Depression of Twitch Response to Stimulation of the Ulnar Nerve during Ethrane Anesthesia in Man

Martin H. Lebowitz, M.D., Casey D. Blitt, M.D.,† Leonard F. Walts, M.D.**

Muscle twitch responses to stimulation of the ulnar nerve during Ethrane anesthesia were studied in 47 adult surgical patients. The responses to an intravenous dose of *d*-tubocurarine or succinylcholine during light anesthesia were measured. The results were compared with results from similar studies measuring the responses to *d*-tubocurarine or succinylcholine during anesthesia with other anesthetics. At low concentrations of Ethrane, marked potentiation of the action of *d*-tubocurarine was observed. No significant effect upon the action of succinylcholine was seen. At high concentrations, Ethrane produced direct depression of twitch response, with fade and posttetanic facilitation. Prostigmine was unable to reverse the direct effects of Ethrane. The authors conclude that the non-curare-like neuromuscular block produced by Ethrane contributes significantly to the profound clinical relaxant effect. (Key words: Ethrane; Muscle twitch response; *d*-tubocurarine; Ulnar-nerve stimulation; Succinylcholine.)

DURING CLINICAL INVESTIGATION of Ethrane (1,1,2-trifluoro-2-chloroethyl difluoromethyl ether) it was found that profound abdominal relaxation was easily obtainable, and small doses of *d*-tubocurarine had prolonged effects.[1] Although the effects of volatile anesthetics upon neuromuscular transmission have been widely studied in animals and in nerve–muscle preparations,[2-12] muscular relaxation during clinical anesthesia in man has had somewhat limited investigation.[12-15] This study of surgical patients during clinical anesthesia was performed to determine the effects of Ethrane upon neuromuscular twitch response and upon neuromuscular blockade produced by *d*-tubocurarine or succinylcholine.

Method

Forty-seven adult surgical patients were studied. Patients were premedicated with combinations of scopolamine, narcotic, barbiturate, or tranquilizer approximately 45 minutes preoperatively. Anesthesia was induced with intravenous thiobarbiturate and maintained with Ethrane in a flow of 4 l/min of 50 per cent nitrous oxide–oxygen, using an Ohio Vernitrol Vaporizer and a semiclosed circle absorption system. Ethrane concentrations from under the mask or from a Rahn End-Tidal Sampler were measured with a portable gas chromatograph, the Mayo Vapor Analyzer. Intubation of the trachea, when required, was facilitated by topical anesthesia. Ventilation was either assisted or controlled, at a minute volume between 6 and 10 l/min, to maintain P_{CO_2} levels within the range of normal. Intravenous fluids included: 5 per cent dextrose in 0.45 per cent saline solution; lactated Ringer's solution; and whole blood.

Neuromuscular twitch response was evaluated by measuring the force of thumb adduction produced in response to supramaximal stimulation of the ulnar nerve at the wrist. The ulnar nerve was stimulated with a Block-Aid nerve stimulator. As described in a previous publication,[16] force of thumb adduction was measured with a Grass (FT03) force-displacement transducer and recorded with a Sanborn recorder. A control twitch response value was obtained for each patient during the administration of thiobarbiturate, nitrous oxide and oxygen. Twitch response was then allowed to stabilize for 30 minutes at a light plane of Ethrane anesthesia (less than 2 per

* Assistant Professor.
† Resident II.
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TABLE 1. Study Groups during Ethrane Anesthesia

	Number of Patients	Mean Age (Years)	Mean Body Surface Area (sq m)	Mean Dose (mg)
Group 1, *d*-tubocurarine 8 mg/sq m	20	47	1.76	14.0
Group 2, succinylcholine 40 mg/sq m	20	35	1.78	70.8
Group 3, no relaxant; Ethrane alone	7	36	1.60	None

cent end-expired). The effect of Ethrane was then evaluated by determining the response to an intravenous dose of *d*-tubocurarine, 8 mg /sq m body surface area (20 patients, Group 1), or succinylcholine, 40 mg/sq m body surface area (20 patients, Group 2).

