

Arterial and Venous Plasma Levels of Bupivacaine Following Epidural and Intercostal Nerve Blocks

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Arterial and peripheral venous plasma levels of bupivacaine were determined in 30 patients following epidural anesthesia using 150 and 225 mg, as well as following intercostal nerve block with 400 mg. Arterial levels were consistently higher than levels in simultaneously sampled venous blood, and the highest levels occurred with bilateral intercostal nerve block. No evidence of systemic toxicity was observed. The results suggest that bupivacaine may have a wider margin of safety in man than is now stated. (Key words: Anesthetics, local, bupivacaine; Anesthetic techniques, peridural; Anesthetic techniques, regional, intercostal.)

BUPIVACAINE (Marcaïne, Winthrop), like all local anesthetics, is used in various concentrations and volumes, depending on the regional block technique employed and on the type of procedure for which it is being performed—*i.e.*, surgery, obstetrics, diagnosis, or therapeutics. For single-dose epidural anesthesia for intra-abdominal surgery, 0.75 per cent bupivacaine must be used in order to provide rapid establishment of surgical anesthesia, to establish complete motor blockade of the abdominal muscles, and to abolish visceral pain during intra-abdominal pelvic manipulations.¹⁻³ Bilateral intercostal nerve block for upper intra-abdominal surgery requires 0.5 per cent bupivacaine to provide rapid onset of surgical anesthesia and complete motor relaxation of the abdominal musculature.^{1,2}

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The purpose of this paper is to report plasma levels of bupivacaine following use of concentrations, volumes, and doses adequate for these forms of regional anesthesia.

Method of Study

Plasma levels of bupivacaine were ascertained following epidural anesthesia and bilateral intercostal nerve blocks in 30 patients. The patients were not screened but were chosen consecutively depending on the operating room schedule and the number of patients that could be studied on any specific day (the study started July 21, 1975, and was completed August 27, 1975).

SELECTION OF PATIENTS AND PREMEDICATION

The subjects of this study were 20 adult patients having epidural anesthesia and ten adult patients having bilateral intercostal nerve blocks. Written informed consent, as approved by the Human Rights Committee of the Virginia Mason Research Center, was obtained from every patient for: the block technique, the arterial and venous blood sampling, and the dosage of bupivacaine.

Premedication was the choice of the resident who was to do the operation. The 20 patients who had epidural anesthesia received no sedation other than the premedication until the surgical procedure began (table 1). The ten patients who had bilateral intercostal nerve blocks received 100–150 mg of a 0.2 per cent methohexital solution intravenously prior to and during administration of the block, in addition to the premedication (table 1). Administration of methohexital was terminated prior to completion of the block, so that the patients were conscious and able to respond to questions within 10 minutes after completion of the block.

TABLE I. Premedication of 30 Patients Whose Plasma Levels Were Studied

Narcotic	Belladonna Derivative	Miscellaneous Agents	Epidural Block	Intercostal Nerve Block
Meperidine 75 mg 100 mg 100 mg 100 mg 125 mg	Atropine, 0.4 mg	Hydroxyzine, 75 mg	2	2
			5	
	Atropine, 0.4 mg Atropine, 0.4 mg		1	2
				1
Morphine 5 mg 8 mg 8 mg 8 mg 10 mg 10 mg 10 mg 10 mg 10 mg 12 mg 15 mg	Scopolamine, 0.6 mg Atropine, 0.4 mg	Diazepam, 10 mg	1	
			1	
	Atropine, 0.4 mg Atropine, 0.4 mg	Diazepam, 10 mg	2	
			2	
	Atropine, 0.4 mg Scopolamine, 0.4 mg Atropine, 0.4 mg	Hydroxyzine, 75 mg	1	
			1	
			1	
	Atropine, 0.4 mg Scopolamine, 0.6 mg		2	
			1	
			2	
			1	
		1		
		2		
		1		
TOTAL			20	10

