

Comparative Neuromuscular Effects of Forane* and Halothane Alone and in Combination with d-Tubocurarine in Man

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In human volunteers, Forane failed to alter twitch height, but increased average neuromuscular refractory period and prevented a sustained response to stimulation at higher frequencies of tetanus. These effects were dose-related. Surgical patients anesthetized with 1.25 MAC Forane were unable to sustain tetanus at more than 120 Hz. In contrast, patients anesthetized with 1.25 MAC halothane were able to sustain tetanus at 200 Hz. In 15 patients anesthetized with 1.25 MAC Forane, the median effective dose of d-tubocurarine needed to produce a 50 per cent depression of twitch height (ED_{50}) was 1.70 mg/m². In contrast, the ED_{50} of d-tubocurarine in 17 patients anesthetized with 1.25 MAC halothane was 5.69 mg/m². Thus, 3.3 times as much d-tubocurarine was needed to produce a 50 per cent depression of twitch height with halothane. (Key words: Forane; Halothane; d-tubocurarine; ED_{50} ; Tetanus; Average refractory period.)

BEFORE INTRODUCTION of a new anesthetic into clinical practice, knowledge of its neuromuscular effects and its interaction with commonly used muscle relaxants is important. Initial clinical investigations of a new inhalation agent (Forane) (1-chloro, 2,2,2-trifluoroethyl difluoromethyl ether, or compound 469) suggested that it produced greater skeletal mus-

cular relaxation than halothane when administered by itself or in combination with d-tubocurarine (dTC). To quantify these impressions we studied the neuromuscular effects of Forane in human volunteers, and compared the neuromuscular depressant actions of equivalent doses of Forane and halothane with and without dTC in surgical patients.

Methods

STUDIES IN HUMAN VOLUNTEERS

Seven unpremedicated human volunteers were informed of the experimental procedure and their consents obtained. The procedures and consent form were approved by the Committee on Human Experimentation of this institution. Anesthesia was induced by inhalation of Forane in 70 per cent nitrous oxide and oxygen until the depth was sufficient for intubation of the trachea without muscle relaxants. Ventilation was controlled to maintain Pa_{CO_2} between 37 and 43 torr. Esophageal temperature was maintained between 36 and 37.5 C.

The ulnar nerve was stimulated with a Grass S-44 stimulator at the wrist through 22-gauge thin-wall needle electrodes, using single stimuli of 0.1-msec duration, which were chosen to avoid repetitive nerve excitation.¹ A voltage at least two times that necessary to evoke a maximal twitch response was used. Force of thumb adduction was measured with a Grass (FT 0.03) force-displacement transducer² and recorded with a Grass polygraph.

Control twitch height and average neuromuscular refractory period were determined while the subjects were awake. The average refractory period was calculated from twitch heights resulting from paired pulses separated by intervals of 0.5 to 6.0 msec.¹ Twitch height, average refractory period, and the

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TABLE 1. Effects of Forane on the Average Neuromuscular Refractory Period in Seven Human Volunteers and Their Ability to Sustain Tetanus

End-tidal Forane (Per Cent)	Average Refractory Period (Msec)*	Per Cent of Subjects Able to Sustain Tetanus			
		50 Hz	120 Hz	160 Hz	200 Hz
Awake†	1.83 ± 0.12	—	—	—	—
0.60	1.96 ± 0.11	100	100	100	57
1.30	2.18 ± 0.11	100	100	43	14
1.90	2.30 ± 0.13	100	56	14	None

* Mean ± SE.

† Ability to sustain tetanus was not determined in awake volunteers.

ability to sustain tetanus at 40, 80, 120, 160, and 200 Hz were determined^{3,4} after at least 15 minutes at 0.60, 1.30, and 1.90 per cent end-tidal Forane with 70 per cent nitrous oxide. Tetanus was defined as unsustained when tetanus height fell more than 2 mm.

STUDIES IN SURGICAL PATIENTS

Thirty-four unpremedicated consenting surgical patients aged 20 to 64 years were studied. Anesthesia was induced and maintained with Forane or halothane without use of other drugs. The trachea was intubated without neuromuscular blocking drugs. End-tidal concentrations were determined by infrared (Forane) and ultraviolet (halothane) analysis and held at 1.5 to 1.6 and 0.95 to 1.05 per cent, respectively. These concentrations are approximately 1.25 MAC for the two agents.^{5,6} Ventilation was controlled to maintain P_{aCO_2} between 33 and 43 torr.

