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Effects of Peridural Block:

V. Properties, Circulatory Effects, and Blood Levels of Etidocaine and Lidocaine

Michael Stanton-Hicks, M.B., B.S., F.F.A.R.C.S., Terence M. Murphy, M.B.; Ch.B., F.F.A.R.C.S.,* John J. Bonica, M.D., F.F.A.R.C.S.,† Peter U. Berges, M.D.,* Laurence E. Mather, Ph.D.‡ Geoffrey T. Tucker, Ph.D.§*

Ten healthy, unpremedicated, male volunteers, aged 21–33 years, were given 20 ml 1 per cent etidocaine with 5 μg/ml epinephrine for peridural analgesia via a catheter placed at L2. On a different occasion they were given 20 ml 2 per cent lidocaine with 5 μg/ml epinephrine in the same manner. Initial onset of sensory analgesia to pin prick was faster for etidocaine (7 min) than for lidocaine (9 min). Analgesia lasted significantly longer after etidocaine with respect to both two-segment regression (177 ± 24 SE min *vs.* 114 ± 8 min) and total duration (379 ±22 min *vs.* 190 ± 8 min). Onset of maximal motor blockade was significantly faster with etidocaine (15.4 ± 2.5 min) than with lidocaine (31.7 ± 3.3 min); blockade lasted longer with etidocaine (331 ± 25 min *vs.* 167 ± 13 min). Changes in mean arterial pressure, cardiac output, central venous pressure, limb blood flows, total peripheral resistance, and stroke volume were similar with the two drugs, although those after etidocaine were more prolonged as a result of the longer blockade. Mean maximum arterial concentrations of etidocaine were 0.96 ± 0.05 SE μg/ml (plasma) and 0.55 ± 0.03 μg/ml (whole blood), achieved at 17 ± 2 min. Mean maximum arterial concentrations of lidocaine were 2.22 ± 0.09 μg/ml (plasma) and 1.85 ± 0.01 μg/ml (whole blood), achieved at 24 ± 2 min. No sign of central toxicity was observed with either drug, although subjects receiving lidocaine tended to sleep, which was not the case with etidocaine. Hematologic screening, blood chemistries, and urinalyses performed 24 hours before and after each study showed no abnormality. (Key words: Anesthetics, local, etidocaine; Anesthetics, local, lidocaine; Anesthetic techniques, peridural; Heart, peridural anesthesia.)

SEVERAL CLINICAL REPORTS[1,2] have recently confirmed animal data[3] indicating the prolonged duration of action of etidocaine (Duranest), a new local anesthetic agent. We have undertaken a comprehensive study of the anesthetic properties, cardiovascular effects, and pharmacokinetic profile of this compound under controlled conditions in human volunteers. The present report concerns a cross-over comparison of etidocaine–epinephrine with a standard agent, lidocaine (Xylocaine)–epinephrine, for peridural analgesia.

Methods

Subjects of the study were 10 healthy, unmedicated, informed, male volunteers, aged 21–33 years. Routine blood chemistries, urinalyses, hematologic screening, and physical examinations were carried out on each subject 24 hours before and 24 hours after each study.

Following placement of appropriate catheters and a rest period of at least 30 min, control measurements of mean arterial pressure (MAP), central venous pressure (CVP), heart rate (HR), cardiac output (CO), leg blood flow (LBF), arm blood flow (ABF), and arterial blood *p*H and P_{CO_2} were obtained, and total peripheral resistance (TPR) and stroke volume (SV) were calculated. The techniques and methods of measurements have been reported.[4–6]

* Assistant Professor.
† Professor and Chairman.
‡ Research Instructor, Anesthesiology and Pharmaceutical Sciences.
§ Research Assistant Professor.
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Address reprint requests to Dr. Stanton-Hicks.

