

Central-nervous-system Toxicity of Local Anesthetic Mixtures in Monkeys

Edwin S. Munson, M.D.,* William L. Paul, M.D.,† William J. Embro, B.S.‡

The central-nervous-system toxicities of local anesthetic mixtures consisting of lidocaine and etidocaine or lidocaine and tetracaine, administered intravenously to four healthy, non-medicated rhesus monkeys, were evaluated. Toxicities were compared by determining seizure dosages for each drug alone and then in a lidocaine-etidocaine or lidocaine-tetracaine mixture. Arterial plasma levels of lidocaine and etidocaine at which electrical seizure activity occurred also were measured when the drugs were administered alone and in combination. The seizure dosages and arterial plasma levels for the drug mixtures studied were equal to the sums of the dosages and thresholds for individual constituents of the mixtures. Under the conditions of this investigation local anesthetic toxicity was additive. (Key words: Anesthetics, local, lidocaine; Anesthetics, local, etidocaine; Anesthetics, local, tetracaine; Brain, seizure thresholds; Toxicity, convulsions.)

LOCAL ANESTHETIC DRUGS are administered in combination with one another with increasing frequency to produce rapid onset and prolonged duration of anesthesia. While the combined administration of large doses of multiple drugs generally is considered an important cause of local anesthetic toxicity, recent clinical reports^{1,2} indicate that local anesthetic solutions containing amide- and ester-type drugs can be used in man without apparent increase in toxicity. However, there are no experimental data that attest to the safe use of local anesthetic mixtures. Data derived from mice,^{3,4} rats,⁵ and dogs⁶ indicate that toxicity resulting from administration of mixtures of amide- and ester-type drugs may be more than additive. Because of differences in methodology and in species, these data cannot be extrapolated properly to man.

Therefore, we studied the central-nervous-system (CNS) toxicity of lidocaine hydrochloride,[§] an amide-type drug, administered intravenously in combination with either etidocaine hydrochloride,[§] another amide-type compound, or tetracaine hydrochloride,[§] an ester-type drug, in rhesus monkeys. CNS toxicities were compared by determining dosages of individual drugs required to produce

seizures alone and in combination, as well as the arterial plasma levels of lidocaine and etidocaine at which electrical seizure activity occurred. In some studies, observations of arterial blood pressure, heart and respiratory rates, acid-base status, and behavioral alterations were made in the pre- and postictal periods.

Materials and Methods

Sixty-eight experiments were performed on four healthy, non-medicated, male *Macaca mulatta*. Each rhesus monkey was placed supine in a restraining chair without medication. The experiments were conducted in three phases over a period of five months.

PHASE I

Thirty-nine experiments were performed on these four animals, which ranged in weight from 4.3 to 6.0 kg (mean 4.9 kg), to determine the dosages of lidocaine, etidocaine, and tetracaine necessary to produce seizures. In each animal a cannula was inserted percutaneously into the small saphenous vein for the continuous infusion of 2.5 per cent glucose and half-strength lactated Ringer's solution. Electrical activity of the brain was recorded from superficial scalp electrodes placed over the sensorimotor cortex, and a single-lead ECG recorded electrical activity of the heart. A pneumograph consisting of expandable rubber tubing, placed over the thoracoabdominal area, recorded ventilatory rate and rhythm. Oxygen was delivered at a rate of 5 l/min into a transparent hood that covered the animal's head ($FI_{O_2} > 0.8$).

All drugs studied were administered in a Latin-square sequence, and intervals of at least a week were allowed between experiments. Lidocaine was obtained from commercially available 2 per cent solutions. Solutions of 0.5 per cent etidocaine were obtained from the manufacturer. Tetracaine solutions of 0.4 per cent were prepared with saline solution and lyophilized crystals prior to each experiment.

Each local anesthetic was administered as a single, rapid intravenous injection into a reservoir of the intravenous cannula. The system then was flushed with saline solution over a 5-second period, and each animal was observed for at least 20 minutes. When no seizure occurred, the drug dosage was increased in 20 per cent increments at weekly intervals until electrical seizure activity resulted.

