ACOG Committee Opinion #797 and the dose of intrapartum vancomycin: a potential danger to mother and newborn alike

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ABSTRACT

Background: Intra-partum (IP) IV vancomycin (VAN) 20 mg/kg every 8 hours is proposed by #797 for the prevention of early onset neonatal group B streptococcal disease (GBS), a recommendation for which the basis of scientific merit is poor. The goal of our study was to analyze the sparsely sampled published data and raise awareness about the underlying risk of VAN toxicity with this dosing approach.
Methods: Plasma and cord-blood concentration-time data of IV VAN given to mothers in the intra-partum period was analyzed. 5000 Monte Carlo runs were conducted to simulate maternal/fetal exposure (AUC_{0-24}, AUC_{24-48}) for doses of 1500, 1750 and 2000 mgs q8h and for possible birth times at two-hour intervals. Neonatal VAN clearance was not possible to determine; hence, we used a validated PK model to calculate exposure for the first 24h of life for gestational ages (GA) of 33 to 40 weeks. The AUC range of 400 – 600, and > 600 mg*h/L were considered for indices of efficacy and toxicity, respectively, during probability of target attainment analysis (PTA).
Results: Estimates from 30 pairs of serum and cord-blood concentrations analyzed with a 2-compartment model are shown in Table 1. Maternal VAN exposures seem acceptable up to 2 IP doses given with mean (SD) AUC0-24 of 394 (140), 474 (167), and 540 (193) mg*h/L for the 1500, 1750 and 2000 mg regimens. Most mothers (up to 83%) who receive three or more doses will be subjected to nephrotoxic exposures (Figure 1.). Neonatal evaluations indicate similarly low PTAs for the three dosing regimens when the efficacy target is considered (Figure 2. A). On the other hand, the PTAs for potentially nephrotoxic exposure is expected to reach undesirable levels when three or more doses were to be administered. The risk is profoundly high in GA of 33 to 35 weeks and birth times beyond 20 hours after the initiation of intra-partum prophylaxis (Figure 2. B).
Conclusion: Current recommendations by #797 for dosing of vancomycin pose significant risk to mother and newborn alike, especially in cases with lengthy duration of preterm labor. Based on our results, maternal therapeutic drug monitoring for all cases requiring more than two doses should be considered as with the proposed dosing regimen going un-adjusted a maximum of 1 out of 4 newborns and 4 out of 5 mothers may be subjected to nephrotoxic exposures in unusually prolonged labor.

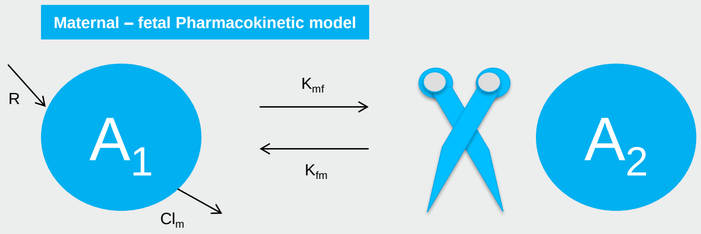
INTRODUCTION AND OBJECTIVES

- Group B streptococcus (GBS) is the leading cause of newborn infection, with two distinct clinical syndromes: early onset disease (within 7 days after birth) secondary to vertical transmission, and late onset disease, which presents between 7 days after birth and 2-3 months[1]
- Various PK/PD monitoring parameters for VAN have been suggested with the AUC/MIC ratio 400-600 best correlating with positive clinical outcomes, and dosing of 15 mg/kg is successfully employed to achieve these standards even in patients with serious infections [2,3]
- For the prevention of GBS sepsis, the updated recommendations by #797 suggest a more aggressive approach of intrapartum VAN at 20 mg/kg every 8 hours, a dosing regimen derived from a study that failed to adapt the use of current day's pharmacometric standards
- The goal of this study was to properly analyze the data used to create this new dosing approach and to raise awareness of the hidden dangers associated with the use of such VAN regimens

METHODS

- The previously published data of 30 pre and full term mothers entering labor who presented with high risk of penicillin allergy and positive GBS culture resistant to clindamycin\erythromycin or with an unknown GBS susceptibility profile were included
- Paired maternal and cord blood samples were collected at the time of delivery
- Pmetrics[6] and ID-ODS[7] tools were used for PK/PD analysis

METHODS



R, represents the infusion rate; CL_m,maternal VAN clearance; A_{1-2}, amount of drug in compartment; K_{mf-fm}, maternal-fetal transfer rate constant

Figure 1. Flow diagram of methods of modelling approaches and statistics adapted in this analysis

RESULTS

Parameter	Population mean	BSV (%)
V, maternal (L)	39.66	49.40
V, fetal (L)	2.07	39.53
CL, maternal (L/h)	4.78	43.64
$K_{m->f}$ (h^{-1})	0.51	31.68
$K_{f->m}$ (h^{-1})	0.36	34.13

