RECOVERY FROM NEUROMUSCULAR BLOCKADE DURING SINGLE SHOCK AND TETANIC NERVE STIMULATION IN CATS

BY

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SUMMARY

Indirectly stimulated gastrocnemius muscles of anaesthetized cats were more sensitive to paralysis by non-depolarizing or competitive agents when tetanic bursts rather than single shocks were employed. This action may be mainly attributable to a reduction in the output of acetylcholine during tetanic stimulation. Recovery from paralysis of equal intensities was similar. Although the twitch response of the gastrocnemius had recovered, respiration was not adequately restored until the tetanus was fully sustained. Hence it is advisable to apply tetanic stimulation when monitoring recovery from neuromuscular paralysis. If reversal of competitive blockade is inadequate, the consequent rapid shallow breathing may lead to apnoea due to recurarization of the muscles concerned. The course of action of depolarizing agents was shorter when tetanic stimulation rather than single shocks were applied to the sciatic nerves. The slower recovery of muscles stimulated by single shocks could be mainly the result of their lower temperature, as recovery was similar when both muscles were maintained at body temperature.

Neuromuscular blockade in experimental animals and in man has often been assessed by the responses of skeletal muscles to indirect stimulation with single shocks. However, muscle movements, including those of respiration, are activated by trains of nerve volleys rather than by single stimuli.

It has been reported by Naess (1950) that the higher the frequency of indirect tetanic stimulation, the greater was the intensity of paralysis by tubocurarine in rabbits. Similarly, Paton and Zaimis (1951) found that during curarization in cats, the responses of the soleus and tibialis muscles to tetanic stimulation of the sciatic nerve were reduced more than the contractions evoked by single shocks, and that respiration was depressed before the twitch response. In contrast, decamethonium reduced the muscle twitches before impairing respiration and the tetanus/twitch ratio was well maintained. Preston and Maanen (1953) observed in rats that when the frequency of stimulation was increased, the doses of tubocurarine, gallamine and decamethonium necessary to produce paralysis were reduced, and the times taken to reach maximum paralysis were shortened, whereas the rate of recovery appeared to be independent of the frequency of stimulation. Blackman (1963), using the rat diaphragm and frog sartorius preparations, found that blockade by tubocurarine was more dependent on the stimulus frequency than was blockade by decamethonium. In anaesthetized patients, Gissen and Katz (1969) used the responses to tetanic stimulation of the ulnar nerve to demonstrate neuromuscular block by tubocurarine since this was not apparent from the twitch responses.

Some of these differences might be explained by temperature effects, as lowered muscle temperature increases and prolongs the action of depolarizing drugs but reduces that of tubocurarine (Bigland et al., 1958). In this context, it may be of importance that the temperature of the limb muscles in anaesthetized cats is usually lower than that of the rest of the body (Bigland and Zaimis, 1958) and the diaphragm (Alderson and Maclagan, 1964), and that the temperature of tetanically stimulated muscle is likely to be higher than that of muscle stimulated by single shocks.

The present experiments were carried out to determine the extent to which the course of paralysis by non-depolarizing and depolarizing neuromuscular blocking agents was dependent on whether the applied stimulus consisted of single shocks or tetanic bursts; the influence of possible differences in muscle temperatures was also investigated.

