Tachyphylaxis to Decamethonium and Reversibility of the Block by Anticholinesterase Drugs

Felix G. Freund, M.D.*

The effect of repeated administration of decamethonium (0.5 mg/kg) was studied by measuring adduction of the thumb in response to stimulation of the ulnar nerve at the wrist in 21 subjects under nitrous oxide-halothane anesthesia. Repeat doses were given when twitch tension had recovered to 75 per cent of control value. Four successive doses of decamethonium reduced twitch tension to 7, 35, 50 and 45 per cent of control value, and maximum tetanic tension to 3.5, 19, 29 and 21 per cent of control value. Neuromuscular transmission always increased when edrophonium (30 mg) or neostigmine (1 mg) was given after two or more doses of decamethonium, but not when edrophonium was given after one dose of decamethonium.

There have been conflicting reports of the degree of tachyphylaxis to depolarizing neuromuscular agents and the reversibility of the neuromuscular block by anticholinesterase drugs. Churchill-Davidson et al.¹ observed tachyphylaxis in all patients given repeated doses or prolonged infusions of depolarizing agents. After development of tachyphylaxis the block always could be reversed by anticholinesterases. Katz et al.² and Cruij et al.³ saw tachyphylaxis only occasionally but were able to reverse the block in most patients. Zaimis found tachyphylaxis and reversibility in several mammalian species⁴ but never in man.⁵

Because of these conflicting reports, a study was performed in man to determine the degree of tachyphylaxis to successive doses of decamethonium (Syncurine) and the reversibility of the block by anticholinesterase drugs.

The results of this study essentially support the conclusions drawn by Churchill-Davidson et al.¹

Methods

Studies were performed in 12 men and nine women, ages 21 to 60 years, undergoing elective surgery. Informed consent was obtained from all patients. Preanesthetic medication consisted of 100 mg pentobarbital (Nembutal) and 0.4 mg scopolamine. Anesthesia was induced with thiopental (sodium Pentothal) (150 to 250 mg) and maintained with 66 per cent nitrous oxide, 33 per cent oxygen and 0.5 to 1 per cent halothane. Tracheal intubation was accomplished without the use of neuromuscular blocking drugs. Body temperature, monitored with an esophageal thermometer probe, was maintained between 35.5 and 37 C. After induction of anesthesia one arm was secured to a splint and two needle electrodes were inserted subcutaneously near the ulnar nerve at the wrist. The nerve was stimulated continuously with rectangular pulses of supramaximal intensity and 0.3-msec duration at a rate of 24/min; a five-second tetanic burst at a rate of 40/sec was interposed every two to three minutes. The strength of the resulting contractions of the adductor pollicis muscle was measured with a Grass FT-10 force transducer attached to the proximal phalanx of the thumb.

Following control records of twitch and tetanic tension, the first dose of decamethonium (0.05 mg/kg) was given intravenously over a period of ten seconds. Subsequent equal doses of decamethonium were given when the twitch tension had recovered to approximately 75 per cent of control value. Four subjects received one, four received two, four received three and nine received four doses of decamethonium.

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Table 1. Effects of Four Successive Equal Doses of Decamethonium on Neuromuscular Transmission*

<table>
<thead>
<tr>
<th></th>
<th>First dose, 21 subjects</th>
<th>Second dose, 17 subjects</th>
<th>Third dose, 13 subjects</th>
<th>Fourth dose, 9 subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Peak effect</td>
<td>Recovery 30 min</td>
<td>Peak effect</td>
<td>Recovery 28 min</td>
</tr>
<tr>
<td>Twitch tension</td>
<td>7.1 ± 7.9</td>
<td>81 ± 22</td>
<td>35 ± 17†</td>
<td>80 ± 22</td>
</tr>
<tr>
<td>(Percent of control)</td>
<td>3.5 ± 3.8</td>
<td>78 ± 21</td>
<td>19 ± 17†</td>
<td>72 ± 24</td>
</tr>
<tr>
<td>Maximum tetanic tension (Percent of control)</td>
<td>41 ± 17</td>
<td>90 ± 11</td>
<td>30 ± 28</td>
<td>79 ± 18</td>
</tr>
</tbody>
</table>

* (Mean ± S.D.). Note the decreasing effect but longer duration of action of each successive dose.

The tetanic tension ratio is the ratio of the final (lowest) to the highest tension with a five-second tetanic contraction. It expresses the reciprocal of muscle fatigue, 100 meaning no fatigue and zero meaning maximal fatigue.

† Significantly different from effect of first dose (p < .01).

Following the last dose, when twitch tension had recovered to approximately 70 per cent of control value, 11 subjects were given 20 mg edrophonium (Tensilon) and ten were given 1 mg neostigmine (Prostigmine) intravenously, the latter preceded by 0.5 mg atropine. Respiration was assisted or controlled as necessary.

