

Critical Care Medicine

Issue: Volume 25(11), November 1997, pp 1933-1934

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Publication Type: [Letters to the Editor]

ISSN: 0090-3493

Accession: 00003246-199711000-00039

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Gentamicin Pharmacokinetics in Neonates With Patent Ductus Arteriosus

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To the Editor:

Dr. Williams et al. [1] recently described the pharmacokinetics of gentamicin in neonates with patent ductus arteriosus (PDA). These authors assert that gentamicin dosing should be altered in newborns with a PDA and that an apparent volume of distribution for gentamicin of 0.7 L/kg may predict the presence of a PDA. We would like to present several points of opposition to these recommendations based on what we believe are important deficiencies in the study design and data analysis.

First, Dr. Williams et al. [1] only provide information on gestational age, birth weight, and Apgar scores for their study population of infants with and without a PDA. Notably absent are critical data such as postnatal or postconceptional age, the time of appearance of the PDA relative to the pharmacokinetic evaluation, and whether or not any drugs were given to close a PDA in those infants with this condition. As well, objective evaluation for PDA was not performed in all infants so as to rule out the presence of a "silent" lesion in those infants in the control group. Postnatal or postconceptional age is a much more important determinant for changes in glomerular filtration rate as compared to gestational age. Additionally, dramatic changes in glomerular filtration rate can be produced both by the duct and by treatment to close a PDA (e.g., indomethacin) [2,3].

Second, the authors [1] state that they were not able to show an effect of gestational age on gentamicin volume of distribution and clearance. A mean difference in gestational age of >3 wks seems in contrast to previous findings with ceftazidime [2,3] since gentamicin elimination in neonates is virtually completely dependent on renal clearance and also correlates with developmental acquisition of renal function [4]. The use of more appropriate statistical methods (e.g., multiple linear regression models) could have shown these relationships if proper covariates were evaluated.

Third, the authors [1] only use a 2-point determination of gentamicin serum concentrations to estimate their pharmacokinetic parameters. While this simplified approach may be suitable for clinical pharmacokinetic evaluations (i.e., drug dosing), variability associated with this restricted sampling paradigm may have introduced artifactual "differences" not truly reflective of the impact of development or disease on gentamicin disposition. Also, the data depicted in Table 2 are confusing. Besides an apparent typographical error (i.e., the K_e of 0.8 for control infants should probably read 0.08), the differences for the pharmacokinetic parameters between the study groups, although statistically significant, may well not be clinically important. Despite the relatively large size of the subject groups, the fact that they were not balanced in size and, perhaps, for postnatal age, makes the comparison between the pharmacokinetic parameters as performed by the authors [1] less valid, particularly if homogeneity of variance in the parameter estimates for both groups was not present.

Finally, we are surprised that the authors [1] implied that the volume of distribution for gentamicin could be used to predict the presence of a PDA. The variability associated with this particular pharmacokinetic parameter in the sick preterm infant (even when calculated using more rigorous pharmacokinetic methods) precludes the accuracy required to effectively diagnose this life-threatening condition. Presently, a very reliable technique (i.e., echocardiography) is routinely available to determine both the presence and the severity of a PDA. Inferior techniques are, therefore, not needed.

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