DOSAGE OF BUPIVACAINE AND BLOCK TECHNIQUE

In 20 patients, epidural anesthesia was administered at the second lumbar interspace with 0.75 per cent bupivacaine with epinephrine, 1:200,000—ten received 20 ml (150 mg) and ten, 30 ml (225 mg). The sixth through the twelfth intercostal nerves were blocked bilaterally in ten patients using 80 ml 0.5 per cent bupivacaine (400 mg) with 0.25 mg epinephrine (1:320,000)—5 ml to each of the 14 nerves for a total of 70 ml, plus an additional 10 ml for skin wheals and subcutaneous infiltration. Because we wanted to complete the intercostal nerve blocks in less than 5 minutes, two anesthesiologists worked simultaneously (one on each side). The techniques used were those previously described.⁴

BLOOD SAMPLING AND PLASMA ANALYSIS

For arterial blood sampling, a 20-gauge, 1½-inch Teflon catheter needle was inserted percutaneously into the radial artery or, when this could not be accomplished, into the brachial artery. For venous sampling a 16-gauge, 2½-inch Teflon catheter needle was inserted in the largest available vein in the

antecubital fossa of the same arm. In the opposite arm a 16-gauge, 2½-inch Teflon catheter was inserted in a vein in the hand through which anesthetic medications were given intravenously.

The blocks were performed in a central induction room, where the patient remained for at least 30 minutes following completion of the block. In no case was the operation begun until after the 45-minute sample was drawn. The blood samples were drawn simultaneously from the artery and vein at 0 time (control) and 5, 10, 15, 20, 25, 30, 45, 60, and 120 minutes from the start of the block—*i.e.*, raising of the skin wheal. Plasma levels of bupivacaine were determined by gas chromatography.⁵

DETERMINATION OF TIME FROM RAISING OF SKIN WHEEL TO COMPLETION OF BLOCK

The time elapsed from the raising of the skin wheal to the completion of the block was coded to the closest minute—*i.e.*, if a block was completed in 3 minutes and 45 seconds, it was coded as 4 minutes, and if completed in 3 minutes and 25 seconds, as 3 minutes. These times, as well as sampling times, were determined by stopwatches.

ANALYSIS OF DATA

Following coding, all data were 1) key-punched into computer cards, 2) verified, 3) read onto tape, and 4) analyzed by the Conversational Computer Statistical System.⁶ The data were submitted to statistical analysis using the test of bivariate correlations.

Results

All 30 blocks produced satisfactory surgical anesthesia, indicating that the solutions of bupivacaine had been placed correctly and in adequate volume and concentration.

TIMES FOR COMPLETION OF BLOCKS

The 20 epidural anesthetics were completed in a mean time of 4 minutes, standard deviation ± 1.5 minutes. The ten bilateral intercostal nerve blocks were completed in a mean time of 4.4 minutes, standard deviation ± 0.97 minutes.

EPIDURAL ANESTHESIA WITH 20 ML OF 0.75 PER CENT BUPIVACAINE (150 MG) CONTAINING 1:200,000 EPINEPHRINE

In ten female patients, 27 to 59 years of age, weighing 113 pounds or more, undergoing gynecologic procedures—nine of which were intra-abdominal—mean peak arterial and venous plasma levels were 1.46 $\mu\text{g/ml}$ (range 1.1–2.32 $\mu\text{g/ml}$) and 1.19 $\mu\text{g/ml}$ (range 0.71–1.73 $\mu\text{g/ml}$), respectively.⁶ These levels occurred 15 to 30 minutes after injection of the agent (fig. 1).

EPIDURAL ANESTHESIA WITH 30 ML OF 0.75 PER CENT BUPIVACAINE (225 MG) CONTAINING 1:200,000 EPINEPHRINE

In six female and four male patients, 31 to 59 years of age, weighing 121 pounds or more, undergoing lower intra-abdominal (six patients) and perineal procedures (four patients), mean peak arterial and venous

plasma levels were 1.49 $\mu\text{g/ml}$ (range 1.12–2.15 $\mu\text{g/ml}$) and 1.25 $\mu\text{g/ml}$ (range 0.78–1.7 $\mu\text{g/ml}$), respectively. Except for one patient whose peak level was 1.25 $\mu\text{g/ml}$ in 60 minutes, peak levels occurred 15 to 30 minutes after injection of the agent (fig. 2).