TABLE 1. Salient Features of Blocks Produced by Etidocaine and Lidocaine, Both with Epinephrine, 5 μg/ml (Mean ± SE)

	Lidocaine	Etidocaine
Sensory Block		
Initial onset	<8.9 min	<6.8 min
Operative onset (± 4 segments)	19 ± 3 min	13 ± 3 min
Complete spread	47 ± 9 min	32 ± 7 min
Maximum number of dermatomes	16.1 ± 0.5	15.5 ± 1.1
Regression 2 segments*	114 ± 8 min	177 ± 24 min
Complete return*	191 ± 8 min	379 ± 23 min
Somatic motor block		
Initial onset	<8.5 min	<6.5 min
Complete onset*	32 ± 3 min	15 ± 3 min
Maximum intensity (0–4)	3.3 ± 0.2	3.7 ± 0.2
Complete return*	168 ± 13	331 ± 26
Sympathetic block		
Disappearance (psychogalvanic reflex, PGR)	7 ± 1 min	7 ± 1 min
Reappearance (psychogalvanic reflex, PGR)	120 ± 18 min	200 ± 18 min

* Significant difference ($P < 0.05$).

On completion of control measurements, peridural block was instituted by injection of local anesthetic solution through a catheter previously positioned with its tip at L2. Etidocaine HCl [20 ml 1 per cent with epinephrine, 5 μg/ml (1:200,000)] and lidocaine HCl (20 ml 2 per cent with epinephrine, 5 μg/ml) were given to each subject on different occasions in random order. At least two weeks were allowed to elapse between studies in individual subjects.

After injection of the anesthetic solution, segmental levels of analgesia and hypalgesia were determined by pin-prick and plotted as a function of time. Motor blockade was scored by the ability of the subject to raise his legs, as described by Bromage.[7] Block of sudomotor fibers was assessed by abolition of the psychogalvanic reflex (PGR) using electrodes placed on the dorsal and plantar aspects of the same foot. To elicit the PGR, a sudden loud noise or pin-prick was used to startle the unsuspecting subject. Vasomotor block was detected by temperature change of the great toe as measured with a skin temperature probe.

Cardiovascular and respiratory variables were measured until complete return of sensation. Serial blood samples were taken via catheters in a brachial artery and in a cephalic vein for measurement of plasma and whole blood local anesthetic concentration by gas chromatography.[8]

The statistical comparison of the two agents was made using Student's t test for paired data.

Results

Etidocaine with epinephrine had a faster onset and a longer duration of anesthetic action than lidocaine with epinephrine (table 1, figure 1). Onset of sensory block occurred in 7 minutes with etidocaine and in 9 minutes with lidocaine, with complete spread of analgesia in 32 and 47 minutes, respectively. The differences were not significant. An index used to determine when surgical preparation might begin is "operative onset," defined as the time when analgesia reached four segments above and below the injection site. The mean values of this index were 12.8 minutes with etidocaine and 18.4 minutes with lidocaine.

Although the maximum spread (total number of dermatomes blocked) with lidocaine was slightly greater and less variable than that with etidocaine, this was not clinically significant. Two-segment regression with etidocaine was significantly longer and duration of residual analgesia was about two and one half times that with lidocaine.

The development of motor block with etidocaine was faster and lasted longer than with lidocaine. For both drugs, motor function returned before full recovery of skin sensation. Recovery from sudomotor blockade with both agents coincided with regression of analgesia in the uppermost two dermatomes. In contrast, recovery from vasomotor block was slower and tended to parallel leg blood flows (figs 1 and 3).

Changes in the cardiovascular variables were similar with the two drugs but, as might be expected, those with etidocaine were more prolonged (table 2, figs 2 and 3). MAP and TPR were significantly less with etidocaine at 210 minutes; leg blood flow was significantly greater with etidocaine beyond 180 minutes.

Mean maximum arterial concentrations of etidocaine were 0.96 ± 0.05 (SE) μg/ml (plasma) and 0.55 ± 0.03 μg/ml (whole blood), and were achieved 17 ± 2 min after injection. Mean maximum arterial concentrations of lidocaine were 2.22 ± 0.09 μg/ml (plasma) and 1.85 ± 0.01 μg/ml (whole blood) and were achieved at 24 ± 2 min. The difference between the times of maximum concentrations of the two drugs was significant, $P < 0.005$. Whereas etidocaine decreased to less than half its maximum value in about 45 minutes, lidocaine took about 95 minutes to decrease to the same extent. A large arteriovenous concentration difference was observed for both drugs in all subjects for one hour or more after injection (fig. 4). The mean maximum plasma concentration of etidocaine was 0.53 ± 0.05 μg/ml and was reached at 33 ± 5 min; that for lidocaine was 1.11 ± 0.08 μg/ml, achieved at 54 ± 0 min. No metabolite of etidocaine was detected in the blood samples, although N-de-ethylated derivatives of lidocaine were found.

