Bupivacaine: Cardiotoxicity or Anesthetic Technique?

To the Editor:—The possibility that bupivacaine exhibits greater cardiotoxicity than shorter-acting local anesthetics has made us all more aware of potential complications of major regional anesthetics. In a case we reported, a seizure and ventricular arrhythmias occurred while attempting epidural anesthesia with bupivacaine.1 Subsequently, Batra et al.2 and Knapp3 were critical of our technique, and the former authors imply that such cases may lead to a short-lived rebirth of regional anesthesia.2

We contend that the techniques utilized in this case, which occurred in March, 1981,1 were not inappropriate at that time, and that such reports provide a basis for improving anesthetic practice. It is knowledge of techniques that may result in systemic toxicity, such as those reported by us1 and others,4–6 that can improve the safety of regional anesthesia. Current recommendations7 concerning epidural administration of bupivacaine include the following: the use of a test dose containing epinephrine to detect intravascular injection, utilizing a "one-shot" technique instead of a catheter technique when giving 0.75% bupivacaine, and avoiding the injection of a large single dose by administering increments of 3–5 ml when 0.5% or 0.75% bupivacaine is used. We agree with the comments2,3 that these procedures would have reduced the chance of systemic toxicity in the case we reported.1

Accepting the importance of the above recommendations, however, does not resolve the controversy as to
the relative cardiotoxicity of local anesthetics. Batra et al. argue that the animal studies we cited cannot be extrapolated to humans to support the thesis of cardiotoxicity. While interspecies variation to drug effects is indisputable, we still feel the results of the animal studies suggest that the cardiotoxicity of bupivacaine is greater than that of lidocaine, although proof of this contention or the contrary in humans may be difficult to obtain. Batra et al. state further that cardiotoxicity, regardless of the drug involved, has been avoided by "... treating it correctly within 60 s." This is consistent with certain case reports they cite in which cardiotoxicity was not observed when ventilation was instituted rapidly. However, our patient developed ventricular arrhythmias for 26 min despite the establishment of a secured airway and ventilation within 1 min. The adequacy of our treatment is attested to by the satisfactory outcome of the mother and infant. Thus, bupivacaine appears to have produced substantial cardiotoxicity even when ventilation was provided within the suggested period of time. Furthermore, under certain conditions, cardiac arrest or fibrillation in humans may be even more resistant to treatment after use of bupivacaine than when shorter-acting agents are used, as, for example, when there is a delay in treatment. The delay may allow hypoxia and acidosis, which occur concomitantly with convulsions in humans, to enhance cardiotoxicity. In this regard, adult sheep exhibit serious cardiac arrhythmias after intravenous administration of bupivacaine but not lidocaine when clinically equivalent doses are used. In hypoxic–acidotic sheep, however, seizures with bupivacaine but not lidocaine resulted in serious cardiotoxicity and death. This may simulate the situation of systemic toxicity in humans followed by a delay in treatment due to difficulty in airway management.

Appropriate treatment of systemic toxic reactions to bupivacaine is mandatory, and oxygen by mask is the recommended first step in management. This treatment, however, will not protect the airway in an obstetric patient who is at significant risk of pulmonary aspiration of gastric contents. The risk of this complication may be even greater in a case such as we reported where a nonselective cesarean section (not elective as implied by Batra et al.) was performed for failure of labor to progress (active labor and use of narcotics for analgesia inhibit gastric emptying). Therefore, in obstetric situations we use cricoid pressure during mask oxygenation and follow with endotracheal intubation to secure the airway.

We would further like to reply to comments of others regarding test doses of chloroprocaine. Batra et al. state that a 2-ml test dose of 3% chloroprocaine (60 mg) is worthless. Our clinical observations are contrary to this statement. We feel that this test dose reliably provides evidence of a subarachnoid injection in obstetric patients. While the effectiveness of a 60 mg test dose of chloroprocaine has not been documented in a controlled clinical experiments, 82.5 mg or 100 mg rapidly produce spinal anesthesia that is adequate for surgical procedures. Total spinal anesthesia, however, has been reported with a 50-kg test dose of this agent in a laboring parturient, thus, the dose should be administered cautiously. Furthermore, we feel that there may have been some misinterpretation of our statement that "... 5 ml of 3% chloroprocaine uniformly produces signs of CNS toxicity." Knapp suggests that this statement "... seems to imply that all parturients respond in a like fashion to a fixed dose of drug." Our intention was to state our clinical observation that all parturients respond to the test dose, not that the signs produced were uniform, which would dispute the pharmacodynamic principle of biologic variation.

In conclusion, we feel that animal experiments and clinical observation suggest that bupivacaine exhibits greater cardiotoxicity than the shorter-acting local anesthetics. However, regardless of the agent selected, utilization of effective test doses and administering local anesthetics incrementally will reduce the incidence of systemic toxicity when performing epidural anesthesia. This is amply demonstrated by the fact that by utilizing these safeguards we have not encountered a convulsion in over 2,000 obstetric epidural anesthetics performed subsequent to the case we reported. In our institution regional anesthesia thrives contrary to the concerns expressed by Dr. Batra and colleagues.

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REFERENCES

3. Knapp RM: Bupivacaine cardiotoxicity may be more related to
Does Almitrine Restore Halothane-induced Depression of Hypoxic Respiratory Drive?

To the Editor:—Clergue et al.1 recently described an 11.5% increase in minute expired ventilation after administration of almitrine to normoxic patients anesthetized with halothane (1.5%). Hyperoxia eliminated this stimulation. Halothane depresses hypoxic sensitivity, and Clergue et al.1 concluded that almitrine reverses this effect. Their conclusion is based on an extrapolation of their measurements because they did not study hypoxia. They did not report alveolar or arterial P\textsubscript{CO\textsubscript{2}}, which greatly affect ventilation and could be involved in the almitrine–halothane interaction. The general depressant effect of halothane has multiple sites of action\textsuperscript{2,3} besides the carotid bodies, so a complete reversal of hypoxic depression by almitrine would be surprising. Although safety and ethical\textsuperscript{4} considerations limit hypoxic experiments in human beings, it is risky to extrapolate data taken in normoxia and hyperoxia into hypoxia. Although their data and that of others\textsuperscript{5} supports a peripheral site of action of almitrine, until almitrine–halothane interaction has been studied during hypoxia, it remains to be shown that halothane-induced depression of hypoxic drive is restored by almitrine.

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REFERENCES

2. Berkenbosch A, de Goede J, Olievier CN, Quanjer PH: Sites of action of halothane on respiratory pattern and ventilatory response to CO\textsubscript{2} in cats. Anesthesiology 57:389–396, 1982

In reply:—Dr. Ward is questioning the validity of the O\textsubscript{2} test of Dejours\textsuperscript{1} as a measure of the hypoxic drive to breathing. In normal resting conditions, when O\textsubscript{2} is administered suddenly to a subject breathing room air, the rapid and transient 10–15% decrease in minute ventilation (\(\dot{V_e}\)) represents the removal of "any residual 'hypoxic' activity of peripheral chemoreceptors."\textsuperscript{12} When this O\textsubscript{2} test is performed in subjects breathing a hypoxic mixture, the O\textsubscript{2}-related fall of \(\dot{V_e}\) is much greater.\textsuperscript{5} The threshold for this O\textsubscript{2}-related stimulation is around