

# Evaluation of the amoxicillin concentrations in amniotic fluid, placenta, umbilical cord blood and maternal serum two hours after intravenous administration

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## Abstract

**OBJECTIVES:** The aims of this study were to evaluate amoxicillin concentrations in amniotic fluid, placenta, umbilical cord blood and maternal blood two hours after intravenous administration to assess obstetric and non-obstetric factors that could have influences on the penetration of the antibiotic into the examined tissues and to analyze the sensitivity to amoxicillin of the most common pathogens isolated from the genital tract.

**METHODS:** A total of 35 full-term pregnant women who qualified for elective Caesarean delivery were included in the study. Amoxicillin at a dose of 1000 mg was administered prior to surgery. Amoxicillin levels were determined by diffusion microbial assay.

**RESULTS:** The drug concentration was highest in umbilical cord blood compared with amniotic fluid, maternal blood and placenta ( $4.20 \pm 1.06$  µg/g versus  $3.96 \pm 0.79$  µg/g,  $3.22 \pm 0.64$  µg/g and  $2.81 \pm 0.64$  µg/g, respectively). Obstetric and non-obstetric factors had no influence on the amoxicillin concentration. The most common bacteria isolated from the genital tracts of pregnant women (*Streptococcus agalactiae*, *Enterococcus faecalis*, *Escherichia coli*) were sensitive to amoxicillin. The MIC for the sensitive strain of *Streptococcus agalactiae* was seen in the majority of tissues of all of the patients; however, the MICs for *E. faecalis* and *E. coli* were not observed in any compartment.

**CONCLUSIONS:** Amoxicillin proved to have good penetration into the fetal tissues and placenta after intravenous administration. The most common bacteria isolated from the genital tracts of pregnant women were sensitive to amoxicillin. Pregnancy complications were not found to have an influence on the amoxicillin concentrations in the examined tissues.

## INTRODUCTION

Amoxicillin is a broad-spectrum beta-lactam antibiotic commonly used in obstetrics due to its low toxicity (Batagol, 1999; Heinonen *et al.* 1997). Amoxicillin is active against Gram-positive strains (*Streptococcus*, *Enterococcus* and non-beta-lactamase-producing *Staphylococcus* strains), as well as certain Gram-negative strains (*Haemophilus influenzae*, *Neisseria gonorrhoeae*, *Escherichia coli*) (Drawz & Bonomo, 2010; Zarowny *et al.* 1974). To reduce the risk of developing bacterial resistance to beta-lactams, some antibiotics are used in combination with beta-lactamase inhibitors (Zarowny *et al.* 1974). The first medication in this class of antibiotic agents was co-amoxiclav, a combination of amoxicillin and clavulanic acid, which has been commonly used since its introduction (Drawz & Bonomo 2010).

The bioavailability of amoxicillin is up to 89% (Zarowny *et al.* 1974). The penetration of antibiotic molecules into pathological tissues could be additionally enhanced by inflammation (increased permeability of cell membranes) (Miller, 2002). Amoxicillin can be administered orally or parenterally. The peak serum concentration following intravenous administration depends on the rate of injection and is achieved 3 to 30 seconds after administration (Brogden *et al.* 1979).

Intravenous amoxicillin is usually used in hospital settings; in obstetrics, common indications include premature amniotic fluid leakage and suspicion or diagnosis of intrauterine infection (Medina & Hill, 2006).

The objectives of this study were to assess amoxicillin levels in amniotic fluid, umbilical blood, placenta and maternal blood two hours after intravenous administration, to attempt the assessment of factors that might influence drug penetration into individual tissues and to assess the drug sensitivity of the most common bacterial strains found within the genital tracts of subjects.

## MATERIALS AND METHODS

The study population consisted of 35 patients who qualified for elective Caesarean section. The most common indications for Caesarean section included fetal macrosomia (8 patients), ophthalmological indications (6 patients), and fetopelvic disproportion (5 patients). The study design initially included the assessment of amoxicillin levels in the amniotic fluid and placenta. However, after obtaining these results from 29 women, a decision was made to expand the scope of assessment to include drug levels in umbilical and maternal blood, which were measured in 6 patients.

The study drug was amoxicillin/clavulanic acid 1000/200 mg, respectively. The inclusion criteria were as follows: full-term pregnancy (week 37-41), maintained integrity of the fetal membrane, informed consent to participate, and no maternal allergy to the drug.

