Population pharmacokinetics of antibiotics to prevent group B streptococcal disease: from mother to neonate

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Chapter 7

Pharmacokinetics of amoxicillin in maternal, umbilical cord and neonatal serum.

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Abstract

The pharmacokinetics of amoxicillin was studied in umbilical cord and neonatal serum relative to maternal concentrations in prevention of neonatal Group B Streptococcus infection. Subjects were 44 pregnant women receiving amoxicillin as 1 or 2 gram intravenous infusion. To measure concentrations, blood samples were obtained from the mother, arterial and venous umbilical cord and neonate. The pharmacokinetics were characterized by a 5-compartment model using nonlinear mixed-effects (population) modeling. The population estimates for the clearance, central volume of distribution and the 2 peripheral maternal volumes of distribution 19.7 +/-0.99 L/h, 6.40+/-0.61 L, and 5.88+/-0.83 L, (mean +/- standard error), respectively. The volume of distribution of the venous umbilical cord and the neonatal volume of distribution were 3.40 L and 11.9 L. The pharmacokinetic parameter estimates were used to simulate concentration-time profiles in maternal, venous umbilical cord and neonatal serum. The peak-concentration in venous umbilical cord serum was 18% of the maternal peak-concentration. It was reached 3.3 minutes after the maternal peak-concentration. The concentration-time profile in neonatal serum is determined by the profile in venous umbilical cord serum, which in turn depends on the profile in maternal serum. Furthermore, the simulated concentrations in maternal, venous umbilical cord and neonatal serum exceeded the minimal inhibitory concentration for group B streptococcus for more than 90% of the 4 hour dosing interval. In first approximation, the 2 gram infusion to the mother appears to be adequate in the prevention of group B streptococcal disease. However, to investigate the efficacy of the prophylaxis, further studies on the inter-individual variability in pharmacokinetics are indicated.

Introduction

Amoxicillin, a penicillin derivative, is an antibiotic used in the prevention of neonatal group B streptococcal (GBS) disease. Neonates from mothers colonized with GBS are at risk for vertical transmission, because they might be exposed to GBS in utero or in the vagina during delivery. While protection of the fetus is the actual objective of the prophylaxis, the procedure in GBS prophylaxis is to administer the antibiotics to the pregnant woman. Since antibiotics reach the fetus only after transport over the placenta via the umbilical cord, adequate concentrations in maternal serum are a prerequisite, but no guarantee, for adequate venous and arterial umbilical cord and fetal serum concentrations. While there are some data on ampicillin concentrations in umbilical cord blood[1,2], data for amoxicillin are not available. The pharmacokinetics of amoxicillin in pregnant women before labor have been described previously and have been shown to exceed the MIC for an adequate percentage of the dosing interval for treatment of the infection in the mother[3]. To assess whether the administration of amoxicillin also protects the fetus from GBS infection, data on the pharmacokinetics in umbilical cord serum or fetal serum are necessary.

Studying the pharmacokinetics in fetal or umbilical cord serum faces ethical and practical difficulties. Because blood sampling of the fetus during delivery is not possible, blood samples of the umbilical cord taken after birth is in most instances the only direct information on fetal concentrations that can be obtained. Unfortunately, these samples can be obtained only at a single point in time for each individual. Alternatively, blood samples of the neonate taken by heel puncture shortly after birth can be considered as a good approximation of the fetal concentration. However, such samples are difficult to obtain because of the poor blood supply to the extremities directly after birth. When neonatal blood samples are taken hours later, these concentrations might not truly reflect the fetal concentrations, because of the differences in the rates and routes of elimination before and after birth.

By necessity the time intervals between the last antibiotic dose and birth will be different for each individual. Therefore presenting either individual or average concentrations in the umbilical cord samples at birth will be of little value. To obtain useful information the pharmacokinetics (i.e. the concentration versus time profile) in the umbilical cord serum should be known. For this purpose population pharmacokinetic modeling is useful, because in this approach all data of the entire study population (i.e. all mothers and fetuses) are taken into account. An important feature of population pharmacokinetic modeling is that it enables the analysis of data from studies with unbalanced designs (e.g. unequal groups) and of incomplete datasets[4,5]. Specifically, Non-Linear Mixed Effects ('population') modeling can be used to connect the sparse data on umbilical cord and neonatal blood concentrations

to the more detailed information on the pharmacokinetics in the mother. A more detailed background of population modeling can be found elsewhere[6,7]. Recently a population pharmacokinetic model of amoxicillin in pregnant women has been proposed[3]. The objective of this study is to describe the concentration-time profile of amoxicillin in umbilical cord and neonatal serum, in relation with the concentration-time profile in maternal serum.

