

- Lewis TL, Alter JH, Chalmers TC, Holland PV, Purcell RH, Alling DW, Young D, Frenkel LD, Lee SL, Lamson ME: A comparison of the frequency of hepatitis-B antigen and antibody in hospital and nonhospital personnel. *N Engl J Med* 289:647-651, 1973
- Maynard JE: Viral hepatitis as an occupational hazard in the health care profession, *Viral Hepatitis*. Edited by Vyas GN, Cohen SN, Schmid R. Philadelphia, Franklin Institute Press, 1978, pp 321-331
- Dienstag JL, Ryan DM: Occupational exposure to hepatitis B virus in hospital personnel: Infection or immunization? *Am J Epidemiol* 115:26-39, 1982
- Denes AE, Smith JL, Maynard JE, Doto IL, Berquist KR, Finkel AJ: Hepatitis B infection in physicians. Results of a nationwide seroepidemiologic survey. *JAMA* 239:210-212, 1978
- Carstens J, Macnab GM, Kew MC: Hepatitis-B virus infection in anaesthetists. *Br J Anaesth* 49:887-889, 1977
- Parry MF, Brown AE, Dobbs LG, Jocke DJ, New HC: The epidemiology of hepatitis B infection in housestaff. *Infection* 6:204-206, 1978
- Berry MD, Isaacson IJ, Hunt D, Kane MA: The prevalence of hepatitis B viral markers in anesthesia personnel. *ANESTHESIOLOGY* 60:6-9, 1984
- Recommendations of the Immunization Practices Advisory Committee (ACIP): Inactivated hepatitis B virus vaccine. *Morbidity and Mortality Weekly Report* 31:317-328, 1982
- Beasley RP, Hwang LY, Lin CC, Stevens CE, Wang KY, Sun TS, Hsieh FJ, Szmuness W: Hepatocellular carcinoma and hepatitis B virus. A prospective study of 22,707 men in Taiwan. *Lancet* 2:1129-1133, 1981
- CDC: Immune globulin for protection against viral hepatitis. Recommendations of the Immunization Practices Advisory Committee. *Ann Intern Med* 96:193-197, 1982
- Krugman S: The newly licensed hepatitis B vaccine. Characteristics and indications for use. *JAMA* 247:2012-2015, 1982
- CDC: The safety of hepatitis B virus vaccine. *Morbidity and Mortality Weekly Report* 32:134-136, 1983
- CDC: Hepatitis B virus vaccine safety: Report of an inter-agency group. *Morbidity and Mortality Weekly Report* 34:465-468, 1982

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Cardiotoxicity of Local Anesthetics—The Plot Thickens

In 1978, an editorial by Albright¹ alerted the anesthetic community to a new complication of regional analgesia, that of sudden circulatory collapse, often resistant to resuscitation, following the accidental intravascular injection of clinical doses of the long-acting anesthetics bupivacaine and etidocaine. In some cases, the cardiac arrest was preceded by convulsions but in others it occurred almost immediately after rapid injection of the drug such as to make antecedent hypoxia unlikely. Albright concluded that "animal studies are urgently needed" to evaluate the relation between central nervous system and cardiac toxicity of the anesthetics. Consequent to this report, Liu and his co-workers² studied the acute intravenous cardiotoxicity of four local anesthetic drugs (2% lidocaine, 0.5% bupivacaine, 3% mepivacaine, 2% and 1% etidocaine) in intact ventilated dogs anesthetized with pentobarbital. The results indicated that all four local anesthetics had the propensity for producing profound circulatory depression and that their relative cardiotoxicity was proportional to their *in vivo* anesthetic potency. These findings appeared to support the role of hypoxemia and acidemia as predisposing factors for the severe cardiac depression observed clinically with bupivacaine and etidocaine, particularly since marked decreases in oxygen

tension, pH, and base change had been demonstrated previously during bupivacaine-induced convulsions.³ However, when the cardiovascular effects of bupivacaine, etidocaine, and lidocaine were compared in lightly anesthetized ventilated cats, intravenous infusions at equiconvulsant rates resulted in the development of nodal and ventricular arrhythmias before or at the onset of the seizure with bupivacaine and etidocaine but not with lidocaine.⁴ The fact that arrhythmias were not seen with subconvulsant doses of lidocaine suggested a specific arrhythmogenic action of bupivacaine and etidocaine, thus corroborating the results of *in vitro* studies on paced perfused rabbit hearts that showed relatively greater cardiotoxic actions of the two long-acting drugs than of lidocaine.*

