SEQUENTIAL CHANGES IN THE FADE OF TETANIC TENSION AFTER THE ADMINISTRATION OF TUBOCURARINE IN ANAESTHETIZED MAN

N. SUGAI, R. HUGHES AND J. P. PAYNE

SUMMARY
Tetanic and single twitch contractions of the adductor pollicis muscle in anaesthetized man were measured continuously following the i.v. injection of tubocurarine 0.2 mg/kg. Tetanic contractions were depressed earlier by tubocurarine and to a greater extent compared with the single twitch. Recovery was also slower for the tetanic contractions. The fade of tetanic tension was also measured throughout the blockade produced by tubocurarine. Fade was expressed in terms of the tetanic tension ratio: the ratio of the magnitude of the muscle tension at the end of 1 s of tetanic contraction compared with its peak height at the beginning of that contraction. Tetanic tension was well maintained during the onset of the neuromuscular block but was less well maintained during the recovery phase. It is suggested that the assessment of tetanic tension fade should be carried out throughout the various stages of curarization.

Since the early observations of Paton and Zaimis (1949, 1951) tubocurarine has been known to produce fade of tetanic tension of skeletal muscles in animals. Such fade is also regarded as a characteristic feature of the neuromuscular blockade produced by non-depolarizing drugs in man (Churchill-Davidson and Wise, 1960).

In the present study, the tetanic tension of the adductor pollicis muscle and its fade were measured continuously following the i.v. injection of tubocurarine in man.

PATIENTS AND METHODS
Five adult male patients were studied before urological surgery and after their informed consent had been obtained on the previous day. Their ages ranged from 48 to 65 yr with a mean of 57.8 ± 6.2 (SD). No premedication was given and anaesthesia was induced with halothane and nitrous oxide in oxygen. Endotracheal intubation was carried out without the use of a neuromuscular blocking agent after spraying the larynx with a 4% lignocaine solution. Anaesthesia was maintained with nitrous oxide and pentazocine in four patients and with nitrous oxide and pethidine in one patient.

Simultaneous measurements of tetanic and single twitch contractions of the adductor pollicis muscle were performed as described previously (Sugai, Hughes and Payne, 1975). One ulnar nerve was stimulated tetanically at 50 Hz for 1 s every 12 s and the other with single square wave pulses of 200 μs duration every 12 s. Recordings were made on a Mingograf ink-jet recorder at a fast speed of 5 mm/s and on a Brush-Clevite recorder at a slow speed of 5 mm/min.

The arterial pressure was measured directly from a polyethylene catheter inserted into the radial artery at the same wrist as that to which single twitch stimuli were applied; heart rate was measured from the electrocardiogram. Arterial blood-gas analyses were performed on the samples taken from this cannula and blood-gases and pH were maintained within normal limits by controlling respiration with a Manley ventilator. The temperature of the hands was monitored by surface probes placed on the palm at the proximal portion of the thumbs and maintained within one degree Centigrade.

At the beginning of the control period tetanic contractions showed a slight decline, but after about 20 min they became stable. After a further 10–20 min tubocurarine 0.2 mg/kg was given i.v. into a forearm vein.

Tetanic tension ratios and the degree of tetanic transmission were determined by an Elliot 903 digital computer from on-line real-time data (Perry et al., 1975). The tetanic tension ratio, which is defined as...
the ratio of the magnitude of the tetanus at the end of tetanic contraction of 1 s duration compared with its initial magnitude and expressed as a percentage, reflects the degree of fade during neuromuscular block. The degree of tetanic transmission was derived from the ratio of the peak tetanic response compared with the control response, tetanus measured during the control period, and expressed as the percentage depression (Perry et al., 1975). During the control period the tetanus, after the initial brief decline, was well maintained and the tetanic tension ratio was virtually 100% in every patient.

Tetanic tension ratios measured during the beginning of the block were compared with those measured during the recovery phase of the tubocurarine block, in order to assess any difference in the degree of tetanic tension fade during these two stages. Single twitch contraction of the thumbs was also measured simultaneously with the tetanic tension and compared throughout the period of the blockade.

**RESULTS**

(1) **Comparison of tetanic and single twitch contractions of the adductor pollicis muscle during the course of action of tubocurarine**

In all the patients studied, the initial sign of depression after tubocurarine occurred earlier and the maximal depression was always greater on the tetanic contraction than on the single twitch contraction. A dose of tubocurarine 0.2 mg/kg caused a mean depression of 95.9 ± 3.2% (SD) of the tetanic contractions and a mean depression of 60.4 ± 18.0% (SD) of the single twitch contractions. Recovery from the maximal depression was seen earlier on the single twitch than on the tetanic contraction (fig. 1).

The relevant quantitative data, together with the appropriate statistical analyses, are presented in table I.

![Figure 1](http://bja.oxfordjournals.org/)  
**FIG. 1.** Slow recording of tetanic and single twitch contractions of the adductor pollicis muscles after the administration of tubocurarine 0.2 mg/kg.