Methods

Patients

In the period between February 7, 2005 and February 28, 2007, all women who needed antibiotic treatment with amoxicillin or amoxicillin/clavulanic acid (Augmentin® or co-amoxiclav) shortly before or during labor were eligible for this study. To take full advantage of all data available to us for the development of a population pharmacokinetic model of amoxicillin in pregnant women, umbilical cord and neonate, the present study includes part of a dataset of a recently published study[3]. 416 blood samples from pregnant women with preterm premature rupture of the membranes were used in a previous study. None of the samples of the umbilical cord or the neonate were previously used. Following local guidelines, women were treated with amoxicillin in the prevention of GBS disease, when no signs of infection were present, but with proven or unknown *Streptococcus agalactiae* carriage, in the presence of generally recognized risk factors for neonatal GBS disease[8]. In case of suspected intra-amniotic infection, women were treated with co-amoxiclav. When signs of infection were present delivery was induced. The study was approved by the Medical Ethics Committee. Written informed consent was obtained from all patients. Women were excluded from the study when i) they had been treated with oral or intramuscular antibiotics within 2 days before starting therapy, ii) were unwilling to comply with the requirements of the study, iii) were known to be allergic to amoxicillin or other penicillins, or iv) were receiving co-medication that exhibits interaction with amoxicillin. All patients were at least 18 years of age.

All patients received a standard work-up which included a medical history, biochemical and hematological examination. Furthermore blood pressure, pulse, oral temperature, and body weight were recorded. The amount of edema was scored semiquantitatively from 0 (no edema) to 3 (above the knee). The weight of the placenta with umbilical cord was measured. From the neonate birth weight and the Apgar-scores after 1, 5 and 10 minutes were recorded.

Drug administration and blood sampling

Before the administration of amoxicillin or co-amoxiclav an intravenous catheter was placed in each arm. Antibiotics were administered following local guidelines.

Treatment with amoxicillin started with an intravenous infusion of 2 gram amoxicillin (50 mg/mL) administered over 30 minutes, followed by a second infusion after 4 hours of 1 gram amoxicillin (50 mg/mL) over 15 minutes. Treatment with co-amoxiclav (consisting of 1 gram amoxicillin (50 mg/mL) with 200mg clavulanic acid) consisted of an infusion for 15 minutes every 8 hours. Blood samples of 2 mL were collected from the second catheter in the contralateral arm at timed intervals beginning at 1 min after the start of the infusion and, at 7 and 15 min (1 gram infusion) or 15 and 30 min (2 gram infusion) during the first two amoxicillin administrations. After the infusion sampling was scheduled at 3, 6, 10, 16 and 36 minutes, and afterwards every 30 minutes until the next antibiotic dosage. Exact sampling times were recorded.

After cord clamping the umbilical cord was cleaned with normal saline and a sponge to prevent contamination of maternal blood in the umbilical cord samples. Both arterial and venous cord samples of 5-10 mL were taken. From the neonate a blood sample of approximately 0.5 mL was obtained by heel puncture after signed informed consent from both parents. These blood samples were taken at least 10 minutes after birth depending on the physical condition of the neonate.

All blood samples were placed immediately on ice, allowed to clot and processed within one hour after collection. The samples were centrifuged at 1200 g for approximately 10 minutes. The supernatants were transferred into plastic storage tubes and frozen at –70° C until analysis.

High-performance liquid chromatography

Amoxicillin concentrations were determined by an isocratic high-pressure liquid chromatography (HPLC) (Shimadzu, Den Bosch, The Netherlands (NL)) method, using an ODS Gemini column (Bester, Amstelveen,NL) with 0.066 M KH_2PO_4 solution containing 10% methanol as a mobile phase. A perchloric acid solution of 0.1 ml was added to the sample in an equal volume and after vortexing, added to 0.56 ml 0.028 M citric acid containing cefadroxil (Sigma, Zwijndrecht,NL) as an internal standard. The assay was linear over the concentration range measured. Controls were included in every run. The lower limit of detection and the lower limit of quantification were 0.2 mg/L and the between run CV < 4%.

Pharmacokinetic analysis

Pharmacokinetic parameters were estimated by means of Non-Linear Mixed Effect (population) Modeling (NONMEM). The model was implemented in the NONMEM ADVAN5 subroutine and the analysis was performed using the FOCE method with INTERACTION. All fitting procedures were performed with the use of the Compaq Visual FORTRAN standard edition 6.6 (Compaq Computer Cooperation, Euston, Texas, USA) and NONMEM® software package (version VI, release 1.2, ICON Development Solutions, Ellicott City, Maryland, USA).

