

The Effects of Small Incremental Doses of *d*-Tubocurarine on Neuromuscular Transmission in Anesthetized Man

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The effects of successive one-mg doses of *d*-tubocurarine on twitch tension before and after tetanus, and fatigue of tension during tetanus, were examined in 28 patients during anesthesia provided by either nitrous oxide-oxygen or methoxyflurane-nitrous oxide-oxygen. Axillary and ulnar block permitted study of awake man and allowed determination of whether antidromic conduction affected the measurements. Depression of twitch tension by *d*-tubocurarine was greater during methoxyflurane than during nitrous oxide anesthesia. Ability to sustain tetanus was better related to the stimulating frequency than to the total amount of *d*-tubocurarine given. Enhancement of posttetanic twitch tension remained constant regardless of the dose of *d*-tubocurarine or the degree of neuromuscular blockade. Antidromic conduction of the electrical stimulus did not affect mechanical response. The measurement of twitch tension furnishes a rational, objective, and reasonably sensitive guide to the effect of *d*-tubocurarine.

DURING ADMINISTRATION of *d*-tubocurarine the mechanical response of muscle to electrical stimulation of a peripheral nerve provides one index of drug effect. A characteristic pattern of decreased twitch tension, inability to maintain tension during tetanic stimulation (fade), and the appearance of posttetanic facilitation has been described.¹ We have made observations during the initial stages of curarization in order to evaluate these measurements.

Our data suggest that: (1) changes in the three mechanical events do not occur simultaneously; (2) ability to sustain tetanus is better related to frequency of stimulation than to the total amount of *d*-tubocurarine given; (3) increased posttetanic twitch tension is present prior to and is not enhanced by the administration of *d*-tubocurarine; (4) antidromic conduction of the electrical stimulus plays no role in determining muscle response; (5) although the response of twitch tension to *d*-tubocurarine was modified by the general anesthetic administered, this measurement offers a sensitive, rational, and objective gauge of the effect of *d*-tubocurarine.

Methods

We studied 28 patients (ASA physical status I) aged 20 to 58 years who were scheduled for lower abdominal or lower extremity surgery. The 22 female and six male patients were free of neuromuscular disease. Informed consent for performance of the investigation was obtained the day before operation.

One or both arms were placed in specially constructed armboards* so that the contractions of the adductor pollicis muscle could be monitored with a force transducer (Grass FT-10 or one of our own construction). Insulated needle electrodes (18-gauge Jelco I.V. catheter) were placed subcutaneously at one or both wrists. The ulnar nerve was stimulated supramaximally at a rate of 0.3 Hz with single pulses of 0.15 msec duration delivered from a square-wave generator (American Electronics Laboratory #104A). A three-sec tetanus of 30 Hz was delivered every five minutes. Five patients receiving methoxyflurane and six patients anesthetized with nitrous oxide were tested with 100-Hz, as well as 30-Hz, tetanus. When both the right and the left hand were being monitored, the nerves were stimulated

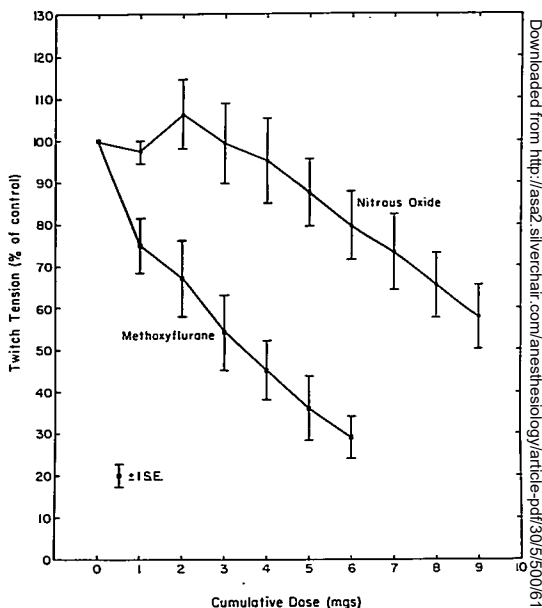
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FIG. 1. Effect of incremental 1-mg doses of *d*-tubocurarine on mechanical twitch tension during nitrous oxide or methoxyflurane anesthesia.



for alternate five-minute periods. The output of the transducers was recorded with a Grass Model 5 Polygraph and pen writer.

Patients received intramuscular premedication consisting of secobarbital (Seconal) (100 mg) and either atropine or scopolamine (0.4–0.5 mg); some patients were given meperidine (Demerol) (75–100 mg) as well.