The study was approved by the Bioethics Committee of the Medical University of Warsaw.

Medical history interviews, physical examinations and cardiotocography (CTG) examinations were performed upon admission to the department. Cervical swabs were collected from each patient for inoculation. After signing the informed consent form, the patients were administered the antibiotic 2 hours before the planned procedure. Before the Caesarean section, maternal blood samples were collected for laboratory analyses, including erythrocyte counts, hemoglobin levels, hematocrit, and leukocyte and platelet counts. The following samples were collected intraoperatively: 20 mL of amniotic fluid, a 100-g fragment of placenta, 9 mL of umbilical blood and 9 mL of maternal blood. Amniotic fluid was collected from each patient for inoculation tests. Twelve hours after the Caesarean section, laboratory analyses as conducted before the procedure were repeated.

The tissue levels of the drug were determined at the National Veterinary Research Institute in Puławy by means of Kundrat microbial diffusion test using Kundrat's agar and *Bacillus stearothermophilus* ATCC 7953 (Merck, cat. no. 1.11499.0001) as the test strain (Kundrat, 1968). Each measurement was repeated 4 or 5 times, depending on the quantity of study material, with arithmetic means calculated from each series of results.

Maternal age and body mass index (BMI), as well as pregnancy weight gain, were the factors that might potentially influence the levels of the drug in the examined tissues. The effects on amoxicillin levels of maternal comorbidities, such as pre-pregnancy hypertension, pre-gestational diabetes, pregnancy-induced hypertension, gestational diabetes, thrombocytopenia, and anemia, were examined. The effects of the presence of pathogens within the cervical canal on the levels of the drug were assessed with consideration of the results of inoculation tests. In addition, tests were conducted to assess the amoxicillin sensitivity of the bacterial strains detected in study subjects.

## RESULTS

The mean age of the mothers was  $30.8 \pm 3.9$  years, the mean BMI was  $24.1 \pm 4.6$  kg/m<sup>2</sup>, and the mean in-pregnancy weight gain was  $13.2 \pm 4.5$  kg. Maternal diseases and pregnancy complications were observed in the following numbers of patients: pre-pregnancy hypertension in 3 patients, pre-gestational diabetes in 3 patients, pregnancy-induced hypertension in 2 patients, gestational diabetes in 8 patients, thrombocytopenia in 7 patients and anemia in 3 patients. Three patients were smokers.

Twenty patients were multiparous, while the other fifteen were primiparous. Sixteen patients had history of Caesarean section; five patients had histories of miscarriage.

**Table 1.** Amoxicillin concentration after intravenous administration in the different compartments

Compartment	X ± SD (mg/g)	Med (Q1 - Q3) (mg/g)	Min (mg/g)	Max (mg/g)	p		
					Cord blood	Placenta	Amniotic fluid
Cord blood	4.20 ± 1.06	4.64 (3.39-4.68)	2.46	5.38		0.004	0.627
Amniotic fluid	3.96 ± 0.79	3.85 (3.21-4.50)	3.13	5.19	0.627	0.021	
Maternal serum	3.22 ± 0.64	3.17 (2.76-3.72)	2.41	4.10	0.046	0.048	0.165
Placenta	2.81 ± 0.64	2.85 (2.34-3.34)	1.86	3.64	0.004		0.021

X – mean concentration; SD – standard deviation; Med - median; Q<sub>1</sub>- lower quartile, Q<sub>3</sub>- upper quartile; Min – minimal concentration; Max – maximal concentration; p – significance level

The mean pregnancy completion time was 38.1±1.2 weeks. The mean birth weight and body length of the neonates were 3543.2±682.9 g and 55.1±2.8 cm, respectively. The birth weight was less than or equal to 3500 g in 18 neonates and greater than 3500 g in 17 neonates. All of the babies were born in good overall condition, with Apgar scores of 8 to 10 one, three, and five minutes after birth. The most common neonatal complications included hypertrophy (14 neonates) and hyperbilirubinemia (2 neonates).

Pre- and post-Caesarean section blood parameters were as follows: erythrocytes 4.1±0.4 vs. 3.82±0.4 M/μL; hemoglobin 12.6±1.0 vs. 11.8±1.1 g/dL; hematocrit 37.5±2.5 vs. 34.8±3.4%; leukocytes 9.1±1.5 vs. 12.0±2.9 K/μL; and platelets 183.8±50.4 vs. 181.2±45.8 K/μL.