To determine the basic structural pharmacokinetic parameters various 3-, 4- and 5- compartment models were tested. The previously described 3 compartment pharmacokinetic population model in pregnant women with PPROM, was used to describe the time course of amoxicillin in maternal blood[3]. Model selection and identification of variability was based on the likelihood ratio test, pharmacokinetic parameter point estimates, and their respective confidence intervals, and goodness-of-fit plots. For the likelihood ratio test on differences between two models, the objective function value (OFV) with a pre-specified level of significance of $P<0.001$ was used. NONMEM minimizes an objective function in performing nonlinear regression analysis. To detect systematic deviations in the model fits the goodness-of-fit plots were visually inspected. The data of individual observations versus individual or population predictions should be randomly distributed around the line of identity. The weighted residuals versus time or population predictions should be randomly distributed around zero. Population values were estimated for the parameters clearance (CL), the volumes of distribution (V) and the intercompartmental clearances (Q).

Individual estimates for pharmacokinetic parameters were assumed to follow a log normal distribution. Therefore an exponential distribution model was used to account for inter-individual variability. The correlations between the various random parameters for inter-individual variability were tested using the forward addition and backward deletion method in the NONMEM Omega block option.

Selection of an appropriate residual error model was based on the likelihood ratio test and inspection of the goodness-of-fit plots. The residual variability between the observed concentrations and those predicted by the model was described using a proportional error model. The residual error term contains all the error terms which cannot be explained and refers to, for example, measurement and experimental error and structural model misspecification.

To refine the model covariate analysis was also performed. The estimated pharmacokinetic parameters were plotted independently against the covariates bodyweight, body mass index, duration of amenorrhea, blood pressure, pulse, oral temperature, and the amount of edema to determine whether this influenced the pharmacokinetics. Covariate analysis was performed by forward addition of each candidate covariate into the model structure until no further improvement of the goodness of fit was observed. A further criterion for acceptance of covariate effects was that the estimated confidence interval of the covariate effect did not overlap zero. Contribution of each covariate to the final model was confirmed by backward elimination of each covariate from the model to account for possible interaction between covariates. The residual intra- and inter-individual variability were visually evaluated.

The accuracy of the final population model for the entire population was established using the bootstrap option in NONMEM, consisting of repeated random

sampling with replacement from the original data. This resampling was repeated 100 times. The estimated parameters from the bootstrap analysis were compared to the estimates from the original data.

Simulations

Simulations were performed to determine the relation in time between the maternal, umbilical cord and neonatal serum concentration-time profiles. The simulations were performed using Berkeley Madonna (version 8.3.5, Berkeley Madonna Inc, University of California, USA). The mean population parameter values of the pharmacokinetic model derived with NONMEM in the first part of the analysis were used in the simulations.

Results

From 44 pregnant patients 53 umbilical cord blood samples were obtained, consisting of 25 arterial and 28 venous samples. Of 23 women both arterial and venous samples were obtained. Four umbilical cord samples of one twin pregnancy were collected. A total of 904 maternal serum samples were collected. Due to the unpredictable and variable duration of labor and to the varying emotional condition of the patient, the number of maternal samples obtained from each patient is variable (range 3-41 samples per patient). The time interval between the last antibiotic dose and birth varied from 24.4 min to 316.8 min. The patients gave birth at gestational ages from 30.0 to 42.4 weeks. Birth weight of the neonates ranged from 1340 gram to 4470 gram. Fourteen blood samples were taken from the neonates between 14.2 min to 199.8 min after birth. The characteristics of the study patients and their neonates are presented in table I.

The concentrations in cord serum range from 1.0-16.8 mg/L in arterial and 1.1-18.0 mg/L in venous umbilical cord serum. The ratio of the arterial and venous umbilical cord serum concentrations is shown in figure 1. The ratio was <1 when the umbilical cord was clamped shortly after the administration of the last antibiotic dose and slightly higher with an increasing interval between the last antibiotic administration and umbilical cord clamping. The differences between the arterial and venous umbilical cord serum concentrations were too small to analyze these concentrations using two separate compartments. Since arterial cord blood originate directly from the fetal circulation, the arterial cord blood concentrations can be considered as fetal blood concentration. Venous cord blood concentrations reach the umbilical cord after passage of the placenta. Therefore these concentrations were analyzed separately.