The direct effects of Ethrane upon muscle twitch responses were evaluated by progressively increasing the alveolar concentration to 6 per cent Ethrane in seven patients who received no neuromuscular blocker (table 1). In two of these patients we compared the muscle twitch responses obtained by stimulating the ulnar nerve with both the Block-Aid and the Grass S-4 stimulators, as follows. A single pair of number 23 needle electrodes was placed over the ulnar nerve at the wrist and connected to both Grass and Block-Aid stimulators via an in-line switch which allowed rapid changes from one stimulator to the other. The Grass stimulator was set to deliver a 0.2-msec single stimulus at 0.25 cycles/sec and a tetanic stimulus at 30 cycles/sec. A fresh pair of batteries was used in the Block-Aid stimulator. Twitch response was measured using a single Grass FT03 Transducer. Supramaximal stimulation of the ulnar nerve was established for each stimulator during light Ethrane anesthesia. The alveolar concentration of Ethrane was then progressively increased as with the other five patients in Group 3 (table 1).

Results

Thirty minutes of light Ethrane anesthesia did not produce depression of twitch response or adequate abdominal relaxation.* The single administration doses of *d*-tubocurarine ranged from 11.5 to 17.3 mg (average 14 mg) and produced 100 per cent depression of twitch responses in 19 of 20 patients studied. Recovery times to 10 per cent of control twitch response heights averaged 66 ± 29 minutes. Walts and Dillon,[15] using a similar technique, studied the effects of other anesthetics upon the action of *d*-tubocurarine. Of the drugs studied, Innovar and nitrous oxide–oxygen had the least effect upon the duration of action of *d*-tubocurarine (10 per cent recovery in 15 ± 6 minutes with 100 per cent twitch depression in 25 per cent of patients) and diethyl ether and nitrous oxide–oxygen had the greatest effect (10 per cent recovery in 30 ± 11 minutes with 100 per cent twitch depression in 65 per cent of patients). Thus, compared with other inhalation agents, Ethrane produces a marked increase in the magnitude and duration of twitch depression produced by intravenous *d*-tubocurarine (table 2).

* Because control twitch response heights had been obtained during thiobarbiturate, nitrous oxide–oxygen anesthesia, nitrous oxide was maintained throughout each study. Thus, our results represent the effects of Ethrane and 50 per cent nitrous oxide.

TABLE 2. Interaction of *d*-Tubocurarine with Ethrane and Other General Anesthetic Agents*

	Number of Patients	Mean Age (Years)	Mean Dose (mg)	10 Per Cent Recovery Time (Mean ± SD in min)	Per Cent of Patients with 100 Per Cent Twitch Depression
Ethrane; nitrous oxide, oxygen	20	47	14.0	66 ± 29	95
Diethyl ether; nitrous oxide, oxygen	20	37	13.5	30 ± 11	65
Innovar; nitrous oxide, oxygen	20	37	13.7	15 ± 6	25

* All groups were statistically similar in age and dose of *d*-tubocurarine. Light Ethrane anesthesia (less than 2 per cent alveolar) produced a significant increase in *d*-tubocurarine effect compared with the other anesthetic agents studied by Walts and Dillon.

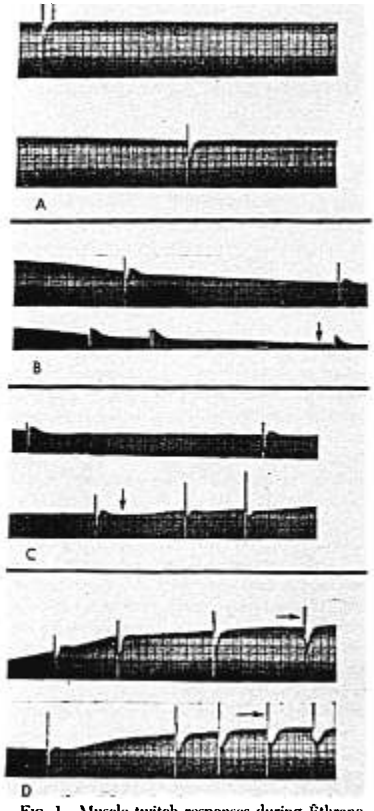

FIG. 1. Muscle twitch responses during Ethrane anesthesia.

