

Bupivacaine Blood Levels during Continuous Interscalene Block

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Winnie and Collins¹ in 1964 described a technique for a block of the brachial plexus by a single injection through the interscalene space.^{2,3} A continuous method of subclavian perivascular block was reported in 1969 by DeKrey *et al.*⁴ His method was used primarily for surgical anesthesia, and the longest duration of block was 9 h. Ansbro was one of the first to suggest that a continuous block of the brachial plexus over several days would be useful in treating upper extremity vascular accidents.⁵ In 1978, a technique of continuous brachial plexus block was described by Manriquez and Pallares,⁶ which has been used routinely and successfully in our institution. This method relies upon intermittent injection of bupivacaine into the interscalene space every 6 h. This provides pain relief and continuous sympathetic blockade in the affected extremity for a period of 4 days or longer. However, the intermittent injection of bupivacaine results in variable peaking blood concentrations of bupivacaine. In addition, intermittent injection of the amide type local anesthetics may result in accumulation of the agent in the blood, possibly resulting in toxic manifestations.⁷⁻⁹ Presumably, if bupivacaine were administered by constant infusion, instead of intermittent injections, peaking blood levels could be avoided and potential toxicity minimized.

Accordingly, we have adopted the routine of administering this agent by constant infusion into the interscalene space when long-term brachial plexus block is

required. Twenty-five patients have received bupivacaine by this method for periods up to 4 days without any apparent complications. This paper presents six cases involving traumatic amputation of the fingers with extensive and prolonged reimplantation surgical procedures. We sought to determine whether the blood level of bupivacaine increased with constant infusion and to what degree.

METHODS

After obtaining their informed consent, we studied six adult patients. The technique of continuous interscalene block, as previously described, was employed.⁶ The initial dose of the anesthetic was 40 ml of 0.6% bupivacaine (240 mg) with epinephrine (1:400,000). A constant infusion of 0.25% bupivacaine without epinephrine at the rate of $0.1 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ was started 4 hours after the initial dose. The constant volume infusion was administered by a Harvard[®] pump through a catheter (Quick-Cath,[®] 20 g \times 1/4", Travenol Laboratories, Inc.) in the interscalene space after the catheter had been secured with sutures.

Sampling of blood for the determination of bupivacaine levels was done from a forearm vein contralateral to the side of interscalene infusion. Aliquots of 5.0 ml of the patient's blood were taken before the initial dose of bupivacaine (blank samples) and at 1, 2, 3, 4, 16, 28, 40, and 52 h after the interscalene block was initiated. The blood was mixed gently for one minute in a 10-ml Vacutainer[®] tube containing potassium oxalate and sodium fluoride (Becton-Dickinson, Rutherford, New Jersey). The tubes containing the blood samples were allowed to stand in the upright position for one hour at 4° C. The plasma was separated from the cells by centrifugation. A Hewlett-Packard[®] Model 5880 gas chromatograph equipped with dual nitrogen-phosphorous detectors, and a capillary column inlet system was employed using the previously described method of Anton *et al.*¹⁰ This chromatographic method does not detect metabolites of bupivacaine.

RESULTS

The plasma levels of bupivacaine obtained after an initial dose of 240 mg followed by a constant infusion

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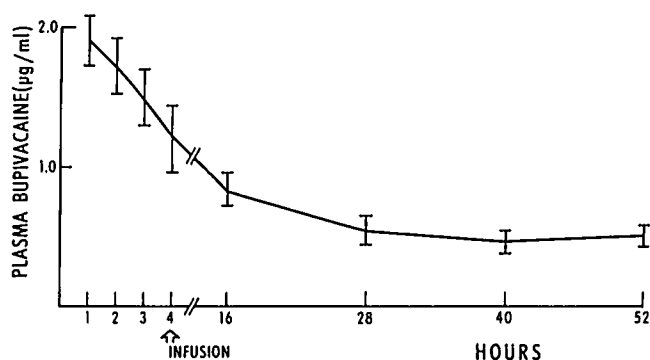


FIG. 1. Plasma concentrations of bupivacaine after the initial injection of 240 mg into the interscalene space followed by a constant infusion of 0.25% bupivacaine beginning at 4 h of 0.1 mg · kg⁻¹ · h⁻¹ (n = 6, mean + SE).

of 0.1 mg · kg⁻¹ · h⁻¹ are shown in figure 1. The plasma level at 1 h following the initial injection of bupivacaine averaged 1.9 ± 0.39 µg/ml. During the constant infusion period, satisfactory anesthesia and sympathetic blockade (as determined by skin temperature) was maintained, during which time the plasma levels of bupivacaine stabilized at 0.5 ± 0.12 µg/ml.