BILATERAL INTERCOSTAL NERVE BLOCKS WITH 80 ML OF 0.5 PER CENT BUPIVACAINE (400 MG) CONTAINING 1:320,000 EPINEPHRINE

In six male and four female patients, 20 to 72 years of age, weighing 109 pounds or more, undergoing upper intra-abdominal surgery, mean peak arterial and venous plasma levels were 3.29 $\mu\text{g/ml}$ (range 1.72–4.0 $\mu\text{g/ml}$) and 2.52 $\mu\text{g/ml}$ (range 1.4–3.45 $\mu\text{g/ml}$), respectively. They occurred 10 to 20 minutes after injection of the agent (fig. 3).

Discussion

SELECTION OF REGIONAL BLOCKS TO BE STUDIED

Single-dose epidural anesthesia was studied because: 1) it is the only technique for which we employ 0.75 per cent bupivacaine; 2) systemic toxic reactions, neuropathy, or both, are more likely to occur when high rather than low concentrations of a local anesthetic agent are injected; 3) excluding spinal anesthesia, it is the most frequently employed form of regional anesthesia.

On the other hand, block of the intercostal nerves bilaterally is done infrequently by most anesthesiologists. It was studied, however, because: 1) we frequently employ it for upper intra-abdominal surgery, particularly for the patient of poor physical status—American Society of Anesthesiologists (ASA) physical status rating 3, 4, or 5; 2) a large volume (60–80 ml) and high concentration (0.5 per cent) of bupivacaine are needed for rapid establishment of surgical sensory anesthesia and for complete motor blockade; 3) most importantly, when it is done rapidly and properly, the plasma levels of local anesthetic agents peak sooner and are higher than with any other

⁶ Mean peak level is the highest microgram concentration attained in the plasma from each of the ten patients.

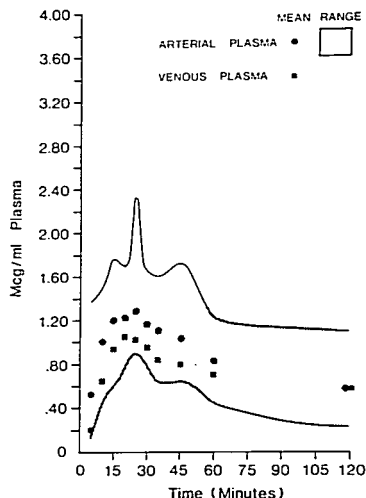


FIG. 1. Means and ranges of arterial and venous plasma levels after 20 ml bupivacaine, 0.75 per cent (150 mg), with 1:200,000 epinephrine following epidural block at the intervals of sampling. ● = mean arterial plasma level; two black lines = ranges (high and low) of arterial plasma levels; ■ = mean venous plasma level; edges of shaded area = high and low venous plasma levels.

gional nerve block studied to date.⁷⁻⁹ Therefore, if a systemic toxic reaction from bupivacaine were to occur from absorption in any block technique, it would be most likely to occur following this block.

DOSAGE OF BUPIVACAINE AND EPINEPHRINE

The volumes and concentrations for these blocks were employed because they are the approximate maxima that might be required to result in effective sensory and motor blockade under any circumstance—*e.g.*, teaching of the technique, etc.

All solutions in this study contained epinephrine. We add epinephrine to most local anesthetic solutions because it lowers the blood levels of such agents; we seldom exceed a dose of 0.25 mg epinephrine,

regardless of the volume of local anesthetic solution injected.^{4,8} The solutions used for the epidural blocks contained what is considered the optimal dose of epinephrine—1:200,000 (0.1 mg in 20 ml and 0.15 mg in 30 ml)—while those employed for the bilateral intercostal nerve blocks could be considered less than optimal—1:320,000 (0.25 mg in 80 ml).^{4,10-12}