A, (above) Light Ethrane (less than 2 per cent alveolar) shows no effect upon twitch height; (below) increasing Ethrane concentration causes twitch height to fall. Fade of twitch response appears at about 2.5 per cent Ethrane.

B, (above) Rapid decrease in twitch response with increasing Ethrane concentration; (below) continuation of recording with 90 per cent twitch depression (arrow) at 6 per cent alveolar Ethrane. Note increasingly prominent fade and posttetanic facilitation.

C, (above) Twitch height maintained at 50 per cent of control; (below) small increase in twitch height without reversal following 3 mg intravenous neostigmine (1-mg increments starting at arrow).

D, Return to control twitch height after discontinuation of Ethrane; (above) before neostigmine; (below) following neostigmine. Note absence of fade (arrows) occurring at approximately 2.5 per cent Ethrane in each recording.

The single-administration doses of succinylcholine ranged from 58 to 90 mg (average 70.8 mg) and produced 100 per cent depression of twitch responses in all patients studied. Recovery times to 10 per cent of control twitch response heights averaged 6.5 ± 1.1 minutes. These results do not differ significantly from the average of 7.2 ± 1.3 minutes to 10 per cent recovery that we have obtained using the same technique with other inhalation agents.

Increasing the Ethrane concentration to above a 2 per cent end-tidal concentration produced a gradual depression of twitch response and excellent abdominal relaxation. Coincident with increasing anesthetic concentration, we observed cardiovascular and ventilatory depression. Therefore, ventilation was controlled in each of the seven patients in Group 3. Blood pressures were supported with intravenous vasopressors and fluids when necessary to maintain systolic blood pressures greater than 75 per cent of control. Arterial P_{CO_2} and *p*H were measured prior to and at peak concentrations of Ethrane so that ventilation could be adjusted to maintain arterial P_{CO_2} and *p*H within the range of normal.

Figure 1*A* shows that light Ethrane anesthesia for 30 minutes is without effect upon twitch response. Increasing the alveolar concentration of Ethrane to above 2 per cent progressively decreased twitch response height. A five-second tetanic stimulation produced fade of twitch response at alveolar concentrations greater than 2.5 per cent. As the anesthetic concentration was increased further (fig. 1*B*), twitch response rapidly decreased; it could be reduced to 10 per cent of control twitch height with an alveolar concentration of 5.5 to 6 per cent Ethrane. Posttetanic facilitation appeared at alveolar concentrations greater than 3.5 per cent Ethrane, becoming more prominent at higher concentrations. Twitch height could be maintained at 50 per cent of control (fig. 1*C*) with an alveolar concentration of 3.5 to 4 per cent. With alveolar concentrations maintained at 3.5 to 4 per cent, we were unable to reverse the 50 per cent block with as much as 3 mg neostigmine administered intravenously (fig. 1*C*). A small increase in twitch height, about 20 per cent, was observed, however, after the first 1 to 2 mg of neostigmine. No change in twitch recovery was observed following the administra-