A total of 8 abnormal results of cervical swab inoculation tests were obtained. A single pathogen was detected in 5 patients, two pathogens were detected in 1 patient, and three pathogens were detected in 2 patients. The most common pathogens included *Streptococcus agalactiae*, *Candida albicans*, *Enterococcus faecalis*, and *Escherichia coli*. The cultured bacteria were amoxicillin-sensitive. A total of 2 abnormal results of amniotic fluid inoculation tests were obtained. Single pathogens were cultured in both cases, namely, *Morganella morganii* (amoxicillin-sensitive) and *C. albicans*.

Two hours after intravenous administration, the highest amoxicillin levels were measured in umbilical blood, reaching 4.20±1.06 μg/g and being significantly higher than in maternal blood (3.22±0.64 μg/g; p<0.046) and placenta (2.81±0.64 μg/g; p<0.004). Placental concentrations were lower than the concentrations within the maternal blood (p<0.048) and amniotic fluid (3.96±0.79 μg/g; p<0.021) (Table 1). The following linear relationships between amoxicillin levels in individual tissues were observed: the higher the maternal serum level was, the higher the placental level was (p<0.046); the higher the placental level was, the higher the amniotic fluid level was (p<0.002) (Figure 1). The highest levels of amoxicillin were detected in most cases in the umbilical blood, regardless of age, parity, surgical history or pregnancy completion time. No effects on drug level were identified for the following factors:

- maternal age (younger than 30 vs. 30-34 vs. 35 years or older);
- smoking;
- parity (primiparous vs. multiparous);
- history of Caesarean section;
- history of miscarriage;
- pre-gestational maternal BMI (BMI <21.0 vs. BMI 21.0-24.9 vs. BMI ≥25.0 kg/m<sup>2</sup>);
- gestational weight gain (<11 kg vs. 11-16 kg vs. >16 kg);
- pregnancy completion time (week 37-38 vs. week 39 and later);
- maternal hypertension;
- pre-gestational and gestational diabetes;
- maternal anemia;
- maternal thrombocytopenia;
- neonatal birth weight (≤3500 g vs. >3500 g);
- neonatal constitutional type (hypertrophic vs. eutrophic vs. hypotrophic); and
- the presence of pathogens within the cervical canal (normal vs. abnormal cervical swab result).

Negative correlations were observed between the drug dose per kilogram of maternal body weight and maternal blood amoxicillin level (r=-0.896; p<0.015; Figure 2), as well as between the platelet counts and umbilical blood amoxicillin level (r=-0.910; p<0.031; Figure 3). The placental amoxicillin levels in female neonates were higher than in male neonates (1.85±0.86 μg/g vs. 1.17±0.84 μg/g; p<0.027; Table 2).

Table 3 presents the compartmental analysis of amoxicillin levels with reference to the minimum inhibitory concentration for a particular bacterial strain. Drug levels greater than or equal to the minimum inhibitory concentration for *Streptococcus agalactiae* were detected in maternal blood, umbilical blood and amniotic fluid in all of the subjects, as well as in the placenta in 97.14% of subjects two hours after intravenous administration. In the cases of *Enterococcus faecalis* and *E. coli*, no MIC was detected in any of the samples 2 hours after intravenous administration of 1000 mg of amoxicillin.

**Table 2.** Amoxicillin concentration after intravenous administration in the different compartments compared to neonatal gender

Compartment	Female		Male		p
	n	X ± SD Med (Q <sub>1</sub> - Q <sub>3</sub> ) (µg/ml)	n	X ± SD Med (Q <sub>1</sub> - Q <sub>3</sub> ) (µg/ml)	
Maternal serum	4	3.10 ± 0.73	2	3.22 ± 0.57	
		3.02 (2.52 - 3.68)		3.22 (2.82 - 3.63)	
Cord blood	4	3.71 ± 1.05	2	4.87 ± 0.53	
		3.94 (2.85 - 4.57)		4.87 (4.49 - 5.25)	
Placenta	19	1.85 ± 0.86	16	1.17 ± 0.84	<b>0.027</b>
		1.82 (1.30 - 2.34)		1.24 (0.42 - 1.59)	
Amniotic fluid	19	3.18 ± 1.51	16	2.52 ± 1.18	0.216
		3.15 (2.04 - 4.28)		2.76 (1.56 - 3.23)	