Systemic toxicity was not observed with either drug. However, all subjects who received lidocaine tended to sleep until aroused by intermittent testing for analgesia. This was not the case with etidocaine, all subjects remaining alert throughout the study.

Results of hematologic screening, blood chemistries and urinalyses showed no abnormality.

Discussion

Etidocaine had a faster onset than lidocaine, particularly in relation to complete motor blockade. Etidocaine differs in this respect from another long-acting local anesthetic, bupivacaine, which has a slower onset than lidocaine.[9] However, there was a general resemblance in the time-segment diagrams of etidocaine and bupivacaine.[9] Lipid solubility (partition coefficient) and plasma (nonspecific) protein binding increase in the order, lidocaine, bupivacaine, etidocaine.[10,11] Penetration of the nerve membrane is accomplished by the lipid-soluble (and non-ionized) form of the drug. Hence, it would be expected that the more lipid-soluble etidocaine would have a faster onset than lidocaine, and this is consistent with the current results. However, bupivacaine has physiochemical properties similar to those of etidocaine, and it is therefore difficult to explain these differences in speed of onset by this mechanism alone. Other factors, including concentration, potency, and perhaps vasomotor activity, must be involved. As with other long-acting local anesthetics, prolonged duration with etidocaine seems to be gained at the expense of predictability, particularly with respect to spread and interpatient reproducibility. It may be that being so lipid-soluble and prone to nonspecific binding, etidocaine may be retained by the first fat or protein it happens to encounter and this may not necessarily be a site of action.

The mean time-segment diagram obtained with etidocaine differed significantly from the familiar one seen with lidocaine. It seems that more of the local anesthetic persists near the site of injection to produce prolonged analgesia in a few segments. This has several implications. First, with the technique used, regression in the upper two segments is a poor predictor of the duration of surgical analgesia in the lower thoracic or lumbosacral segment. Second, the pattern suggests that the greatest benefit from this drug, so far as duration is concerned, will be obtained with segmental blocks. For example, for surgery of the abdomen and for control of postoperative pain in this area, the catheter tip should be placed at T8, for labor pain at

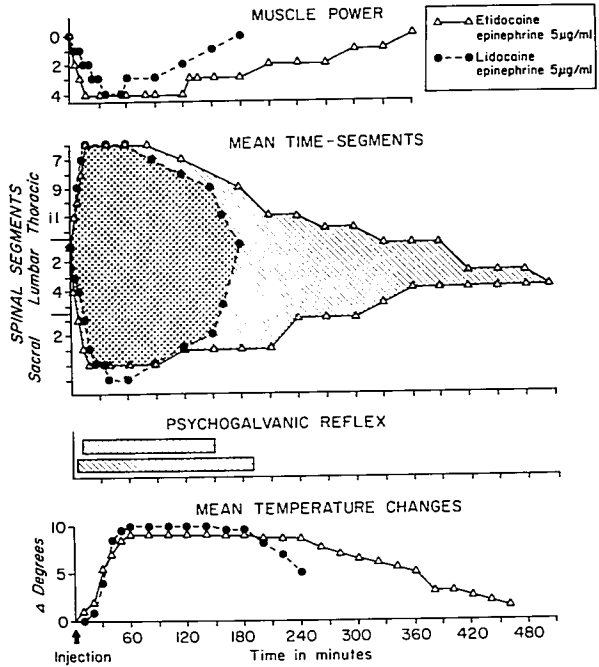

FIG. 1 *Upper*, motor power as measured by the subject's ability to raise leg, using a scale of 1–4 (Bromage[7]). *Lower*, mean time-segment diagram and mean temperature changes of peridural block in which etidocaine HCl, 1 per cent, with epinephrine, 5 µg/ml, and lidocaine HCl, 2 per cent, with epinephrine, 5 µg/ml, are compared. The areas circumscribed in the time-segment diagrams indicate "analgesia" as determined by loss of sensation to pin-prick. Block of the sympathetics is shown by mean temperature change plotted from measurements at the L5 dermatome, and psychogalvanic reflex depicted by the horizontal hatched bars representing the period during which it was unobtainable.