**METHOD**

Cats of either sex and weighing between 2.7 and 3.8 kg were used. Anaesthesia was induced with 4–8 per cent halothane in oxygen at a flow rate of 4 l./min from a calibrated Fluotec vaporizer and maintained with chloralose (60 mg/kg i.v.) after cannulation of a jugular vein. Both sciatic nerves were exposed between the thigh muscles, crushed centrally and placed on shielded bipolar platinum electrodes. The hind limbs were secured to a rigid frame by steel drills through the knee joints and by clamps at the ankle joints. The limbs were kept warm by radiant heat from a 60-watt electric lamp. The tendon of each gastrocnemius muscle was cut and attached to a Grass FT10 force displacement transducer. Rectangular pulses of supramaximal voltage and 0.05–0.1 msec duration were applied to the sciatic nerves. The right muscle was indirectly stimulated with 1 shock/10 sec through a 1:1 isolation transformer; the maximum tension developed was 1.25 kg. The left gastrocnemius muscle was indirectly stimulated with a tetanus of 30 shocks/sec for 1 sec every 10 sec through an rf isolation unit so that there was no common connection between the stimulating electrodes; the maximum tension developed was 3.5 kg. Tetanic fusion occurred at a frequency of 15–29 shocks/sec and the tetanus employed was the maximum which could be applied without causing severe muscle fatigue during a 6–8-hr experiment. Carotid blood pressure was recorded with a pressure transducer, and respiration was registered by a thermistor bead fixed inside a polyethylene cannula inserted into the trachea to ensure constancy of ventilation. Heart rate was recorded from the electrocardiogram using a cardiotachometer. Additional experiments were carried out using six patas monkeys (3–4.8 kg) prepared in a similar manner. Multichannel recordings were made on a Polygraph (Grass Instruments). During neuromuscular paralysis adequate ventilation was maintained with a Starling Ideal respiration pump (Palmer); periodically the pump was disconnected to assess whether breathing had returned. Oesophageal, rectal and muscle temperatures were sometimes compared using an electro-thermometer (Light Laboratories). In other experiments the temperature of both gastrocnemius muscles were maintained at body temperature by surrounding each limb with a heating coil made from polyvinyl tubing through which warm water was circulated using a thermostatically controlled Circotherm water heater and pump.

**RESULTS**

In a preliminary series of experiments using groups of four to seven anaesthetized cats, intravenous doses of tubocurarine (0.21 mg/kg), dimethyl tubocurarine (0.019 mg/kg), gallamine (1.1 mg/kg) and benzoquinonium (0.13 mg/kg), sufficient to cause partial paralysis (54–67 per cent) of the right gastrocnemius muscle stimulated by single shocks, greatly reduced or abolished (96–100 per cent) the sustained contraction of the left muscle stimulated tetanically. The tetanus declined more rapidly than the twitch and recovery took at least twice as long. Breathing was not usually fully restored until the tetanically stimulated muscle had nearly recovered; this effect was best illustrated in an experiment carried out with tubocurarine in a monkey (fig. 1).

During neuromuscular blockade by suxamethonium (0.07 mg/kg i.v.) in five cats, the tetanus was well sustained and its depression (88 per cent) was only slightly greater than that of the single twitches (73 per cent); blockade by decamethonium (0.03 mg/kg i.v.) in four cats was similar (80 per cent) whether tetani or twitches were applied. Such paralyzing doses of these drugs did not arrest respiration. The rate of recovery of the tetanically stimulated muscle was about twice that of the muscle stimulated by single shocks. Similar results were obtained using anaesthetized monkeys.

Further experiments were carried out in which partial neuromuscular blockade of similar intensity was produced in both gastrocnemius muscles of the same cat. As the tetanically stimulated muscle was usually more sensitive to
TABLE I

Comparison in anaesthetized cats of onset and recovery times of indirectly stimulated gastrocnemius muscles from neuromuscular paralysis of similar intensities of (a) the twitch responses of one muscle stimulated with single shocks every 10 sec and (b) the sustained contractions of the other muscle stimulated tetanically with 30 shocks/sec for 1 sec every 10 sec. Blood pressure at the time of maximum change is shown as percentage of initial. Mean values and ranges are quoted. Differences between mean doses causing similar paralysis of (a) and (b), and corresponding mean recovery times, when indicated * and ** were significant at the 5 and 1 per cent levels respectively.