* Professor of Anesthesiology.

† Assistant Professor in Anesthesiology.

‡ Laboratory Technologist II.

Received from the Department of Anesthesiology, University of Florida College of Medicine, Box J-254, J. Hillis Miller Health Center, Gainesville, Florida 32610. Accepted for publication October 15, 1976. Supported in part by USPHS Grant No. GM00427-15 and Astra Pharmaceutical Products, Inc.

Address reprint requests to Dr. Munson.

§ The salts of the local anesthetics are stated only the first time they appear in the text.

TABLE 1. Seizure Dosages (mg/kg) for Lidocaine, Etidocaine, and Tetracaine (Phase I), and for Lidocaine-Etidocaine and Lidocaine-Tetracaine Mixtures (Phase II) When Administered as Rapid Intravenous Injections

	Lidocaine	Etidocaine	Lidocaine-Etidocaine	Lidocaine Equivalent†	Tetracaine	Lidocaine-Tetracaine	Lidocaine Equivalent†
Monkey 1	14.4 (3)	3.0 (3)	8.7-1.8 (3)	17.3	4.2 (4)	8.7-2.5 (2)	17.3
Monkey 2	17.3 (5)	2.5 (4)	7.2-1.0 (2)	14.4	2.4 (3)	7.2-1.0 (2)	14.4
Monkey 3	14.4 (2)	3.6 (4)	6.0-1.5 (2)	12.0	3.5 (2)	7.2-1.7 (3)	14.4
Monkey 4	14.4 (3)	3.0 (3)	5.0-1.0 (3)	10.0	3.5 (3)	6.0-1.4 (2)	12.0
Mean ± SD	15.1 1.5	3.0 0.5	6.7-1.3 1.6-0.4	13.4 3.1	3.4 0.7	7.3-1.7 1.1-0.6	14.5 2.2

* Combination contains half the seizure dosage of each drug.

† Lidocaine-mixture dosages expressed in terms of lidocaine equivalents (see text).

() Number of injections required to determine dosage values.

TABLE 2. Seizure Dosages (mg/kg) and Arterial Plasma Concentrations ($\mu\text{g/ml}$) for Lidocaine and Etidocaine and a Lidocaine-Etidocaine Mixture When Administered as Intravenous Infusions* (Phase III)

	Seizure Dosage (mg/kg)				Plasma Concentration ($\mu\text{g/ml}$)			
	Lidocaine	Etidocaine	Lidocaine-Etidocaine	Lidocaine Equivalent†	Lidocaine	Etidocaine	Lidocaine-Etidocaine	Lidocaine Equivalent†
Monkey 1	23.2	6.2	16.0-4.0	30.9	14.4	3.7	7.4-2.1	15.6
Monkey 2	16.4	3.8	8.1-2.0	16.7	13.4	4.3	6.5-1.6	11.5
Monkey 3	—	—	7.8-2.0†	15.1	—	—	6.5-1.8†	13.0
Monkey 4	18.4	5.9	10.4-2.6	18.5	13.2	3.3	6.7-1.7	13.5
Mean ± SD	19.3 3.5	5.3 1.3	10.6-2.7 3.8-0.9	20.3 7.2	13.7 0.6	3.8 0.5	6.8-1.8 0.4-0.2	13.4 6.7

* Infusion rates: lidocaine, 4 mg/kg/min; etidocaine, 1 mg/kg/min; lidocaine-etidocaine mixture, 2.0 and 0.5 mg/kg/min.

† Lidocaine-mixture dosages expressed in terms of lidocaine equivalents (see text).

‡ Calculated from group mean control values.

When seizures occurred, the drug dosage was decreased in 20 per cent decrements in subsequent experiments until no seizure activity resulted. Seizure dosage was determined in mg/kg of body weight as the amount that produced electrical seizure activity. When seizures occurred, a single intravenous injection of diazepam, 0.1 mg/kg, was administered 5 minutes after onset of seizure activity.