In population modeling data of concentrations in maternal, arterial and venous umbilical cord, and neonatal serum were analyzed simultaneously. Of all

Maternal patient characteristics	units	mean	SD	Number of patients
Maternal age	y	30.0	6.85	44
Maternal weight	kg	79.4	13.9	43
Body Mass Index	kg/m^2	29.4	5.3	43
Edema (no/around the ankle/up to knee)	-	-	-	29/12/3
Leucocytes	x 10^9/L	12.8	5.14	44
Creatinin	µmol/L	47.4	11.5	44
Amenorrea	weeks	36 6/7	2.7	44
Nulliparity	-	-	-	22
Twin pregnancy	-	-	-	3
Mode of delivery (vaginal/vacuum extraction/ emergency caesarean section)	-	-	-	23/1/3*
Placental weight	gram	546.5	165.0	40
Birth weight neonate	gram	2887.4	627.9	46
Apgar score 1 min	-	8.7	1.05	41
Apgar score 5 min	-	9.6	0.84	41
Apgar score 10 min	-	9.8	0.59	40

* Only patients from whom umbilical cord serum was obtained.

***Table I**: characteristics of the study patients, placental weight and their neonates*

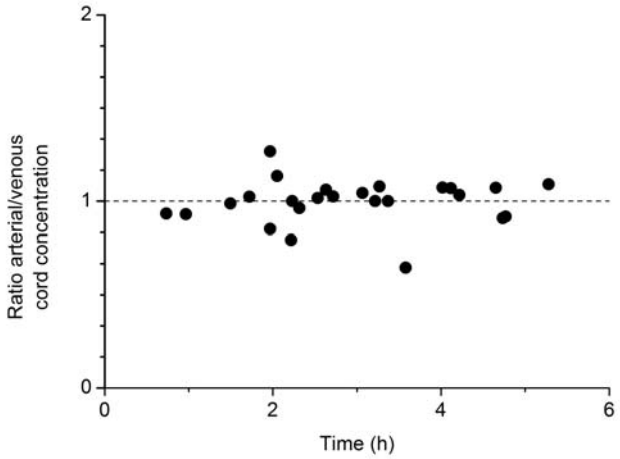

***Figure 1**: ratio of arterial and venous umbilical cord serum concentrations as function of the time.*
The ratio of the arterial and venous umbilical cord serum concentrations was plotted versus the time interval between the last antibiotic administration to the mother and child birth.

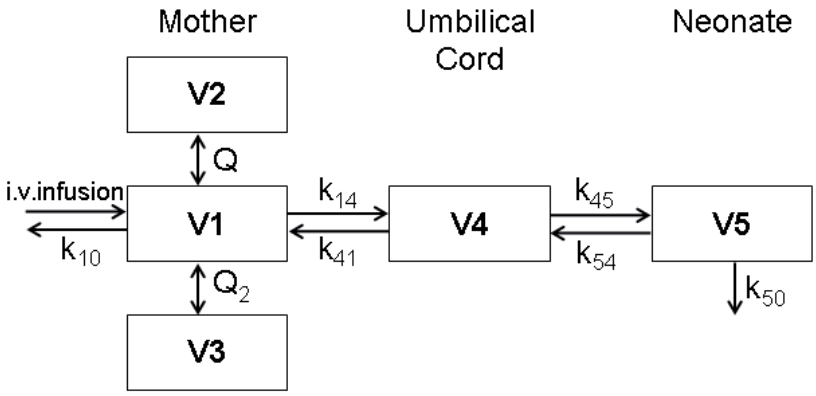

***Figure 2:** 5-compartment model*
Structure of the final 5-comparment model consisting of a central volume of distribution of the mother (V_1), peripheral volumes of distribution of the mother (V_2 and V_3), a volume of distribution of the umbilical cord (V_4) and a volume of distribution of the neonate (V_5). The k-values represent the intercompartmental exchange rate constants.

models tested a multicompartment pharmacokinetic model with three compartments for the mother, 1 compartment for the venous umbilical cord, and 1 compartment for the neonate best described the data (figure 2). The peripheral compartments 2, 3 and 4 were connected to the central compartment. Compartment 5 is attached to compartment 4 and antibiotics in compartment 5 are transferred back to compartment 4, and eliminated from the system. During the analysis the values of the volumes of distribution V_2 and V_3 of compartment 2 and 3 were comparable (difference in the final model with separate estimates for V_2 and V_3 <0.5 L). The %CV of these estimates exceeded 51% and therefore for the final analysis V_3 was assumed to be equal to V_2. The inter-individual variability was mainly due to differences in clearance, V_1 and the residual error. A correlation between the random parameters for inter-individual variability was found and accounted for in the model. The residual error was found to be proportional to the blood concentrations.

