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ORIGINAL ARTICLE

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

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Abstract

OBJECTIVES: Amoxicillin is a broad-spectrum beta-lactam antibiotic. Due to its low toxicity, it is commonly used in obstetrics. The objective of this study was to assess amoxicillin concentrations in amniotic fluid, umbilical blood, placenta and maternal serum two hours following oral administration among pregnant women at term and to assess obstetric and non-obstetric factors that might affect amoxicillin's penetration of these tissues.

MATERIALS AND METHODS: A total of 30 full-term pregnant women who qualified for elective Caesarean delivery were included in the study. Amoxicillin at a dose of 500 mg was administered prior to surgery. Amoxicillin levels were determined by diffusion microbial assay.

RESULTS: The maternal serum, placental, umbilical blood and amniotic fluid levels of amoxicillin two hours after oral administration were 2.18±1.30 μg/g, 1.00±0.71 μg/g, 1.00±0.73 μg/g, and 0.67±0.59 μg/g, respectively (Table 2). Maternal serum levels of amoxicillin were significantly higher compared to other tissues ($p<0.05$).

CONCLUSION: If the target tissues for the use of antibiotic drugs in pregnant patients are the fetus and/or the placenta, the drug should be administered in a higher-than-standard dose than that used to treat infections in non-pregnant patients. Considering that there is a maximum absorbable dose following oral administration, intravenous administration should be considered to prevent failure of antibiotic treatment. A higher dose of amoxicillin should be considered in obese mothers.

INTRODUCTION

Amoxicillin is a broad-spectrum beta-lactam antibiotic. Due to its low toxicity, it is commonly used in obstetrics. Amoxicillin is administered via an oral or parenteral route. Following oral administration, 80–90% of the drug is absorbed by the gastrointestinal system. The process is independent from the time of meals and the type of diet (Zarowny *et al.* 1974; Sabto *et al.*

1973; Miller 2002), and the drug is resistant to gastric juice. Gastrointestinal absorption appears to be dose-dependent; serum levels do not increase beyond doses larger than 1000 mg (Paintaud *et al.* 1992; Sjovall *et al.* 1992). The maximum absorbable quantity of the drug from a single dose is 2 grams (Arancibia *et al.* 1988). Following oral administration, the serum level peaks at approximately 2 hours. After administration of 500 mg of amoxicillin, the peak blood level is 5 μg/mL, while after administration of 1 g, it rises to 10 μg/mL (Hoffler 1974; Lawson *et al.* 1974). According to the manufacturer's data, the peak serum level following administration of 400 mg of amoxicillin is in the range of 5 to 6 μg/mL (SmithKline Beecham Pharmaceuticals 2003).

Amoxicillin is characterized by very good bioavailability of up to 89% (Zarowny *et al.* 1974). Plasma protein-bound amoxicillin constitutes 15 to 25% of the total amount (Sutherland *et al.* 1972). Amoxicillin is a hydrophilic antibiotic. It is inactive in intracellular infections due to its reduced ability to penetrate cell membranes (Szałek *et al.* 2012). It is characterized by a good ability to penetrate into the uterus, ovaries, placenta, amniotic fluid and breast milk (Zarowny *et al.* 19741). Inflammation resulting in increased permeability of cell membranes increases the penetration of amoxicillin into inflamed tissues (Miller 2002).

The objective of this study was to assess amoxicillin concentrations in amniotic fluid, umbilical blood, placenta and maternal serum two hours following oral administration among pregnant women at term and to assess obstetric and non-obstetric factors that might affect amoxicillin's penetration of these tissues.

MATERIALS AND METHODS

The study was conducted in 30 randomly selected pregnant patients at term (37–40 gestational weeks) who were undergoing elective cesarean delivery in the 2nd Department of Obstetrics and Gynecology at Warsaw Medical University. Following admission and provision of informed consent, participants' medical history was acquired, general medical and obstetric examinations were performed, and maternity notes were obtained (Table 1). For all patients, cervical swabs were obtained at admission for microbial analysis.

Prior to delivery, subjects received a 500-mg tablet of amoxicillin orally. During the cesarean section, 15 mL of amniotic fluid, a 100-g piece of placenta, 9 mL of umbilical blood, and 9 mL of maternal blood were collected for laboratory tests to assess the concentration of amoxicillin. Additionally, 5 mL of amniotic fluid was collected for culture. The tissue samples were frozen below –20 °C and sent in monthly intervals to the National Veterinary Research Institute in Puławy, where the antibiotic concentrations were determined.