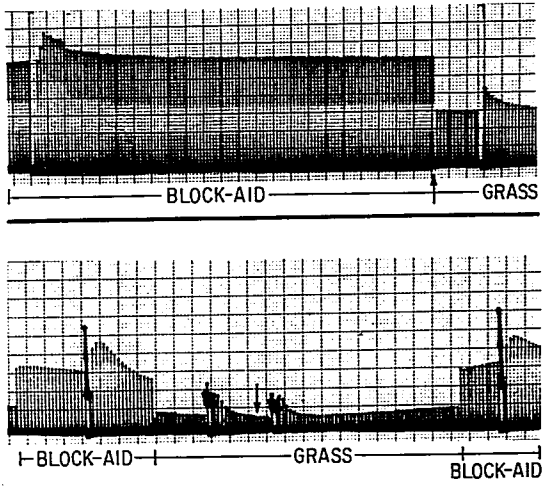

FIG. 2. A comparison of muscle twitch response to ulnar-nerve stimulation by the Grass S-4 stimulator and the Block-Aid Monitor during Ethrane anesthesia. *A*, (above) light Ethrane anesthesia showing switch from Block-Aid stimulator to Grass S-4 (arrow). Five-second tetanic stimulation is exhibited for each stimulator. *B*, (below) increasing the Ethrane concentration caused twitch depression with either stimulator. Five per cent alveolar Ethrane produced a 78 per cent block with the Grass stimulator (arrow). Fade and posttetanic facilitation are evident with both stimulators.

tion of neostigmine, with all evidence of neuromuscular block disappearing when the alveolar concentration of Ethrane fell below 2.5 per cent. Figure 1*D* compares recovery with control levels before and after neostigmine.

In the two patients in whom twitch tensions were measured with both Block-Aid and Grass stimulators, twitch tensions with the Grass stimulator were approximately half those produced by the Block-Aid stimulator during light Ethrane anesthesia (fig. 2*A*). As Ethrane concentrations increased, twitch tensions decreased almost simultaneously with the two stimulators. Per cent twitch depression was always slightly greater with the Grass stimulator. At approximately 5 per cent alveolar Ethrane, a 78 per cent reduction in twitch height was seen with the Grass stimulator, while twitch depression with the Block-Aid stimulator was only 56 per cent (fig. 2*B*). Fade and posttetanic facilitation, although different in magnitude, were noted with both stimulators (fig. 2*B*).

Discussion

All measurements of twitch responses to Ethrane in this study were made during the course of surgical operations. Measurements of twitch response were compared with control twitch heights obtained during thiobarbiturate and nitrous oxide–oxygen anesthesia. In previous trials with other inhalation anesthetics, we found that nitrous oxide had no significant effect upon the action of *d*-tubocurarine. To determine if a direct interaction of nitrous oxide and Ethrane occurred, we discontinued administration of nitrous oxide to one patient after a block with 50 per cent nitrous oxide–Ethrane–oxygen had been established and we added 50 per cent nitrous oxide to the gases being administered to another patient after a block had been established with Ethrane–oxygen. No effect upon twitch height was observed so long as the alveolar concentration of Ethrane remained stable.

Epstein *et al.*[17] found that the muscular contractions produced by stimulation of the ulnar nerve with the Block-Aid Monitor were similar to those produced by a pair of stimuli of 0.1-msec duration separated by an interval of 5 msec. Because the twitch depression we obtained using this paired stimulus might have differed from the response a conventional laboratory stimulator produces, we administered Ethrane to two patients (table 1, Group 3) to compare the muscle twitch responses obtained by stimulating the ulnar nerve with the Block-Aid and Grass S-4 stimulators. Twitch tension was progressively decreased by increasing the concentration of Ethrane with either

monitor. Indeed, the percentages of twitch depression with the Grass stimulator were consistently greater than values obtained simultaneously with the Block-Aid monitor.

Therefore, the neuromuscular effects observed in this study were a direct result of the action of Ethrane. A spectrum of depression of neuromuscular transmission ranging from potentiation of *d*-tubocurarine at low concentrations of Ethrane to direct depression of muscle twitch responses at higher concentrations was produced. The lack of interaction with succinylcholine and the failure of neostigmine to reverse the direct effects suggest that the neuromuscular block produced by Ethrane is not curare-like, yet is nondepolarizing.