Twitch tension and tetanic tension were measured in grams and computed as percentages of control values. The ability of the muscle to maintain a tetanic contraction during five seconds was expressed as the percentage ratio of the lowest (final) to the highest tension within each tetanic contraction. The tetanic tension ratio represents the reciprocal of muscle fatigue, 100 meaning no fatigue and zero meaning complete exhaustion. Student's t test for paired data was used for statistical analysis.

Results

Decamethonium produced a maximum neuromuscular blocking effect five to seven minutes after injection. The onset of the block was preceded by potentiation of the twitch in three of 60 administrations of decamethonium. Tachyphylaxis developed in all subjects. Whereas the first dose of decamethonium reduced twitch tension to a mean of 7 per cent of control value, the second, third and fourth doses reduced it to only 35, 50 and 45 per cent, respectively (table 1). Likewise, maximum tetanic tension fell to 3.5 per cent of control value with the first dose, but to only 19, 29 and 21 per cent with the subsequent three doses. Figure 1 illustrates the decreasing neuromuscular block produced by three consecutive doses in one patient. Unlike twitch tension and maximum tetanic

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**Fig. 1.** From top to bottom, effects of three successive equal doses of decamethonium on twitch tension (left) and tetanic tension (right). Tetanic tension records were obtained when depression of twitch tension was maximal. Note different scales on right. The second and third doses of decamethonium were much less effective than the first.
tension, the tetanic tension ratio (reciprocal of fatigue) showed no significant difference between the first and the subsequent doses of decamethonium. From a control value of 97 ± 2.1 per cent, the tetanic tension ratio fell to 41, 30, 30 and 28 per cent with each of four consecutive doses of decamethonium, indicating poorly sustained tetanus.

As the neuromuscular blocking effect of successive doses of decamethonium decreased, the duration of action increased. Figure 2 shows progressively longer recovery of neuromuscular transmission, so that 20 minutes after peak effect of each of four consecutive doses of decamethonium, twitch tension had recovered to 81, 72, 58 and 51 per cent, respectively, of control. Recovery of maximum tetanic tension and tetanic tension ratio followed a similar course (table 1).

The administration of edrophonium or neostigmine after two or more doses of decamethonium always increased twitch tension, maximum tetanic tension and tetanic tension ratio (table 2). The peak effect of edrophonium occurred within two to three minutes of injection, but often was not sustained. The action of neostigmine developed gradually over 15 minutes after injection and was sustained for the period of observation, 30 to 45 minutes. The effects of these drugs were always greater on maximum tetanic tension and tetanic tension ratio than on twitch tension (fig. 3). Of four patients given edrophonium after one dose of decamethonium, two showed no effect and two had a 20 per cent decrease in twitch tension that lasted 30 to 40 seconds and did not appear to alter the recovery rate.

Discussion

The development of tachyphylaxis to repeated doses of decamethonium and reversibility of the neuromuscular block by anticholinesterase drugs in all subjects confirms the results obtained by Churchill-Davidson et al. in man anesthetized with thiopental and nitrous oxide. Decamethonium evidently has in man the same action reported for other mammals. The similarity of findings in different species with various anesthetic agents (thiopental-nitrous oxide, chloralose, pentobarbital, ether) suggests that the use of

| Table 2. Peak Effects of Edrophonium and Neostigmine on Neuromuscular Transmission after Two, Three and Four Equal Doses of Decamethonium*
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<tbody>
<tr>
<td></td>
<td>Twitch Tension (Percentage of control)</td>
<td>Maximum Tetanic Tension (Percentage of control)</td>
<td>Tetanic Tension Ratio (Per cent)</td>
</tr>
<tr>
<td>Decamethonium</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Second dose (17 subjects)</td>
<td>06±7±</td>
<td>52±10.5</td>
<td>55±5.1</td>
</tr>
<tr>
<td>Anticholinesterase effect (13 subjects)</td>
<td>75±5.5</td>
<td>82±8.2</td>
<td>85±3.3</td>
</tr>
<tr>
<td>Decamethonium Third dose (9 subjects)</td>
<td>52±22</td>
<td>44±36</td>
<td>51±42</td>
</tr>
<tr>
<td>Anticholinesterase effect</td>
<td>66±4.3</td>
<td>74±3.5</td>
<td>84±0.7</td>
</tr>
<tr>
<td>Decamethonium Fourth dose</td>
<td>64±10</td>
<td>50±21</td>
<td>61±33</td>
</tr>
<tr>
<td>Anticholinesterase effect</td>
<td>50±12</td>
<td>81±15</td>
<td>88±14.3</td>
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* (Mean ± S.D.). Note that the anticholinesterase always improved neuromuscular transmission and that the effect was greater on the tetanic muscle response than on single-twitch tension. For the meaning of the tetanic tension ratio see legend to table 1. 
† P < .05. 
‡ P < .01.
halothane did not affect the results of this study. Moreover, the effect of a single dose of decamethonium in the presence of halothane was of the magnitude and duration measured in unanesthetized man by Poulsen and Hougs. Finally, although halothane has been shown to decrease the number of miniature end-plate potentials in isolated frog muscle and to increase the magnitude and duration of action of tubocurarine in man, there is no evidence that it affects the nature of neuromuscular block in man.

