OBSTETRICS

Transplacental passage of vancomycin from mother to neonate

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OBJECTIVE: The objective of the study was to analyze a large number of patients receiving vancomycin chemoprophylaxis and evaluate the maternal and neonatal cord blood levels at the time of delivery.

STUDY DESIGN: Every mother who entered labor with a positive group B streptococcal culture and a high-risk penicillin allergy with resistance to clindamycin or unknown sensitivity was consented to participate in the study. In the initial phase of the study, patients received the standard intravenous dose of 1 g every 12 hours. Based on the results, this was changed to a dosing of 15 mg/kg every 12 hours in the second phase and then further modified to 20 mg/kg every 8 hours in the third phase. Maternal and cord blood vancomycin levels were obtained at delivery and evaluated.

RESULTS: A total of 55 patients consented to participate in the study, with 31 in phase I, 12 in phase II, and 12 in phase III. For the standard-dosing phase I group, only 32% of maternal and 9% of cord blood samples were therapeutic at delivery. For phase II, 50% of maternal and 33% of cord blood values were therapeutic; however, in phase III, 83% of mothers and neonates had therapeutic levels at the time of delivery.

CONCLUSION: With standard dosing, only 9% of neonates have therapeutic vancomycin levels at delivery. By using a regimen of 20 mg/kg intravenous every 8 hours (maximum individual dose 2 g), the newborn therapeutic level increases above 80%. The pharmacological pattern shows that transplacental passage occurs with fetal levels equaling maternal levels, but transplacental transport is somewhat slow in both directions.

Key words: group B streptococcus chemoprophylaxis, infections in pregnancy, neonatal sepsis, vancomycin in pregnancy

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Early-onset group B streptococcus (GBS) is still a common cause of neonatal sepsis, even though the prevalence of this disorder has decreased from its high in the 1960s and 1970s at 2/1000 live births to 0.96/1000 live births in 1996 and to 0.34/1000 live births in 2004.[1]

A major factor in producing this decline is from following recommended protocols and guidelines devised and published by the Centers for Disease Control and Prevention and the American College of Obstetricians and Gynecologists.[2,3] One aspect of these guidelines discusses the use of specific chemoprophylaxis treatments based on sensitivities of the organism and what antimicrobial agents should be administered. In the setting of high-risk penicillin allergies, the guidelines recommend the use of clindamycin as the antibiotic of choice as long as there is no demonstrated resistance to clindamycin or erythromycin.[2,3] For isolates that do not display sensitivity to both clindamycin and erythromycin, vancomycin is recommended with a dosing schedule of 1 g intravenous every 12 hours.

In evaluating the literature, very little information exists regarding the transplacental passage of vancomycin and the blood levels obtained in the neonate at the time of delivery. Two ex vivo placental perfusion studies demonstrated minimal transfer of the antibiotic.[4,5] Three other studies with a total of 16 patients have reported on transplacental passage of vancomycin, but 14 were found to have subtherapeutic levels and only 9 received the full 1 g dose.[6-8] Of these 16 patients, 15 received the standard 1 g intravenous dose and 1 was administered a dose of 15 mg/kg.

Because of the limited data that currently exist on this topic and the discrepancy seen between ex vivo placental perfusion studies and clinical cases, estimating an accurate patient sample size was difficult. Therefore, our study objective was to analyze a minimum of 50 patients receiving vancomycin chemoprophylaxis and evaluate the maternal and neonatal cord blood levels at the time of delivery. Interim analyses would occur as the study progressed and dosing modifications would be made if indicated. Our hypothesis was that the recommended standard dosing of 1 g intravenous every

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12 hours would result in subtherapeutic newborn levels.

Materials and Methods

Every mother who entered labor with a positive GBS culture and a high-risk penicillin allergy and resistance to clindamycin or unknown sensitivity was prospectively consented. Women were also prospectively consented if they were less than 37 weeks in gestation and their GBS status was unknown and again they had a high-risk penicillin allergy. The study was reviewed and approved by the University of Tennessee Medical Center Institutional Review Board and spanned a little more than 2 years.

The initial part of the study lasted 13 months and began with the standard dosing of 1 g of vancomycin administered intravenously every 12 hours. After evaluation of this subset, a second phase (that lasted 6 months) was introduced whereby the dosing regimen was modified to 15 mg/kg intravenous every 12 hours. This study addendum was resubmitted to the institutional review board and was reviewed and approved. Upon completion of this second phase, a third and final phase was developed that changed the dosing regimen to 20 mg/kg intravenous every 8 hours, and this phase had a 7-month duration. Again, this third phase was resubmitted to the institutional review board and was reviewed and approved.