In the meantime, additional fatal cardiac arrests occurred sporadically in healthy parturients scheduled for cesarean section after intended epidural injection of bupivacaine. None of these was publicized as a case report, but one parturient, whose circulatory collapse followed administration of 12 ml 0.75% bupivacaine, was included in an 18-month review of deaths during anesthesia reported to the Office of Medical Examiner in New York City.† The major abnormality found on her autopsy was

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* Block A, Covino BG: Effect of local anesthetic agents on cardiac conduction and contractility. *Regional Anesthesia* 6:55-61, 1981.

† Chalon J: Causes of death during anesthesia (Editorial). *Survey of Anesthesia* 26:257-258, 1982.

a large hematoma in the sacrospinalis muscle adjacent to the site of entry of the epidural needle; puncture of the ligamentum flavum was not detected.‡

Concerned with the rising incidence of maternal mortality, the Section on Anesthetic and Life Support Drugs of the Food and Drug Administration of the Department of Health and Human Services convened a meeting of its Advisory Committee on May 3, 1982, to reevaluate the "dose related adverse experience of long-acting, highly protein bound, local anesthetics," *i.e.* bupivacaine and etidocaine. Much of the discussion centered around the need for "well-constructed laboratory investigations" of the differential central nervous system and cardiac effects of these agents in an appropriate animal model.§ The article by Kotelko *et al.*,⁵ in this issue, fulfills these criteria. The animal species chosen, the adult sheep, permitted monitoring of all variables necessary to determine seizure threshold, cardiac effects, associated local anesthetic drug concentrations, as well as changes in arterial pressures, blood gases, and electrolyte values. By using awake, unpremedicated animals and by calculating the "low" doses to approximate those employed clinically, the study simulated human conditions *par excellence*. The results thus showed that convulsant doses of bupivacaine, but not lidocaine, produced severe ventricular arrhythmias in the absence of hypoxemia, acidemia, or hyperkalemia. In subsequent experiments undertaken by the same research group⁶ under the same laboratory conditions, sheep were rendered hypoxic-acidemic and then randomly assigned to receive either bupivacaine or lidocaine in low or high dose over a 10-s period. All animals developed electroencephalographic evidence of convulsive activity within 30 s. They immediately were treated to terminate the seizures so that arterial blood gas and acid-base values normalized within 5 min. Serious arrhythmias and conduction changes occurred after both low- and high-dose bupivacaine but not lidocaine. Most importantly, despite the rapid correction of the acidemia, cardiopulmonary resuscitation failed in all animals given high-dose bupivacaine and one animal given low-dose bupivacaine but in none injected with low- or high-dose lidocaine. Similar findings were obtained in another well-known laboratory. Morishima and her associates⁷ also compared the effects of equipotent doses of lidocaine and bupivacaine in sheep but added pregnant ewes to the study. They found not only that the margin of safety between convulsions and circulatory collapse was smaller with bupivacaine than lidocaine but that pregnant sheep required a smaller dose of bupivacaine than the nonpregnant animal to produce symptoms of cardiovascular depression.

‡ Chalon J: Personal communication.

§ Transcript of Fourth Meeting of the Anesthetic and Life Support Drug Advisory Committee, May 3, 1982, pp 3, 153, 160.