T12, and for herniorrhaphy and lower abdominal surgery at L1. In addition to producing more specific and more prolonged analgesia, this would require less drug. Third, since block after about 300 minutes with etidocaine involved only a few segments and therefore would be clinically useless, "operative analgesia" can be considered to last about 210 minutes for lower limb surgery and 300 minutes for surgery limited to the lumbar segments.

The muscle paralysis obtained with etidocaine was more profound than that seen with bupivacaine peridural block, and in intensity resembled that seen with subarachnoid block.

It remains unclear why the resumption of sympathetic activity as measured by the PGR and as measured by change of temperature in the same dermatome should differ. Perhaps preganglionic fibers subserving sudomotor function in the foot arise above T10 spinal

TABLE 2. Circulatory Responses to Peridural Block with Etidocaine HCl (1 Per Cent) and Lidocaine HCl (2 Per Cent), Both Solutions Containing Epinephrine, 5 μg/ml (Means ± SE)

	Mean Arterial Pressure (mm Hg)	Central Venous Pressure (cm H_2O)	Cardiac Output (l/Min)	Heart Rate (Beats/Min)	Stroke Volume (ml)	Total Peripheral Resistance (dynes/sec/cm^{-5})	Arm Blood Flow (ml/100 ml Tissue/Min)	Leg Blood Flow (ml/100 ml Tissue/Min)
Control								
Etidocaine	87.7 ± 2.7	7.4 ± 0.8	6.3 ± 0.3	59 ± 2	106 ± 5	1,149 ± 68	1.41 ± 0.22	0.77 ± 0.13
Lidocaine	87.4 ± 2.0	8.7 ± 1.1	6.0 ± 0.3	59 ± 2	103 ± 5	1,182 ± 60	1.22 ± 0.25	0.84 ± 0.14
5 min								
Etidocaine	79.8 ± 3.4*	7.3 ± 1.0	9.5 ± 0.5*	75 ± 3*	127 ± 3*	677 ± 47*	0.96 ± 0.18	1.35 ± 0.21
Lidocaine	84.0 ± 2.5* †	8.8 ± 1.1	92. ± 0.8	73 ± 4*	124 ± 6*	769 ± 49*	0.89 ± 0.23	1.66 ± 0.29*
15 min								
Etidocaine	76.5 ± 4.3*	6.8 ± 1.3	9.9 ± 0.4*	72 ± 3*	137 ± 6*	627 ± 73*	1.11 ± 0.25	1.77 ± 0.20*
Lidocaine	78.0 ± 1.4*	8.1 ± 1.2	9.2 ± 0.6*	71 ± 3*	128 ± 4*	699 ± 37*	1.03 ± 0.29	2.42 ± 0.35*
30 min								
Etidocaine	76.4 ± 3.6*	6.7 ± 1.2	8.8 ± 0.3*	66 ± 2*	135 ± 4*	693 ± 31*	1.12 ± 0.22	1.93 ± 0.18*
Lidocaine	79.2 ± 1.8	7.4 ± 1.2*	8.4 ± 0.7*	67 ± 3*	126 ± 7*	783 ± 43*	0.74 ± 0.13	2.45 ± 0.27*
60 min								
Etidocaine	78.4 ± 2.9*	6.8 ± 1.3	7.2 ± 0.3	66 ± 2	118 ± 3	893 ± 57*	0.72 ± 0.10	1.89 ± 0.28*
Lidocaine	82.3 ± 2.3	6.9 ± 1.1*	6.7 ± 0.5	62 ± 3	109 ± 6	985 ± 59	0.81 ± 0.13	2.27 ± 0.27*
90 min								
Etidocaine	78.5 ± 3.3*	6.3 ± 1.4	7.1 ± 0.4	62 ± 2	115 ± 5*	910 ± 62	0.78 ± 0.19*	1.93 ± 0.26*
Lidocaine	78.8 ± 2.1	6.4 ± 1.2*	6.5 ± 0.5	60 ± 3	108 ± 7	1,028 ± 76	0.82 ± 0.24	2.00 ± 0.26*
120 min								
Etidocaine	78.6 ± 3.0	5.2 ± 1.1	7.0 ± 0.3	62 ± 2	113 ± 4	915 ± 58	0.87 ± 0.10	1.82 ± 0.30*
Lidocaine	82.3 ± 1.8	7.7 ± 1.0	6.1 ± 0.5	59 ± 3	104 ± 6	1,128 ± 85	0.79 ± 0.12	1.85 ± 0.23*