After induction with a sleep dose of thiopental, anesthesia was maintained in one of two ways: (1) 12 patients were studied during anesthesia with nitrous oxide (5 l/min) and oxygen (2 l/min) supplemented with meperidine and thiopental (henceforth termed nitrous oxide); (2) 16 patients were studied while inhaling nitrous oxide (4 l/min), oxygen (2 l/min), and methoxyflurane delivered from an in-circle #8 Ohio vaporizer (henceforth termed methoxyflurane).

Respiration was assisted or controlled as necessary. Anesthetic depth was adjusted to provide satisfactory operating conditions. The

only neuromuscular blocker administered was *d*-tubocurarine.

After suitable control recordings had been obtained, one-mg increments of *d*-tubocurarine were given intravenously at five-minute intervals. Twitch response was recorded continually, a three-sec tetanus (30 Hz) was delivered prior to each injection of *d*-tubocurarine. Recordings were made prior to, during, or after operation as individual requirements demanded.

Nine individuals received axillary and ulnar block of one arm using 2 per cent lidocaine (Xylocaine) and epinephrine (1:200,000) to produce both motor and sensory block; this prevented antidromic conduction of the electrical stimulus and also allowed some patients to be studied prior to induction of anesthesia. In five of these patients the response of the blocked arm was examined after injection of thiopental, during a ten-minute administration of nitrous oxide, and during ten minutes of

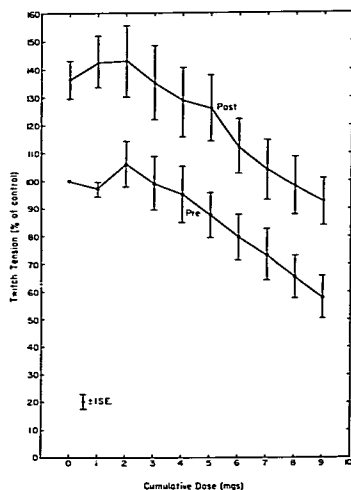


FIG. 2. Effect of incremental 1-mg doses of *d*-tubocurarine on mechanical twitch tension before and after tetanic stimulation during nitrous oxide anesthesia.

methoxyflurane, but prior to administration of *d*-tubocurarine. (In three of these the response was measured prior to induction of anesthesia as well). In the remaining four patients with axillary block, measurements were obtained during either nitrous oxide or methoxyflurane.

Bilateral stimulation and recording were performed in two patients who had not received axillary or ulnar block to evaluate the uniformity of mechanical response in both arms. There was no observed difference between arms during administration of *d*-tubocurarine.

Results

In this study, we have related all measurements of pre- and posttetanic * twitch tension to the control (no *d*-tubocurarine given) pretetanic twitch tension. Figure 1 illustrates the effect of *d*-tubocurarine on mechanical twitch tension during anesthesia with either nitrous

* The highest twitch tension recorded in the ten-sec period following the end of tetanus.

oxide or methoxyflurane. The depression of twitch tension produced by all doses of the neuromuscular blocker was greater during methoxyflurane anesthesia. Figures 2 and 3 show the parallel responses of pre- and posttetanic twitch tension when *d*-tubocurarine was administered during inhalation of either nitrous oxide or methoxyflurane.

The ability to sustain tetanus, as evidenced by mechanical tension, was best related to frequency of stimulation. The mean twitch tension in patients anesthetized with methoxyflurane was reduced to 35 per cent of control after the fifth mg of *d*-tubocurarine; yet, at the same time, 63 per cent of these patients failed to demonstrate fade when stimulated at 30 Hz. In those patients in whom a total of 5 mg of *d*-tubocurarine given over 25 minutes had reduced twitch tension to less than 10 per cent of control, the majority still did not evi-

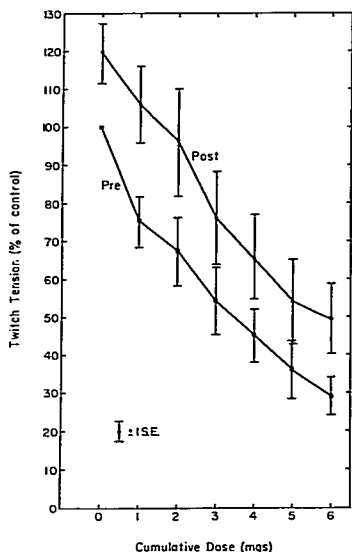


FIG. 3. Effect of incremental 1-mg doses of *d*-tubocurarine on mechanical twitch tension before and after tetanic stimulation during methoxyflurane anesthesia.

dence fade with a 30-Hz tetanus. Conversely, all patients stimulated at 100 Hz showed fade after the third mg of curare, regardless of the anesthetic agent or the reduction of twitch tension. Fade was not seen in tetanus produced by the 100-Hz stimulus during the control periods.

