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Bupivacaine Cardiotoxicity Is Related to Increased Brain Sensitivity

To the Editor:—We are puzzled by one of the conclusions reached by Morishima *et al.* in their study of bupivacaine toxicity in pregnant and nonpregnant ewes.[1] They found that pregnant ewes suffered circulatory collapse at a significantly lower total dose and blood level of bupivacaine than nonpregnant ewes. In their discussion, the authors state, "The cardiac tissue/blood concentration ratio of bupivacaine was approximately 3.5 in nonpregnant ewes and 3.3 in pregnant ewes." They go on to suggest that in pregnancy, "enhanced cardiotoxicity may be related to greater sensitivity of the myocardium." However, the data presented in their paper do not support this conclusion. The blood concentration of bupivacaine at circulatory collapse was 5.5 $mg \cdot ml^{-1}$ in pregnant ewes and 8.0 $mg \cdot ml^{-1}$ in nonpregnant ewes ($P < 0.05$). The cardiac tissue concentrations at circulatory collapse (derived from fig. 4) were: 19 $mg \cdot g^{-1}$ in pregnant ewes *versus* 25 $mg \cdot g^{-1}$ in nonpregnant ewes (NS) yielding tissue/blood concentration ratios of 3.5 in pregnant ewes and 3.1 in nonpregnant ewes, not 3.3 and 3.5, respectively. This suggests lesser, not greater, sensitivity of the pregnant myocardium to the depressant effects of bupivacaine. Their data also suggest greater myocardial uptake of bupivacaine in the pregnant ewe (higher tissue concentration of drug at lower plasma levels).

Their data do suggest an alternate explanation for the enhanced sensitivity of pregnant ewes to bupivacaine toxicity, *i.e.*, significantly lower brain concentrations of bupivacaine at circulatory collapse in gravid ewes. Brain/blood concentration ratios at circulatory collapse are 1.9 in nonpregnant ewes *versus* 1.3 in pregnant ewes, suggesting increased CNS sensitivity to bupivacaine toxicity in pregnant ewes. That this could result in circulatory collapse is not unreasonable in light of work by Heavner,[2] showing that very small doses of bupivacaine can cause severe ventricular arrhythmias following intracerebral ventricular injection. Severe terminal ventricular arrhythmias also occurred in the ewes studied by Morishima *et al.*[1] Combining the results of these two studies suggests that the increase in sensitivity to bupivacaine toxicity observed in pregnant ewes may be due not to increased myocardial sensitivity but rather to increased CNS sensitivity.

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In reply:—We thank Dr. Norris for his interest in our article. Our conclusion that enhanced cardiotoxicity of bupivacaine in pregnant sheep may be related to greater sensitivity of the myocardium was based primarily on the fact that nonpregnant animals required approximately twice as much drug and twice as high plasma concentrations of the drug, while the myocardial bupivacaine uptake was similar in pregnant and nonpregnant ewes. The values for bupivacaine concentrations in the heart and for heart–blood concentration ratios, which were not significantly different between groups, were quoted to imply a comparable drug uptake in the heart. The values calculated by Dr. Norris are at variance with ours because he calculated a ratio of means for tissue and blood concentrations of bupivacaine, while we calculated a mean of ratios in individual animals. Similarly, our calculation of mean brain–blood concentration ratios indicates that these were not significantly different (2.1 ± 0.2 in the nonpregnant, and 1.6 ± 0.3 in the pregnant). Even though the absolute concentration of bupivacaine was lower in the brain of pregnant ewes, it is unlikely that the greater cardiotoxicity noted in these animals was related to brain uptake of the drug.

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