PHASE II

Nineteen experiments were performed on the four monkeys to determine the dosages of lidocaine-etidocaine and lidocaine-tetracaine mixtures necessary to produce seizures. The animals now ranged in weight from 5.3 to 6.7 kg (mean 5.9 kg). The experimental procedures and preparation of the animals were the same as in Phase I. The mixtures were prepared for each animal by combining half of the seizure dosages, as determined in Phase I, for the two local anesthetics. For example, when

the lidocaine seizure dosage was 14.4 mg/kg and the etidocaine dosage was 3.0 mg/kg, the mixture was prepared by combining the drugs in the proportion of 7.2 mg/kg lidocaine and 1.5 mg/kg etidocaine. The ratio of drug dosage established for each animal in Phase I was maintained during subsequent tests. Seizure dosage of the mixture was determined in subsequent experiments by rapid intravenous injections in 20 per cent increments or decrements at weekly intervals until the smallest dosage of the mixture that induced electrical seizure activity was found. In order to compare the toxicity of the mixture with those of the drugs administered individually (Phase I), the composition of the mixture was expressed in terms of lidocaine equivalents. For example, the algebraic sum of the seizure dosages of a mixture containing 7.2 mg/kg lidocaine and 1.5 mg/kg etidocaine would be equivalent to 14.4 mg/kg lidocaine. When seizures occurred, a single intravenous injection of 0.1 mg/kg diazepam was administered 5 minutes after the onset of seizure activity. In Monkeys 2 and 4, activity rates

for pseudocholinesterase were determined on plasma samples, using 50 μM tetracaine as substrate.

PHASE III

Ten experiments were performed in the same four monkeys to determine the arterial plasma concentrations at the onset of seizures for lidocaine, etidocaine, and a mixture of the two. The combination of lidocaine and tetracaine was not studied. The animals ranged in weight from 5.5 to 6.7 kg (mean 6.1 kg). The drugs were administered intravenously by an infusion pump at rates of 4 mg/kg/min for lidocaine and 1 mg/kg/min for etidocaine, and at half these rates (2 and 0.5 mg/kg/min) for the lidocaine-etidocaine mixture, until electrical seizure activity began. In addition to the preparation of the animals described in Phase I, a cannula was inserted into the saphenous artery (on the side opposite the intravenous cannula) after local infiltration of 0.5 per cent procaine solution.⁷ This permitted us to monitor arterial blood pressure continuously, as well as to withdraw blood for measurements of local anesthetic, respiratory blood-gas tensions, and pH. Arterial blood samples were obtained prior to drug infusion, at 1-minute intervals during drug infusion, and at the onset of seizure activity. When seizures occurred, a single intravenous injection of either 0.1 mg/kg diazepam or 1.0 mg/kg ketamine was administered 5 minutes after the onset of seizure activity. Arterial blood-gas tensions and pH values were measured 1, 5, and 15 minutes after onset of seizures. Measurements of Pa_{O_2} , Pa_{CO_2} , and pH_a were performed with a Radiometer (BMS-3) blood-gas analyzer. Arterial non-carbonic acid-base state (base deficit) was calculated using the method of Siggaard-Andersen⁸ as modified by Severinghaus.⁹ Concentrations of local anesthetic in arterial plasma were measured by gas chromatography.¹⁰ Retention times for lidocaine and etidocaine were sufficiently different to permit the quantitative analysis of each drug in each plasma sample. Data were analyzed with Student's t-test for paired data when appropriate.

Results

PHASE I

Seizure dosages (mean \pm SD) determined from single intravenous injections were: lidocaine, 15.1 \pm 1.5 mg/kg; etidocaine, 3.0 \pm 0.5 mg/kg; tetracaine, 3.4 \pm 0.7 mg/kg (table 1). Therefore, the ratio of seizure toxicities for lidocaine, etidocaine, and tetracaine was 1:5:4.4. The local anesthetic drugs induced varying degrees of preictal behavioral depression, depending on dosage. Subseizure dosages resulted in little or no depression, and recovery usually appeared complete within a few minutes. With larger dosages, seizures were char-

acterized by a tonic phase followed by a clonic phase, with bursts of electrical activity interspersed with electrically silent periods. In 14 of 17 experiments, 0.1 mg/kg diazepam was effective in terminating electrical seizure activity. In one etidocaine and in two tetracaine studies, thiopental or additional diazepam was required.

