

Editorial Views

Anesthesiology
51:285-287, 1979

Cardiac Arrest Following Regional Anesthesia with Etidocaine or Bupivacaine

ANESTHESIOLOGISTS have generally believed that cardiac arrest following injection of clinical doses of local anesthetics could be prevented by prompt oxygenation and, if necessary, blood pressure support. However, this may not always be the case in susceptible individuals who have been given inadvertent intravascular injections of clinical doses (100–200 mg) of potent, highly lipid soluble and protein-bound amide local anesthetic agents such as etidocaine and bupivacaine.

The report by Prentiss of sudden cardiac arrest following caudal anesthesia with etidocaine¹ is the sixth anecdotal case to my knowledge of sudden cardiovascular collapse immediately after the presumed intravascular injection of clinical doses of bupivacaine and now etidocaine. The other cases also occurred in the operating room under the direct supervision of anesthesiologists and following negative aspiration tests. Sudden cardiovascular collapse (ventricular fibrillation or ventricular tachycardia, cardiac asystole, or complete heart block with P waves only) occurred almost immediately after rapid injection of the local anesthetic agent, so that antecedent hypoxia probably was not an etiologic factor. Resuscitation has generally been difficult, with cardiac massage needed for 45 min or longer. Only two of these cases have been previously reported. Cardiac arrest was attributed to a "total spinal" in the first case.² This diagnosis is questionable since ventricular fibrillation occurred immediately after removal of the needle from the interscalene space after injection of bupivacaine, 0.5 per cent, 40

ml. Hodgkinson³ reported ventricular tachycardia at cesarean section after an epidural injection of bupivacaine, 0.75 per cent, 2 ml, and 10 ml 5 min later. There was an immediate onset of severe convulsions. Endotracheal intubation was performed after administration of succinylcholine, 100 mg, and the patient ventilated with pure oxygen. Ventricular tachycardia developed approximately 3 min after the onset of seizures, which responded to DC electric shock. Cardiac resuscitation was rapid in the latter two cases.

The other three cases occurred at: 1) Stanford Medical Center, bupivacaine, 0.5 per cent, 40 ml, for axillary block; 2) Santa Clara Valley Medical Center, bupivacaine, 0.5 per cent, 40 ml, for interscalene block; 3) Oakland Naval Hospital, bupivacaine, 0.5 per cent, 25 ml, with chloroprocaine, 2 per cent, 15 ml, for Bier block, in which the tourniquet suddenly deflated. In addition, a maternal death secondary to convulsions and cardiovascular collapse occurred following administration of bupivacaine, 0.5 per cent, for caudal anesthesia (test dose 5 ml followed by 15 ml). This patient, however, had three seizures over a 3-min period before cardiovascular collapse was ascertained, so that hypoxia may well have been a contributory factor.

The cardiovascular system is considered more resistant than the central nervous system (CNS) to local anesthetic toxicity. When artificial ventilation is maintained, the dose needed to produce cardiovascular collapse may be several times larger than that which causes respiratory paralysis.⁴ However, the relative cardiovascular toxicity of local anesthetic agents does not parallel that for the respiratory system. Steinhaus⁵ demonstrated that for procaine the cardiovascular depressant dose was more than

Accepted for publication February 20, 1979.

Key words: Anesthetic techniques: regional. Anesthetics, local: bupivacaine; etidocaine. Complications: arrest, cardiac.

four times the respiratory depressant dose in rabbits, but the difference between these two doses for dibucaine (a more potent amide anesthetic) was slight. The toxicity ratio for procaine to dibucaine was 1:80, using cardiovascular failure as the end point, compared with 1:20 by ordinary toxicity determinations of respiratory failure.⁶ More importantly, there was complete recovery following procaine administration, and no recovery following dibucaine toxicity.