ARTERIAL AND VENOUS PLASMA LEVELS

Arterial levels were measured for comparison with peripheral venous levels because they more closely reflect changes in drug levels in well-perfused vital organs and are more sensitive to change in drug absorption or disposition.¹³ Venous sampling is more prone to variability and artifact due to local circulatory changes at the sampling site, in which case the resultant blood

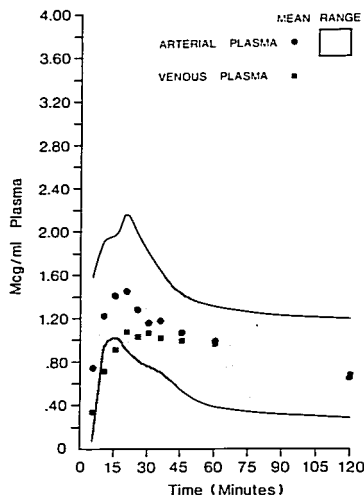


FIG. 2. Means and ranges of arterial and venous plasma levels after 30 ml bupivacaine, 0.75 per cent (225 mg), with 1:200,000 epinephrine following epidural block at the intervals of sampling. ● = mean arterial plasma level; two black lines = ranges (high and low) of arterial plasma levels; ■ = mean venous plasma level; edges of shaded area = high and low venous plasma levels.

concentration profile may lead to erroneous conclusions.¹¹ For these reasons, toxic effects may be more reliably associated with arterial than with venous drug levels.^{11,12} The mean peak plasma levels and ranges, as anticipated, were markedly higher following bilateral intercostal nerve blocks using 400 mg than following epidural anesthesia with either 150 or 225 mg. Although not anticipated, and at present unexplainable, the mean peak plasma levels and ranges with epidural blocks did not vary significantly, despite the 75-mg difference in dosages.

Comparison of the arterial and venous plasma levels obtained in this investigation with those reported in other studies, including those previously reported by us, is difficult and probably meaningless, because in previous studies: 1) volumes and concentrations and, therefore, total milligram doses were less; 2) dosages were based on milligrams per pound of body weight, estimated on clinical need for the specific blocks, or on predetermined therapeutic indices, as opposed to a fixed maximum milligram dosage for a particular block technique; 3) the numbers of patients studied were small; 4) arterial sampling was not done in most instances; 5) some of the studies were studies of the parturient; 6) bupivacaine was given intravenously; 7) the techniques of gas chromatography differed; or 8) all of these.^{1,2,15-20}

SYSTEMIC TOXICITY

The convulsive plasma levels of bupivacaine in man have been reported to be 4 $\mu\text{g/ml}$ or more.¹³ In only one of the present 30 patients did the arterial plasma level peak at 4.0 $\mu\text{g/ml}$ 15 minutes following a bilateral intercostal nerve block. No systemic toxic reaction was observed in the 30 patients. We did not expect any such reaction—unless during epidural anesthesia bupivacaine had been injected inadvertently intravenously—because: 1) we have employed 0.75 per cent bupivacaine with epinephrine, 1:200,000, or without epinephrine in dosages

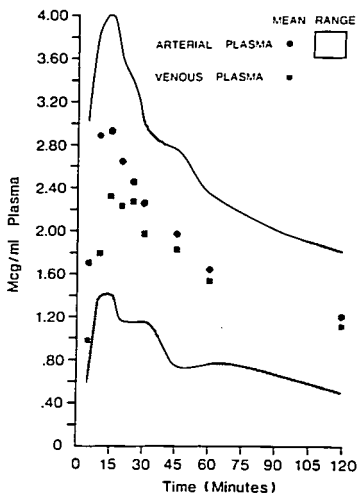


FIG. 3. Means and ranges of arterial and venous plasma levels after 80 ml bupivacaine, 0.75 per cent (400 mg), with 1:320,000 epinephrine following bilateral intercostal nerve block at the intervals of sampling. ● = mean arterial plasma level; two black lines = ranges (high and low) of arterial plasma levels; ■ = mean venous plasma level; edges of shaded area = high and low venous plasma levels.

as high as 200 mg for single-dose epidural anesthesia for surgical procedures in 1,312 patients with only one systemic toxic reaction from an inadvertent intravascular bolus dose of 18 ml; 2) 0.25–0.5 per cent solutions and dosages of 200–525 mg with epinephrine, 1:200,000 to 1:320,000, or without epinephrine were used in 787 patients for bilateral intercostal nerve block for surgical procedures with no systemic toxic reaction.

