 2).

Finally, in the patients who received cefoperazone, the mean ± S.D. maternal blood concentration was 67.97 ± 12.31 μg/mL, the fetal venous blood concentration was 8.19 ± 2.85 μg/mL and the fetal arterial blood concentration was 6.59 ± 2.42 μg/mL. The transplacental and transfetal passage rates were determined as 12.68% and 79.78%, respectively.

When cases were grouped as having received either a quinolone or cephalosporin, the transplacental passage rate of either quinolone was significantly higher than that of either cephalosporin ($P < 0.001$). However, no difference was found between the two groups with respect to the transfetal passage rate ($P = 0.089$).

When transplacental and transfetal passage rates of the two quinolones were compared, no statistically significant differences were found ($P = 0.075$ and $P = 0.262$, respectively). When the two cephalosporins were compared, the transplacental passage rate of cefoperazone was significantly lower than that of cefepime ($P = 0.006$), but the transfetal passage rates were found to be similar ($P = 0.744$).

4. Discussion

Antibiotic use may have different indications and, for prophylaxis against surgical infections, long-acting, inexpensive and usually narrow-spectrum agents are preferred. However,

Table 2
Maternal and fetal arterial and venous blood levels of moxifloxacin, levofloxacin, cefepime and cefoperazone at the time of delivery.

	Concentration (μg/mL)			Transplacental passage rate (%)	Transfetal passage rate (%)
	Maternal	Fetal venous	Fetal arterial		
Moxifloxacin					
Mean	4.96	3.57	3.23	74.84	90.78
S.D.	1.36	0.53	0.49	12.39	11.64
S.E.	0.43	0.17	0.16	3.92	3.68
Levofloxacin					
Mean	8.18	5.44	4.54	66.53	84.22
S.D.	1.68	1.23	0.93	6.96	10.68
S.E.	0.48	0.35	0.27	2.01	3.08
Cefepime					
Mean	37.33	8.63	6.72	23.21	79.17
S.D.	7.13	3.17	2.76	8.60	17.56
S.E.	2.38	1.06	0.92	2.87	5.85
Cefoperazone					
Mean	67.97	8.19	6.59	12.68	79.78
S.D.	12.31	2.85	2.42	5.79	11.73
S.E.	3.89	0.90	0.76	1.83	3.71

S.D., standard deviation; S.E., standard error.

postpartum infections are commonly polymicrobial in origin and the pathogens isolated from infected areas usually include both Gram-positive and Gram-negative bacteria and even some anaerobes [11,12]. Some new and extended-spectrum antibiotics may be the preferred choice both for therapeutic and prophylactic measures. However, the maternal and fetal levels of these agents should be known for their safe use in pregnant women for different purposes. These four antibiotics have a wide spectrum with acceptable cost and side-effect profiles.

Regarding the transplacental passage of quinolones, studies have generally focused on ofloxacin and ciprofloxacin. To our knowledge, there are no studies describing the placental transfer of levofloxacin and moxifloxacin in vivo. In one in vitro placental perfusion study conducted by Polachek et al. [13] it was observed that the steady-state concentrations of levofloxacin in maternal and fetal sites were 6.3 ± 0.9 μg/mL and 0.5 ± 0.1 μg/mL, respectively. From these levels, the placental passage rate can be calculated as 7.94% (percentage of umbilical level to maternal level). Unlike their in vitro study, in the current study we determined a placental passage rate for levofloxacin of 66.53 ± 6.96% and for moxifloxacin of 74.84 ± 12.39%. It can be clearly seen that nearly three-quarters of moxifloxacin and levofloxacin can cross the placenta in vivo. The difference between the passage rates of these two quinolones was not found to be significant ($P = 0.075$). When the transfetal passage rates were examined, it was observed that 85–90% of levofloxacin and moxifloxacin pass through the fetus, leaving 10–15% in the fetus. The transfetal passage rates of moxifloxacin and levofloxacin did not differ significantly.

There are no data regarding fetal blood levels of cefepime, and data regarding fetal blood levels of cefoperazone are scarce. In one study, following a 1 g i.v. dose of cefoperazone, cord blood levels were observed to be 34.4% of maternal blood [14]. Peak concentrations were observed at the first hour and produced peak cord blood concentrations averaging ca. 45% of maternal serum at 70 min [15]. However, in our study we observed that the fetal plasma levels were 12.68% of maternal serum at nearly 26 min. This may be an explanation for the low transplacental passage rate.

The goal of prophylaxis is to obtain therapeutic levels of antibiotic agents in tissues at the time of microbial contamination [4]. However, the common practice during Caesarean is to administer the agent after clamping of the cord to avoid transplacental passage. Therefore, to achieve the desired level of antibiotics in the tissue at the time of incision will not be possible. Antibiotics with a low transplacental passage rate and proven safety may be considered for administration before clamping of the cord. Among the agents studied here, cefepime has a lower and cefoperazone the lowest transplacental passage; therefore these two antibiotics may be used safely for this purpose. On the other hand, both levofloxacin and moxifloxacin have high transplacental passage rates. This may have a prophylactic benefit when there is a suspicion of subclinical infection involving fetal structures as in early rupture of membranes. Moreover, these two antibiotics have an excellent coverage against the commonly isolated pathogens in such conditions.

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