The Effect of Depth of Anesthesia on the Neuromuscular Refractory Period of Anesthetized Man

R. A. Epstein, M.D., and S. H. Jackson, M.D.†*

The average neuromuscular refractory periods in 13 subjects anesthetized with diethyl ether, fluroxene, halothane, or methoxyflurane were determined. Increasing depth of anesthesia increased the refractory periods in all subjects. Depth of anesthesia had little or no effect on the indirectly-evoked twitch response. This demonstrates a direct effect of these anesthetics on the neuromuscular junction in man despite an absence of neuromuscular blockade. The effect of anesthetics on the refractory period is opposite that of the nondepolarizing neuromuscular blockers. (Key words: Anesthetics; Diethyl ether; Fluroxene; Halothane; Methoxyflurane; Neuromuscular transmission; Neuromuscular refractory period; Twitch tension.)

IT HAS LONG BEEN SUSPECTED that general anesthetics impair neuromuscular transmission in man. However, since anesthetics in clinically-used concentrations have little or no effect on the evoked twitch response, investigators have turned to indirect methods, such as the study of potentiation of neuromuscular blockers by anesthetics, to demonstrate effects on neuromuscular transmission.[1] We have commented upon the use of the neuromuscular refractory period as a sensitive indicator for the investigation of the pharmacology of the human neuromuscular junction *in vivo*.[2] This paper presents findings from a study of the effect of depth of anesthesia on the neuromuscular refractory period in man.

Methods

Thirteen healthy patients receiving no drugs known to affect neuromuscular transmission were studied during anesthesia administered for surgical operations. They were either unmedicated or were given atropine sulfate (0.007 mg/kg, im). Anesthesia was induced and maintained with diethyl ether (three subjects), fluroxene (two subjects), halothane (five subjects), or methoxyflurane (three subjects), all in 60 per cent nitrous oxide. No other drug was administered. The tracheas of all patients were intubated. A nonrebreathing anesthetic circuit was used. Ventilation was controlled with a volume-limited ventilator and a constant minute ventilation was maintained. Thenar muscle temperature was measured (Yellow Springs Instrument Company, Yellow Springs, Ohio, hypodermic probe no. 524) and varied no more than 0.2 C during a study period. Control measurements were made after a constant inspired anesthetic concentration sufficient to produce a "light" plane of anesthesia, as judged by clinical signs, had been administered for one hour. The inspired concentration of the anesthetic was then increased and maintained constant at the new level for 20 to 30 minutes so as to produce a "deep" level of anesthesia. Measurements were then repeated. The anesthetic was then discontinued, and recovery data during light anesthesia were obtained 20 to 30 minutes later.

The methods used to study neuromuscular transmission have been detailed previously.[2, 3] In brief, the ulnar nerve was stimulated at the wrist through bare needle electrodes, using single or paired stimuli of 0.1-msec duration. A voltage two times that necessary to evoke a maximal twitch response was used. Paired pulses were separated by intervals of 0.5 to 10.0 msec. The evoked adductor pollicis tension was plotted as a function of the pair interval. The average neuromuscular refractory period (ARP) was derived from this function. *The ARP is defined as that pair interval which determines that tension which is the average of the tension evoked by a single stimulus and the maximum tension which can be evoked by*

* Assistant Professor, Columbia University.
† Assistant Professor, Stanford University.
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Direct all correspondence to: R. A. Epstein, M.D., Department of Anesthesiology, Room PH 18-6, The Presbyterian Hospital, New York, New York 10032.

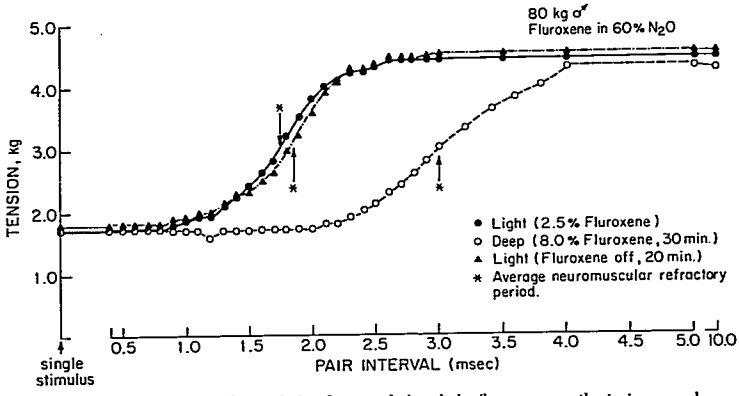

FIG. 1. Tension curves during light, deep, and then light fluroxene anesthesia in one subject. Deepening anesthesia caused the curve to shift to the right and ARP to increase from 1.75 to 3.00 msec. With the return to light anesthesia, there was a return to the control level. The evoked twitch response to the single stimulus was not affected by the depth of anesthesia.

a paired stimulus.[1] Preliminary studies indicated that in patients maintained at constant levels of anesthesia and minute ventilation ARP remains constant (within 0.1 msec) for periods exceeding 90 minutes. The compound action potentials of the adductor pollicis muscles of 11 subjects were photographed from an oscilloscope. The recording bare needle electrodes were positioned so that the electromyogram (EMG) evoked by a single stimulus had a single major upright deflection. Paired stimuli with pair intervals greater than the refractory period of some or all of the neuromuscular units evoked EMG's with an additional (second) upright deflection. (Subjects manifesting repetitive muscle firing in response to single indirect stimuli were not admitted to the study.[4]) The ulnar nerve compound action potentials of two of these 11 subjects were recorded antidromically at the elbow with bare needle electrodes. The preamplifier frequency response was generally set at 0.8 to 10,000 hertz for muscle recordings and 0.8 to 1,000 hertz for nerve recordings.