In patients with axillary block, the induction and maintenance of anesthesia (either nitrous oxide or methoxyflurane) produced no changes in twitch tension in the blocked arm. The effects of *d*-tubocurarine on all parameters measured were equal in the blocked and unblocked arms. The enhanced twitch tension following tetanus persisted in the blocked arm; therefore, enhancement does not depend on events occurring at a spinal level.

Discussion

The schedule of drug administration (1 mg/5 min) was chosen deliberately to permit measurement of twitch tension and response to tetanus in man during varying degrees of curarization. Figures 1, 2, and 3 indicate the effect of each dose on the mechanical response of muscle and illustrate the sensitivity of this approach. Other workers have used a single weight-related, rather than a cumulative-dose, technique.^{2,3} We felt that the goals of the present investigation were best met by obtaining a dose-response relationship. Since tremendous variability in response of man to *d*-tubocurarine has been demonstrated,⁴ we elected to express all data in terms of absolute rather than weight-related doses of *d*-tubocurarine. Regression analysis showed no statistically significant relationship between the effect of a given dose of *d*-tubocurarine and the patient's weight in any group studied.

Data obtained from patients with axillary block prior to induction of anesthesia showed that neither thiopental, nitrous oxide, nor methoxyflurane depressed twitch tension. Other studies have also demonstrated no change in twitch tension during anesthesia with halothane or diethyl ether, although awake control recordings were not obtained.^{2,3} On the other hand, a direct effect of inhalation anesthetics on neuromuscular transmission has been shown *in vitro*.⁵⁻⁷ Furthermore, diethyl ether is known to decrease twitch tension *in vivo*, both in cats when intra-arterial injection was used

to obtain high concentrations of the agent at the neuromuscular junction, and in *deeply* anesthetized man.³ Thus, although neither nitrous oxide nor methoxyflurane by themselves decreased twitch tension, the differences in response of the two anesthetized groups probably represent a direct anesthetic effect on either the neuromuscular junction or muscle, which becomes evident only after injection of *d*-tubocurarine (*vide infra*).

EFFECT OF D-TUBOCURARINE ON TWITCH TENSION

The effect of *d*-tubocurarine on mechanical response to electrical stimulation was greater during anesthesia with methoxyflurane than during nitrous oxide. Similar effects of halothane and diethyl ether have been described.^{2,5} Surgical relaxation produced by general anesthesia results from suppression of spinal reflex activity rather than from a direct effect of the drug upon the neuromuscular junction.^{8,9} It is important, therefore, to know whether the observed enhancement of *d*-tubocurarine's effect by methoxyflurane derives from a central or peripheral effect of this anesthetic. Antidromic propagation of the electrical stimulus applied to the peripheral nerve may activate spinal reflexes. If spinal reflex pathways play a role in altering the mechanical twitch tension, one would expect a difference in response when antidromic conduction is prevented by axillary block. However, in all patients investigated, the behavior patterns of the blocked and unblocked arms were similar. We conclude, therefore, that changes in spinal reflex activity cannot explain differences in response to *d*-tubocurarine when methoxyflurane is compared with nitrous oxide anesthesia. These differences very likely represent interaction of *d*-tubocurarine and the anesthetic at the neuromuscular junction. These findings apply only to antidromic conduction elicited by a supramaximal externally-supplied electrical stimulus, and do not obviate the importance of spinal reflex pathways in providing surgical relaxation.

EFFECT OF D-TUBOCURARINE ON POSTTETANIC TWITCH TENSION

The enhanced mechanical response seen in normal uncurarized man after tetanic stimula-

tion¹⁰ is a different phenomenon from that observed in the partially curarized muscle. The former is not accompanied by an increase in the compound muscle action potential, and reflects a change in the contractile mechanism. In the partially curarized muscle, however, the increased response is accompanied by an increase in the compound muscle action potential when compared with the immediate pretetanus control. The change seen in normal muscle is properly called posttetanic potentiation. Any changes in mechanical activity associated with a changed action potential (as seen in a curarized muscle) is referred to as posttetanic facilitation. Thus, complete information cannot be obtained unless both electrical and mechanical recordings are obtained.