PHASE II

Seizure dosages for the lidocaine mixtures, expressed as lidocaine equivalents, were lidocaine-etidocaine, 13.4 \pm 3.1 mg/kg, and lidocaine-tetracaine, 14.5 \pm 2.2 mg/kg. These values represent decreases of 15 per cent for lidocaine-etidocaine ($P > 0.3$) and 5 per cent for lidocaine-tetracaine below the lidocaine control dosage. The proportions of lidocaine on a weight basis ranged from 4.0:1 to 6.9:1 in the lidocaine-etidocaine mixture, and from 3.4:1 to 7.2:1 in the lidocaine-tetracaine mixture. No correlation between the proportion of lidocaine present and the individual lidocaine equivalency value was observed for either drug mixture.

The seizures induced by the drug mixtures were electrically and somatically similar to those observed with the individual drugs. Behavioral and seizure responses were similar to those found in Phase I. Diazepam, 0.1 mg/kg, was effective in terminating electrical and motor seizure activity in each of the seven experiments in which it was administered. Tetracaine hydrolysis rates in Monkeys 2 and 4 were 0.11 and 0.19 $\mu\text{mol/hr/ml}$ plasma, respectively.[¶]

PHASE III

Seizure dosages (mean \pm SD) for lidocaine and etidocaine when infused alone were: lidocaine, 19.3 \pm 3.5 mg/kg; etidocaine, 5.3 \pm 1.3 mg/kg (table 2). The seizure dosage of the lidocaine-etidocaine mixture, expressed as a lidocaine equivalent, was 20.3 \pm 7.2 mg/kg. Plasma levels (mean \pm SD) at which seizures occurred were: lidocaine, 13.7 \pm 0.6 $\mu\text{g/ml}$; etidocaine, 3.8 \pm 0.5 $\mu\text{g/ml}$. Plasma concentration of the mixture, expressed as a lidocaine equivalent, was 13.4 \pm 6.7 $\mu\text{g/ml}$.

Seizure activity was promptly terminated by diazepam, 0.1 mg/kg, iv, in six experiments, and by ketamine, 1.0 mg/kg, iv, in two experiments. One animal (Monkey 1) that received etidocaine and another (Monkey 3) that received the lidocaine-etidocaine mixture did not respond to anticonvulsant treatment and died after prolonged periods of hypotension, hypoxemia, hyperthermia, and metabolic acidosis.

[¶] Mean hydrolysis rate for tetracaine in a normal human pool in the same laboratory is 0.29, range 0.06 to 0.50, $\mu\text{mol/hr/ml}$ plasma.

TABLE 3. Respiratory and Acid-Base Values (Mean \pm SD) before and after Seizures Induced by Local Anesthetics (N = 10)

	P _{aO₂} (torr)	P _{aCO₂} (torr)	pH _a	Base Deficit (mEq/l)
Control	393 \pm 75	29.1 \pm 5.1	7.51 \pm .06	-1.0 \pm 1.3
At seizure	401 \pm 51	30.0 \pm 5.0	7.52 \pm .07	+0.3 \pm 1.8
After Seizure 1 min	334* \pm 71	59.4* \pm 9.6	7.25* \pm .11	-3.7* \pm 2.5
5 min	250* \pm 119	97.1* \pm 21.4	6.97* \pm .06	-7.3* \pm 2.9
15 min	275 \pm 109	66.9* \pm 23.9	7.08* \pm .11	-8.7 \pm 3.1

* $P < 0.01$, difference from previous group values.