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

Amoxicillin concentrations were determined by means of Kundrat's agar diffusion test with *Bacillus stearothermophilus* ATCC 7953 (Merck, cat. Np. 1.11499.0001) as the test strain (Kundrat 1968). The culture medium composition was as follows: peptone – 17.0 g/L, NaCl – 3.0 g/L, D-(+)-glucose – 3.0 g/L, starch – 3.0 g/L, gelatin – 2.5 g/L, bromocresol purple – 0.016 g/L, agar – 10.0 g/L; and pH of 6.8. The principle of the assay is the inhibition of the growth of the test strain *Bacillus stearothermophilus* spore suspension in the presence of an antibiotic in the sample. Samples were incubated for 3 hours at 64 °C. Antibiotic concentration was determined from the diameter of the test strain growth inhibition zone compared to the reference curve established in an antibiotic-free material. The reference curve for the determination of amoxicillin concentration within the tested samples was established using the reference standard obtained from Sigma (cat. No. A/8523 containing ≥900 μg/g – FDA recognized consensus standard).

The study examined potential correlations between drug levels in individual tissues and determined the amoxicillin levels determined in relation to minimum inhibitory concentrations (MIC) for the bacterial strains most commonly isolated from the cervical canal and the amniotic fluid.

Statistics

Concentrations of amoxicillin were standardized before statistical analyses using specific gravity of serum of 1.026 g/mL and specific gravity of amniotic fluid of 1.006 g/mL (Pawelski and Maj 1987). The results are presented in Table 2. The study also examined potential correlations between drug levels in individual tissues. Correlation analyses were performed to identify statistically significant correlations between drug levels in pairs of tissues (Figure 1).

The statistical analyses were repeated for various subgroups. The purpose of these exploratory analyses was to identify factors that could explain any correlations identified in the full set of subjects and to identify subgroups in whom particularly good or poor tissue penetration was observed (Figure 2).

The amoxicillin levels were determined in relation to minimum inhibitory concentrations (MIC) for the bacterial strains most commonly isolated from the cervical canal and the amniotic fluid (Table 3).

Non-parametric methods were used for both types of analyses mentioned above. The analyses were carried out using the following procedures: MEANS (calculations of medians, means, quartiles, and standard deviations), NPAR1WAY (Wilcoxon and Kruskal-Wallis tests), and UNIVARIATE (signed-rank test and the Shapiro-Wilk, Kolmogorov-Smirnov, Cramer-von Mises, and Anderson-Darling tests to assess conformity to a Gaussian distribution). Separate comparisons were made to identify inter-group differences in qualitative parameters. In these cases, Fisher's exact test was

used (calculations were performed using the FREQ procedure with the EXACT option). The power of correlations is expressed by Spearman's correlation coefficient. The lines on the charts, which were calculated by linear regression methods, are purely illustrative as they reflect the direction of the identified correlations.

Tab. 1. Maternal and neonatal characteristics.

Variable [unit]	Mean±SD or n (%)	Median	Min	Max
Age [years]	31.8±5.2	32.0	22.0	42.0
Pre-pregnancy weight [kg]	63.3±10.0	60.5	46.0	88.0
BMI [kg/m^2]	23.1±3.7	22.4	16.9	32.7
Gestational weight gain [kg]	14.3±4.9	15.5	6.0	21.0
Multiparas	13 (43.4)			
History of cesarean section	10 (33.3)			
Pre-existing hypertension	0			
Pregnancy-induced hypertension	1 (3.3)			
Pre-existing diabetes	3 (10.0)			
Gestational diabetes	4 (13.3)			
Thrombocytopenia	5 (16.6)			
Serum hemoglobin level [g/dL]	12.7±1.2	11.8	10.1	14.8
Red blood cell count [mln/µl]	4.2±0.3	3.9	3.49	4.68
Presence of bacteria in the cervix	10 (30.0)			
Gestational age at delivery [weeks]	38.5±1.0	38.0	37.0	41.0
Birth weight [g]	3535.3±567.8	3600.0	1980.0	4620.0
Body length [cm]	55.1±2.9	55.0	45.0	60.0
Boys	18 (60.0)			
SGA	3 (10.0)			
LGA	9 (30.0)			
Smoking	4 (13.3)			

SD - standard deviation; Min - the minimal value of variable; Max - the maximal value of variable; SGA - small for gestational age; LGA - large for gestational age

The CORR and REG procedures were used in these calculations.