<table>
<thead>
<tr>
<th>Drug</th>
<th>No. of cats</th>
<th>Dose (mg/kg) i.v.</th>
<th>Blood pressure (initial = 100)</th>
<th>Gastrocnemius paralysis (%)</th>
<th>Onset (min)</th>
<th>Recovery time (min)</th>
<th>Dose (mg/kg) i.v.</th>
<th>Blood pressure (initial = 100)</th>
<th>Gastrocnemius paralysis (%)</th>
<th>Onset (min)</th>
<th>Recovery time (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tubocurarine</td>
<td>5</td>
<td>0.22* (0.13-0.40)</td>
<td>79</td>
<td>72</td>
<td>6</td>
<td>20</td>
<td>0.07 (0.02-0.13)</td>
<td>95</td>
<td>73</td>
<td>4.8</td>
<td>23</td>
</tr>
<tr>
<td>Dimethyl-</td>
<td>5</td>
<td>0.027* (0.015-0.034)</td>
<td>108</td>
<td>82</td>
<td>7.5</td>
<td>28</td>
<td>0.010 (0.005-0.013)</td>
<td>105</td>
<td>83</td>
<td>6</td>
<td>30</td>
</tr>
<tr>
<td>Gallamine</td>
<td>5</td>
<td>1.0** (0.6-1.6)</td>
<td>102</td>
<td>82</td>
<td>5</td>
<td>30</td>
<td>0.41 (0.29-0.65)</td>
<td>106</td>
<td>82</td>
<td>5.5</td>
<td>28</td>
</tr>
<tr>
<td>Benzoquinonium</td>
<td>4</td>
<td>0.15** (0.13-0.20)</td>
<td>109</td>
<td>81</td>
<td>5</td>
<td>18</td>
<td>0.03 (0.02-0.04)</td>
<td>109</td>
<td>81</td>
<td>3.5</td>
<td>20</td>
</tr>
<tr>
<td>Suxamethonium</td>
<td>5</td>
<td>0.06 (0.04-0.12)</td>
<td>111</td>
<td>93</td>
<td>2</td>
<td>18**</td>
<td>0.04 (0.03-0.09)</td>
<td>100</td>
<td>95</td>
<td>1</td>
<td>8</td>
</tr>
<tr>
<td>Decamethonium</td>
<td>4</td>
<td>0.04 (0.01-0.06)</td>
<td>103</td>
<td>86</td>
<td>7.5</td>
<td>61</td>
<td>0.04 (0.01-0.06)</td>
<td>98</td>
<td>84</td>
<td>4</td>
<td>36</td>
</tr>
</tbody>
</table>
Record from a patas monkey, 4.3 kg; chloralose anaesthesia. An intravenous dose of 0.10 mg/kg tubocurarine arrested breathing and abolished the tetanic contractions of the gastrocnemius muscle stimulated with 30 shocks/sec every 10 sec, while the single twitches of the contralateral muscle were only partially suppressed. Respiration was not restored until the tetanic responses had recovered.

paralysis, after its recovery a higher dose was given to produce the same degree of block in the muscle stimulated with single shocks. Decamethonium was exceptional in that only one dose was required.

Mean intravenous doses of non-depolarizing agents required to cause similar blockade (c. 80 per cent) of the single twitches of one muscle, and of the sustained tetanic contractions of the contralateral muscle, were respectively (table I): tubocurarine, 0.22 and 0.07 mg/kg; dimethyltubocurarine, 0.027 and 0.010 mg/kg; gallamine, 1.0 and 0.41 mg/kg; benzoquinonium, 0.15 and 0.03 mg/kg. The differences between the mean doses of these agents causing similar blockade of the twitch and the tetanus were significant at the 1 or 5 per cent level as indicated in table I. Breathing was apparently unimpaired by doses of these drugs which reduced the tetanic contractions by about 80 per cent but was arrested by the larger doses necessary to cause similar blockade of the twitch. Although not significant, recovery of the tetanus took slightly longer than that of the single twitches after paralysis by tubocurarine (23 and 20 min) (fig. 2a, b), dimethyltubocurarine (30 and 28 min) and benzoquinonium (20 and 18 min), whereas recovery after gallamine (28 and 30 min) was often slightly shorter in this respect (table I).

