Anesthesiology
V 40, No 1, Jan 1974

Evaluation of Etidocaine, A New Local Anesthetic Agent, with a Modified Bilateral Ulnar-nerve-block Technique

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Etidocaine, a new local anesthetic, was evaluated in a double-blind study using ulnar-nerve block. In addition, electromyography for the assessment of peripheral nerve motor blockade was investigated. Ten volunteers received bilateral ulnar-nerve blocks, in three series, to compare: 0.25 per cent etidocaine with 1 per cent lidocaine, each containing epinephrine 1:200,000; 0.5 per cent etidocaine with 1 per cent lidocaine, each containing epinephrine 1:200,000; 0.5 per cent etidocaine with 1 per cent lidocaine, both without epinephrine. The two anesthetics had similar rapid onsets of action. Etidocaine, 0.25 per cent, appeared equivalent to lidocaine 1 per cent and had approximately the same duration of action. Etidocaine, 0.5 per cent, twice the equivalent concentration, and lidocaine, 1 per cent, both with epinephrine, produced analgesia lasting 583 and 262 min, and motor block lasting 653 and 294 min, respectively. The same solutions without epinephrine provided analgesia for 320 and 165 min, and motor block for 358 and 139 min, respectively. Electromyography allowed determination of all phases of motor blockade. (Key words: Anesthetics, local: etidocaine; Anesthetic techniques: regional: ulnar block; Muscle, skeletal: electromyography; Measurement, techniques: electromyography.)

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Received from the Department of Anesthesiology, College of Physicians and Surgeons, Columbia University, New York, New York 10032, and the Astra Research Laboratories, Worcester, Massachusetts. Accepted for publication June 14, 1973. Supported in part by grant GM 09069 of the National Institutes of Health and by a grant from Astra Pharmaceutical Products, Inc., Worcester, Massachusetts. A preliminary report of this investigation was presented at the Annual Meeting of the American Society of Anesthesiologists, Boston, October 1972.

ULNAR-NERVE BLOCK in man has been previously employed for the initial evaluation of local anesthetic agents.[1] This technique has the advantage of producing a well recognizable, circumscribed area of analgesia and motor blockade. Albért and Lõfström observed that a fairly accurate estimation of the latency and duration of analgesia and motor blockade, as well as the penetrating power and potency of a local anesthetic, can be achieved by this method.[1] The bilateral ulnar-nerve block technique will allow simultaneous comparison of two local anesthetics in the same subject. Moreover, since the amount of drug required for this procedure is relatively small, the danger of systemic toxicity is minimal. The technique has disadvantages, in that both sensory and motor block are evaluated subjectively. Although more objective testing procedures have been described,[2,3] no advantage over the simple standardized pin prick or pinch test for pain has been found, while for the evaluation of motor blockade the cooperation of the subject is still necessary.

The present investigation pursued two goals. First, it served as the initial controlled study in humans of the actions of a new local anesthetic, etidocaine (W-19053), in comparison with those of lidocaine. Second, the feasibility of electromyography as an objective test of peripheral nerve motor blockade was critically examined.

Etidocaine, (±)-2-(N-ethylpropylamino)-2',6'-butyroxylidide hydrochloride, is a local anesthetic chemically related to lidocaine (fig. 1). The purpose of its synthesis was to develop a long-acting local anesthetic. Animal studies indicate that with comparable modes of administration, etidocaine has a duration of action two to three times as

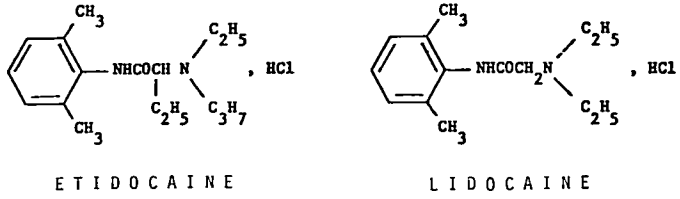

FIG. 1. Chemical structures of etidocaine and lidocaine.

long as that of lidocaine, and possesses potency approximately four times greater. However, etidocaine is four times more toxic than lidocaine when administered by rapid intravenous injection.[4] Thus, the two drugs appear to have similar therapeutic ratios. Etidocaine may therefore find clinical application when regional anesthesia of moderately long duration is desired.