Statistical analyses were based on L.D. Fisher's and Gerald van Belle's manuals (Lioyd *et al.* 1993) and were carried out using the SAS system (SAS/STAT® 9.3, User's Guide, Volume 1, 2, 3. SAS Institute Inc., Cary, NC, USA, 2011).

RESULTS

Both maternal and neonatal characteristics are presented in Table 1. Microbial presence in the cervical canal was detected in 10 subjects (most commonly isolated species included *Candida albicans*, *Streptococcus agalactiae*, and *Enterococcus faecalis*), and presence in the amniotic fluid was detected in 3 subjects (*Enterococcus faecalis* in all samples). No neonatal infections were observed. All babies were born in good general condition with Apgar scores of 8 to 10.

The maternal serum, placental, umbilical blood and amniotic fluid levels of amoxicillin two hours after oral administration were 2.18±1.30 µg/g, 1.00±0.71 µg/g, 1.00±0.73 µg/g, and 0.67±0.59 µg/g, respectively (Table 2). Maternal serum levels of amoxicillin were significantly higher compared to other tissues (p<0.05).

The higher the maternal serum levels, the higher the umbilical blood levels (p<0.0001, r=+0.769) (Figure 1). Greater maternal pre-pregnancy BMI was associated with higher maternal serum levels of the antibiotic (p<0.016) (Figure 2). A similar correlation (approaching the statistical correlation threshold, p<0.053) was observed between maternal weight at delivery and the maternal serum levels of amoxicillin.

Amoxicillin concentration in the amniotic fluid was significantly higher in the group with low gestational weight gain (below 11 kg) compared to subjects with moderate gestational weight gain (11–16 kg) (p<0.031). Significantly higher drug concentrations were detected in the amniotic fluid of subjects with hemoglobin levels above 11 mg/dL compared to subjects with hemoglobin levels of 11 mg/dL or less (0.75±0.57 µg/mL vs. 0.21±0.22 µg/mL; p<0.038).

No statistically significant differences were observed in tissue amoxicillin levels in relation to the following parameters:

Tab. 2. Amoxicillin concentration in different tissues.

Tissue µg/g	n	Med (Q_1–Q_3)	Mean ± SD	Min	Max	*p*-value		
						UC	PL	AF
Maternal blood	28	2.17 (1.18–2.79)	2.18±1.30	0.20	5.25	0.0001	0.0004	0.0001
Umbilical cord	28	0.86 (0.38–1.33)	1.00±0.73	0.01	2.40		0.981	0.059
Placenta	28	0.94 (0.59–1.23)	1.00±0.71	0.01	3.31			0.019
Amniotic fluid	28	0.48 (0.19–1.06)	0.67±0.59	0.01	2.01			

Med– median; SD – standard deviation; Min – the minimal value of variable; Max – the maximal value of variable; UC– umbilical cord, PL– placenta, AF– amniotic fluid

- parity
- smoking status
- maternal gestational and pre-gestational diabetes mellitus
- maternal thrombocytopenia
- bacterial colonization of the maternal cervical canal
- gestational age at delivery
- maternal numbers of leukocytes and platelets prior to cesarean delivery
- neonatal birth weight

Table 3 presents the amoxicillin levels in relation to MIC for the bacterial strains most commonly isolated from the cervical canal and the amniotic fluid. The MIC for *Streptococcus agalactiae* was achieved in most compartments, while the MIC for *Enterococcus faecalis* was not achieved in any of the tissues.

DISCUSSION

We chose to assess the penetration abilities of amoxicillin, which is one of the most common antibiotics used by pregnant women, at a dose of 500 mg, which is very common for oral administration. Amoxicillin levels were determined in all tissues two hours following administration, when, according to the literature, peak serum levels of the drug are achieved. We wanted to determine these levels in pregnant women and to examine the relationships between these levels and the levels found in other tissues.

Tab. 3. The pathogens most often isolated from the cervix and amniotic fluid and the concentration of amoxicillin higher or equal to MIC.