V, volume of distribution; CL, clearance; $K_{m->f}$ –$K_{f->m}$, transfer rate constants from mother to fetus and back

Table 1. Final models parameters

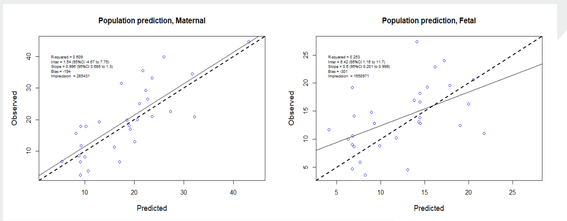


Table 2. Observed versus predicted concentrations

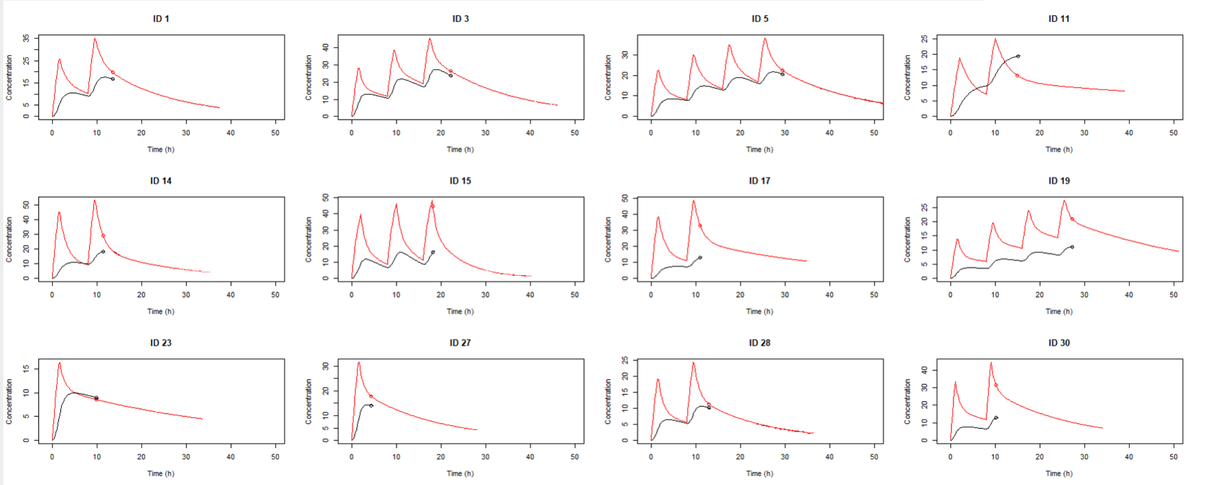


Figure 2. Individual observed versus predicted VAN concentrations

RESULTS

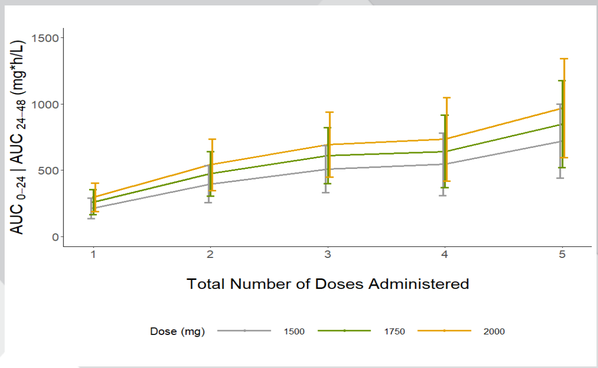


Figure 3. Simulated maternal VAN exposure for select dosing regimens at 8 hour intervals

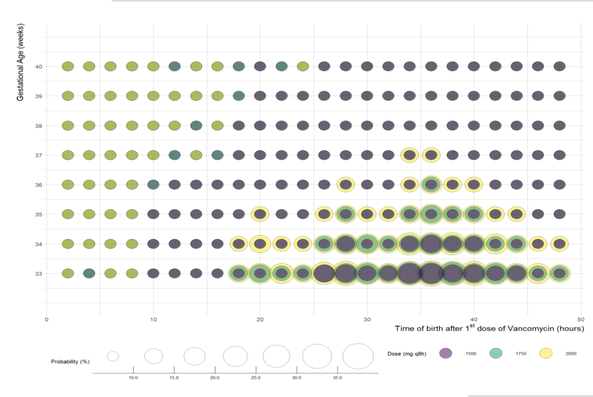


Figure 4. Neonatal probability of AUC_{0-24} > 600 mg*h/L as a function of gestational age and time of birth

CONCLUSION

- Pharmacometric analysis of the published sparsely sampled data suggest excessive exposure both in the mother and fetus alike when these new dosing regimens are utilized
- The risk becomes especially profound in prolonged labor lasting more then 16 hours and in infants with gestational age of 35 weeks or less
- Results of a pharmacokinetic study currently on going at our centers will shed light on the dosing design which provides maximum acceptable maternal – fetal exposure for the prophylaxis of GBS in the intrapartum period

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