In 17 patients anesthetized with Forane for at least 60 minutes, we measured the ability to sustain tetanus at 40, 80, 120, 160, and 200 Hz.³ The patients were then given *d*-tubocurarine chloride, 0.75, 1.50, 3.0, or 6.0 mg/m², intravenously. Maximum depression of twitch tension, time from administration of relaxant to maximum depression of twitch tension (onset of neuromuscular block), and time to 10 per cent recovery of twitch height were determined. The other 17 patients anesthetized with halothane were studied in an identical manner except that the dose of *d*TC was 3.0, 6.0, or 7.5 mg/m². Only one dose of *d*TC was given to each patient.

The median effective dose (ED_{50}) of *d*TC (dose of *d*TC which resulted in 50 per cent depression of twitch tension) during halothane

or Forane anesthesia was estimated by the method of Litchfield and Wilcoxon.⁷ This method allowed quantitative comparison of the effects of Forane and halothane on the neuromuscular blockade by *d*TC with determination of 95 per cent confidence limits of the ED_{50} , and tests of goodness of fit and parallelism of the two dose-response curves.

Results

STUDIES IN HUMAN VOLUNTEERS

In volunteers, twitch height was not altered by Forane, but the average refractory period increased with increasing end-tidal concentrations (table 1). The ability to sustain tetanus

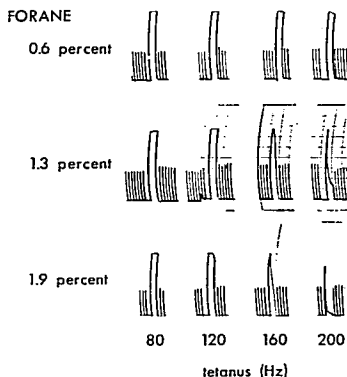


FIG. 1. Relationship between end-tidal concentration of Forane and the ability of human volunteers to sustain tetanus five seconds in duration.

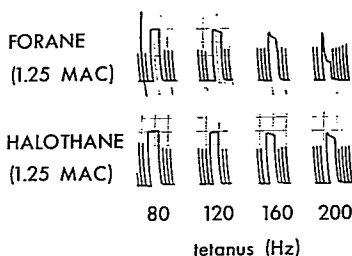


FIG. 2. Comparative abilities of patients to sustain tetanus while anesthetized with 1.25 MAC Forane and 1.25 MAC halothane. With the Forane-anesthetized patient tetanus was not sustained at 160 and 200 Hz. Unsustained tetanus was defined as a decrease of more than 2 mm in tetanus height. Only two of 17 patients anesthetized with halothane were unable to sustain tetanus at 200 Hz, of which the above is an example.

at higher Hz decreased at higher Forane concentrations (table 1; fig. 1).

STUDIES IN SURGICAL PATIENTS

In surgical patients, tetanus was not sustained at 1.25 MAC Forane, but was well maintained at 1.25 MAC halothane (fig. 2).

With Forane all patients stimulated at 200 Hz, 12 of 17 stimulated at 160 Hz, and five of 17 patients stimulated at 120 Hz were unable to sustain tetanus. In contrast, all patients anesthetized with halothane were able to sustain tetanus except two stimulated at 200 Hz.

During halothane anesthesia, 3.3 times as much dTC was necessary to produce a 50 per cent reduction in twitch height as during Forane anesthesia. The ED_{50} of dTC during halothane anesthesia was 5.60 mg/m^2 , compared with 1.70 mg/m^2 during Forane anesthesia giving a potency ratio of $5.60/1.70$, or 3.3 (fig. 3). The difference between ED_{50} values was significant ($P < 0.05$). Deviation from parallelism of the two curves was not significant.

All doses of dTC had shorter onsets and longer durations (time to 10 per cent recovery) during Forane than during halothane anesthesia ($P < 0.01$) (fig. 4; tables 2 and 3).