	C ≥ MIC			
	Maternal blood	**Umbilical cord**	**Placenta**	**Amniotic fluid**
Streptococcus agalactiae	96.70%	90.01%	82.76%	72.41%
Enterococcus faecalis	0%	0%	0%	0%

C ≥ MIC – concentration of amoxicillin higher or equal to MIC

The highest concentrations of the drug were observed in maternal blood. Daschner *et al.* studied amoxicillin's penetration to pleural fluid following oral administration of a dose of 750 mg in 9 patients undergoing thoracic surgery (Daschner *et al.* 1981). Maximum serum amoxicillin concentration was achieved after 4±0.87 hours and amounted to 4.52 μg/mL in the serum. In pleural fluid, the peak level was achieved after 5.33±1.99 hours and amounted to 1.56 μg/mL. The authors had expected the higher serum levels and attributed their results to the condition of patients on the second day after surgery.

Strausbaugh *et al.* studied amoxicillin's penetration to cerebrospinal fluid (CSF) in 19 patients with tuberculous meningitis (Strausbaugh *et al.* 1978). Two hours after oral administration of a dose of 1 g of amoxicillin, the concentration was 0.1 to 1.5 μg/mL. Following intravenous administration of a dose of 2 g of amoxicillin, after 90 minutes the concentration was 2.9 to 40.0 μg/mL, compared to 2.6 and 27 μg/ml after four hours. The CSF levels of amoxicillin following oral administration were not markedly different from the range observed in our study, though reaching 40.0 μg/mL at 90 minutes following intravenous administration is significantly higher than any of our results. It has been reported that ongoing infection can lead to better drug penetration and higher drug levels, which likely explains this result (Miller 2002; Canafax *et al.* 1998).

Brazilian researchers (Pires de Abreu *et al.* 2003) assessed amoxicillin levels following administration

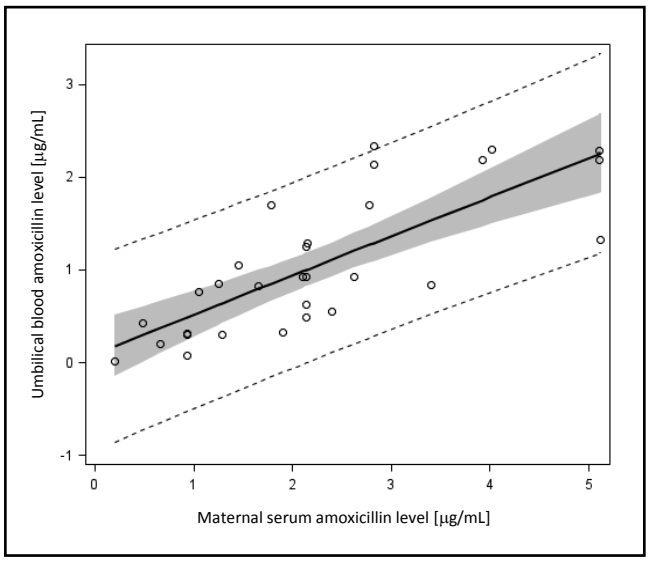

Fig. 1. Correlation between the umbilical blood and maternal serum amoxicillin levels.

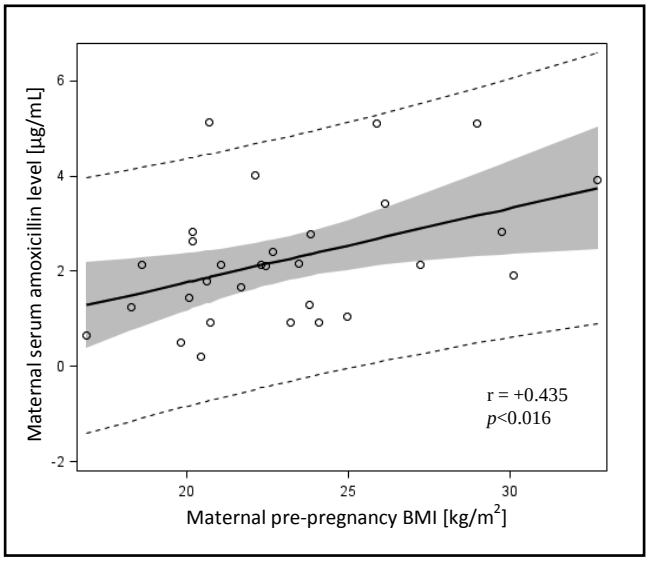

Fig. 2. Correlation between maternal pre-pregnancy BMI and serum amoxicillin level.

of two doses of 500 mg administered to 24 volunteers in one-week intervals. The drug was produced by different manufacturers. The authors observed that the maximum blood levels achieved two hours after oral administration were similar and amounted to 8.1 μg/mL (5.1–12.1) and 8.15 μg/ml (3.8–13.9) depending on the source of the drug.

