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

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Chapter 8

Evaluation of dosing regimen on amoxicillin exposure in pregnant women with preterm premature rupture of the membranes using Monte Carlo Simulation.

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Abstract

Objective: To determine whether the probability of target attainment differs significantly between commonly used amoxicillin dosing regimens and whether inaccuracies in antibiotic administration influence the probability of target attainment.

Study Design: Population pharmacokinetic parameter estimates and their inter-individual variability in patients with premature rupture of the membranes were obtained from a previous investigation. Monte Carlo Simulations were then used to determine the influence of differences in the dosing of amoxicillin on the percentage of time that serum concentrations of the unbound drug remained above the Minimum Inhibitory Concentration (%*f*T>MIC).

Results: When administering 1 gram as a bolus injection, %*f*T>MIC was approximately 4% lower than after infusion over 15 minutes. Simulating the administration of 1 gram amoxicillin bolus injections every 6 hours, the %*f*T>MIC at steady state for the average population is 92%, for a value of 0.25 mg/L as MIC of group B streptococcus (GBS). When the lower 99% confidence interval (CI) was taken into account, this percentage decreased to 46%. After decreasing the dosing interval to 4 hours, the %*f*T>MIC for the average population and the lower 99% CI were 99% and 70%, respectively.

Conclusion: Minor differences in the probability of achieving effective concentrations were detected between the different dosing regimens of amoxicillin. A dosing schedule of 1 gram bolus injections every 6 hours is adequate to prevent GBS infections and minor inaccuracies in the administration are not influencing its predicted efficacy. An initial dose of 2 gram is has no added value.

Introduction

During labor, especially after rupture of the membranes, pregnant women and their fetuses are at risk for ascending infections from the vagina. An important part of these infections is caused by group B streptococcus (GBS, *Streptococcus agalactiae*). Up to 35% of pregnant women are colonized with GBS in the rectovaginal tract[1,2]. To protect neonates of these mothers from infection, prevention strategies have been implemented[3,4]. Antibiotics are used in the management of pregnant patients to eliminate GBS from the site of infection. Proper dosing of antibiotics is essential to prevent both mother and fetus from infection.

Although several dosing regimen recommendations exist and are currently used, the rationale behind these regimens is not always clear. Specifically, limited information on the pharmacokinetics of antibiotics in pregnancy in general and in the peripartal period in particular, is available. In addition, at the time these regimens were designed less information was available with respect to the pharmacokinetic/pharmacodynamic properties of the drugs used. This may lead, or may have lead, to therapeutic failure. Cases of neonatal GBS infection after maternal antibiotic therapy have been described[5,6]. In the literature different dosing regimens for the prevention of GBS infection are recommended. Guidelines to prevent neonatal GBS disease issued by the Centers for Disease Control and Prevention (CDC) recommend the use of an initial dose of 2 gram ampicillin and subsequent doses of 1 gram every 4 hours[4]. The Cochrane Library on the other hand describes a dosing regimen of ampicillin 1 gram intravenously every 6 hours as the usual regimen[7]. Because the consequences of changes in antibiotic dosing are unknown, it is not possible to study different regimens in pregnant women. Computer-simulations using data of the prescribed regimens are an accepted alternative, particularly when detailed information on the pharmacokinetics and the inherent inter-individual variation is available.

Monte Carlo Simulation (MCS) is used to evaluate the probability of achieving therapeutic concentrations of different dosing schedules. MCS is performed using pharmacokinetic parameters, data on the concentration-effect relationship and on the inter-individual variability[8-13]. The relationship between pharmacokinetic properties, the susceptibility of the microorganism (as reflected in the Minimum Inhibitory Concentration, MIC) and clinical effects is increasingly well understood. Specifically, the efficacy of the penicillins such as ampicillin and amoxicillin, has been shown to be primarily correlated to the percentage of time that serum concentrations of the unbound drug remain above the MIC (%*f*T>MIC)[14-16]. In general, the therapeutic goal to cure infections caused by Gram-positives is a %*f*T>MIC of at least 40%, which corresponds to an in vivo static effect in animal studies. The pharmacokinetic behavior of drugs differs for each individual. The recommended dosing schedule should be adequate in preventing infections for the

entire population. Therefore, inter-individual variability is a determining factor in the prediction of the outcome of therapy in individual patients. To predict the probability of success of treatment, the %*f*T>MIC should be at least 40% for each individual within the population.