Adequate oxygenation was maintained in all animals, but significant respiratory and metabolic acidosis developed after the onset of seizure activity (table 3). Heart rate and mean arterial pressure were maintained at near-normal values during all experiments, while respiratory rates decreased significantly during periods of seizure activity (table 4). The infusion of lidocaine, alone and in combination with etidocaine, produced greater behavioral changes of sedation and drowsiness in the preictal period than were observed during infusion of etidocaine alone.

Discussion

Our observations indicate that mixtures of lidocaine-etidocaine and lidocaine-tetracaine, in proportions equal in potency, have approximately the same CNS toxicity in rhesus monkeys as either drug administered alone. That is, anesthetic toxicity is additive. Unfortunately, direct comparison with previous work cannot be made since other studies have used species such as mice,^{3,4} rats,⁵ and dogs,⁶ in which the hydrolysis rates of serum esterase may be slow or absent.¹¹ *Macaca mulatta* has been reported by Reidenberg¹¹ to be one of a few monkey species that are similar to man in this regard. Indeed, hydrolysis rates of tetracaine in two of our animals were within the normal range for man. We are not aware of other reports of measurements of blood levels of local anesthetics during seizures produced by the simultaneous intravenous infusion of two amide-type local anesthetic drugs. It is interesting that the two fatalities were associated with the relatively slow infusions of lidocaine and etidocaine rather than with rapid bolus administrations. While the exact cause of these deaths is unknown, presumably the larger seizure dosages of these amide-type drugs would delay redistribu-

TABLE 4. Heart Rate, Mean Arterial Blood Pressure, and Respiratory Rate Values (Mean \pm SD) before and after Seizures Induced by Local Anesthetics (N = 10)

	Heart Rate (Beats/Min)	Mean Arterial Blood Pressure (torr)	Respiratory Rate (Breaths/Min)
Control	195 \pm 23	128 \pm 18	70 \pm 18
At seizure	192 \pm 15	136 \pm 20	54 \pm 11
After seizure 1 min	206 \pm 17	129 \pm 33	14* \pm 7
5 min	209 \pm 21	133 \pm 32	27* \pm 7
15 min	192 \pm 25	112 \pm 24	61* \pm 11

* $P < 0.01$, difference from previous group values.

tion and increase tissue uptake, thereby increasing CNS toxicity and possibly circulatory toxicity as well.

The animal studies reporting synergistic toxicities of local anesthetics have combined various ester- and amide-type drugs as well as routes of administration. Undoubtedly, variations in the rates of drug absorption, distribution, and elimination are significant factors in the interpretation of such studies. The rapid intravenous injections that we employed minimizes the influence of kinetic factors in the production of toxicity. The additive effects of the local anesthetics studied suggest that these drugs probably act in similar manners on the central nervous system, without significant interaction. However, we can only speculate in this conclusion, since only a narrow relationship of drug dosages was investigated. It is known that local anesthetic interactions may vary as a function of drug dosage levels.⁴ The lack of correlation between the proportions of lidocaine in the mixtures studied and the combined toxicities of the mixtures (Phase II) suggests that a significant interaction did not occur in the production of the combined drug toxicity. Our previous work also indicates that repeated administration of local anesthetics cannot of itself alter seizure dosage or threshold.¹²⁻¹⁴

Our results are clinically applicable to the high levels of drugs in the blood occurring after accidental rapid intravascular injection, rather than those resulting from the relatively slow absorption of drugs following regional block procedures. In the latter situation the clinical tolerance of local anesthetics could be increased following regional and peripheral nerve blocks and the potential for toxicity diminished if the compounded drugs selected had different kinetic or metabolic characteristics. For example, high levels in the blood of ester derivatives such as procaine and tetracaine

are limited by the actions of the serum cholinesterases, while amide derivatives like lidocaine are subject to slower processes of redistribution, hepatic metabolism, and elimination. The clinical reports of Moore and colleagues¹ and Cunningham and Kaplan² attest to the safety of such ester-amide mixtures.

The authors gratefully acknowledge the assistance of Dr. Daniel Bush, Astra Pharmaceutical Products, Inc., Worcester, Massachusetts, for the analysis of local anesthetic concentrations; Ms. Ann M. Deery and Dr. Francis F. Foldes, Montefiore Hospital, The Bronx, New York, for the determinations of the hydrolysis rates of tetracaine; and Dr. Jerome H. Modell for his encouragement and advice.