Suarez-Kurtz *et al.* studied the pharmacokinetics of amoxicillin following oral administration of 500 mg of amoxicillin as a capsule or as a suspension (Suarez-Kurtz *et al.* 2001). The maximum serum concentration following administration of a capsule was 5.4±2.2 μg/mL and took 1.54 ±0.42 hours to be achieved. In case of the drug being delivered as a suspension, the respective values were 5.0±1.5 μg/mL and 1.33±0.49 hours.

Chilean researchers published a study comparing amoxicillin levels following intravenous and oral administration of 500 mg of amoxicillin (Arancibia *et al.* 1980). The mean serum concentration peaked 5 minutes after intravenous administration and amounted to 42.6±7.7 μg/mL (52.1–30.1), and it fell to 4.9±1.4 μg/mL two hours after administration. Following oral administration, maximum serum drug levels were observed 90 to 120 minutes after administration and amounted to 9.5±3.8 μg/mL and 8.8±2.0 μg/mL, respectively. All of these results exceeded the levels measured in our study, though it is important to note that these studies were conducted in non-pregnant volunteers.

Several studies of penicillin levels have been conducted in the past century. Angeta Philipson studied the serum levels and urinary excretion of ampicillin in 26 women during pregnancy, *post-partum* and after the lactation period (Philipson 1977). The pregnant subjects received 500 mg of the drug intravenously or orally at intervals of at least one week. After delivery (3–12 months) and after the lactation period, the subjects received the same dose of the drug, first intravenously and then orally. The author observed that peak serum concentrations following intravenous administration did not differ between the pregnant and non-pregnant periods. Following oral administration, peak serum levels were much lower during pregnancy than during the non-pregnant period (2.2±1.0 μg/mL vs. 3.7±1.5 μg/mL, $p<0.001$). In both groups, maximum serum levels were usually observed 2 hours after oral administration; however, a trend towards faster buildup of the maximum serum level was observed during the non-pregnant periods. Mean serum levels during pregnancy were nearly 50% lower than those during non-pregnant periods both after intravenous and oral administration. In addition, the biological half-life following intravenous administration was significantly lower during pregnancy than during the non-pregnant periods, amounting to 39.2±8.1 minutes compared to 44.4±6.8 minutes. The author attributed the elevated results to increased plasma and water volumes during pregnancy. She also highlighted possible differences in the binding of ampicillin by the plasma proteins and peripheral tissues. The author concluded that because the objective of administrating an antibiotic is to achieve bacterial MIC, which was not achieved during pregnancy, higher doses should be considered in pregnant patients.

In 2007, Andrew *et al.* published a study of pharmacokinetics following oral administration of 500 mg of amoxicillin to 16 female subjects in the second (18–22 weeks) and third (30–34 weeks) trimesters of pregnancy and at three months *post-partum* (Andrew *et al.* 2007). The authors observed that the maximum serum levels of the drug in the second (6.17±1.9 μg/mL) and third trimester (5.27±1.6 μg/mL) were significantly lower than those after delivery (7.87±2.7 μg/mL). The time to achieve the peak serum level did not differ significantly between the groups. Compared to after delivery, the calculated renal clearance of amoxicillin was significantly higher in pregnancy, while the quantity of unchanged drug excreted in urine and the half-life of amoxicillin was significantly lower. The authors assessed the pharmacokinetics of amoxicillin with respect to exposure to Anthrax bacilli. According to the US Department of Health standards, pregnant women exposed to these bacilli should prophylactically receive 500 mg of amoxicillin for 60 days. According to Clinical and Laboratory Standards Institute (CLSI) recommendations, the MIC for penicillin-sensitive Anthrax bacilli is ≤0.12 μg/mL. According to FDA recommendations, serum amoxicillin levels should be maintained above the MIC for 75–100% of the periods between the individual doses. Taking into account the obtained results, the authors concluded that in order to meet these recommendations, amoxicillin should be administered every 4 hours.

According to Welling et al., absorption of amoxicillin following oral administration to fasting patients is affected by the amount of water taken with the drug (Welling *et al.* 1977). Reducing the amount of water from 250 mL to 25 mL led to significantly lower levels of the drug in the blood serum. In our study, patients took the 500 mg dose of the drug with approximately 10 mL of water as they awaited the cesarean section procedure. Thus, under other conditions, including taking the drug with more water, the tissue levels of the drug would have probably been higher.