Ngai *et al.*[11] correlated muscle relaxation in the cat with depression of spinal and cephalic reflexes. Decreased tibialis twitch response to indirect stimulation was observed only with diethyl ether, but at an inspired concentration much higher than that necessary to produce areflexia. Katz,[12] studying the effects of diethyl ether in the cat and man, found no depression of neuromuscular transmission at a time when the abdomen was well relaxed. However, a few patients did have 10–30 per cent depression during deep ether anesthesia. deJong *et al.*,[13] studying electrically evoked monosynaptic reflexes (H reflexes) in man during anesthesia with various agents, found a statistically significant relationship between reflex depression and observable muscle relaxation. All these investigators concluded that muscle relaxation during inhalation anesthesia is predominately a result of central nervous system or spinal reflex depression rather than myoneural blockade.

Volatile anesthetics do increase the effect of *d*-tubocurarine, however, and have been shown to depress muscle twitch responses to indirect stimulation *in vitro*.[2, 5–9] Yet, Watland *et al.*[10] and Ngai *et al.*[11] were unable to produce muscle twitch depression *in vivo* with agents other than diethyl ether. This apparent discrepancy may simply reflect the effects of differences in concentration and potency. If so, the effect of Ethrane upon neuromuscular transmission is not unique, but represents the result of a significantly greater potency. Thus, as we observed, low concentrations of Ethrane produced greater potentiation of *d*-tubocurarine than other anesthetic agents. Higher concentrations of Ethrane produced surgical relaxation as well as depression of muscle twitch response. Profound abdominal relaxation generally required an alveolar concentration of approximately 3 per cent, which correlated with an EEG pattern of burst suppression and a neuromuscular block of approximately 30 per cent. Further depression of twitch response could be achieved, but only at concentrations of Ethrane much greater than those required for ordinary maintenance of anesthesia. Nevertheless, the magnitude of the twitch depression we were able to obtain *in vivo* with Ethrane suggests a potency of neuromuscular blockade far greater than those reported for other volatile anesthetics. We conclude that, although an appreciable central effect no doubt occurs, the potent depression of muscle twitch response produced by Ethrane contributes significantly to the profound clinical relaxant effect.

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Obstetrics and Pediatrics

PENTAZOCINE IN LABOR A double-blind trial of the effects of pentazocine and pethidine in patients in labor showed that the analgesic effects of the two drugs were similar. The levels of analgesic drug in cord blood were higher after pethidine. The one-minute Apgar scores were best in infants of mothers to whom no analgesic drugs had been given. Approximately the same degrees of neonatal depression were seen with pentazocine and with pethidine. Both drugs caused maternal peripheral vasodilatation and slowing of respiratory rate. The second stage of labor was shorter in women given pentazocine than in those given pethidine. (*Duncan, S. L., Ginsburg, J., and Morris, N. F.: Comparison of Pentazocine and Pethidine in Normal Labor, Amer. J. Obstet. Gynec. 105: 197 (Sept.) 1969.*)

NEONATAL DISTRESS Thirty-four premature infants with Wilson-Mikity syndrome were seen during a seven-year period. Mild respiratory symptoms usually began insidiously after the first week of life. The symptoms became increasingly severe and reached maximum intensity four to eight weeks later. A fourth of the infants died during this stage. In survivors, the respiratory symptoms cleared slowly over the next month; they had disappeared completely in all but one infant by two years of age. Roentgenograms of the chest were consistent and distinctive. Diffuse, streaky infiltrates with small cystic areas appeared during the first stage and progressed as the clinical symptoms increased. The second stage was characterized by basilar hyperaeration with residual strands in the upper lobes. These changes slowly cleared as the clinical symptoms disappeared. Eleven lung biopsies were examined, and all 12 infants who died were autopsied. The prominent findings were patchy areas of hyperinflation and collapse in the first stage and diffuse overinflation during the second stage. The infants had pulmonary fibrosis. The most likely pathogenesis of the syndrome is an abnormal air distribution with disturbance in ventilation–perfusion ratios secondary to immature lung. (*Hodgman, J. E., and others: Chronic Respiratory Distress in the Premature Infant, Pediatrics 44: 179 (Aug.) 1969.*)