The demographic and clinical characteristics of the patients were examined as potential covariates on the parameters CL, V_1, K_{45} and the residual error. According to the specified OFV change criterion, gestational age (ΔOFV = - 10.5) and body mass index (ΔOFV = - 8.5) both influenced the volume of distribution. Although a correlation was noted between gestational age and body mass index, incorporation of these two covariates on the volume of distribution did not result in a significant decrease in OFV (ΔOFV = - 3.3). Because the decrease in OFV was larger after incorporation of gestational age then after incorporation of body

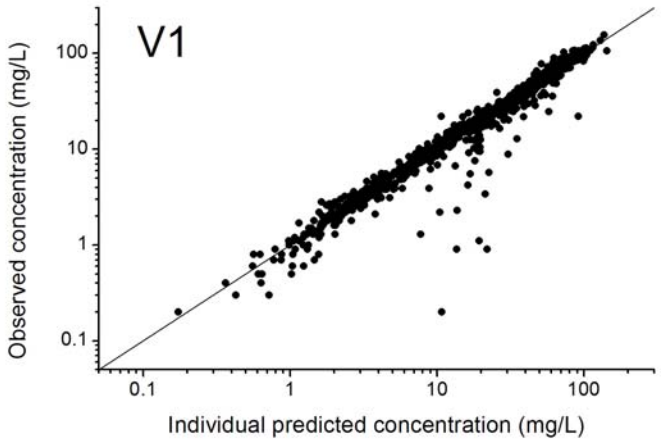

Figure 3: *Individual predicted vs observed concentrations of amoxicillin for the central compartment of the mother (V_1), the umbilical cord (V_4) and neonatal compartment (V_5).*

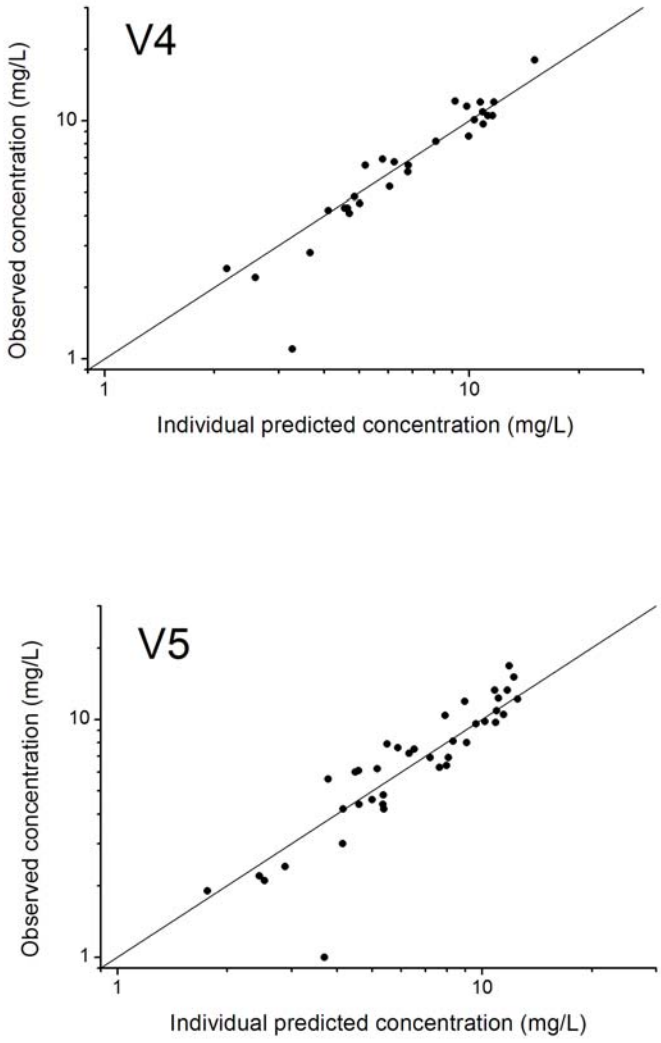

Figure 3: *Individual predicted vs observed concentrations of amoxicillin for the central compartment of the mother (V_1), the umbilical cord (V_4) and neonatal compartment (V_5). Scatter plots of the individual predicted vs observed concentrations of amoxicillin for 44 patients (V_1), 53 measures of the umbilical cord (V_4) and 14 neonatal measures (V_5). The figures show the individual data points and the line of identity (x=y).*