Human volunteers receiving continuous intravenous infusions of bupivacaine have not demonstrated toxic symptoms at venous plasma bupivacaine levels of 2.6 to 4.5 $\mu\text{g/ml}$.⁷ However, constant-infusion studies have more clinical application to rapid absorption from the injection site than to accidental intravascular injection, since the dose of drug tolerated by the volunteers decreased with the speed of infusion. Unfortunately there are a paucity of experimental or clinical data delineating the effects of bupivacaine and etidocaine on the cardiovascular system above the convulsive threshold. Comparative LD_{50} studies of acute toxicity from rapid intravenous injections reported by Adams *et al.*⁸ are not applicable (artificial respiration was not maintained), since respiratory arrest occurs before marked cardiovascular depression. Widman⁹ found no CNS or circulatory effects following the rapid injection (3–4 sec) of bupivacaine, 0.5 per cent, 0.75 mg/kg, (approximately 10 ml in a 70-kg man) intravenously in six volunteers. Larger doses have not been studied in man for ethical reasons. Seizures or cortical irritation have been reported after presumed intravascular injection of small doses of bupivacaine (50 mg,¹⁰ 75 mg,¹¹ 100 mg,¹² three cases 100 mg,¹³ 120 mg¹² and 135 mg,¹⁴) and etidocaine, 15 mg,¹⁵ and 100 mg.¹⁶

The relative toxicity of etidocaine and presumably bupivacaine is disproportionately high (twofold) when administered intravenously, compared with absorption from injection sites, because these drugs have high lipid solubility.¹⁵ At 1 $\mu\text{g/ml}$ bupivacaine and etidocaine are 95 per cent bound in plasma, with a rapid decrease in the percentage bound as the plasma concentration exceeds 4–5 $\mu\text{g/ml}$, thereby increasing the fraction of free base available to cross the nerve membrane.¹⁷ If cardiac toxicities of bupivacaine and etidocaine are similar to that of dibucaine, a steep dose–response curve would be anticipated, with marked cardiovascular depression occurring at plasma levels only slightly above that for CNS toxicity. Additionally, cardiac resuscitation would be expected to be difficult, with prolonged cardiac massage to allow for redistribution and metabolism of the offending agent.

Lund *et al.*¹⁸ reported two seizures from 2,206 instances of regional anesthesia using etidocaine, presumably from intravascular injections. One of the affected patients (etidocaine, 1.5 per cent, 30 ml epidurally) had “acute cardiovascular collapse . . . a prolonged resuscitation and a stormy postanesthetic period.” Moore *et al.*¹⁹ reported systemic toxic reactions in 15 patients after 11,080 blocks using bupivacaine. Unrecognized intravascular injections were responsible for the reactions in 13 patients, and rapid absorption after intercostal nerve blocks with typical doses in two young, healthy patients. These two cases may have been the result of low “individual toxic thresholds.”¹⁹ Hodgkinson³ also reported the occurrence of generalized seizures 15 min after the epidural injection of bupivacaine, 0.75 per cent, 20 ml, preparatory to cesarean section. Since this primigravida demonstrated CNS toxicity at an unusually low blood level of bupivacaine, she might have had a cardiac arrest if the drug had been administered intravascularly.

The newer local anesthetic agents (bupivacaine, etidocaine) may result in almost simultaneous seizures and cardiovascular collapse without antecedent hypoxia from typical clinical doses administered inadvertently intravascularly. The true incidence of this phenomenon, if real, needs to be determined. How many other cases have occurred and not been reported? Since resuscitation may be difficult and outcome poor (45 min or longer to establish spontaneous cardiac rhythm), medical opinion would immediately suspect “preventable hypoxia” as a necessary etiologic factor, which may not be the case. Animal research studies are urgently needed to evaluate: 1) the slope of the dose–response curve between CNS and cardiac toxicity during maintenance of artificial respiration; 2) the most effective means of cardiac resuscitation when direct cardiac depression is the result of toxicity with these potent amide local anesthetic agents. The value of membrane stabilizers such as lidocaine, procainamide, and diphenylhydantoin as used by Prentiss needs to be established.

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