150 min								
Etidocaine	81.4 ± 3.5	5.5 ± 1.1*	7.1 ± 0.4	64 ± 4	112 ± 3	933 ± 58	0.70 ± 0.15*	1.91 ± 0.27*
Lidocaine	83.3 ± 1.9	7.4 ± 1.0	5.9 ± 0.4	58 ± 3	101 ± 5	1,183 ± 86†	1.07 ± 0.23	1.54 ± 0.26*
180 min								
Etidocaine	82.3 ± 4.6	5.4 ± 1.1*	7.2 ± 0.4	64 ± 3	112 ± 4	939 ± 64	0.90 ± 0.14	1.86 ± 0.16*
Lidocaine	85.0 ± 2.7	7.1 ± 1.0	6.5 ± 0.4	62 ± 3	104 ± 3	1,081 ± 63	1.01 ± 0.16	1.11 ± 0.12†
210 min								
Etidocaine	84.5 ± 3.8	5.8 ± 1.3	7.6 ± 0.5	66 ± 4	116 ± 4	922 ± 68*	0.95 ± 0.17	1.82 ± 0.22*
Lidocaine	90.4 ± 2.6†	7.2 ± 1.3	6.5 ± 0.5	61 ± 3	104 ± 5	1,193 ± 92†	1.25 ± 0.15	1.06 ± 0.12†
240 min								
Etidocaine	83.4 ± 3.6	4.9 ± 1.1*	7.1 ± 0.4	64 ± 4	111 ± 4	975 ± 69	1.20 ± 0.23	1.60 ± 0.23*
Lidocaine	93.9 ± 3.5†	8.0 ± 1.1	6.5 ± 0.4	62 ± 3	105 ± 4	1,161 ± 49	1.44 ± 0.23	1.18 ± 0.64
270 min								
Etidocaine	85.3 ± 3.6	5.1 ± 1.1*	7.6 ± 0.5*	67 ± 4	113 ± 4	937 ± 72	1.32 ± 0.21	1.68 ± 0.21*
Lidocaine	—	—	—	—	—	—	—	—
300 min								
Etidocaine	86.3 ± 3.8	5.2 ± 1.3*	7.4 ± 0.3	66 ± 4	114 ± 5	957 ± 60*	1.22 ± 0.21	1.51 ± 0.26
Lidocaine	—	—	—	—	—	—	—	—
330 min								
Etidocaine	86.6 ± 3.9	5.5 ± 1.1*	7.4 ± 0.4	65 ± 4	115 ± 4	961 ± 64*	1.44 ± 0.24	1.30 ± 0.25
Lidocaine	—	—	—	—	—	—	—	—
360 min								
Etidocaine	87.4 ± 3.8	5.2 ± 1.3*	7.1 ± 0.3	65 ± 4	110 ± 4	1,011 ± 63	1.43 ± 0.21	1.24 ± 0.19
Lidocaine	—	—	—	—	—	—	—	—

* $P < 0.05$.
† Etidocaine vs. Lidocaine, $P < 0.05$.