X – mean concentration; SD – standard deviation; Med - median; Q<sub>1</sub> - lower quartile; Q<sub>3</sub> - upper quartile; p – significance level

**Table 3.** Amoxicillin concentration higher or equal MIC for the most common cervical pathogens

Pathogen	C ≥ MIC			
	Maternal serum	Cord blood	Placenta	Amniotic fluid
Streptococcus agalactiae	100%	100%	97.14%	100%
Enterococcus faecalis	0%	0%	0%	0%
Escherichia coli	0%	0%	0%	0%

MIC – minimal inhibitory concentration

C ≥ MIC - amoxicillin concentration higher or equal MIC

## DISCUSSION

Amoxicillin is one of the antibiotics that is most commonly used in pregnant women. The study subjects were given co-amoxiclav (combination of amoxicillin and clavulanic acid) prior to Caesarean section due to the drug's broad spectrum of activity in terms of the prevention of perioperative infections. Only amoxicillin levels were assessed, because single-agent amoxicillin is most commonly used in pre-term pregnancy when co-amoxiclav might increase the risk of necrotic enterocolitis in neonates (Kenyon *et al.* 2001- ORACLE I; Kenyon *et al.* 2001- ORACLE II). According to the available studies, clavulanic acid has no effect on tissue penetration by amoxicillin (Adam *et al.* 1982; Muller *et al.* 2009). An amoxicillin dose of 1000 mg was used in the study because this dose is most commonly administered by intravenous route at our study site. Amoxicillin levels were assessed two hours after administration while bearing in mind that, rather than the peak levels (which are attained shortly after administration), the measured levels were those after one half-life period

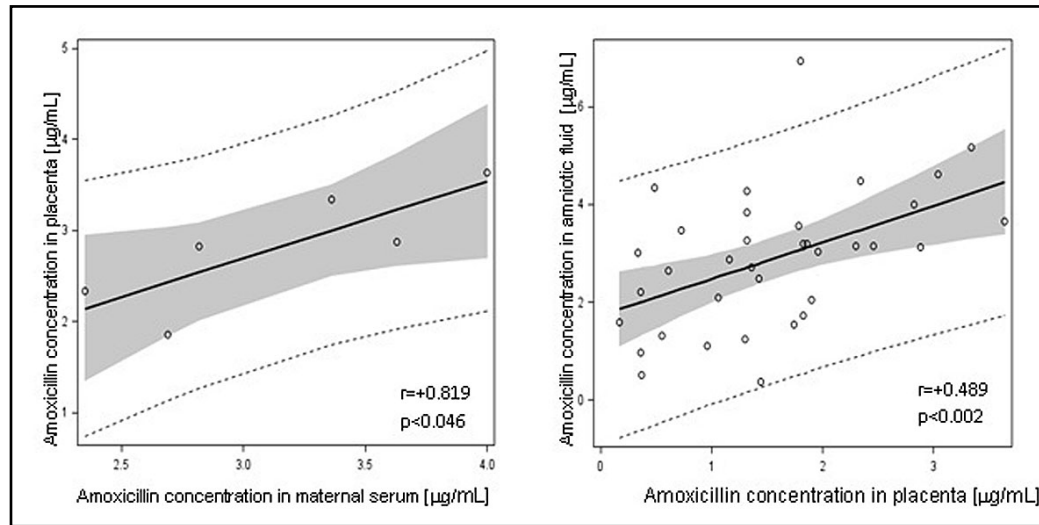
of the antibiotic drug and typical for one half of the time interval between consecutive doses, when used in the prevention of *Streptococcus agalactiae* infections.

Single samples of umbilical blood, maternal blood, placenta and amniotic fluid were collected from each patient, in every case 2 hours after administration of the drug. Thus, there was no possibility to assess the changes in drug levels as a function of time. Such attempts have been undertaken by other authors who assessed amoxicillin levels in patients at different time points following administration; however, the results from different patients are not always sufficient for drawing unambiguous conclusions (Muller *et al.* 2008- Br J Clin Pharmacology; Muller *et al.* 2009).