In animal species the anticholinesterases relieved the block produced by the first dose of decamethonium. In the present study these drugs were effective only after the second dose of decamethonium. The difference may be related to the use of smaller amounts of decamethonium in this study.

The present observations contrast with those of Zaimis, who reported that regardless of the number of doses or the total amount of decamethonium given to man, tachyphylaxis never developed and anticholinesterase drugs always were ineffective or increased the magnitude of the block. The discrepancy is not readily explainable. Unfortunately, the number of doses and the total amount of decamethonium used by Zaimis are not clear. The infrequent finding of tachyphylaxis to succinylcholine by Katz et al.2 and Crul et al.3 may be related to the difficulty of maintaining a stable level of neuromuscular block with this drug, owing to rapid hydrolysis. It was for this reason that decamethonium, a longer-acting drug, was chosen for this study.

After prolonged exposure of the muscles to depolarizing agents recovery of neuromuscular transmission can be very slow, as shown by this study (table 1 and fig. 2) and by the numerous reports of prolonged apnea following use of succinylcholine. Every subject in this study was given either edrophonium or neostigmine during the recovery phase of the block. Neuromuscular transmission always improved when these drugs were given after two or more doses of decamethonium (see table 2 and fig. 3). Transmission decreased, though transiently only, when the anticholinesterase was given after a single dose of decamethonium.

It would seem reasonable to test the response to anticholinesterases in any patient exhibiting a prolonged block after administration of repeated doses or continuous infusions of depolarizing agents. It is important, however, that some respiratory effort or muscle response to electrical nerve stimulation be present in order to permit evaluation of the efficacy of the anticholinesterase. When using a nerve stimulator for this purpose, it may be advisable to place greater reliance on the character of the tetanic responses than on the strength of single twitches. As shown in table 2 and figure 3, the anticholinesterases had greater effects on both magnitude and maintenance of tetanic tension than on single-twitch tension.

From a clinical point of view, it is worth emphasizing the effect of anticholinesterase drugs on tetanic tension. Because skeletal muscle is physiologically activated by neurons discharging at near-tetanic rates, the response...
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of a muscle to tetanization is a more useful indication of mechanical performance than the single-twitch response.

References


Anesthesia

“AWAKE” CANNULATION In the course of surgical treatment of severely ill cardiac patients, the period between induction of general anesthesia and establishment of cardiopulmonary bypass following thoracotomy is a critical one. A technique was devised to protect the patient during that period. Femoral vessels were exposed bilaterally under local or continuous peridural (level of T12) analgesia. Cannulae were inserted through femoral veins into the right atrium and inferior vena cava. One femoral artery was cannulated and the other ligated. Cardiopulmonary bypass could thus be instituted at any time if circulatory failure occurred. General anesthesia was then induced and the operative procedure started. This technique was used in 20 severely ill patients with no deaths prior to the definitive surgical procedure. (Danielson, G. K., Hasbrouck, J. D., and Bryant, L. B.: Cannulation Under Local or Regional Anesthesia for the “Salvage” Cardiac Patient, J. Thorac. Cardiovasc. Surg. 55: 894 (June) 1968.)

PARACERVICAL BLOCK Varying incidences of fetal bradycardia and depression at the time of birth have been reported after paracervical block for pain relief in the first stage of labor. This report describes the deaths of two infants following mepivacaine paracervical block. The first experienced prolonged bradycardia unmodified by maternal oxygen administration and was stillborn. The second had bradycardia which coincided with maternal analgesia and died at 45 hours of age after repeated episodes of convulsions. Chromatographic analysis of this infant’s urine at 36 hours revealed 6.2 µg/ml mepivacaine. Rapid passage of mepivacaine into the fetal circulation and impaired detoxification during the newborn period may have produced high fetal blood levels of mepivacaine. (Rosefsky, J. B., and Petersol, M. E.: Perinatal Deaths Associated with Mepivacaine Paracervical Block Anesthesia in Labor, New Engl. J. Med. 278: 530 (March) 1968.)