What can be advocated to avoid morbidity and mortality resulting from the accidental intravascular injection of bupivacaine and etidocaine? The simplest approach would be the substitution of a less cardiotoxic local anesthetic. There are, however, situations in which the prolonged duration of bupivacaine and etidocaine may provide advantages. Two recommendations have been made to increase their safety. The first, fractionation of the injectate, is uniformly applicable. Injections should be made intermittently in up to 30 mg increments of bupivacaine or equivalent doses of etidocaine followed 1–2 min later by a careful search for the classic signs and symptoms of local anesthetic toxicity (jitteriness, heart rate changes, slurred speech, ringing in ears, metallic taste in mouth). The second recommendation, that of adding epinephrine to the test dose, may not always be helpful. Recent sheep experiments⁸ have confirmed the empiric observation that the magnitude and duration of cardiovascular changes from small doses of intravenous epinephrine may be so insignificant as to make their recognition difficult. Furthermore, intravascular injections of local anesthetic have occurred with top-up doses after an uneventful initial dose.⁹ In the pregnant woman, epinephrine 1:200,000 added to the test dose is safe (except perhaps in a severe preeclamptic gravida), but the drug should not be added to the total dose because of its propensity for decreasing uterine blood flow. In gravid sheep, this effect was found to be dose related.⁸ And in a study of 12 parturients by means of the ¹³³xenon clearance technique before and after epidural administration of 10 ml 2-chloroprocaine with epinephrine 5 µg/ml, intervillous blood flow decreased in three of the women (–21%, –30%, and –58%, respectively),¹⁰ obviously an unpredictable phenomenon.

In conclusion, bupivacaine appears to be more cardiotoxic than lidocaine, and this toxicity seems to be aggravated by antecedent hypoxia-acidemia as well as by pregnancy. In the clinical application of bupivacaine, a test dose containing epinephrine should be employed, the therapeutic dose should be fractionated, and drugs and equipment for immediate treatment of adverse effects always must be at hand.

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References

1. Albright GA: Cardiac arrest following regional anesthesia with etidocaine or bupivacaine (Editorial). *ANESTHESIOLOGY* 51:285–287, 1979
2. Liu P, Feldman HS, Covino BM, Giasi R, Covino BG: Acute cardiovascular toxicity on intravenous amide local anesthetics

- in anesthetized, ventilated dogs. *Anesth Analg* 61:317-322, 1982
3. Moore DC, Crawford RD, Scurlock JE: Severe hypoxia and acidosis following local anesthetic-induced convulsions. *ANESTHESIOLOGY* 53:259-260, 1980
 4. de Jong RH, Ronfeld RA, DeRosa RA: Cardiovascular effects of convulsant and supraconvulsant doses of amide local anesthetics. *Anesth Analg* 61:3-9, 1982
 5. Kotelko DM, Shnider SM, Dailey PA, Brizgys RV, Levinson G, Shapiro WA, Koike M, Rosen MA: Bupivacaine-induced cardiac arrhythmias in sheep. *ANESTHESIOLOGY* 60:10-18, 1984
 6. Thigpen JW, Kotelko DM, Shnider SM, Foutz SE, Levinson G, Koike M, Rosen MA: Bupivacaine cardiotoxicity in hypoxic-acidotic sheep (Abstract). *ANESTHESIOLOGY* 59(Suppl):A204, 1983
 7. Morishima HO, Pedersen H, Finster M, Tsui A, Hiraoka H, Feldman HS, Arthur GR, Covino BG: Is bupivacaine more cardiotoxic than lidocaine? (Abstract). *ANESTHESIOLOGY* 59(Suppl):A409, 1983
 8. Hood DD, Dewan DM, Rose JC, James FM III: Maternal and fetal effects of intravenous epinephrine containing solutions in gravid ewes (Abstract). *ANESTHESIOLOGY* 59(Suppl):393, 1983
 9. Ryan DW: Accidental intravenous injection of bupivacaine: A complication of obstetrical epidural anaesthesia. *Br J Anaesth* 45:907-908, 1973
 10. Albright GA, Jouppila R, Hollmen AI, Jouppila P, Vierola H, Koivula A: Epinephrine does not alter human intervillous blood flow during epidural anesthesia. *ANESTHESIOLOGY* 54:131-135, 1981