(2) **Evaluation of the changes in tetanic tension ratio after the injection of tubocurarine**

The tetanic tension ratio was calculated for each tetanic contraction after the injection of tubocurarine (fig. 2) and plotted as shown in figure 3. The tetanic tension ratios at 30% and 50% of tetanic transmission were determined for every patient studied from graphs of this type. The tetanic tension ratio was always higher during the onset of the depressant

<table>
<thead>
<tr>
<th>Time intervals for recovery and percentage maximal depression after i.v. injection of tubocurarine 0.2 mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient</td>
</tr>
<tr>
<td>----------</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>3</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>4</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>5</td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

Table 1. Time intervals for recovery and percentage maximal depression after i.v. injection of tubocurarine 0.2 mg/kg

Time for initial effect and recovery is expressed in seconds.

Maximal depression is expressed as percentage of the control.

\[P < 0.01, 0.9 < P < 0.1, 0.02 < P < 0.05, 0.01 < P < 0.02\]
action of tubocurarine on the tetanic contractions, compared with the later recovery phase.

The relevant information together with the statistical interpretation of the results are listed in Table II. It will be seen that the tetanic tension ratios during the onset of the blockade were significantly higher than those during the recovery phase at both 30% and 50% tetanic transmission.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Onset</th>
<th>Recovery</th>
<th>Onset</th>
<th>Recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>91.8</td>
<td>36.9</td>
<td>96.0</td>
<td>76.4</td>
</tr>
<tr>
<td>2</td>
<td>67.7</td>
<td>22.9</td>
<td>87.4</td>
<td>62.8</td>
</tr>
<tr>
<td>3</td>
<td>93.6</td>
<td>31.2</td>
<td>99.0</td>
<td>67.7</td>
</tr>
<tr>
<td>4</td>
<td>94.3</td>
<td>40.2</td>
<td>97.5</td>
<td>88.7</td>
</tr>
<tr>
<td>5</td>
<td>98.7</td>
<td>52.5</td>
<td>99.8</td>
<td>94.2</td>
</tr>
<tr>
<td>Mean</td>
<td>89.2</td>
<td>36.7</td>
<td>95.9</td>
<td>78.0</td>
</tr>
<tr>
<td>SD</td>
<td>12.3</td>
<td>11.0</td>
<td>5.0</td>
<td>13.4</td>
</tr>
</tbody>
</table>

P < 0.01

Tetanic tension ratio is expressed as percentage.

P = significance of difference between onset and recovery.

(3) Cardiovascular effects

No significant change in heart rate was seen after the injection of tubocurarine, but in three of the five patients the mean arterial pressure decreased by an average of 8.1% (6.5%, 8.1%, 9.7%).

DISCUSSION

It has been argued that the tetanic contraction of skeletal muscle in man is a more sensitive index of the neuromuscular blockade produced by tubocurarine than is the single twitch contraction (Gissen and Katz, 1969; Epstein and Epstein, 1973). The present results confirm and amplify this observation. The onset of the neuromuscular blockade occurred earlier with tetanic contractions than with single twitch contractions, the maximal depression of the tetanus was more marked and the recovery of the tetanus was slower especially after the 50% recovery point had been attained. The present study has also demonstrated that, compared with the later recovery phase, the extent of tetanic fade was less and the tetanus was better maintained during the onset of blockade.

Recently, the concept that tetanic tension fade is an important clinical criterion in the diagnosis of neuromuscular blockade by tubocurarine in man (Churchill-Davidson and Wise, 1960) has been challenged. Heisterkamp, Skovsted and Cohen (1969), who studied tetanic tension fade after administering 1-mg incremental doses of tubocurarine, were unable to demonstrate tetanic tension fade.
fade in 63% of the patients stimulated at 30 Hz. It was concluded that the ability to sustain tetanus was better related to the stimulus frequency than to the dose of tubocurarine and that the measurement of twitch tension furnished a rational, objective and reasonably sensitive guide to the effect of tubocurarine.

Katz (1973) also investigated this problem in man by testing the tetanic response at 74% and 36% of the single twitch depression compared with the control after incremental doses of 0.05 mg/kg of tubocurarine. Evidence of fade was found in five of the six patients studied at the greater degree of block, but only in three of the five at the lesser degree of block. Although Katz studied the tetanic response at different degrees of depression of the single twitch contractions, a detailed examination of tetanic tension fade throughout the entire course of the action of tubocurarine was not carried out.

The absence of fade in most patients in the study of Heisterkamp and his colleagues and in some of the patients in Katz' study might indicate that it is important to evaluate the tetanic tension fade at different stages of curarization. The dose of tubocurarine and the method of administration must be known also. Heisterkamp and his colleagues used small incremental doses while Katz used large incremental doses. In the present investigation a relatively large single dose was given and the results suggest that tetanic tension fade always occurs when a substantial amount of tubocurarine is applied to the neuromuscular junction for a sufficient length of time.