Mean doses of the depolarizing agent suxamethonium, which caused similar paralysis of the single twitches (93 per cent) and of the sustained tetanus (95 per cent), were 0.06 and 0.04 mg/kg i.v. respectively (table I). The mean recovery time of the tetanically stimulated muscle (8 min) was considerably shorter than that of the muscles stimulated with single shocks (18 min) (fig. 3a, b); this difference was significant at the 1 per cent
Record from a cat, 2.7 kg; chloralose anaesthesia.

(a) An intravenous dose of 0.04 mg/kg tubocurarine reduced the sustained contractions (heavy tracing) of the gastrocnemius muscle stimulated tetanically with 30 shocks/sec every 10 sec. Breathing and the single twitches of the contralateral muscle were unimpaired.

(b) A subsequent intravenous dose of 0.37 mg/kg tubocurarine caused similar paralysis of the single twitches of the contralateral muscle, as that produced previously by 0.4 mg/kg i.v. of the drug in the tetanically stimulated muscle. Rates of recovery on both occasions were similar. The higher dose of 0.37 mg/kg tubocurarine i.v. caused apnoea and abolished the contractions of the tetanically stimulated muscle.
RECOVERY FROM NEUROMUSCULAR BLOCKADE

(a) An intravenous dose of 0.05 mg/kg suxamethonium greatly reduced the responses of the gastrocnemius muscle to single shocks and abolished the contractions of the tetanically stimulated muscle. Respiration was unimpaired.

(b) A subsequent intravenous dose of 0.027 mg/kg suxamethonium caused similar paralysis of the tetanic contractions of the muscle stimulated with 30 shocks/sec every 10 sec, as that produced previously by 0.05 mg/kg i.v. of the drug in the contralateral muscle stimulated by single shocks. The tetanus recovered more rapidly than the twitch. Respiration was unimpaired.

FIG. 3
Record from a cat, 3.3 kg; chloralose anaesthesia.

FIG. 4
Record from a cat, 3.3 kg; chloralose anaesthesia. An intravenous dose of 0.06 mg/kg decamethonium caused similar paralysis of the tetanic contractions of the gastrocnemius muscle stimulated with 30 shocks/sec every 10 sec, and the twitch responses of the contralateral muscle to single shocks every 10 sec. The tetanus recovered more rapidly than the twitch. Breathing was unimpaired.
level. During paralysis by decamethonium, the
tetanic contractions were fully sustained and the
same dose (0.04 mg/kg i.v.) caused similar block-
ade (84 and 86 per cent) in both muscles (table I).
Recovery of the tetanically stimulated muscle
(36 min) was considerably quicker than that of
the contralateral muscle stimulated by single
shocks (61 min) (fig. 4). Although not significant
because of the large variation in recovery times,
this effect occurred in each of the four tests car-
ried out. Breathing was apparently unimpaired by
the doses of the depolarizing agents used.

In four experiments, oesophageal, rectal, right
gastrocnemius (single shocks) and left gastroc-
nemius (tetanus) temperatures were continuously
monitored. The temperature of the tetanically
stimulated muscle was within 1°C of the oeso-
phageal and rectal temperatures (which were
similar), but was 1.5–2.0°C above that of the
muscle stimulated by single shocks. During
neuromuscular paralysis by suxamethonium and
tubocurarine the mean fall in temperature of the
tetanically stimulated muscle was 0.5 and 1.0°C
respectively while the temperature of the muscle
stimulated by single shocks was unchanged.

In three other experiments the temperature of
both limbs was maintained at body temperature
(c.36.9°C) even during blockade. The mean
intravenous dose of tubocurarine required to
cause similar paralysis (81 per cent) of the single
twitches of one muscle, and of the sustained con-
traction of the contralateral muscle, were 0.13
and 0.30 mg/kg; respective recovery times were
24 and 26 min. Similarly with gallamine, cor-
responding doses were 1.05 and 1.28 mg/kg i.v.,
and recovery times were 37 and 35 min res-
pectively. When apnoea occurred, breathing did
not return until the tetanically stimulated muscle
had almost recovered. However, intravenous
doses of 0.05 and 0.06 mg/kg respectively of
suxamethonium caused similar paralysis (82 per
cent) of the twitch and tetanic responses. The
mean recovery time of the tetanically stimulated
muscles (9 min) was only slightly shorter than
that of the muscles stimulated with single shocks
(11 min). Similarly, a dose of 0.04 mg/kg i.v.
decamethonium caused equal paralysis in both
muscles (70 per cent) and the respective recovery
times were 19 and 21 min.