Outside the US, intravenous amoxicillin is often used in the prevention of neonatal GBS disease. Amoxicillin dosing regimens have been derived from studies using ampicillin, a beta-lactam antibiotic closely related to amoxicillin[17, 18]. Differences in dosing regimens, as well as inaccuracies in the administration of the antibiotic might influence the %*f*T>MIC and the associated efficacy in preventing GBS infections. The purpose of this study was therefore to perform MCS for amoxicillin concentrations in pregnant women to assess whether the probability of target attainment (PTA) differed significantly between the recommended dosing regimens and to examine the influence of inaccurate antibiotic administration on PTA. To this end, we used the population pharmacokinetic model for amoxicillin in pregnant women with preterm premature rupture of the membranes (PPROM) as previously described[19].

Materials and Methods

Dosing schedules

The different dosing regimens used for the MCS are shown in table 1.

Simulated dosing regimen			
	amount	**infusion**	**interval**
Single dose			
	1 gram	15 min	4 h
	1 gram	Bolus	4 h
	1 gram	Bolus	6 h
	2 gram	30 min	4 h
Steady state			
	1 gram	Bolus	4 h
	1 gram	Bolus	6 h
Inaccuracies			
	1 gram	Bolus	8 h
	1 gram	Bolus	12 h
	1 gram	30 min	4 h
	1 gram	Rate 66.7 mg/min	-

Table 1: *Simulated dosing regimens.*

Study population and pharmacokinetic modeling

The population pharmacokinetic model of the amoxicillin serum concentrations in pregnant women with PPROM has been described previously[19]. The amoxicillin was administered intravenously. The initial dose of 2 gram was infused over 30 minutes and the subsequent 1 gram doses were infused over 15 minutes. Population pharmacokinetic parameter estimates were based on a population analysis of plasma concentrations in 17 patients using NONMEM. A total of 416 blood samples was obtained and used in the modeling procedure. A 3-compartment open model best described the concentration-time curves. Inter-individual variability was very small and largely explained by variations in the parameters clearance and volume of distribution of one of the peripheral compartments. The main demographic characteristics and pharmacokinetic estimates are summarized in table 2.

	Demographic characteristics			Structural model parameters		
	mean	SD	range		mean	SE
Maternal age (y)	29.42	4.64	19.6-35.1	CL (L/h)	22.8	1.03
Gestational age (wk)	35.1	1.63	29.4-36.9	V_1 (L)	5.59	0.826
Body mass index (kg/m^2)	29.1	3.87	21.5-35	V_2 (L)	7.43	1.06
Weight (kg)	80.9	12.03	56.2-98.9	V_3 (L)	8.61	0.768
Leucocytes x10^{9}L	11.8	4.43	6-25.9	Q (L/h)	60	18.5
Creatinin µmol/L	44.4	10.11	37-74	Q_2 (L/h)	7.72	1.72

Table 2: *Main demographic characteristics and pharmacokinetic estimates of the 17 pregnant women with PPROM.*
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: intercompartmental clearance between V_1 and V_2, Q_2: intercompartmental clearance between V_1 and V_3. More details can be found in Muller et al.[19].

Monte Carlo Simulation

The estimates of the pharmacokinetic parameters and measures of dispersion were used to simulate various dosing regimens and obtain %*f*T>MIC as a function of MIC[13]. An amoxicillin protein binding of 22% was used in the simulations. MCS was performed using the MICLAB version 2.36 program (Medimatics, Maastricht, the Netherlands) simulating 10.000 subjects for each regimen. The program allows inclusion of the covariance matrix (or correlation matrix) of the parameter

estimates used in the simulations. The output consisted of a probability distribution, a cumulative probability distribution, and specific confidence intervals over user defined MIC and %*f*T>MIC ranges. MIC breakpoint of GBS for amoxicillin of 0.25 mg/L was used according to the susceptibility breakpoints determined by the European Committee on Antimicrobial Susceptibility Testing (EUCAST)[20].