Material and Methods

Ten healthy men, 23 to 45 years old, volunteered for the study. The procedure, with its possible risks, effects, and discomfort, was explained to them in detail well before consent was obtained. The subjects underwent a physical examination that included blood pressure determination, ECG recording, urinalysis, complete blood count, and blood chemistry tests prior to and 24 hours after each experiment. No premedication was given to the subjects. During performance of the ulnar-nerve block, they lay supine with the arm abducted and the elbow bent. After the ulnar groove had been located, an attempt was made to palpate the nerve. Following aseptic preparation of the skin, a 25-gauge needle was inserted slightly proximal to the ulnar groove. It was advanced until paresthesias corresponding to ulnar-nerve distribution could be elicited. The needle was then slightly withdrawn to prevent intraneural injection, after which 5 ml of the anesthetic solution was slowly administered. This usually caused some paresthesias, but not immediate onset of block. In this respect, the method for this investigation was a modification of the original bilateral ulnar-nerve block technique[1] in that the anesthetic was injected extraneurally rather than intraneurally.

The bilateral ulnar-nerve blocks were performed in a double-blind fashion according to a randomized code. In each subject one nerve was anesthetized with lidocaine and the contralateral one with etidocaine. Three different solutions of etidocaine were evaluated in three series of experiments undertaken at one-week intervals in all volunteers, and compared with solutions of 1 per cent lidocaine. Lidocaine in the 1 per cent concentration is commonly used for this procedure, and was therefore selected as the standard for comparison.

In the first series, a 0.25 per cent solution of etidocaine containing 1:200,000 epinephrine was compared with 1 per cent lidocaine containing epinephrine 1:200,000. In the second series, 0.5 per cent etidocaine with epinephrine 1:200,000 was compared with 1 per cent lidocaine with epinephrine 1:200,000. For the third series of experiments, 0.5 per cent etidocaine and 1 per cent lidocaine were used without epinephrine.

Following the performance of the block, onset of analgesia was determined by pinching the fifth finger and hypothenar with a surgical clamp at 1–2-minute intervals until pain sensation had disappeared. The duration of the analgesia was determined by applying the clamp at approximately 15-minute intervals until complete recovery of sensation had occurred. Those experiments in which onset times of 30 minutes or longer, or durations of one hour or less, occurred were rejected for statistical analysis since they were considered clinical failures.

Electromyography was employed for objective determination of the onset and duration of the ulnar-nerve motor blockade (fig. 2). A pair of stimulating electrodes was placed over the ulnar nerve proximal to the site of the blockade. A TECA model TE4 electromyograph was used to deliver a single constant square-wave stimulus of 200 mV lasting 2 msec. Two recording surface electrodes were taped on the skin of the hypothenar area. The evoked muscle action potential was recorded on light-sensitive paper. Prior to injection of the local anesthetic agent, two to four control electromyograms were recorded. Electromyographic recordings were made at 1–2-minute intervals after the block had been performed until the amplitude of the action potential had been reduced by at least 50 per cent. Thereafter, tests for motor activity were performed at approximately 15-minute intervals until the amplitude of the action potential had returned to 90 per cent of the control value. This was taken for the end point of the motor blockade. Concurrently, and in accordance with the method as originally described,[1] the motility and muscle strength of the fifth finger were noted. These subjective observations were then compared with the electromyographic recording. As with sensory analgesia, those experiments in which the onset time of the motor blockade exceeded 30 minutes or the duration was less than one hour were considered clinical failures and excluded from the series.

Results

Analgesia

A total of 60 ulnar-nerve blocks was performed. Complete analgesia was obtained in 58 instances, and only one bilateral technical failure occurred. In addition, five subjects had one ulnar-nerve block each that was classified a clinical failure because the onset of analgesia exceeded 30 minutes or its duration was less than one hour.

There was no statistically significant difference between times to onset of analgesia with etidocaine and with lidocaine in the three experiments. However, significant differences between durations of analgesia ($P < 0.05$) were obtained in experiments II and III (table 1). In experiment II, 0.5 per cent etidocaine with epinephrine, 1:200,000, blocked sensation for 583 ± 126.6 minutes, compared with a mean duration of 262 ± 24.9 minutes for 1 per cent lidocaine with epinephrine, 1:200,000. In experiment III, 0.5 per cent etidocaine without epinephrine had a significantly longer duration of action (320 ± 62.8 minutes) than 1 per cent lidocaine without epinephrine (165 ± 21.8 minutes). Thus, when no epinephrine was added to the

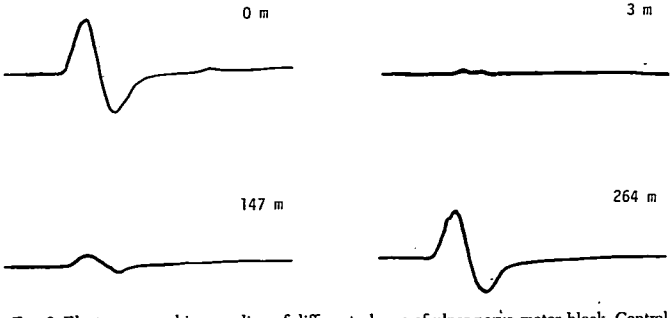

FIG. 2. Electromyographic recording of different phases of ulnar-nerve motor block. Control recording, prior to injection of anesthetic (0 min); virtual absence of action potential and total block (3 min after injection); first return of muscle activity (147 min); restoration of control activity (264 min).