For statistical analysis the results with the various anesthetics were pooled. Student's *t* test for paired data was used to test the significance of differences between ARP values in light (control) and deep anesthesia, and also in control and recovery periods.

Results

Effect of Anesthetic Depth on ARP

In the 13 subjects ARP was derived from the tension curves obtained during light, deep, and then light, anesthesia. The results of one such study are shown in figure 1. During light fluroxene anesthesia (2.5 per cent, inspired), ARP was 1.75 msec. Deepening anesthesia (8.0 per cent, inspired for 30 minutes) caused the tension curve to shift to the right. ARP increased to 3.00 msec. Twenty minutes after discontinuation of fluroxene, the tension curve and the derived ARP returned to control levels. In all 13 subjects deepening anesthesia increased ARP. The mean ARP increased from 1.77 to 2.33 msec ($P < 0.001$) (table 1). With re-establishment of a light plane of anesthesia ARP returned to the control level. Deepening anesthesia had no effect on the evoked muscle response to a single nerve stimulus (twitch tension) except in two of the diethyl ether studies, in each of which there was a 10 per cent decrease in evoked tension.

Effects of Depth of Anesthesia on the Evoked Electromyogram and Nerve Action Potential

EMG's of 11 of the 13 subjects were also recorded. Results from one study are shown in figure 2. During light fluroxene anesthesia, the EMG possessed a second upright deflection characteristic of double muscle firing at stimulus pair intervals of 1.0 msec or more. During deep anesthesia the least pair interval that produced a second positive deflection increased to 2.4 msec, and the height of the second positive deflection evoked at pair intervals of 2.4 to 4.0 msec was decreased. Similar changes were observed in all 11 subjects, reflecting the increase in ARP. Increased depth of anesthesia had no effect on the configuration of the EMG evoked by a single stimulus except in the two diethyl ether studies, in which small decreases in muscle twitch tension evoked by a single stimulus were observed. Here, the height of the positive deflection decreased approximately 10 per cent, while the duration of this deflection increased by about 10 per cent.

In one halothane and one fluroxene study, the ulnar nerve compound action potentials were also recorded. In both studies changes in depth of anesthesia had no effect on the configuration of the nerve action potentials, the nerve refractory period remaining at 0.6 to 0.8 msec (fig. 2).

Discussion

The neuromuscular effects of anesthetics have intrigued investigators for well over half a century. Indeed, various investigators, using diverse preparations, have reported that anesthetics increase, decrease, or do not affect the indirectly-evoked twitch response. A relevant discussion of the subject is found in a recent review.[1]

In this study we have attempted to control some of the factors which have contributed to the conflicting results. Some comments concerning methodologic problems are pertinent. Our studies were done in man. Anesthetic agents were studied in clinically-used concentrations. To avoid extraneous drug interactions, we administered no drugs other than the anesthetic agents themselves, except atropine for premedication in some subjects. We considered it important to avoid the use of muscle relaxants even for intubation because subtle effects of such drugs may persist despite return of twitch tension to control levels. A stimulus of 0.1-msec duration was selected to avoid exciting the nerve repetitively, such as may occur with a stimulus of longer duration. It is possible that in earlier studies, where a stimulus of longer duration was used with consequent repetitive stimulation, an increase in anesthetic depth decreased the evoked tension by increasing the refractory period.[6] This could have been interpreted incorrectly as neuromuscular blockade. Other phenomena may also simulate neuromuscular blockade. On occasion during clinical anesthesia we have recorded repetitive muscle contraction in response to a single brief nerve stimulus.[4] Factors which increase or decrease this phenomenon will alter the evoked tension without necessarily signifying a change in neuromuscular blockade. For this reason we have not included in this report subjects who manifested repetitive muscular activity upon stimulation with a single stimulus. Finally, factors which affect the coordination of contraction of the muscle fibers or the contractile process itself may alter the evoked tension without necessarily altering neuromuscular transmission.[5] These phenomena may be differentiated *in vivo* from true neuromuscular blockade only by recording in detail the compound muscle action potential (EMG) as well as the evoked tension.

The indirect twitch response (both tension and EMG) was not affected by changes in depth of fluroxene, halothane or methoxyflurane anesthesia. With deep diethyl ether anesthesia we detected small decreases in evoked tension in two of three subjects. These slight decreases in twitch tension do not necessarily imply the presence of neuromuscular blockade, but rather a change in the coordination of contraction of the muscle fibers (unpublished observations).* The lack of neuromuscular blocking effect in no way contradicts the fact that synaptic depression is a

* Our results with the four anesthetics studied should not be extended to all anesthetics. Cyclopropane, for example, may increase the evoked twitch tension in man (unpublished observation).