Results

The values for %*f*T>0.25 mg/L for the dosing regimens obtained from the MCS are shown in table 3. After an initial bolus injection of 1 gram the %*f*T>MIC was approximately 4% lower compared to the value after a 15 minutes infusion. The use of a loading dose of 2 gram administered over 30 minutes increased the %*f*T>MIC for the population including the 99% CI with 19%, but both values remained above the targeted value of 40%.

The most frequently used dosing intervals (4 and 6 hours) were also simulated in a steady state situation. Figure 1 shows the %*f*T>MIC for these 2 dosing intervals. Simulating the administration of 1 gram amoxicillin every 6 hours as bolus injection the %*f*T>MIC in maternal serum for the average population was 92%, given the MIC of GBS. When the lower 99% CI was taken into account, this percentage decreased to 46%. For the dosing interval of 4 hours as recommended

Simulated dosing regimen				%*f*T>0.25 mg/L		
	amount	**infusion**	**interval**	**average**	**95% CI**	**99% CI**
Single dose						
	1 gram	15 min	4 h	99.3	88.1	73.2
	1 gram	Bolus	4 h	99.1	84.5	69.4
	1 gram	Bolus	6 h	91.4	56.8	47.9
	2 gram	30 min	4 h	99.9	99.6	88.8
Steady state						
	1 gram	Bolus	4 h	99.1	84.2	69.7
	1 gram	Bolus	6 h	91.5	55.7	46.3
Inaccuracies						
	1 gram	Bolus	8 h	77.8	42.2	34.9
	1 gram	Bolus	12 h	53.3	28.2	23.3
	1 gram	30 min	4 h	99.4	90.1	74.6
	1 gram	Rate 66.7 mg/min	-	-	-	-

Table 3: *Simulated dosing regimens with the %fT>0.25 mg/L. The MIC of amoxicillin for GBS was determined by the EUCAST.*

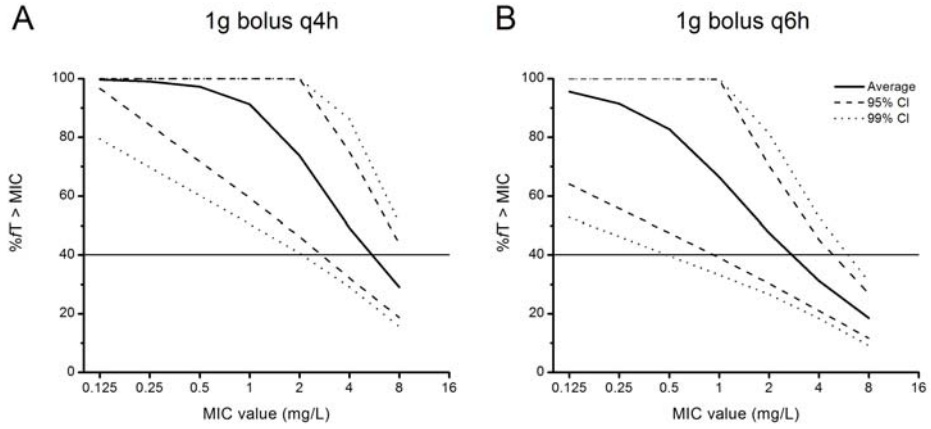

Figure 1: *Percent of time the unbound fraction of amoxicillin remained above the MIC (%fT>MIC) as a function of the MIC for two dosing intervals, 4 hours (figure 1a) and 6 hours (figure 1b), in pregnant women with PPROM in steady state situation.*