Discussion

The study in surgical patients demonstrated that Forane has greater neuromuscular depressant effects alone and in combination with dTC than equivalent doses of halothane. The inability of patients to sustain tetanus at higher

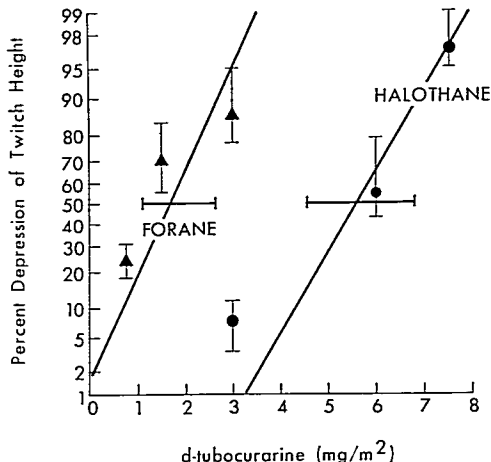


FIG. 3. Dose-response curves for d -tubocurarine in patients anesthetized with Forane and halothane plotted on log-probit paper using the method of Litchfield and Wilcoxon.⁷ The horizontal brackets represent 95 per cent confidence limits for the ED_{50} of d -tubocurarine. The vertical brackets represent \pm one standard error of the response of twitch to a given dose of d -tubocurarine. The Forane curve does not include the two patients who received 6 mg/m^2 of dTC .

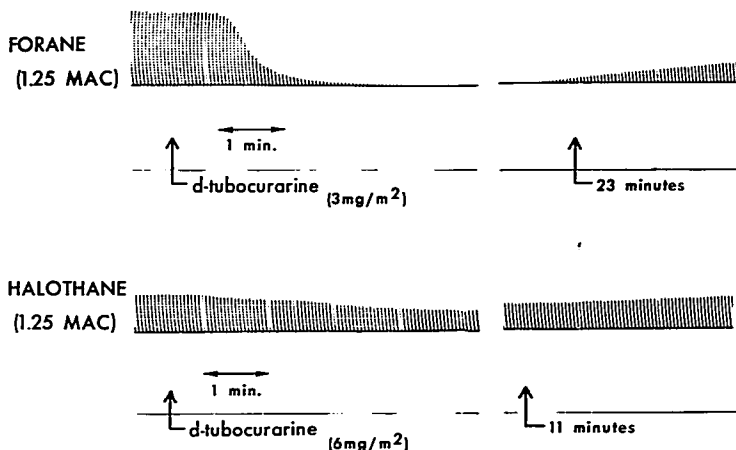


FIG. 4. The effect of *d*-tubocurarine on twitch height in patients anesthetized with 1.25 MAC Forane and 1.25 MAC halothane. In the patient anesthetized with Forane, 3 mg/m² of *d*-tubocurarine resulted in a greater depression of twitch height and longer duration than did 6 mg/m² in a patient anesthetized with halothane.

frequencies of stimulation during Forane anesthesia suggests a greater neuromuscular depressant effect of 1.25 MAC Forane compared with 1.25 MAC halothane. Most halothane-anesthetized patients were able to sustain tetanus at 200 Hz. The ability of Forane-anesthetized patients to maintain control twitch heights when they were unable to sustain tetanus emphasizes the greater sensitivity of response to tetanus in evaluating depression of neuromuscular transmission.³

Forane appears to potentiate *d*TC more than any other inhalation agent, including diethyl ether.⁸ Walts *et al.*⁹ gave 8 mg/m² of *d*TC to patients anesthetized with diethyl ether and nitrous oxide and found a 100 per cent depression of twitch height, with a 10 per cent recovery time of 30 minutes in 66 per cent of these patients. Sixty per cent of our Forane-anesthetized patients had depressions of twitch height of 95 per cent or more and a mean 10 per cent recovery time of 25.6 minutes with only 3 mg/m² of *d*TC. However, the above comparison may not be completely valid because anesthetic depths in the two studies probably were different.

Results of studies in volunteers suggest that Forane has neuromuscular effects qualitatively similar to those of other inhaled anesthetics. Twitch height was not altered. However, the average neuromuscular refractory period increased and the ability to sustain tetanus decreased with higher Forane concentrations. Whether Forane alters the average neuromuscular refractory period and the ability to sustain tetanus to a greater or lesser extent than those anesthetics evaluated by Epstein¹ and Cohen⁴ cannot be determined because of differences in measuring anesthetic dose.

There are some possible deficiencies in our data. Although 1.25 MAC of Forane is clearly different from 1.25 MAC of halothane in neuromuscular effect or interaction with *d*TC, this does not mean that the same relationship will hold at higher or lower anesthetic doses. Complete dose (MAC)-response (neuromuscular effect) curves for each agent are needed to answer this criticism.