TABLE 1. Effect of Depth of Anesthesia on the Average Neuromuscular Refractory Period

Subject	Sex	Age (Years)	Weight (kg)	Anesthetic Tested	Light (Control)		Deep (Experimental)			Light (Recovery)	
					ARP (msec)	F_I (per cent)	ARP (msec)	F_I (per cent)	Δ (msec)	ARP (msec)	Δ (msec)
1†	♂	37	65	Ether	1.80	2.0	2.50	9.0	+0.70	1.90	+0.10
2†	♂	54	78	Ether	2.25	1.6	3.00	10	+0.75	2.35	+0.10
3†	♀	65	26	Ether	2.65	2.5	3.70	10	+1.05	2.65	0.00
4†	♂	28	58	Fluroxene	1.65	1.2	2.40	10	+0.75	1.65	0.00
5†‡	♂	26	80	Fluroxene	1.75	2.5	3.00	8.0	+1.25	1.85	+0.10
6†	♀	50	82	Halothane	1.20	1.0	1.90	2.5	+0.70	1.15	−0.05
7	♂	55	75	Halothane	2.15	0.5	2.45	1.5	+0.30	1.90	−0.25
8	♀	35	55	Halothane	1.65	0.8	1.95	2.5	+0.30	1.65	0.00
9†	♀	24	35	Halothane	1.80	1.0	2.10	2.5	+0.30	1.70	−0.10
10†‡	♀	57	53	Halothane	1.45	1.0	1.70	2.5	+0.25	1.40	−0.05
11†	♀	41	40	Methoxyflurane	1.80	0.4	2.10	1.0	+0.30	1.95	+0.15
12†	♀	57	64	Methoxyflurane	1.70	0.3	1.85	1.2	+0.15	1.55	−0.15
13†	♂	37	65	Methoxyflurane	1.15	0.3	1.65	0.8	+0.50	1.25	+0.10
MEAN ±SE					1.77		2.33		0.56 ±0.09§	1.77	0.00 ±0.03

ARP = average neuromuscular refractory period; F_I = inspired concentration of anesthetic agent (in 60 per cent N_2O); Δ = change from control. The deep ARP was obtained 20–30 min after the increase in F_I. Recovery occurred 20–40 min after discontinuation of the anesthetic agent.

† EMG recorded.

‡ Nerve action potential recorded.

§ $P < 0.001$.

FIG. 2. Muscle and nerve compound action potentials obtained from the subject in figure 1. Increasing the depth of anesthesia increased the least pair interval at which there was a second positive electromyographic deflection from 1.4 to 2.4 msec, which returned to the control level with lightening of anesthesia. Depth of anesthesia did not affect the electromyographic response to the single stimulus, nor did it affect the nerve compound action potentials elicited by single or paired stimuli.

general property of anesthetic agents. Because of the margin of safety of neuromuscular transmission,[7] a considerable change at the neuromuscular junction must occur before actual failure of transmission. Previous investigators have provided indirect evidence for such an effect at the neuromuscular junction in man by showing that anesthetics potentiate the effect of neuromuscular blockers.[5, 9]

We have used the neuromuscular refractory period as a sensitive means to provide direct evidence for a neuromuscular effect of anesthetics in man. With all four anesthetics studied, increasing depth of anesthesia reversibly increased the neuromuscular refractory period. It may be useful to study the effects of anesthetics on the refractoriness of other physiologic systems. Thus, Kitahata has shown that, in the cat, anesthetics, in concentrations which do not depress the amplitude of the cortical evoked response, depressed the auditory recovery cycle.[10]

The mechanisms by which anesthetics increase the neuromuscular refractory period are not known. The prolongation of the duration of the endplate potential by ether *in vitro* may be a related phenomenon.[11] The inhibition by anesthetics of active transport of sodium, which is involved in the recovery after excitation and depolarization, may also be relevant.[12]

Our data do not reveal the precise site at which anesthetics act to increase the refractory period. It is not the nerve trunk itself, because we showed that the nerve compound action potentials were not affected. This is consistent with *in vitro* studies. Karis *et al.*[11] have demonstrated that the neuromuscular junction is more sensitive to the actions of anesthetics than is the nerve trunk or the muscle fiber away from the endplate. The most sensitive site appears to be the postjunctional membrane, which is desensitized by anesthetics.[11] It is noteworthy that other drugs which desensitize the endplate also increase the neuromuscular refractory period. These include the anticholinesterases [2] and the depolarizing muscle relaxants (unpublished observations). In contrast, other drugs such as *d*-tubocurarine, gallamine and hexafluorenium, which are active at, but do not depolarize, the neuromuscular junction, decrease the refractory period.[2, 13] Thus, although diethyl ether and other volatile anesthetics affect neuromuscular transmission, their effect is opposite to that of the nondepolarizing muscle relaxants, and therefore cannot be said to be "curare-like."

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