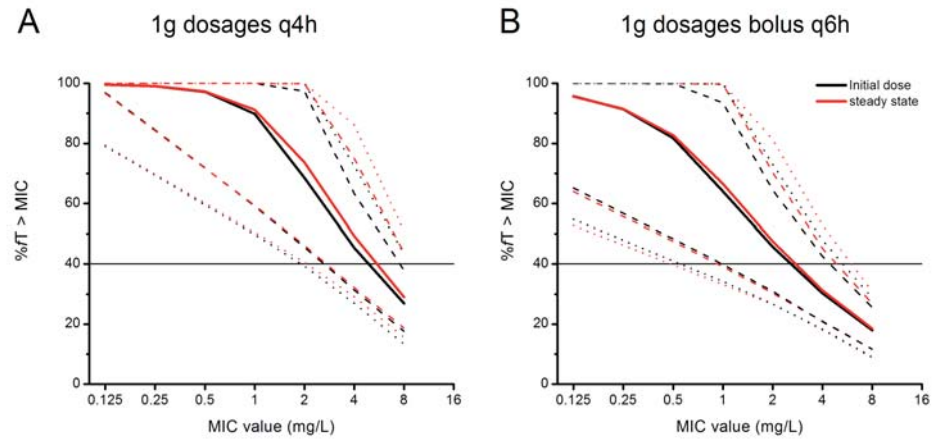

Figure 2: *Percent of time the unbound fraction of amoxicillin remained above the MIC (%fT>MIC) as a function of the MIC for two dosing intervals, 4 hours (figure 2a) and 6 hours (figure 2b), in pregnant women with PPROM after the inital dose (black lines) and in steady state situation (red lines). (See color inlay for a full color version of this figure.)*

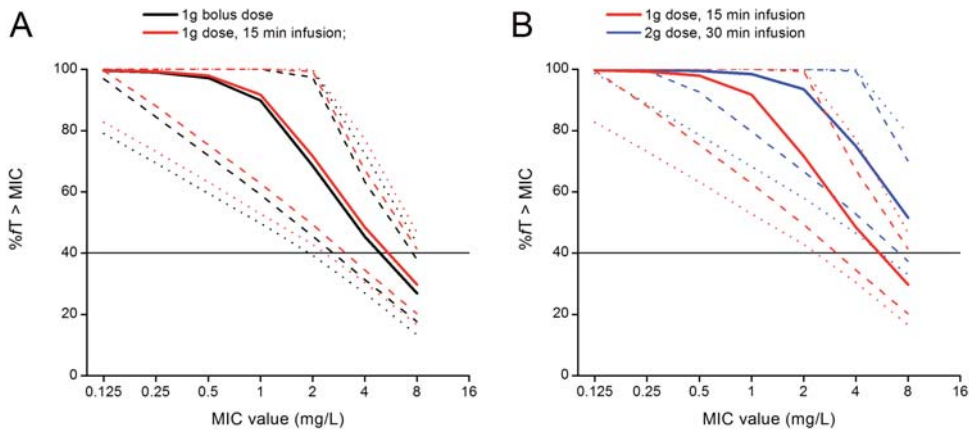

Figure 3: *Percent of time the unbound fraction of amoxicillin remained above the MIC (%fT>MIC) as a function of the MIC for three different initial doses for a 4 hours dosing interval in pregnant women with PPROM. In figure 3A the %fT>MIC for a dose of 1 gram administered as bolus (black lines) and the 1 gram dose administered over 15 minutes (red lines) are shown. In figure 3B the %fT>MIC for the 1 gram dose administered over 15 minutes (red lines) and the 2 gram dose administered over 30 minutes (blue lines) are shown. The solid lines are the values for the average pregnant women; the interrupted lines represent the 95% confidence intervals and the dotted lines the 99% confidence intervals. (See color inlay for a full color version of this figure.)*

by the CDC the %*f*T>MIC for the average population and the lower 99% CI were 99% and 70% at steady state, respectively. Therefore the probability of target attainment of amoxicillin administered every 6 hours would probably be lower than when administered every 4 hours, but the %*f*T>MIC for all patients exceeded the target percentage of 40%. As shown in figure 2, there are minor differences in the shape of the curves for initial dose and for doses administered at steady state at dosing intervals of 6 hours and 4 hours. In figure 3, the %*f*T>MIC for the three different initial doses is shown (1 gram bolus, 1 gram infusion over 15 minutes and 2 gram infused in 30 minutes). This indicates that the use of a loading dose of 2 gram amoxicillin is not beneficial to achieve adequate concentration-time profiles in maternal serum to prevent GBS disease.

During daily patient care, the ideal infusion time is sometimes hampered by small accidents, overlooks or other misfortunes, resulting in possibly inadequate concentration profiles. We simulated some of these possible adverse regimens. In the first simulation the interval was extended to 8 hours and 12 hours respectively, predictably resulting in decreased %*f*T>MICs. Given the MIC of GBS, the %*f*T>MIC for the average population is 78% for an interval of 8 hours and 53% with an

interval of 12 hours. However, when the 99% CI was included in the analysis of a dosing interval of 8 hours and 12 hours the %*f*T>MIC decreased to values below the 40%. Another problem frequently occurring is obstruction during infusion. When an obstruction in the infusion system results in a slower administration the %*f*T>MIC is increased. When amoxicillin was administered with a rate of 66.7 mg/min (1 gram over 15 minutes) with a dosing interval of 4 hours, the %*f*T>MIC was >50% for the population with the 95% CI included when the infusion is stopped after 2 minutes.

