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

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Chapter 1

Population pharmacokinetics of antibiotics to prevent group B streptococcal disease.

Scope and outline of the investigations.

The objective of the investigations in this thesis was to characterize the pharmacokinetics of antibiotics in the prevention of group B streptococcal (GBS) infections in pregnancy with emphasis on the possible changes which may occur in the perinatal period. A specific objective was to assess the implications of potentially altered maternal pharmacokinetics on the exposure of the infant.

Group B streptococcus (GBS, *Streptococcus agalactiae*) has been known as a human pathogen since 1938[1]. It is a gram-positive coccus, growing in chains or as diplococci. Because GBS causes complete destruction of red blood cells on sheep blood agar, colonies produce a characteristic appearance with narrow surrounding zone of β-hemolysis. Based on the expression of antigenic capsular carbohydrates, GBS is classified into nine serotypes: Ia, Ib and II-VIII. Recently a tenth serotype has been proposed[2]. Like carbohydrates, proteins are also expressed on the bacterial surface. Differences in the expression of carbohydrates and surface proteins account for differences in the pathogenesis of infection and possibly clinical presentation[3,4]. Factors playing a role in the development of invasive infection have been elucidated to some extent[3].

In pregnancy GBS may cause a variety of serious infections in both mother and neonate. Most commonly known is neonatal GBS disease. GBS disease in the neonate is classified according to the age at which the first symptoms occur. Early-onset GBS disease (GBS-EOD) presents within the first week of life and late-onset disease (GBS-LOD) presents from 7 to 90 days of life. GBS is a major cause of neonatal morbidity and mortality. Diseases caused by GBS include sepsis, pneumonia and meningitis. GBS-EOD is usually acquired during delivery by neonates born from mothers colonized with GBS in the rectovaginal tract. Up to 35% of pregnant women is colonized with GBS in the rectovaginal tract, most often without having symptoms[5,6]. Fortunately, only 1% of neonates of colonized mothers develop GBS-EOD. The occurrence of maternal GBS infections is often disregarded.

Intravenous administration of antibiotics is now the cornerstone of the prevention of GBS-EOD and of the treatment of intra-amniotic infection during pregnancy, shortly before and during labor. During pregnancy, antibiotics are administered intravenously to the mother, with the fetus as actual target of prophylaxis of neonatal GBS disease. Antibiotics are administered as short infusions and reach the fetus after transplacental transport. To protect both mother and neonate from GBS infections, the concentration-time profiles of the prescribed antibiotics have to be adequate in both maternal and fetal serum. A limitation of the current dosing regimens as recommended by the Centers of Disease Control and Prevention (CDC) is that they are not evidence-based in the sense that the actual exposure profiles have not been determined.

To study the efficacy of the recommended dosing regimens for GBS-EOD prevention, knowledge of the disposition of drugs in the body is necessary.

Pharmacology (Greek 'φαρμακος' for medicine or drug and 'λογος' for study) is the science of the interactions of chemicals with the human body[7]. These interactions are divided into two classes: pharmacokinetics (PK) and pharmacodynamics (PD). Pharmacokinetics is the study of how the body absorbs, distributes, metabolizes and excretes drugs. The calculation of various rates at which these processes occur brings a quantitative component to assessing drug action[8]. PD is the study of the biochemical and physiological effects of drugs, the mechanisms of drug action and the relationships between drug concentration and effect. The effects of drugs are related to the time course of the drug concentration in plasma, albeit that these relationships may be complex[9,10].