Parameter	Units	Mean	SE	95% confidence interval
Structural model parameters				
CL	L/h	19.7	0.99	17.8 – 21.6
V_1	L	6.4	0.61	5.2 – 7.6
V_2	L	5.88	0.83	4.2 - 7.5
V_3	L	5.88	0.83	4.2 – 7.5
Q_1	L/h	56.6	9.5	38.0 – 75.2
Q_2	L/h	10.7	2.2	6.3 – 15.1
K_{14}		0.76	0.28	0.21 – 1.3
K_{41}		1.4	0.31	0.83 – 2.1
K_{45}		5.1	2.0	1.1 – 9.1
K_{54}		1.4	0.31	0.83 – 2.1
K_{50}		0.16	0.033	0.098 – 0.23
Variance model parameters				
Interindividual variability in CL		0.076	0.026	0.026 – 0.13
Interindividual variability in V_1		0.038	0.013	0.014 – 0.063
Residual variability		0.030	0.0040	0.022 – 0.037

***Table 2**: Population model parameter values.*
CL: clearance, V_1: volume of distribution of the central compartment, V_2: volume of distribution of the first peripheral compartment, V_3: volume of distribution of the second peripheral compartment, Q_1: intercompartmental clearance between V_1 and V_2, Q_2: intercompartmental clearance between V_1 and V_3, SE: Standard error

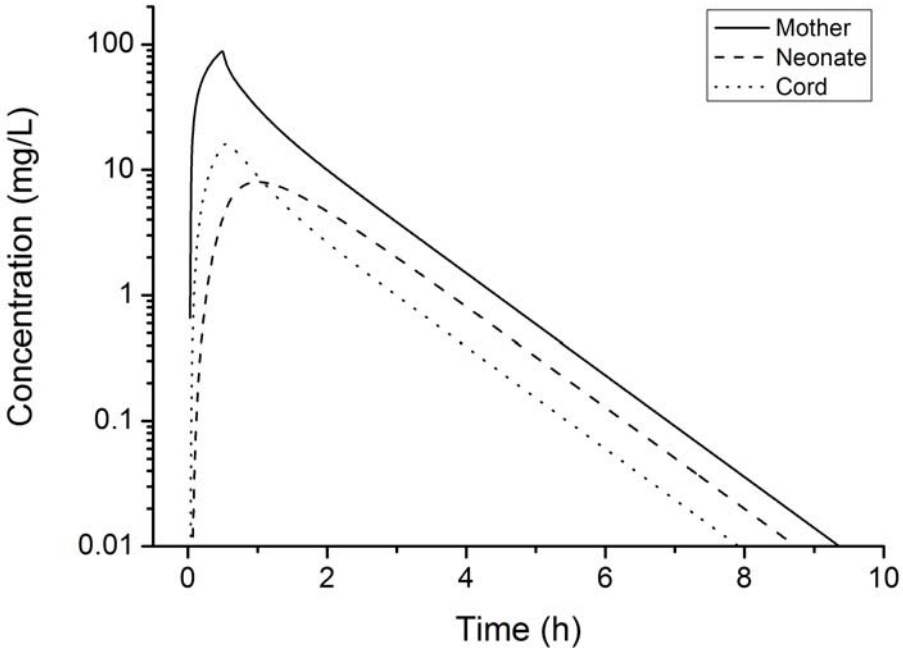

Figure 4: *Simulated concentration-time profiles for the mother, umbilical cord and neonate.*
Concentration-time profile of amoxicillin in maternal, umbilical cord and neonatal serum simulated after a single dose of 2 gram amoxicillin infused over 30 minutes. The simulations were performed with PK parameter estimates based on the final 5-compartment model and carried out for 12 hours after a single antibiotic dose. (See color inlay for a full color version of this figure.)

mass index, only gestational age was incorporated in the final model. The effect of other potential covariates was also assessed. This resulted in maximum decreases of OFV of –0.5 for body weight, -0.3 for the blood pressure, and -0.2 for pulse. All model with the temperature incorporated resulted in running-errors. The following equation represents the covariate model in the final model including the gestational age as covariate for the volume of distribution.

$$V_1 = \theta_2 \cdot (1 + \theta_{12} \cdot (GA - 36.8)) \cdot \exp(\eta_2)$$

In which V_1 is the volume of distribution of the central compartment, θ_2 is the estimate for V_1, θ_{12} is the estimate for the effect of gestational age and GA is the gestational age centered by its median value in the study population (36.8 weeks).