Discussion

We determined the effect of the use of different dosing regimens on the probability of achieving therapeutic concentrations in the entire group of pregnant women with PPROM. Monte Carlo simulation using pharmacokinetic estimates and a three-compartment model showed that both the dosing regimen as recommended by the CDC[4] and the regimen mentioned in the Cochrane Library[7] result in adequate concentration-time profiles in maternal serum. For both regimens accidentally missing a single dose results in a %*f*T>MIC above the threshold for efficacy for the majority of the population. Inaccuracies in the rate of the infusion of amoxicillin did not have clinically relevant changes on the PTA, primarily because the MIC of GBS is relatively low.

The CDC recommends an initial dose of 2 gram of ampicillin[4]. For the average population the %*f*T>MIC after such a loading dose for amoxicillin as well as after a bolus infection of 1gram is >99%. Taking into account the 99% CI this difference was 19%, but the values were above the target of 40%. Adequate concentrations were reached almost immediately after the start of the administration. Therefore the use of a 2 gram loading dose does not seem to be beneficial for reaching adequate maternal concentration-time profiles.

The rate of the administration of 1 gram amoxicillin does not have major influences on the %*f*T>MIC of the concentration-time profiles. The %*f*T>MIC after a bolus injection is only slightly lower compared to the standard infusion over 15 minutes. It is only when amoxicillin infusions are extended to hours, that major differences will result (results not shown). This is in line with the half life of amoxicillin.

An obstruction in the infusion system occurs regularly and in clinical practice finally the total amount of antibiotic is administered. Using MCS, it is not possible to simulate this particular situation. The best alternative is to simulate an infusion 1 gram with a constant rate of infusion and stop the infusion prematurily. In this way, a minimal infusion time was determined needed to reach the target %*f*T>MIC of 40%. This target was reached for the majority of the population after

2 minutes of infusion, but in clinical practice the infusion will only be temporarily blocked resulting in much higher values for %*f*T>MIC.

Studies showing a clear relationship between exposure to amoxicillin and its efficacy in preventing GBS infections in pregnant women are not available. To our opinion it is reasonable that in this patient group the exposure should correspond to exposures that correlate to a 1 to 2 log drop of colony forming units in various models, and thus be bactericidal rather than bacteriostatic. Thus, for amoxicillin the %*f*T>MIC should therefore be at least 40%.

Only the unbound fraction of the total drug concentration is active. Therefore, the percentage of protein binding is implemented in the MCS. Values for protein binding of amoxicillin vary between 18-20%[21,22]. Protein binding might even decrease in pregnant women[23]. It is likely that the protein binding of 22%, as used in our analysis, underestimates the active fraction of amoxicillin in pregnant women. The use of 22% is therefore a conservative estimate. This may lead to slightly underestimated %*f*T>MICs resulting from the simulations.

When prevention of GBS infection fails and the fetus gets infected, adequate fetal serum levels and probably amniotic fluid levels are required as well. Amoxicillin reaches the fetus after transplacental transfer from the mother. Consequently, adequate maternal serum levels are a prerequisite for adequate levels in fetal serum. Concentrations in fetal serum are lower compared to concentrations in maternal serum; therefore these simulations can not guarantee that these dosing regimens are adequate for the prevention of GBS infection in the fetus.

In conclusion, we present MCS using a three-compartment model. Both the dosing regimen as recommended by the CDC and as mentioned in the Cochrane Library will result in adequate concentrations in maternal serum. A two gram loading dose does not seem to be beneficial and the 1 gram doses can safely be administered by bolus injection increasing the comfort of the patient and facilitating prophylaxis. For the majority of the population considerable inaccuracies in the infusion of amoxicillin will not interfere with its predicted efficacy in preventing infections with GBS in the mother. A dosing regimen of bolus injections of 1 gram every 6 hours was predicted to be adequate for the prevention GBS infection in pregnant patients.

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