To describe the pharmacokinetics of a specific drug in a target patient group, it is important to take inter-individual variability into account. To this end advanced data-analysis techniques such as non-linear mixed effects modeling are increasingly applied. This is often referred to as the "population approach". Using population pharmacokinetics the data of a group of individuals is simultaneously analyzed and the sources and correlates of variability in drug concentrations among individuals are studied. Specifically, in this manner patient demographical and therapeutical characteristics which might influence the pharmacokinetics are included in the analysis as covariate(s). A further advantage is that the population approach allows the analysis of data from unbalanced study groups[11,12]. This is particularly important for pharmacokinetic studies in pregnant women, because blood sampling might be limited due to practical and emotional problems. Typically, the number of blood samples collected from pregnant women during labor will be less compared to women before onset of labor. The number of umbilical cord blood samples is even more limited, because they can be collected only once for each patient. Thus, population pharmacokinetics describes the pharmacokinetics of a population of subjects. Furthermore, it tries to identify in a quantitative manner the factors that influence the pharmacokinetics. As such population pharmacokinetics constitutes a basis to adjust drug dosages in specific patient populations.

The description of the pharmacokinetics obtained in the population analysis, can be used to evaluate the efficacy of therapy and to optimize dosing regimens. Monte Carlo Simulation (MCS) is a technique used to evaluate the probability of achieving therapeutic concentrations using different dosing regimens. MCS is performed using pharmacokinetic parameters, data on the parameters describing the drug concentration-effect relationship and data on the inter-individual variability in these parameters[13-18]. To study the efficacy of antibiotics, the susceptibility of the micro-organisms is of importance. The susceptibility of bacteria is indicated by the Minimum Inhibitory Concentration (MIC). For the antibiotics used in the prevention of GBS-EOD, the efficacy is determined by the time the antibiotic concentration exceeds the MIC (time-dependent mechanism of action)[19-21].

The aim of the research presented in this thesis was to describe the pharmacokinetics of the antibiotics used in the prevention of GBS-EOD. Preventing GBS-EOD requires an adequate concentration-time profile in both the mother and the fetus. To this end the effects of various dosing regimens and inaccuracies in the antibiotic administration on the efficacy of the amoxicillin were evaluated. Finally after birth, adequate dosing in (preterm) neonates with a suspected infection is essential. This requires knowledge of the pharmacokinetics in neonates. In this respect the pharmacokinetics of penicillin G in neonates was studies as well.

Part I of this thesis reviews background information on the prevention of GBS-EOD and maternal GBS infections. In **chapter 2** a detailed review of the use of antibiotics in the era of the prevention of GBS-EOD is presented. The available evidence on the pharmacokinetics of antibiotics used as intrapartum prophylaxis in relation to infection parameters and GBS-EOD incidence is described, to evaluate the efficacy and safety of currently advised prophylaxis. The efficacy of the prophylaxis is mainly attributed to a lowering of the incidence figures of GBS-EOD. However, incidence figures are influenced by many factors and may therefore not be considered conclusive proof. The available data on the changes in incidence figures, as well as data on the interruption of vertical transmission of GBS carriage, support the idea that antibiotics prevent GBS-EOD. But to advise antibiotic prophylaxis to approximately 35% of all pregnant women during labor, more data are needed on the pharmacokinetics of the antibiotics and on the unintended consequences for both mother and neonate.

Guidelines on the prevention of GBS disease focus on infections of the fetus. The fact that GBS also causes infections in pregnant women is less appreciated. Various maternal GBS infections, their characteristics, associated neonatal morbidity, and prevention and treatment strategies during pregnancy, delivery, and in the postpartum period are reviewed in **chapter 3**. GBS infections in the mother cause less morbidity than neonatal infection, but occur more commonly. Especially during the course of pregnancy and labor, GBS can endanger both mother and the fetus. Postpartum mastitis can also threat mother and the neonate, because it may be a cause of late-onset or recurrent neonatal GBS disease. With early recognition and proper treatment, maternal and neonatal severe morbidity and mortality due to GBS infections are rare.