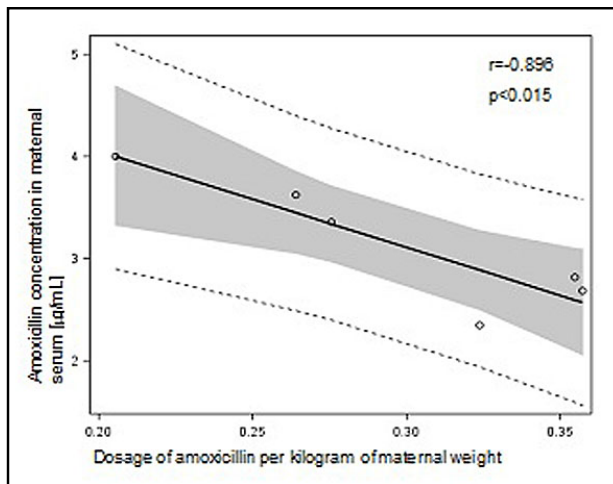
The highest levels of amoxicillin were detected in umbilical blood, regardless of maternal age, parity, surgical history or pregnancy completion time. The lowest levels were achieved within the placenta. One might therefore conclude that, following intravenous administration, amoxicillin is characterized by good penetration of fetal tissues, allowing it to reach levels higher than the respective maternal levels 2 hours after administration. Similar results were presented by Colobomo for ampicillin (Colobomo *et al.* 2006): 80 minutes after intravenous administration, umbilical blood levels of ampicillin were higher than the maternal blood levels.

As revealed by the studies of Chilean researchers (Aranzibia 1980), mean serum concentration of amoxicillin was the highest 5 minutes after intravenous administration at 42.6±7.7 µg/mL (30.1-52.1). After 2 hours, the serum concentration was 4.9±1.4 µg/mL which exceeded the serum antibiotic levels measured in our patients; however, it must be mentioned that the aforementioned study was conducted in non-pregnant volunteers.

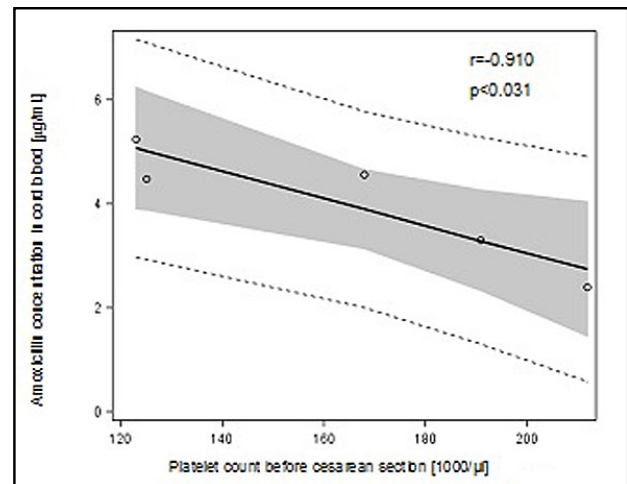
According to Philipson (Philipson, 1977), who studied the pharmacokinetics of ampicillin after intravenous administration of 500 mg to pregnant women and subsequently to the same women after puerperium and the lactation period, although peak serum levels did not differ between pregnant and non-pregnant women, the mean serum levels were nearly 50% lower in pregnant women. The author explained these results by the increased serum volumes and higher body water content in pregnant women, while indicating the need to use higher doses of antibiotics in this group of patients, consistent with the reports by other authors (Kmieciak-Kołada, 1998; Szałek *et al.* 2012).



**Fig. 1.** Comparison between amoxicillin concentration in different compartments.



**Fig. 2.** Comparison between dosage of amoxicillin per kilogram of maternal weight and amoxicillin concentration in maternal serum.



**Fig. 3.** Comparison between amoxicillin concentrations in cord blood with platelet count before cesarean section.

In our study, we observed positive linear correlations between amoxicillin levels within the maternal serum and placenta, as well as between amoxicillin levels between the placenta and the amniotic fluid. Other researchers (Colobomo *et al.* 2006) observed a linear relationship between the ratio of umbilical to maternal serum ampicillin levels and time: the higher the value, the longer the time between drug administration and Caesarean section; the mean ratio of umbilical to maternal serum ampicillin levels was  $1.74 \pm 2.52$ . According to our data, the umbilical and maternal serum amoxicillin level ratio 2 hours after administration of the drug was  $1.30 \pm 0.32$ .

Muller *et al.* (Muller *et al.* 2008- Am J Obstet Gynecol) administered 2 g of amoxicillin, followed by another 1 g of amoxicillin, to 17 pregnant women and observed no differences in pharmacokinetics depending on the dose, gestational age, maternal body weight, BMI, arterial blood pressure, heart rate, body temperature, or the presence of maternal edema. Additionally,

we did not observe in our study any effects on amoxicillin levels within the tested tissues for factors including maternal age, parity, obstetrical history, BMI, gestational weight gain, age at pregnancy completion, or the presence of pregnancy complications (hypertension, diabetes, anemia, thrombocytopenia).