The mechanism of tetanic tension fade is speculative; one possibility is the involvement of the presynaptic action of tubocurarine in the development of tetanic fade. According to Standaert (1964), tubocurarine has a depressant effect on the motor-nerve terminals of the cat and this effect might contribute to its neuromuscular blocking action. Tetanic tension fade can be interpreted as a failure of the motor-nerve terminal to produce a sustained supply of acetylcholine to maintain the tetanic contraction. This can only occur when the drug has reached the motor-nerve terminal where it exerts its action. Immediately after tubocurarine is injected i.v. the plasma concentration of the drug is high but decays rapidly with a half-life of 5.7 min (Kalow, 1959). This high concentration of tubocurarine would provide enough drug in the postsynaptic area to block tetanic transmission, but the initial process of blockade would probably not prevent accumulation of acetylcholine at the motor-nerve terminal in response to tetanic stimulation. However, as the concentration of the drug around the presynaptic region increases, the motor-nerve terminal would be unable to release sufficient acetylcholine to maintain the response to tetanic stimulation. In this context it is worth emphasizing that hemicholinium, which blocks neuromuscular transmission by presynaptic action, exerts its neuromuscular blocking action after a latent period (Schueler, 1955).

In conclusion, it has been demonstrated that tetanic tension evaluation is a more sensitive index than the single twitch for the assessment of the neuromuscular blocking action of tubocurarine, that during the onset of neuromuscular block by tubocurarine, tetanic tension is relatively well maintained compared with the later recovery phase in man and that the continuous evaluation of tetanic tension and its fade provides useful information about the nature of neuromuscular blockade.

ACKNOWLEDGEMENTS

We are indebted to Mrs Jennifer Eccles, s.r.n., and Mr R. Worsley for technical assistance; to Mr R. Bartholomew and his staff for the illustrations; to our surgical and nursing colleagues for their tolerance and patience, and to our volunteers without whom the study would have been impossible. N. S. was the holder of a Wellcome-Japanese Travelling Research Fellowship while this work was being carried out.

REFERENCES


FADE OF TETANIC TENSION AFTER TUBOCURARINE


CHANGEMENTS SEQUENTIELS DANS LA DISPARITION PROGRESSIVE DE LA TENSION TETANIQUE APRES ADMINISTRATION DE TUBOCURARINE SUR UN HOMME ANESTHESIE

RESUME
On a mesure d'une manièere continue les contractures tétniæques et les crisptions nerveuses du muscle adducteur pollicis sur un homme anesthésié après une injection intraveineuse de tubocurarine à raison de 0,2 mg/kg. Les contractures tétniæques ont été réduites par la tubocurarine plus vite et dans une plus grande mesure que les crisptions nerveuses. La récupération a aussi été plus lente pour les contractures tétniæques. La disparition progressive de la tension tétniæque a également été mesurée pendant toute la durée du blocage produit par la tubocurarine. La disparition progressive a été exprimée en terme de rapport de la tension tétniæque: le rapport de la magnitude de la tension musculaire à la fin d'une seconde de contracture tétniæque par comparaison à son point le plus élevé au commencement de cette contracture. La tension tétniæque s'est bien maintenue pendant les débuts du blocage neuromusculaire, mais elle s'est moins bien maintenue pendant la phase de récupération. On suggère dans cet article de procéder à une évaluation de la disparition progressive de la tension tétniæque pendant les divers stades de la curarisation.

SEQUENZANDERUNGEN IM ABFLAUFEN TETANISCHER SPANNUNGEN NACH VERABREICHUNG VON TUBOCURARIN AN NARKOTISIERTE PATIENTEN

ZUSAMMENFASSUNG

CAMBIOS SUCESIVOS EN LA AMORTIGUACION DE LA TENSION TETANICA TRAS ADMINISTRACION DE TUBOCURARINA EN EL ANESTESIADO

SUMARIO
Las contracciones tetánicas y de espasmo único del músculo aductor del pulgar en el anestesiado fueron medidas continuamente tras la inyección i.v. de 0,2 mg/kg de tubocurarina. Las contracciones tetánicas fueron deprimidas anteriormente mediante tubocurarina y en un grado mayor comparadas con el espasmo único. La recuperación fue también más lenta para las contracciones tetánicas. La amortiguación de la tensión tetánica fue medida también durante todo el bloqueo producido por la tubocurarina. La amortiguación se expresó en términos de la proporción de tensión tetánica: la proporción de la magnitud de la tensión muscular al final de 1 seg de contracción tetánica comparada con su valor máximo al comienzo de dicha contracción. La tensión tetánica se mantuvo bien durante el bloqueo neuromuscular en su comienzo, pero su mantenimiento no fue tan bueno durante la fase recuperativa. Se sugiere que la valoración de la amortiguación de la tensión tetánica debiera efectuarse durante todas las diversas etapas de la curarización.