Age, weight, underlying disease, etc., have been said to be important factors in determining whether a systemic toxic reaction develops.^{4,10,11} However, the importance of these factors, if any, needs documentation. Correlations between these factors and maximum plasma levels of each patient were not found in a previous study with mepivacaine, whose chemical structure resembles that of

** Tucker GT, Mather LE: Personal communication of research now in preparation for publication.

bupivacaine.⁸ Likewise, in the small patient population reported herein (30 patients), the simple bivariate correlations between predictor variables (sex, age, height, weight, and physical status) and each of the criterion variables (peak arterial plasma level, peak venous plasma level, time to peak arterial plasma level, and time to peak venous plasma level) were not statistically significant. Perhaps the principal factors in determining dosages that may be used without resulting in a systemic toxic reaction are not age, weight, etc., but the specific regional block technique itself—that is, the area of the body into which the solution is injected, its vascularity, and the possibility of an intravascular injection from a needle whose position is not changed during injection of a large dose of the local anesthetic agent.

SHIVERING

Shivering has been cited as possible evidence of a mild systemic toxic reaction following administration of bupivacaine.^{1,2,20} Therefore, this sign was carefully observed, both in the induction room, where all blocks were performed and where the temperatures were 74 F or more and in the operating rooms, where the temperatures were 70 F or less. In the induction room, none of the patients shivered. In the operating rooms, shivering occurred in three of the ten patients who received bilateral intercostal nerve blocks and in five of the 20 patients who received epidural anesthesia. In a previous study of parturients, shivering was higher with 0.25 per cent than with 0.5 per cent solutions of bupivacaine—that is, the lower dosage resulted in the higher incidence of shivering.²⁰ In both instances, shivering occurred when temperatures in the rooms were significantly below 74 F—that is, 65–70 F. Shivering may occur regardless of the local anesthetic agent injected, and the etiology of shivering probably involves many factors, the least influential of which may be the local anesthetic agent.²⁰

SYSTEMIC TOXICITY AND PACKAGE INSERTS

In countries other than the United States, where only 0.25 and 0.5 per cent concen-

trations of bupivacaine are available, the dosage of bupivacaine is 2 mg/kg, with the maximum of 100 mg without epinephrine and 150 mg with epinephrine, 1:200,000.¹¹ In the United States, where 0.25, 0.5, and 0.75 per cent solutions of bupivacaine are available, no maximum dose is defined in the package insert, which states: 1) "Most experience to date is with single doses of Marcaine up to 225 mg with epinephrine 1:200,000, and 175 mg without epinephrine; more or less drug may be used depending on individualization of each case;" and 2) "In clinical studies to date, total daily doses have been up to 400 mg. Until further experience is gained, this dose should not be exceeded in 24 hours."¹¹ However, some physicians misinterpret the first of these statements to mean that the doses stated represent the maximum amounts that should be given.

From our clinical experiences with bupivacaine from 1966 through March 1975, involving 5,880 patients, as well as from the plasma studies reported herein, it appears that such statements may be unnecessarily restrictive and in need of revision because 1) bupivacaine apparently has a greater margin of safety in man than the package insert indicates, and 2) dosages as stated in the inserts limit the use of this versatile, long-acting local anesthetic agent in single-dose epidural and peripheral nerve blocks.

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¹¹ As stated in 1) package inserts from Australia, Brazil, England, France, Germany, Japan, Netherlands, and New Zealand; 2) *British Pharmaceutical Codex*, Pharmaceutical Press of London, 1973; 3) *Martindale: The Extra Pharmacopoeia*, 26th edition, Pharmaceutical Press of London, 1967. Copies supplied on request.

¹¹ Package insert of Winthrop Laboratories (revised October 1974), 90 Park Avenue, New York, New York 10016.

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