η_2 estimates the inter-individual variability on V_1. An increase in V_1 of 4.2% per week was found and incorporated into the model. The scatter plots of the observed concentrations versus model-predicted concentrations were randomly distributed, illustrating the unbiased model fit for maternal, umbilical cord and neonatal serum concentrations (figure 3). Table 2 shows the estimated values for the pharmacokinetic parameters of the final model. The volumes of distribution of the venous umbilical cord and the neonate were calculated (3.4 L for the umbilical cord and 11.9 L for the neonate).

The bootstrap validation of the model of the entire population was performed with 100 runs. The bootstrap validation was successful for 91 runs. The mean parameter estimates of the runs obtained from the bootstrap analysis deviated 1 to 36% from the predicted values from the NONMEM PK analysis, indicating that the accuracy of the final model is good.

The parameter estimates obtained by the population modeling analysis were used to simulate concentration-time profiles of amoxicillin in maternal, venous umbilical cord and neonatal serum after a single dose of 2 gram amoxicillin. Figure 4 shows the obtained concentration-time profiles for the initial dose of 2 g amoxicillin infused to the mother over 30 minutes. Maternal peak concentration was reached at the end of the antibiotic infusion at 30 minutes (88.7 mg/L). Peak concentration in venous umbilical cord serum was lower and delayed compared to the maternal peak concentration. Peak concentration in venous umbilical cord serum was 16.0 mg/L (18% of the maternal peak concentration) and was reached 3.3 minutes after the maternal peak concentration.

The sparse neonatal concentrations were analyzed simultaneously with the maternal and umbilical cord serum concentrations. The restricted blood supply to the extremities directly after birth and the need of an informed consent of both parents, were the main reasons for the limited number of samples from the neonates. Peak-concentration after the 2 gram infusion to the mother in neonatal serum was 8.0 mg/L (compared to 16.0 mg/L in venous umbilical cord serum). Similar concentrations were reached 1.1 h after the start of the infusion and afterwards the neonatal serum concentrations exceeded venous umbilical cord serum concentrations.

An intrapartum dose of 2 gram amoxicillin is commonly used to prevent neonatal GBS disease by achieving bactericidal concentrations in the fetus for a sufficient amount of time. According to the clinical breakpoints as determined by the EUCAST, for GBS, concentrations of at least 0.25 mg/L should be reached 9. The simulations show that the concentration of amoxicillin after a single 2 gram dose in the maternal, the venous umbilical cord and the neonatal serum, exceeds the minimally inhibitory concentration for more than 90% of the dosing interval.

Discussion

This collection of data from the mother, umbilical cord and neonate, was a unique opportunity to develop a 5-compartment model to describe the overall concentration versus time profile in maternal plasma, umbilical cord and neonatal plasma. Peak- concentrations in umbilical cord and neonatal serum were lower and delayed compared to the maternal peak-concentration. Approximately 1 hour after the start of the antibiotic administration the neonatal concentration reached its highest level, and thereafter exceeded the concentrations in venous umbilical cord. In a first approximation, simulation of a 2 gram infusion on basis of the developed pharmacokinetic model demonstrated that amoxicillin concentrations in maternal, venous umbilical cord and neonatal serum exceeded the minimal inhibitory concentration for >90% of the dosing interval.

Studies on the pharmacokinetics in umbilical cord serum are scarce. For ampicillin, an antibiotic closely related to amoxicillin, two studies have been performed in women during elective caesarean section[1,2]. Due to differences in study design direct comparison to our study is not possible. Because physical changes during labor might influence the transplacental blood flow, the transfer of amoxicillin across the placental barrier might be different during vaginal delivery. Furthermore, data in both studies were not analyzed using a population pharmacokinetic approach. Nevertheless, results of both studies are in line with our results. The ampicillin concentrations in cord serum exceeded the MIC for GBS during the study periods of 7-71 minutes[1] and 32- 343 minutes[2] after the start of the antibiotic infusion. Colombo et al.[2] focused on the ratio of the concentration in cord serum and maternal serum. They reported that initial cord serum concentrations were lower than maternal concentrations, but after approximately 80 minutes the concentrations in umbilical cord serum exceeded the maternal serum concentrations. In our study the venous cord concentrations did not exceed the maternal concentrations.

Both patients receiving amoxicillin and co-amoxiclav were included in the study. In the literature it has been described that the addition of clavulanic acid does not influence the pharmacokinetics of amoxicillin after intravenous administration[10-12]. Our data confirmed this finding (unpublished observations). Therefore, the pharmacokinetics of amoxicillin in these patients was assumed to be similar and all patients were analyzed simultaneously.