Figures 2 and 3 show parallel responses of pre- and posttetanic twitch tension (elicited by a single square-wave stimulus) as neuromuscular blockade is increased. Thus, both in the normal muscle and during all stages of curarization, there was a constant absolute increase in twitch tension following tetanus. During clinical anesthesia, increased twitch tension following tetanus becomes apparent when it is superimposed upon a sufficiently small pretetanic response. For example, when pretetanic tension is ten arbitrary units and posttetanic tension is 13, a visual difference may not be observed. After a sufficient dose of curare has been administered, a posttetanic tension of 5 units following a pretetanic tension of two will be obvious although the absolute magnitude to change (three units) has remained constant. Similar changes were found by de Jong and Freund, who stated that during the administration of depolarizing blockers, "posttetanic facilitation becomes more apparent as the neuromuscular block is made more profound."¹¹

De Jong and Freund¹¹ considered posttetanic facilitation "meaningful" only when the posttetanic response was 200 per cent greater than that appearing before tetanus. Visual inspection of a stimulated muscle group may result in what appears to be the sudden appearance of posttetanic facilitation. However, since the enhancement of twitch tension following tetanus remains constant in the face of an increasing neuromuscular blockade (*i.e.*, fewer muscles are contributing to an unchanging re-

sponse), the phenomenon is continuous. Thus, enhanced response following tetanus is "significant" the moment neuromuscular blockade is evidenced by decreased pretetanic twitch tension.

Finally, enhanced posttetanic twitch tension depends on the stimulating waveform¹² and may not even be observed when the Block-Aid monitor provides the stimulus (see illustration in reference 13). We therefore believe that to insist that the response be obvious to visual inspection, or demand that posttetanic exceed pretetanic tension by 200 per cent before curarization is termed "significant," is without justification.

EFFECT OF D-TUBOCURARINE ON FADE

The degree of curarization is not the sole determinant of the occurrence of mechanical fade during tetanic stimulation. The frequency and duration of the stimulus are of major importance.¹⁴ In the absence of *d*-tubocurarine, neither awake nor anesthetized man showed fade when stimulated at either 30 or 100 Hz. The presence or absence of fade during clinical anesthesia is commonly evaluated in this country during a tetanus of 30 Hz. The majority of patients anesthetized with either nitrous oxide or methoxyflurane showed no fade at 30 Hz at a time when twitch tension had been significantly decreased by *d*-tubocurarine; this has been observed by Katz with other anesthetics.¹⁵ However, in all patients receiving a total of 3 mg of *d*-tubocurarine within 15 minutes, fade could be demonstrated when a stimulus of 100 Hz was used. Some patients showed fade after as little as 1 mg of *d*-tubocurarine. Thus, a stimulus of 30 Hz will not consistently elicit fade, although twitch height has been significantly reduced. On the other hand, stimulation at 100 Hz produces fade when twitch tension is totally unaffected. If tetanus is used as a gauge of curarization, it becomes incumbent upon the anesthetist to select a stimulating frequency providing the required sensitivity, and to ensure that the apparatus delivers tetanus at this rate.¹³

Clinical Implications

The use of electrical stimulation can give reliable and useful clinical information to the

anesthetist. Of the three parameters we have discussed, twitch tension appears to be the most useful single index of the action of *d*-tubocurarine. (The effect of even one-mg doses could be detected in our study.) The ability to sustain tetanus and visual examination of posttetanic twitch tension are considerably less important, for reasons we have discussed.

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Drugs

MASSIVE HEPATIC NECROSIS This abstract is a summary of a clinicopathologic conference from Washington University School of Medicine. A 67-year-old woman underwent percutaneous translumbar aortography, followed seven days later by superficial femoral popliteal artery bypass, which was followed two weeks later by left femoral endarterectomy. For all operations, anesthesia consisted of halothane, nitrous oxide, oxygen and thiopental. Four days after the third operation, the patient became jaundiced. Despite treatment, the jaundice deepened; she became obtunded, oliguric, and hypotensive, and died 24 days later. Autopsy revealed lobar pneumonia, acute massive hepatic necrosis, renal tubular necrosis, and pneumococcal meningitis. The admonition is made to avoid a second use of halothane anesthesia in any patient exhibiting fever and jaundice after one exposure to halothane. In addition, repeated frequent exposure to halothane is not recommended. (*Clinicopathologic Conference: Massive Hepatic Necrosis Following Multiple Exposures to Halothane*, *Amer. J. Med.* 45: 589 (Oct.) 1968.)