After recalculating the amoxicillin dose per 1 kg of body weight, we observed that the higher the dose was, the lower the observed maternal serum levels were. Bearing in mind that every patient received the same dose of amoxicillin, one might assume that lower serum drug levels were observed in leaner patients. Being a hydrophilic drug, amoxicillin poorly penetrates adipose tissue, which is more abundant in individuals with higher BMI values (Bearden & Rodvold, 2000; Hanley *et al.* 2010; Falagas & Karageorgopoulos, 2010); in addition, obese individuals are characterized by lower tissue perfusion (Hanley *et al.* 2010), which might explain the observed results.

According to global data, infection leads to better penetration of amoxicillin and higher drug concentrations in pathologically changed tissues (Brogden *et al.* 1979; Canafax *et al.* 1998). In a study comparing amoxicillin levels in middle ear fluid collected from children with otitis media, the highest drug levels were observed in cases of bacterial infections. Lower values were measured in mixed bacterial and viral infections, while the lowest levels were observed in viral infections, as well as in cases with negative bacteriological and virological screening results (Canafax *et al.* 1998). In our study, we were unable to demonstrate that the presence of pathogens within the cervical canal had any effect on concentrations of amoxicillin in the tested compartments. Unfortunately, no similar analysis could be observed in the aspect of amniotic fluid infection because this complication occurred only in two cases, with one of them being of fungal origin.

Higher amoxicillin levels were observed in placental tissue in cases of female neonates. No similar results were reported in the international literature, and the underlying cause remains unclear. There is a possibility of a hitherto unknown effect of hormonal factors. In our study, we observed a linear relationship between maternal platelet counts before the Caesarean section and umbilical blood amoxicillin level following intravenous administration: lower concentrations of the antibiotic were observed with higher maternal platelet counts. Unfortunately, no reports are available on this subject in the international literature, although the effects of rheological blood parameters on amoxicillin levels are not impossible to assess. As shown by our study assessing the penetration of amoxicillin into the amniotic fluid, placenta, umbilical blood and maternal blood following intravaginal administration, higher amniotic fluid concentrations were achieved in women with higher hemoglobin levels and higher erythrocyte counts (Zareba-Szczudlik *et al.* 2014).

The strongest antibacterial effect of beta-lactam antibiotics is observed when their concentrations in pathologically changed tissues reach four times the minimum inhibitory concentration (MIC) (Hoffman *et al.* 1998). In our study, the levels of amoxicillin, as measured two hours after administration, were found to be greater than or equal to the MIC for *Streptococcus agalactiae* in maternal blood, umbilical blood and amniotic fluid in all of the subjects, as well as in the placenta in 97.14% of the subjects. In the cases of *E. faecalis* and *E. coli*, no MIC was detected in any of the samples. When planning efficient intravenous antibiotic therapy for *E. faecalis* and *E. coli* infections, amoxicillin doses should be higher than these used in our study.

To conclude, amoxicillin proved to have good penetration into the fetal tissues and placenta after intravenous administration. The most common bacteria isolated from the genital tracts of pregnant women were sensitive to amoxicillin. Pregnancy complications were

not found to have an influence on the amoxicillin concentrations in the examined tissues.

## STATISTICS

1. Tissue concentrations of the drug were calculated based on the serum specific gravity value of 1.026 g/mL and the amniotic fluid specific gravity value of fluid 1.006 g/mL for the purpose of standardization of the results before subjecting them to statistical analyses (Pawelski & Maj, 1987).
2. Patient groups were compared in terms of drug concentrations using the Mann-Whitney U-test.
3. The results are presented as 1st quartiles, medians, and 3rd quartile values; however, for the sake of potential reference to results obtained in other studies, mean  $\pm$ SD values were also included.
4. Qualitative parameters were compared between the patient groups using Fisher's exact test.
5. The strength of correlations between quantitative factors was described by Spearman's correlation coefficient (Lloyd *et al.* 1993).
6. Statistical analyses were performed using SAS software (SAS Institute, Cary, NC, USA, 2011).

## CONFLICTS OF INTEREST

The authors have no potential conflicts of interest to disclose.

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