In our study, we were able to observe a linear correlation between the maternal serum levels of amoxicillin following oral administration and pre-pregnancy maternal BMI (Figure 2). The greater the pre-pregnancy BMI, the higher the serum drug levels. According to the international literature, hydrophilic drugs such as amoxicillin poorly penetrate into adipose tissue, which is more prevalent in individuals with higher BMI (Cheymol 2000). In addition, tissue perfusion may be lower in individuals with excessive body weight (Falagas *et al.* 2010). Gastrointestinal absorption of these drugs is the same in obese and normal-weight patients (Cheymol 2000; Wurtz *et al.* 1997). Considering the fact that obe-

sity has no effect on absorption, poorer penetration of tissues in obese patients remains the only explanation of our results. According to most authors, the levels of hydrophilic drugs may be lower in obese patients due to the aforementioned factors, and thus higher doses of these drugs are required in these patients (Cheymol 2000; Falagas et al.2010; Wurtz *et al.* 1997). These prior studies were conducted with ertapenem, piperacillin with tazobactam, and other antibiotics; unfortunately, none were conducted with amoxicillin. Muller *et al.* studied the pharmacokinetics of amoxicillin and observed no relationship between maternal serum levels of the drug following intravenous administration and maternal BMI (Muller *et al.* 2008). We were also able to observe a correlation between gestational weight gain and amoxicillin's penetration into amniotic fluid. Subjects who gained less than 11 kg during pregnancy were characterized by lower drug levels in the amniotic fluid compared to subjects who gained 11 to 16 kg (0.95±0.60 vs. 0.18±0.19 μg/mL; $p< 0.031$). This was probably due to the mechanism described above; subjects who gained more weight during pregnancy were characterized by a higher percentage of adipose tissue, leading to poorer penetration of a hydrophilic drug.

The levels of amoxicillin in the amniotic fluid were lower in patients with anemia and low hemoglobin levels. The worldwide literature provides very little data on the impact of anemia and changes in the erythropoietic system on the pharmacokinetics of antibiotics and other drugs. The only study on the subject addresses the pharmacokinetics of amikacin, an aminoglycoside antibiotic, in 10 patients with hematological disorders and immunosuppression and 1 patient with aplastic anemia (Kaojarern *et al.* 1989). The authors compared their results to previously published studies of the pharmacokinetics of amikacin in healthy volunteers. They found that in patients suffering from hematological disorders, not excluding aplastic anemia, an increase was seen in amikacin's volume of distribution and clearance, though the mechanism responsible for these findings remains unknown. In our study of amoxicillin levels following intravaginal administration, a similar phenomenon was observed, with higher drug concentrations in the amniotic fluid among patients with higher hemoglobin levels (Zareba-Szczudlik *et al.* 2015).

According to the literature, the bactericidal activity of beta-lactam antibiotics is significantly higher when the drug concentration is four-fold greater than the MIC value (Hoffman *et al.* 1998), and high antibiotic concentrations reduce the risk of developing resistance. Another important parameter is the MIC maintenance time (t>MIC), which should be in the range of 30–40% of the interval between individual doses for efficient treatment of Gram-positive bacterial infections and 60–70% of the interval between individual doses for efficient treatment of Gram-negative bacterial infections (Szałek *et al.* 2012). Keeping in mind amoxicillin's short biological half-life and that it is absorbed mainly from the small intestine and poorly absorbed from the large intestine, in order to achieve the therapeutic objective, one should use the drug not only at an appropriate dose but also with an appropriate frequency to maintain appropriate therapeutic concentration in serum and tissues. When analyzing the obtained amoxicillin levels in the context of the MIC for *Enterococcus faecalis*, we arrived at results similar to these obtained by Dr. Philipson, with no MIC being achieved in most patients and in most compartments and similar to our previous study evaluating the amoxicillin concentration after intravenous administration (Zareba-Szczudlik *et al.* 2016). A study published in 2014 examined whether a 1000-mg intravenous dose of amoxicillin combined with 200 mg of clavulanic acid was sufficient to achieve 40% t>MIC for a bacterial strain with MIC of 8 μg/mL (as in the case of *Enterococcus faecalis*) (Haeseker M *et al.* 2014). Unfortunately, the goal was achieved only in 65% of patients. Following a computer simulation, the authors decided to increase the frequency of drug administration to 6 times per day, which permitted the 40% t>MIC value to be achieved in 95% of patients. In a Dutch study, patients with acute exacerbations of chronic obstructive pulmonary disease received oral doses of 500 mg of amoxicillin and 125 mg of clavulanic acid three to four times a day or intravenous doses of 1000 mg of amoxicillin and 200 mg of clavulanic acid four times a day (Brusse-Keizer *et al.* 2015). The authors observed that the sputum and blood levels of the drug were lower than the MIC at which 90% of potential pathogen growth is inhibited (MIC 90) in 78% and 30% of patients, respectively; in light of these findings, the authors suggested that the drug dosage should be optimized. The case was somewhat different for the *Streptococcus agalactiae* strain. In this case, MIC was achieved (amounting to 0.25 μg/mL) 2 hours after oral administration in a vast majority of patients.