Data collection included maternal demographics, the gestational age on admission for delivery, the maternal GBS status, a history of a high-risk maternal penicillin allergy, maternal height and weight, vancomycin dose, number of doses administered, time from the completion of the last dose to delivery, the maternal and cord blood vancomycin levels at delivery, and any adverse maternal events experienced during or shortly after the drug administration. Neonatal data included birthweight, Apgar scores, brainstem auditory-evoked response results, and overall neonatal outcome including any signs of sepsis. In addition, all neonates born to mothers with known positive GBS have their urine tested for GBS antigen and these data were collected.

Any patient who required in excess of 4 vancomycin doses would have a trough level drawn 30 minutes prior to the initiation of the fifth dose. The maternal height and weight information was used to determine a body mass index (BMI) at the time of labor. The vancomycin infusion protocol in our institution is at a rate of 1 g per hour. For the second and third phases, infusion bags of more than 1 g were produced by the pharmacy in 250 mg increments (ie, 1.25 g, 1.5 g, 1.75 g, and 2 g). Therefore, patients receiving weight-based dosing were rounded to the closest 250 mg dosing bag. All patients administered 1.25 and 1.5 g vancomycin doses received their infusion over 90 minutes, and all patients given 1.75 and 2 g vancomycin doses received their infusion over 2 hours. No patient received more than 2 g in a single dose.

Because greater than 80-90% of vancomycin is recovered unchanged in the urine within 24 hours of a dose,[9] and larger doses would be administered in phase 3, a serum creatinine level was obtained and an estimated creatinine clearance was determined using the Cockcroft and Gault equation. This equation utilizes the patient's age, weight, and serum creatinine to estimate the glomerular filtration rate.[10,11]

Vancomycin primarily circulates as a free drug with a variable amount of protein binding ranging from 10% to 50%.[9] A therapeutic level is between 10 and 40 μg/mL, and this is used for both adults and neonates.[9,12] The vancomycin level is assessed as the total drug identified in the patient's serum. Statistical analysis included a χ^2 and Fisher exact test where appropriate and a value of $P <$ .05 was considered significant. All tests were considered against a 2-sided alternative hypothesis where appropriate.

Results

A total of 56 gravid patients were consented for the study, with 55 being analyzed. The one excluded case is discussed in the following text. Of the 55 patients, 31 received the standard treatment of 1 g of vancomycin intravenous every 12 hours. In this group was one set of twins for a total of 32 neonates. A total of 10 maternal levels (32%) had therapeutic levels at delivery and only 3 cord blood values (9%) were therapeutic. There were 12 patients in the second phase of the study who received 15 mg/kg intravenous every 12 hours. Of these, 6 maternal values (50%) and 4 cord blood levels (33%) reached therapeutic levels.

In analyzing the time from the completion of the last dose to delivery and therapeutic levels, patients in phases 1 and 2 were combined together. Of the 43 patients, 16 mothers had therapeutic levels at delivery, and of these, 14 (88%) delivered less than 6 hours of completion of the last dose and 15 (94%) delivered less than 8 hours from the last dose. In the 27 cases that did not have therapeutic maternal levels at delivery, only 6 (22%) delivered less than 6 hours from the last dose and 12 (44%) delivered less than 8 hours from the last dose. These differences were both statistically different with $P <$ .001 for less than 6 hours and $P =$ .002 for less than 8 hours. There were 7 cord blood levels that had therapeutic values and 6 (86%) of these delivered less than 6 hours. Of the 37 newborns with subtherapeutic levels, 17 (46%) delivered less than 6 hours, but this did not reach significance with $P =$ .06.

In evaluating the number of doses received prior to delivery, again the patients in phases 1 and 2 were combined. A total of 25 (58%) received 1 dose prior to delivery, 12 (28%) received 2 doses, 4 (9%) received 3 doses, and 2 (5%) received 4 doses. Only 7 of the 25 who received a single dose (28%) had therapeutic maternal levels vs 9 of 18 (50%) who received 2 or more doses prior to delivery, but this also was not significant at $P =$ .25. Of the 7 cord blood levels that had therapeutic levels, 4 (57%) received 2 or more doses.

Lastly, regarding BMI, in phase 1, there were 22 patients with a BMI of greater than 30 kg/m^2 at the time of labor, and only 6 of these (27%) had therapeutic maternal levels at delivery. In phase 2 there were 5 patients with a BMI greater than 30 kg/m^2 at the time of labor, and 3 (60%) had therapeutic levels at delivery but this was not significant at $P =$ .36. Of the cord blood values, 5 of the 7 therapeutic levels were seen