In the final analysis, the arterial umbilical cord and neonatal concentrations were considered similar. Several differences exist between these concentrations. Before clamping the umbilical cord antibiotics are eliminated from the fetus by transplacental transport to the mother and by fetal renal excretion. After cord clamping elimination of amoxicillin from the neonate takes place only by neonatal renal excretion. Because elimination from the neonate to the mother was included

in the model, the model predicted neonatal concentrations might be lower compared to the observed concentrations. Furthermore, many physiological changes occur immediately after birth in the neonate. These changes might influence the PK in the neonate. However, since all concentrations taken from the neonate and the arterial umbilical cord are distributed randomly around the line of identity, these differences do not seem to have a major influence on the PK within the first hours after birth

Blood samples in venous umbilical cord serum are sometimes used as a representative for concentrations in fetal serum. In the simulated concentration-time profiles the neonatal serum concentration is slightly higher than the concentrations in venous umbilical cord. This might be explained by a change in elimination route after birth. Before umbilical cord clamping the amoxicillin was eliminated both by the mother and fetus. After birth the amoxicillin is eliminated only by the neonate. Together with the decreased glomerular filtration rate in neonates, this results in a slower elimination rate and higher serum concentrations. This indicates that venous umbilical cord amoxicillin concentrations will not overestimate the concentrations in fetal serum.

In our study the simulated concentration-time profiles in maternal, venous umbilical cord and neonatal serum are used to describe the PK in relation to each other. In a first approximation, an amoxicillin infusion of 2 gram seems to be adequate to prevent neonatal GBS disease in the average patient. But to evaluate the efficacy of the dosing regimen as recommended by the CDC[8] for all pregnant women and to investigate possible improvement of the dosing regimen, further studies are needed. Such studies should take into account the inter-individual variability, correlation between the PK parameter estimates and knowledge of the concentration-effect relationship.

Acknowledgments

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References

1. Bloom SL, Cox SM, Bawdon RE, Gilstrap LC. Ampicillin for neonatal group B streptococcal prophylaxis: how rapidly can bactericidal concentrations be achieved? Am J Obstet Gynecol 1996;175:974-6.

2. Colombo DF, Lew JL, Pedersen CA, Johnson JR, Fan-Havard P. Optimal timing of ampicillin administration to pregnant women for establishing bactericidal levels in the prophylaxis of Group B Streptococcus. Am J Obstet Gynecol 2006;194:466-70.

3. Muller AE, DeJongh J, Oostvogel PM, Voskuyl RA, Dorr PJ, Danhof M, Mouton JW. Amoxicillin pharmacokinetics in pregnant women with preterm premature rupture of the membranes. Am J Obstet Gynecol 2008;198:108 e1-6.

4. Liefaard LC, Ploeger BA, Molthoff CF, Boellaard R, Lammertsma AA, Danhof M, Voskuyl RA. Population pharmacokinetic analysis for simultaneous determination of B (max) and K (D) in vivo by positron emission tomography. Mol Imaging Biol 2005;7:411-21.

5. Schoemaker RC, Cohen AF. Estimating impossible curves using NONMEM. Br J Clin Pharmacol 1996;42:283-90.

6. Sheiner BL, Beal SL. Evaluation of methods for estimating population pharmacokinetic parameters. II. Biexponential model and experimental pharmacokinetic data. J Pharmacokinet Biopharm 1981;9:635-51.

7. Bonate PL. Recommended reading in population pharmacokinetic pharmacodynamics. Aaps J 2005;7:E363-73.

8. Schrag S, Gorwitz R, Fultz-Butts K, Schuchat A. Prevention of perinatal group B streptococcal disease. Revised guidelines from CDC. MMWR Recomm Rep 2002;51:1-22.

9. Eucast. (European Committee on Antimicrobial Susceptibility Testing) Clinical breakpoints and epidemiological cut-off values: clinical breakpoints. see website http://217.70.33.99/Eucast2/. Last accessed 23-03-2008.

10. Reed MD. Clinical pharmacokinetics of amoxicillin and clavulanate. Pediatr Infect Dis J 1996;15:949-54.

11. Adam D, de Visser I, Koeppe P. Pharmacokinetics of amoxicillin and clavulanic acid administered alone and in combination. Antimicrob Agents Chemother 1982;22:353-7.

12. Weber DJ, Tolkoff-Rubin NE, Rubin RH. Amoxicillin and potassium clavulanate: an antibiotic combination. Mechanism of action, pharmacokinetics, antimicrobial spectrum, clinical efficacy and adverse effects. Pharmacotherapy 1984;4:122-36.