Zero or 100 per cent responses may skew a dose-response curve. This is because a 100 per cent response is the limit of response; a higher or lower dose might cause the same re-

TABLE 2. Interaction of *d*-Tubocurarine (*d*TC) with Forane (1.25 MAC)

Dose of <i>d</i> TC	No. Patients	Body Surface Area (sq m)*	Per Cent Depression of Twitch Height*	Onset Time (Min)*	10 Per Cent Recovery Time (Min)*	No. Patients with 100 Per Cent Depression of Twitch Height	No. Patients with No Depression of Twitch Height
0.75 mg/m ²	5	1.54 ± 0.06	24.0 ± 7.2	3.17 ± 0.96	10.1 ± 3.10	None	None
1.5 mg/m ²	5	1.72 ± 0.07	70.0 ± 14.8	3.82 ± 0.63	12.2 ± 1.90	1	None
3.0 mg/m ²	5	1.64 ± 0.18	86.0 ± 9.0	2.94 ± 1.41	25.6 ± 3.25	2	None
6.0 mg/m ²	2	1.51	100	2.1	57.85	2	None

* Mean ± SE.

TABLE 3. Interaction of *d*-Tubocurarine (*d*TC) with Halothane (1.25 MAC)

Dose of <i>d</i> TC	No. Patients	Body Surface Area (sq m)*	Per Cent Depression of Twitch Height*	Onset Time (Min)*	10 Per Cent Recovery Time (Min)*	No. Patients with 100 Per Cent Depression of Twitch Height	No. Patients with No Depression of Twitch Height
3 mg/m ²	7	1.66 ± 0.08	17.6 ± 6.5	4.20 ± 0.94	8.40 ± 0.81	None	4
6 mg/m ²	5	1.75 ± 0.07	54.2 ± 12.4	3.62 ± 0.55	17.14 ± 6.1	None	None
7.5 mg/m ²	5	1.75 ± 0.09	97.0 ± 2.0	3.18 ± 1.0	38.84 ± 6.1	3	None

* Mean ± SE.

sponse. It was for this reason that the two Forane-anesthetized patients receiving 6 mg/m² of *d*TC were not included in the probit-analysis. Some of our patients (particularly those in the 3 mg/m² dose group for both anesthetics) had zero or 100 per cent depressions of twitch height (tables 2 and 3). If they were eliminated, the dose-response curves would be more vertical with greater separation. Goodness of fit would be still more significant.

The potency ratio ED₅₀ halothane/ED₅₀ Forane indicates that 3.3 times as much *d*TC is necessary to produce a 50 per cent depression of twitch height during halothane anesthesia. Our clinical experience in ten Forane anesthetizations for intra-abdominal surgery is that 3 to 5 mg of *d*TC produce sufficient skeletal muscle relaxation. This accords with the results of this study concerning the potentiation of *d*TC by Forane.

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References

- Epstein RA, Jackson SH: The effect of depth of anesthesia on the neuromuscular refractory period of anesthetized man. *ANESTHESIOLOGY* 32:494-499, 1970
- Watts LF, Lebowitz MH, Dillon JB: A means of recording force of thumb adduction. *ANESTHESIOLOGY* 29:1054-1055, 1968
- Gissen AJ, Katz RL: Twitch, tetanus, and post-tetanic potentiation as indices of nerve-muscle block in man. *ANESTHESIOLOGY* 30:481-487, 1969
- Cohen PJ, Heisterkamp DV, Skovsted P: The effect of general anaesthetics on the response to tetanic stimulus in man. *Brit J Anaesth* 42:543-546, 1970
- Saidman LJ, Eger EI II: Effect of nitrous oxide and of narcotic premedication on the alveolar concentration of halothane required for anesthesia. *ANESTHESIOLOGY* 25:302-306, 1964
- Stevens WC, Dolan WM, Miller RD, et al.: Unpublished data.
- Litchfield JT Jr, Wilcoxon F: A simplified method of dose-effect experiment. *J Pharmacol Exp Ther* 96:99-113, 1949
- Lebowitz MH, Blatt CD, Watts LF: Depression of twitch response to stimulation of the ulnar nerve during Ethrane anesthesia in man. *ANESTHESIOLOGY* 33:52-57, 1970
- Watts LF, Dillon JB: The influence of the anesthetic agent on the action of curare in man. *Anesth Analg* 49:17-21, 1970