CONCLUSION

To sum up these findings, we would like to note that if the target tissues for the use of antibiotic drugs in pregnant patients are the fetus and/or the placenta, the drug should be administered in a higher-than-standard dose than that used to treat infections in non-pregnant patients. Considering that there is a maximum absorbable dose following oral administration, intravenous administration should be considered to prevent failure of antibiotic treatment. A higher dose of amoxicillin should be considered in obese mothers. Further studies are required to assess the potential impacts of other factors on amoxicillin levels in pregnant women.

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REFERENCES

1 Andrew MA, Easterling TR, Carr DB, Shen D, Buchanan ML, Rutherford T *et al.* (2007) Amoxicillin pharmacokinetics in pregnant women: modeling and simulations of dosage strategies. Clin Pharmacol Ther. **81**(4): 547–56.
2 Arancibia A, Guttmann J, González G, González C (1980) Absorption and disposition kinetics of amoxicillin in normal human subjects. Antimicrob Agents Chemother. **17**(2): 199–202.
3 Arancibia A, Icarte A, Gonzalez C, Morasso I (1988) Dose-dependent bioavailability of amoxicillin. Int J Clin Pharmacol Ther Toxicol. **26**(6): 300–3.
4 Brusse-Keizer M, VanderValk P, van der Zanden RW, Nijdam L, van der Palen J, Hendrix R, Movig K. (2015) Amoxicillin concentrations in relation to beta-lactamase activity in sputum during exacerbations of chronic obstructive pulmonary disease. Int J Chron Obstruct Pulmon Dis. **10**: 455–61.
5 Canafax DM, Yuan Z, Chonmaitree T, Deka K, Russlie HQ, Giebink GS. (1998) Amoxicillin middle ear fluid penetration and pharmacokinetics in children with acute otitis media. Pediatr Infect Dis J. **17**(2): 149–56.
6 Cheymol G (2000) Effects of obesity on pharmacokinetics implications for drug therapy. Clin Pharmacokinet. **39**(3): 215–31.
7 Daschner FD, Gier E, Lentzen H, Kaiser D, Bamberg P (1981) Penetration into the pleural fluid after bacarapicillin and amoxicillin. J Antimicrob Chemother. **7**(5): 585–8.
8 Falagas ME, Karageorgopoulos DE (2010) Adjustment of dosing of antimicrobial agents for bodyweight in adults. Lancet. **375**(9710): 248–51.
9 Haeseker M, Havenith T, Stolk L, Neef C, Bruggeman C, Verbon A (2014) Is the standard dose of amoxicillin-clavulanic acid sufficient? BMC Pharmacol Toxicol. **15**: 38.
10 Hoffler D (1974) The pharmacokinetics of amoxicillin. Adv Clin Pharmacol. **7**: 28–30.
11 Hoffman A, Danenberg HD, Katzhendler I, Shuval R, Gilhar D, Friedman M (1998) Pharmacodynamic and pharmacokinetic rationales for the development of an oral controlled-release amoxicillin dosage form J Control Release. **54**(1): 29–37.
12 Kaojarern S, Maoleekoonpairoj S, Atichartakarn V (1989) Pharmacokinetics of amikacin in hematologic malignancies. Antimicrob Agents Chemother. **33**(8): 1406–8.
13 Kundrat W (1968) Methoden zur Bestimmung von Antibiotika-Ruckstanden in tierischen Produkten. Z. Anal. Chem. 624–630.
14 Lawson DH, Henderson AK, McGeachy RR (1974) Amoxycillin: pharmacokinetic studies in normal subjects, patients with pernicious anaemia and those with renal failure. Postgrad med J. **50**(586): 500–3.