When the catheter was removed from the interscalene space, after 52 h, there were no signs of infection, bleeding, or hematoma.

DISCUSSION

Studies in mice, rabbits, and humans show that toxic reactions from anilide-local anesthetics often are delayed and that these drugs have a cumulative effect when given for continuous peridural anesthesia by intermittent injections.^{7-9,11-13} Rosenblatt *et al.* reported that the blood levels of bupivacaine increased during the second day of constant infusion in a patient given axillary block.¹⁴ In our patients the plasma concentration of bupivacaine at 1 h (1.9 ± 0.39 µg/ml) following the initial "loading" dose is consistent with the results reported by Wildsmith *et al.*¹⁵ These investigators also reported no evidence of systemic toxicity with bupivacaine at a peak plasma concentration of 2.0 µg/ml. A plasma concentration above 4 µg/ml would be expected to produce objective toxic reactions.¹⁶ Furthermore, the plasma concentrations in our patients decreased to one-fourth the initial concentration, and no accumulation of bupivacaine was noted throughout the infusion period.

Tachyphylaxis has been described when a continuous epidural nerve block is employed over a long period of time using an intermittent administration of the local anesthetic if the sensory block is allowed to relapse.^{7,17} It is our clinical impression that a similar phe-

nomena occurred with intermittent injections of bupivacaine during continuous brachial plexus block.⁶ The timing of injections is evidently a prime consideration that determines whether tachyphylaxis follows. It is less likely to occur if a blocking agent is reinjected soon after the first signs of returning sensation. If a delay of 10 min or more after the return of sensation occurs, then more drug must be given to offset tachyphylaxis. We have employed the constant infusion technique for interscalene block in 25 patients without evidence of tachyphylaxis.

Between 28 and 52 h, bupivacaine reached a steady state concentration in the plasma as indicated by the relatively constant plasma concentration during this period. Accordingly, the clearance of bupivacaine can be calculated by dividing the average infusion rate (0.146 mg/min) by the average steady state plasma concentration (0.5 ± 0.12 µg/ml). The calculated clearance of bupivacaine, 0.29 l/min, contrasts with the higher values reported by Tucker *et al.* (0.47–0.58 l/min).^{7,18} However, it may be inappropriate to compare the clearance value obtained in the present study to clearance calculations from data obtained after the intravenous bolus injection of bupivacaine.

In conclusion, constant infusion of (0.25%) bupivacaine after an initial 240-mg block avoids high peak blood concentrations and maintains the anesthetic concentration below toxic levels throughout the duration of the block.

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Plasma Levels of Beta-blocking Drugs prior to Coronary Artery Bypass Surgery

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The duration of action of beta-adrenergic blocking drugs such as propranolol and metoprolol is determined by the dose administered and by the plasma half-life. Propranolol has a half-life of approximately 2-5 h^{1,2} and metoprolol one of 3-6 h,^{2,3} and although the half-lives are relatively long, effects may be short lasting following small drug doses. This study was undertaken to determine whether or not commonly prescribed but relatively small dose schedules of propranolol and metoprolol, when continued until the day before or morning of coronary artery bypass graft surgery, reliably resulted in beta-blocker plasma levels within the therapeutic range at the time of anesthesia and surgery.

A therapeutic beta blocker plasma range has been proposed for awake patients with coronary artery disease, and, in both awake and anesthetized patients, a

relationship between the logarithm of plasma propranolol level and beta-blocking effect has been demonstrated.^{2,4-7} In awake patients, therapeutic effects of propranolol and metoprolol have been observed in the range of approximately 50-100 ng/ml,^{8,9} although propranolol plasma levels from about 30 ng/ml have been reported to reduce the frequency of angina attacks,⁵ and metoprolol levels above the 50-100 ng/ml range may be required to suppress heart rate (HR) exercise response in healthy volunteers.¹⁰ A therapeutic range during anesthesia and surgery has not been established, although propranolol 50-100 ng/ml has been shown to significantly ameliorate the hemodynamic responses to stressful perioperative stimuli.⁷

METHODS

Sixty-eight patients, (57 men and 11 women, ages 40-75 yr) who chronically took propranolol or metoprolol, and who were scheduled for elective coronary artery bypass graft surgery, were investigated following institutional approval and informed consent. Patients had been taking either propranolol, 10 mg, 20 mg, or 40 mg, four times a day, or metoprolol, 50 mg, twice a day, for the preceding 1 month to 10 years. Beta-blocker therapy was continued until the day before or morning of surgery. In addition to beta blockers, 68 patients took dipyridamole (Persantine®), and 64 took nitrates. Patients taking cimetidine, phenothiazines, or heparin were excluded from the study, as these drugs alter propranolol kinetics,^{11,12} and patients with renal, hepatic, gastrointestinal, or thyroid

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