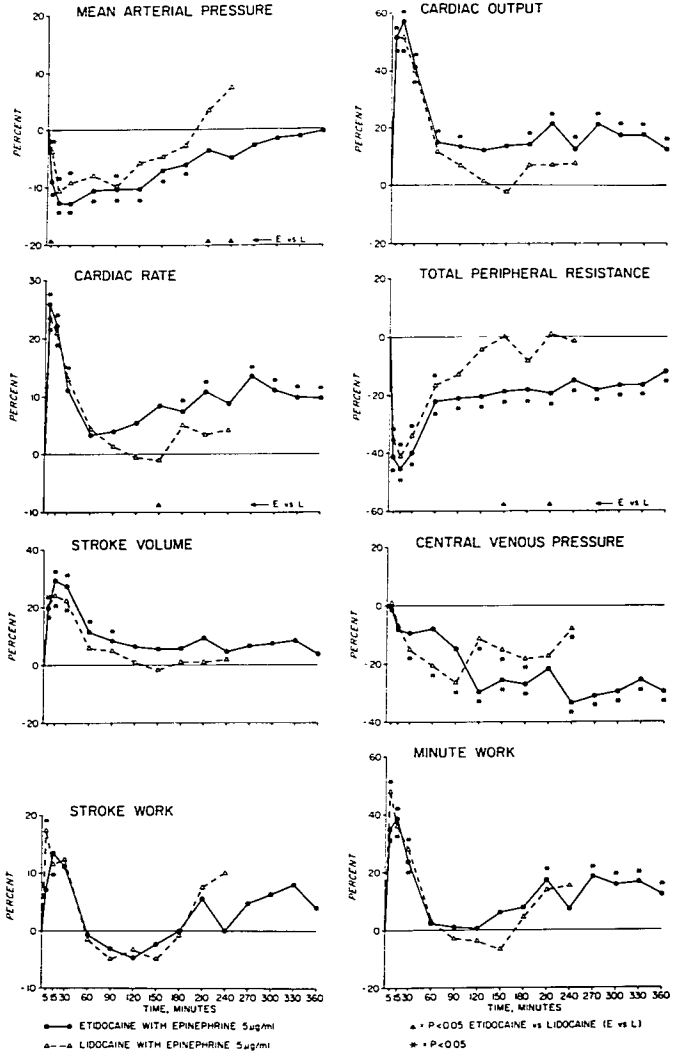

FIG. 2. Circulatory responses to peridural analgesia. Each point represents the mean change from control in all ten subjects, using crossover technique. Significant changes from controls are indicated by "*" on each graph. Significant differences between the changes produced by etidocaine HCl, 1 per cent, and lidocaine HCl, 2 per cent, both with epinephrine, 5 μg/ml, are indicated by "Δ" along the time axis.

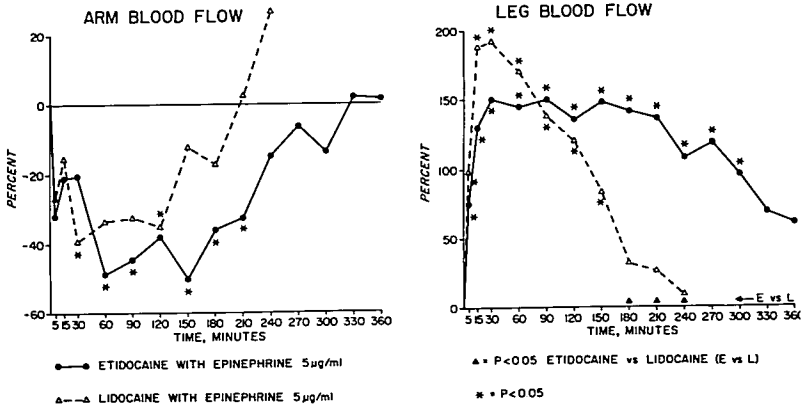

FIG. 3. Circulatory responses to peridural analgesia. Meanings of symbols are described in the legend to figure 2.

cord segments (as classically taught), and they may even have their origins as high as the mid thoracic segments. This possibility finds support from the fact that the PGR, and therefore sudomotor activity, returned in the foot at the same time as analgesia regressed in the uppermost dermatomes. More difficult to explain, however, is why vasomotor function as measured by temperature change should not closely parallel sudomotor function. We believe that the slow time course for cooling of the foot was not merely a function of the specific heat of the tissues but truly reflected the vascular tone at the time. Use of temperature monitoring of the great toe as a clinical tool to observe the circulatory status, and in particular, cardiac output, is described, and lends support to our thesis.[12,13]

Changes in cardiovascular variables were essentially similar with the two drugs and manifested the usual circulatory adjustments to peridural blockade and the beta-adrenergic effects of epinephrine.[4,5] Prolongation of circulatory effects of etidocaine was presumably related to the longer duration of blockade.