15 Lloyd D. Fisher, Gerald van Belle. Biostatistics. A Methodology for the Health Sciences. John Wiley & Sons, Inc., New York, 1993.
16 Miller EL (2002). The penicillin: a review and update (2002) J Midwifery and Women's Health. **47**(6): 426–433.
17 Muller AE, Dörr PJ, Mouton JW, De Jongh J, Oostvogel PM, Steegers EA, *et al.* (2008) The influence of labour on the pharmacokinetics of intravenously administered amoxicillin in pregnant women. Br J Clin Pharmacol. **66**(6): 866–74.
18 Paintaud G, Alvan G, Dahl ML, Grahnen A, Sjovall J, Svensson JO (1992) Nonlinearity of amoxicillin absorption kinetics in human. Eur J Clin Pharmcol. **43**(3): 283–98.
19 Pawelski S, Maj S (1987). The standards and clinical interpretation of diagnostics tests in medicine. Warsaw, PZWL, p. 35.
20 Philipson A (1977) Pharmacokinetics of ampicillin during pregnancy. J Infect Dis. **136**(3): 370–6.
21 Pires de Abreu LR, Ortiz RM, de Castro SC, Pedrazzoli J (2003) HPLC determination of amoxicillin comparative bioavailability in healthy volunteers after a single dose administration. J Pharm Pharm Sci. **6**(2): 223–30.
22 Sabto J, Carson P, Morgan T (1973) Evaluation of amoxicillin – a new semisynthetic penicillin. Med J Aust. **2**(11): 537– 41.
23 SAS/STAT® 9.3, User's Guide, Volume 1, 2, 3. SAS Institute Inc., Cary, NC, USA, 2011.
24 Sjovall J, Alvan G, Akerlund JE, Svensson JO, Paintaud g, Nord CE *et al.* (1992) Dose-dependent absorption of amoxicillin in patients with an ileostomy. Eur J Clin Pharmacol. **43**(3): 277–81.
25 SmithKline Beecham Pharmaceuticals (2003) Amoxil. Product information.
26 Strausbaugh LJ, Girgis NI, Mikhail IA, Edman DC, Miner WF, Yassin MW (1978) Penetration of amoxicillin into cerebrospinal fluid. Antimicrob Agents Chemoter. **14**(6): 899–902.
27 Suarez-Kurtz G, Ribeiro FM, Vicente FL, Struchiner CJ (2001) Development and validation of limited-sampling strategies for predicting amoxicillin pharmacokinetic and pharmacodynamic parameters. Antimicrob Agents Chemother. **45**(11): 3029–36.
28 Sutherland R, Croydon EA, Rolinson GN (1972) Amoxycillin: a new semi-synthetic penicillin. Br Med J. **3**(5817): 13–6.
29 Szałek E, Tomczak H, Seremak-Mrozikiewicz A, Bartkowiak-Wieczorek J, Grześkowiak E (2012). Optimization of antibiotic therapy in pregnancy--clinical implications. Gin Pol. **83**: 462–68.
30 Welling PG, Huang H, Koch PA, Craig WA, Madsen PO (1977) Bioavailability of ampicillin and amoxicillin in fasted and nonfasted subjects. J Pharm Sci. **66**(4): 549–52.
31 Wurtz R, Itokazu G, Rodvold K (1997) Antimicrobial dosing in obese patients. Clin Infect Dis. **25**(1): 112–8.
32 Zareba-Szczudlik J, Romejko-Wolniewicz E, Lewandowski Z, Rozanska H, Malinowska-Polubiec A *et al.* (2016) Evaluation of the amoxicillin concentrations in amniotic fluid, placenta, umbilical cord blood and maternal serum two hours after intravenous administration. Neuro Endocrinol Lett. **37**(5): 403–409.
33 Zaręba-Szczudlik J, Romejko-Wolniewicz E, Lewandowski Z, Różańska H, Czajkowski K (2015) Concentration of amoxicillin in maternal serum, cord blood, amniotic fluid and the placenta after vaginal administration.J Matern Fetal Neonatal Med. **28**(17): 2048–52.
34 Zarowny D, Ogilve R, Tamblyn D, Macleod C, Ruedy J (1974) Pharmacokinetics of amoxicillin. Clin Pharmacol Ther. **16**(6): 1045–51.