The penicillins, such as amoxicillin, are antibiotics of first choice in the prevention of GBS-EOD during pregnancy and delivery. As an alternative, clindamycin is used. In **part II** the pharmacokinetics of amoxicillin is described. It is used as prototype to study all issues related to the prevention of GBS infection in pregnant women. In **chapter 4** the pharmacokinetics of amoxicillin in pregnant women with preterm premature rupture of the membranes (PPROM) is described. Pharmacokinetic parameter estimates for patients with PPROM were all within the ranges reported in the literature for healthy non-pregnant individuals. **Chapter 5**

focuses on the influence of labor on the pharmacokinetics of amoxicillin. To this end the pharmacokinetics were determined in patients before the onset of labor, during labor and in the immediate postpartum period. An effect of labor was seen on the peripheral volume of distribution. A decrease in the peripheral volume of distribution was seen during labor and even more in the immediate postpartum period. In case of suspected intra-amniotic infection, co-amoxiclav, a combination of amoxicillin and clavulanic acid is used. When drugs are administered simultaneously, there is a possibility that these drugs influence their pharmacokinetic behavior. The influence of co-administration of clavulanic acid on the pharmacokinetics of amoxicillin is presented in **chapter 6**. In agreement with observations from earlier studies in healthy subjects it is shown that clavulanic acid has no effect on the pharmacokinetics of amoxicillin in pregnant women. Because the fetus is the actual target of the prophylaxis, the transfer of drugs over the placenta is an important factor. The investigations in **chapter 7** aim therefore characterization of the concentrations of amoxicillin in umbilical cord serum and neonatal serum in relation to the concentrations in maternal serum. Approximately 1 hour after the start of the intravenous administration 2 gram amoxicillin over 30 min to the mother the neonatal concentration reached its highest level, and thereafter exceeded the concentrations in venous umbilical cord blood. Finally the population model of the amoxicillin pharmacokinetics in pregnant women with PPROM was used in **chapter 8** to evaluate the probability of target attainment (as indicated by the MIC) after various dosing regimens and inaccuracies in the administration of the amoxicillin using Monte Carlo Simulations. Both regimens recommended by the CDC as well as the regimen described in the Cochrane Library result in adequate maternal concentration-time profiles[22,23].

Most patients included in our study were relatively healthy. To describe the influence that co-morbidity might have on the pharmacokinetics we present a case-report of a pregnant women with PPROM and severe vomiting in **chapter 9**. We hypothized that the extreme vomiting had resulted in additional physiological changes and thereby changing the distribution of the amoxicillin.

In **part III** pharmacokinetics of other antibiotics used in prevention or treatment of GBS infections are presented. Patients allergic to penicillins may not be treated with amoxicillin and in this condition clindamycin is used instead. Moreover in patients who need endocarditis prophylaxis, clindamycin is prescribed as well. Clindamycin should be studied in a similar manner as described for amoxicillin, but limited data were available. In **chapter 10** the pharmacokinetics of clindamycin in pregnant women is described. A limited number of patients was available to study the pharmacokinetics in pregnant women and the transfer over the placental barrier. The results of our preliminary investigations show that for the average pregnant women the recommended dosing regimen is adequate, but it is doubtful whether the concentrations in the fetus are also adequate.

Despite the prophylactic measures, neonates may still acquire GBS-EOD, partly because mothers of these neonates were not selected for antibiotic prophylaxis. In some neonates an overwhelming intra-amniotic infection had already developed at the time the antibiotics are prescribed. In both occasions, neonates have to be treated with antibiotics after birth. In this respect it is important that especially, preterm neonates are vulnerable for the development of GBS-EOD. For several drugs the pharmacokinetics in preterm neonates has been found to be different from older children and adults[24-26]. In **chapter 11** therefore, the pharmacokinetics of penicillin G in very preterm neonates is described. The pharmacokinetics in neonates with a gestational age of less than 32 weeks differs from that in adults and older infants, which is indicated by a prolonged terminal half-life.

In the general discussion (**part IV, chapter 12**) all results of the various investigations are discussed and future perspectives are presented.

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