References

1. Moore DC, Bridenbaugh LD, Bridenbaugh PO, et al: Does compounding of local anesthetic agents increase their toxicity in humans? *Anesth Analg (Cleve)* 51:579-585, 1972
2. Cunningham NL, Kaplan JA: A rapid-onset, long-acting regional anesthetic technique. *ANESTHESIOLOGY* 41:509-511, 1974
3. Akamatsu TJ, Siebold KH: The synergistic toxicity of local anesthetics. *ANESTHESIOLOGY* 28:238, 1967
4. Brecher MJ, Greenberg RA, Greene NM: Drug interactions

- (toxicity) associated with drug combinations. *Acta Anaesthesiol Scand* 16:22-26, 1972
5. Daos FG, Lopez L, Virtue RW: Local anesthetic toxicity modified by oxygen and by combination of agents. *ANESTHESIOLOGY* 23:755-761, 1962
 6. Adriani J, Zepemick R, Hyde E: Influence of the status of the patient on systemic effects of local anesthetic agents. *Anesth Analg (Cleve)* 45:87-92, 1966
 7. Munson ES: Arterial cannulation in awake restrained monkeys. *Lab Anim Sci* 24:793-795, 1974
 8. Siggaard-Andersen O: Blood acid-base alignment nomogram. *Scand J Clin Lab Invest* 15:211-217, 1963
 9. Severinghaus JW: Siggaard-Andersen alignment nomogram, Respiration and Circulation. Edited by PL Altman, DS Dittmer. Bethesda, Maryland, Federation of American Societies for Experimental Biology, 1971, p 222
 10. Keenaghan JB: The determination of lidocaine and prilocaine in whole blood by gas chromatography. *ANESTHESIOLOGY* 29:110-112, 1968
 11. Reidenberg MM: The procaine esterase activity of serum from different mammalian species. *Proc Soc Exp Biol Med* 140:1059-1061, 1972
 12. Munson ES, Wagman IH: Acid-base changes during lidocaine induced seizures in *Macaca mulatta*. *Arch Neurol* 20:406-412, 1969
 13. Munson ES, Wagman IH: Elevation of lidocaine seizure threshold by gallamine. *Arch Neurol* 28:329-333, 1973
 14. Ausinsch B, Malagodi MH, Munson ES: Diazepam in the prophylaxis of lignocaine seizures. *Br J Anaesth* 48:309-313, 1976

Asepsis

CLEAN AIR AND INFECTION The effect of clean air on wound infection was studied in patients undergoing total hip replacement. A plastic surgical isolator that allowed only the wound to be surrounded continuously by a flow of sterile air was used in 109 cases. A standard plenum-ventilated operating room was used in 108 cases. Bacteriologic samples were obtained from the nose, throat and perineum of each patient on admission to the hospital. Samples were taken from skin over the hip before and after application of tincture of iodine, as well as from edges of freshly incised skin. Biopsies of the edge of the wound were taken at the beginning and end of each operation. Instruments, cement, prosthesis and aerosol adhesive were sampled after operation. Blood cultures were taken at the beginning of operation and then 0.5, 1, 4, and 24 hours postoperatively. Drain fluid was cultured at the wound

closing and at 48 hours when the drain was removed. All wounds were swabbed 14 days after operation. Air in the isolator was sampled and found essentially sterile, while air in the opening operating room grew an average of 21 colonies per hour, almost entirely saprophytic cocci. Two major wound infections occurred in each group. Five minor wound infections occurred in the isolator group and three in the non-isolator group. All infections were caused by intestinal-type flora, indicating the secondary nature of infection occurring in the postoperative period. It was concluded that provision of sterile air did not in any way modify the occurrence of postoperative wound infections. (McLauchlan J, and others: *The role of clean air in wound infection acquired during operation. Surg Gynecol Obstet* 143:6-8, 1976.)