TABLE 1. Analgesia Obtained with Etidocaine and Lidocaine in Three Series of Experiments Involving Bilateral Ulnar-nerve Blocks in Ten Volunteers*

	Anesthetic Agent		Time of Onset (Min) Mean ± SE	Duration of Analgesia (Min) Mean ± SE	
Experiment I	Etidocaine c epinephrine	0.25 per cent 1:200,000	3 ± 1.0 n = 9	410 ± 66.7 n = 7	
	Lidocaine c epinephrine	1 per cent 1:200,000	3 ± 1.3 n = 9	379 ± 20.1 n = 7	
Experiment II	Etidocaine c epinephrine	0.5 per cent 1:200,000	4 ± 1.3 n = 8	583 ± 126.6 n = 10	†
	Lidocaine c epinephrine	1 per cent 1:200,000	7 ± 2.5 n = 8	262 ± 24.9 n = 10	†
Experiment III	Etidocaine	0.5 per cent	3 ± 0.7 n = 8	320 ± 62.8 n = 7	†
	Lidocaine	1 per cent	3 ± 0.7 n = 8	165 ± 21.8 n = 7	†

* n = the number of clinically successful blocks accepted for statistical analysis.
† Significantly different at the 0.05 level.

solutions, significant reductions in the mean durations of analgesia were seen with both agents. In experiment I, where 0.25 per cent etidocaine with epinephrine was compared with 1 per cent lidocaine with epinephrine, the average durations of sensory block were similar for the two compounds.

MOTOR BLOCKADE

The failure rate of ulnar-nerve motor blockade was much higher than that for the sensory block. Of the 60 ulnar-nerve blocks performed, 19 failed to meet the criteria for successful motor blockade. This was probably due in part to the technical difficulty involved in performing the block, since occasionally it was not possible to elicit the desired paresthesias. Since the n values in the various experiments were relatively small, only limited statistical analysis of the data was possible. Therefore, table 2 indicates the means and the ranges of the data obtained in those subjects in whom the electromyographic results met our criteria. However, the studies did yield much valuable information. It appeared that etidocaine had a shorter and more consistent time to onset of motor blockade than did lidocaine in those experiments in which epinephrine-containing solutions were used. In addition, the durations of motor blockade produced by the 0.5 per cent etidocaine solutions were consistently longer than those produced by the lidocaine solutions (table 2). In experiment II the data did lend themselves to statistical analysis. Etidocaine, 0.5 per cent, with epinephrine, 1:200,000, produced a significantly longer duration of motor blockade (653 minutes) than 1 per cent lidocaine with epinephrine (294 minutes), $P < 0.05$.

Electromyographic recording of the compound action potentials evoked by ulnar-nerve stimulation afforded registration of all phases of the motor blockade and their relative intensities (fig. 2). In contrast, subjective testing indicated only the presence of partial or total blockade, or the absence thereof, but, in general, the findings correlated with the electromyographic evaluation. It was noted that on occasion some electrical activity could still be detected when, clinically, there was complete paralysis of the fifth finger.

The two agents were well tolerated by all subjects. No local irritant or inflammatory effect was seen. There was no change in the electrocardiogram, pulse rate, or blood pressure. No sign of systemic toxicity was observed throughout the study. After the blocks had worn off, complete restoration of sensory

TABLE 2. Motor Blocks Obtained with Etidocaine and Lidocaine in Three Series of Experiments Involving Bilateral Ulnar-nerve Blocks in Ten Volunteers*

	Anesthetic Agent		Time of Onset (Min) Mean (Range)	Duration of Motor Block (Min) Mean (Range)	
Experiment I	Etidocaine c̄ epinephrine	0.25 per cent 1:200,000	3 (1–4) n = 4	338 (216–345) n = 5	
	Lidocaine c̄ epinephrine	1 per cent 1:200,000	10 (1–30) n = 6	292 (145–360) n = 7	
Experiment II	Etidocaine c̄ epinephrine	0.5 per cent 1:200,000	2 (1–4) n = 8	653 (440–1193) n = 6	†
	Lidocaine c̄ epinephrine	1 per cent 1:200,000	5 (1–18) n = 5	294 (205–400) n = 6	†
Experiment III	Etidocaine	0.5 per cent	8 (1–21) n = 3	358 (303–493) n = 4	
	Lidocaine	1 per cent	6 (1–20) n = 5	139 (90–213) n = 5	

* n = the number of clinically successful blocks accepted for statistical analysis.
† Significantly different at the 0.05 level.

and motor functions ensued. Urinalysis, complete blood count, and clinical chemistry tests performed 24 hours after each procedure remained unchanged from control values.