Measurement of arterial plasma and arterial whole blood concentrations of etidocaine and lidocaine indicated a significant difference between the blood/plasma concentration ratios for the two agents (*viz.*, on average, 0.58 for etidocaine and 0.84 for lidocaine (see fig. 4). This difference reflects the greater extent of plasma binding of etidocaine (95 per cent) compared with lidocaine (70 per cent).[10,11] Although peripheral venous samples are of little or no value in reflecting the kinetics of local anesthetic agents, they are included because this method is used by many investigators and the data therefore have considerable comparative value.[14] Of interest was the large

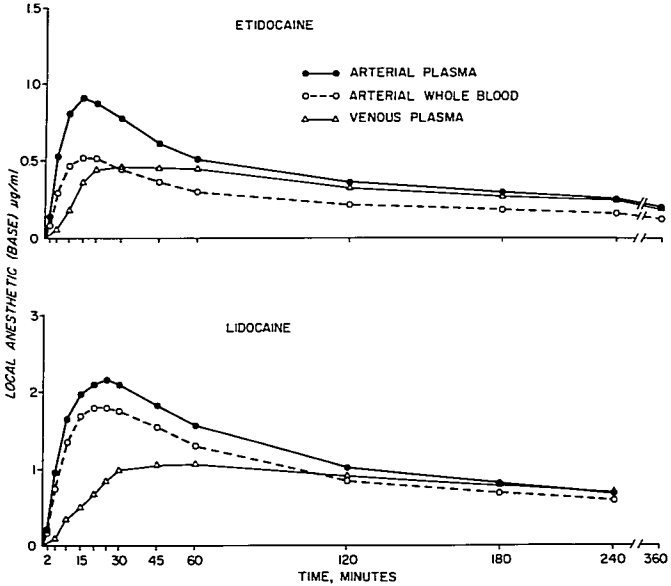

FIG. 4. Concentrations of local anesthetic in arterial plasma, arterial whole blood, and venous plasma following peridural administration of 400 mg lidocaine HCl or 200 mg etidocaine HCl, both with epinephrine, 5 µg/ml, using subject crossover technique.

arteriovenous drug concentration difference observed with the two agents. This difference was significantly greater in this group of volunteers than in a group of premedicated patients receiving the same dose of local anesthetic prior to surgery. Since volunteers developed prompt compensatory vasoconstriction in the upper torso and limbs, we speculate that premedicants alter the time course of peripheral distribution of the local anesthetic by modifying arm blood flow.

The occurrence of sedation with lidocaine but not with etidocaine may be related to differences in dose and blood concentrations of the agents, or to pharmacologic differences. It has been reported that the pre-seizure EEG and behavior effects of the two drugs differ in monkeys. On infusion of equipotent doses of etidocaine and lidocaine, pre-seizure activity was preceded by drowsiness with lidocaine but not with etidocaine. (Munson ES, Tucker WK and Embro W.: Personal communication. These results are consistent with current observations in man.

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Drugs and Their Use

MORPHINE IN HEROIN DEATHS In sudden deaths after intravenous administration of narcotic drugs, failure of toxicologic analysis consistently to demonstrate significant narcotic substance in body tissues and fluids suggests that hypersensitivity reactions and/or toxic effects of adulterants may contribute to mortality. The present study examines 22 autopsy-confirmed cases of fatal intravenous heroin narcotism. Only blood drug level gave precise information on recent drug intake. Histologic examination of the lung indicated that death occurred within three hours of drug injection in 13 instances (minimal to severe pulmonary hemorrhage and edema without leukocytic infiltration). The highest blood morphine concentrations (50, 50 and 93 μg/100 ml) produced rapid death without significant pulmonary edema.

In all cases blood morphine levels were elevated, and no evidence of hypersensitivity reaction was found. The authors conclude that careful measurement of blood morphine levels indicate that death from intravenous narcotics is nearly always due to drug overdosage. *(Garriott, J. C., and Sturner, W. Q.: Morphine Concentrations and Survival Periods in Acute Heroin Fatalities. N Engl J Med 289:1276–1278, 1973.)*