

CORRESPONDENCE

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Should Epinephrine Be Used to Treat Local Anesthetic-induced Cardiotoxicity?

To the Editor:—Recently, Butterworth *et al.*¹ showed that ropivacaine, bupivacaine, and mepivacaine are approximately equipotent in directly inhibiting cyclic AMP (*i.e.*, forskolin-stimulated cAMP production), expressing skepticism that direct inhibition of cAMP by local anesthetics is important in clinical toxicity. We agree. On the other hand, they demonstrated that the concentrations of the local anesthetics that reduce epinephrine-induced cAMP production by 50% more closely fit the relative toxicity ratio usually assumed. From this they suggest there is a clinically meaningful local anesthetic effect at a more proximal step in the cAMP synthesis pathway. In a separate abstract, Butterworth and Pang² reported that bupivacaine displaces β -adrenergic receptor ligands from receptors at concentrations associated with cardiovascular toxicity. Although not conclusive, the findings from both reports indicate that the area deserves further study to determine relevance to defining the use of pharmacologic agents to treat local anesthetic-induced cardiotoxicity.

We are concerned that there is no evidence from the studies that the interaction between local anesthetics and epinephrine is competitive. In fact, the data show noncompetitive (insurmountable) inhibition of epinephrine-stimulated cAMP production. This would not support the authors' recommendation to increase the epinephrine dose but would indicate another therapeutic approach should be used.

More to the point of our concern is that large doses of epinephrine may worsen the clinical problem rather than improve it. In pilot studies (unpublished), we have noted that aggressive use of epinephrine to resuscitate rats from bupivacaine-induced cardiac asystole can produce marked hypertension and dangerous and often terminal ventricular arrhythmias (V tach, fibrillation). Feldman *et al.*³ con-

cluded from their study and review of the literature that the use of epinephrine to treat cardiovascular collapse after bupivacaine overdose is controversial and that vasopressor drugs with less direct cardiac effects than epinephrine may be more beneficial in the treatment of local anesthetic-induced hypotension.

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In Reply:—Heavner *et al.* are concerned that there is little evidence (in our studies) that an increased initial dose of epinephrine is superior to a standard dose for resuscitation. We agree. They assert that we did not show a competitive interaction between bupivacaine and epinephrine. We agree. They cite several animal studies in which epinephrine produced adverse effects. Finally, they assert that vasoconstrictors other than epinephrine "may be more beneficial in the treatment of local anesthetic-induced hypotension." Again, we agree. We were speaking not of local anesthetic-induced hypotension but of local anesthetic-induced cardiac arrest. Our point was that, if

a standard dose of epinephrine proved to be unsuccessful, clinicians should consider using a larger dose, because bupivacaine clearly inhibited the ability of epinephrine to stimulate cyclic AMP formation. In the face of bupivacaine-induced cardiac arrest, what would be the alternative?

Our recommendation regarding an increased dose of epinephrine (when an initial dose is ineffective) is also consistent with the ACLS protocols of the American Heart Association,¹ to which we recommend adherence. These guidelines have been developed at national consensus conferences where the relevant animal and clinical re-