Discussion

The continuing research in the field of local anesthetics is aimed at synthesizing compounds with characteristics different from and more desirable than those offered by existing drugs. Etidocaine has been developed as a long-acting local anesthetic. Animal studies showed that it provided a longer duration of analgesia than lidocaine without exceeding the latter's therapeutic ratio.[4] It appeared that etidocaine was approximately three to four times as toxic as lidocaine following rapid intravenous administration, but that its anesthetic potency was also increased by the same factor. For example, the intravenous LD_{50} of etidocaine in mice was 6.7 (5.7–8.5) mg/kg, compared with 26 (23–33) mg/kg for lidocaine. However, etidocaine in a concentration of 0.5 per cent provided anesthesia similar in frequency to 2 per cent lidocaine in various animal tests, while the duration of analgesia was two to three times longer for etidocaine.[4]

The bilateral ulnar-nerve block method described by Albért and Löfström[1] allows evaluation of the anesthetic characteristics of local anesthetic agents with minimum risk to the subjects, since relatively small amounts of the drug are employed. For example, in this study the maximum dose of etidocaine used was 25 mg, or less than 0.4 mg/kg, which is far below the reported acute toxic dose of this agent in animals. This is important when a drug whose toxicity in man is not yet fully established is administered. The technique also allows simultaneous evaluation of two drugs, one being a standard.

Lidocaine, 1 per cent, was selected as the reference anesthetic for this investigation because this drug, in this concentration, is frequently employed for ulnar-nerve block at the elbow. It seemed that by using this single standard solution—with or without addition of epinephrine—meaningful information for the clinician could best be provided, even when etidocaine was tested in two different concentrations. Furthermore, the experimental design of an initial study in man should be kept simple. On must bear in mind that data previously gained from *in vitro* and animal experiments, in general, do not entirely apply to human experimentation.

The method employed in the present study differed in two aspects from the one originally described.[1] 1) We chose to deposit the drugs extraneurally rather than intraneurally to limit the possibility of trauma to the ulnar nerve.[5-6] The lack of immediate onset of block suggests the absence of intraneural injection. It should be pointed out that extraneural deposition of the agent is associated with a somewhat lower success rate in blocking the nerve, and requires a larger dose of anesthetic.[1] 2) Our technique also differs from that of Albért and Löfström in that, rather than testing the motor blockade subjectively, it was primarily evaluated objectively by means of hypothenar electromyography. The onset and intensity of blockade and the degree of recovery could be measured with precision in those subjects in whom the nerve block was satisfactorily performed. In contrast, subjective testing of the muscle strength, while indicating the presence or absence of a motor block, did not allow accurate determination of the latency, intensity, or duration of the block. Thus, electromyography proved very useful and may become an important technique for evaluation of motor blockade. The reason for the presence of electrical activity in a few instances when, clinically, motor power seemed eliminated is difficult to explain. A dissociation of mechanical and electrical activity has been previously demonstrated for the diaphragm[7] and also for the muscles of the hand.[8]

The comparison of 0.25 per cent etidocaine and 1 per cent lidocaine with epinephrine showed similar durations of action in terms of analgesia and motor blockade. The two solutions produced equally rapid onsets of anesthetic effect. Thus, 0.25 per cent etidocaine appeared equivalent to 1 per cent lidocaine, a result which confirmed previously reported animal data.[4]

A longer-lasting anesthetic action than produced by our standard solution of 1 per cent lidocaine could be obtained by using etidocaine in twice the equivalent concentration. Etidocaine, 0.5 per cent, with epinephrine produced analgesia and motor blockade with durations twice as long as those obtained with 1 per cent lidocaine with epinephrine, 1: 200,000. When epinephrine was not added to either solution, 0.5 per cent etidocaine still had a 100 per cent longer action, but in absolute terms the durations of action of both agents were significantly shorter. This suggests that, like lidocaine, etidocaine possesses vasodilator properties and that it is preferable to use this anesthetic in conjunction with a vasoconstrictor, at least for peripheral nerve blocks. The 0.5 per cent etidocaine solutions had the same rapidity of onset as 1 per cent lidocaine. It is of interest that etidocaine does not follow the general trend for long-acting agents to have slow onsets.

This study indicates that etidocaine is a reliable local anesthetic for peripheral nerve block. It has a rapid onset of action and, in a 0.5 per cent concentration, produces an ulnar-nerve conduction block of moderately long duration. Addition of epinephrine, 1: 200,000, to the anesthetic solution prolongs its action considerably.

It is also evident that electromyography constitutes a useful means for the objective evaluation of the action of local anesthetics upon the propagation of motor impulses in peripheral nerves.

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