**DISCUSSION**

In anaesthetized cats, the responses of the gas-
tronemius muscles to tetanic stimulation of the
sciotic nerve were poorly sustained during
development of neuromuscular paralysis by non-
depolarizing blocking agents but were well
maintained during that by depolarizing drugs.
Similar observations have been reported by Paton
and Zaimis (1951) and Wislicki and Benzakein
(1963). The intensity of neuromuscular paralysis
by non-depolarizing blocking agents was found to
be greater when the gastrocnemius muscles were
stimulated tetanically than when single shocks
were applied. It has been concluded by other
investigators (Guyton and Reeder, 1949; Naess,
1950; Preston and Maanen, 1953; Wislicki, 1958;
Blackman, 1963) that an increase in the frequency
of stimulation resulted in a decrease in the
amount of drug required to produce the same
degree of block; this effect has been attributed to
a reduction in the output of acetylcholine per
nerve impulse (Paton, 1951; Straughan, 1960;

In contrast, it was found that the intensity of
paralysis by the depolarizing agent suxameth-
onium was only slightly increased during tetanic
stimulation, while blockade by decamethonium
was similar whether the gastrocnemius muscles
were stimulated either tetanically or by single
shocks. The initial stimulant action of decame-
thonium summates with that of acetylcholine
(Paton, 1951), and blockade is less dependent on
stimulus frequency because many endplates still
permission transmission might be depolarized to
such an extent that even when the output of
acetylcholine is reduced, as during tetanic stimu-
lation, the muscle fibres are still activated (Black-
man, 1963).

Recovery times from equal degrees of blockade
by non-depolarizing agents were similar for single
twitches and tetanic contractions. However, the
course of paralysis by suxamethonium and
decamethonium was considerably shorter when
tetanic stimulation rather than single shocks were
applied to the gastrocnemius muscles; this differ-
ence was almost negligible when both limbs were
maintained at body temperature. Thus, the
slower recovery of the muscles stimulated by
single shocks could be mainly attributed to their
lower temperature, as Bigland and associates
(1958) have demonstrated in cats, and Cannard and Zaimis (1959) in man, that cooling prolongs the action of depolarizing drugs.

After paralysis by non-depolarizing agents, respiration was not usually adequately restored until the contractions of the tetanically stimulated muscles were fully sustained, although the twitch responses had already recovered. Respiratory muscles are activated by bursts of tetani which cannot be maintained under the influence of tubocurarine (Paton and Zaimis, 1951; Zaimis, 1962). The limb muscles are usually colder than the respiratory muscles and this factor may also contribute to the smaller degree of block produced in the limb muscles, as tubocurarine is less effective at lower muscle temperatures (Alderson and Maclagan, 1964). Gissen and Katz (1969) concluded that the response to repetitive stimulation in man was a more accurate index of the level of blockade by tubocurarine than twitch or post-tetanic potentiation. In view of these observations it is advisable to apply tetanic stimulation rather than single shocks when monitoring the recovery of patients from neuromuscular paralysis.

In contrast, breathing was apparently unimpaired by neuromuscular paralyzing doses of suxamethonium and decamethonium in cats when the body temperature was higher than that of the limbs. However, when the limb temperatures were brought to the same level the paralyzing action of decamethonium was usually similar in the respiratory and limb muscles. These conclusions were in agreement with those of Alderson and Maclagan (1964).

It would be expected from the observed differences between the responses to muscle twitch and tetanus, that exercise might delay recovery from neuromuscular blockade by non-depolarizing agents, but may hasten that by depolarizing drugs. It has in fact been demonstrated in man that exercise prolongs paralysis by tubocurarine and gallamine, but facilitates recovery after decamethonium and suxamethonium (Churchill-Davidson and Richardson, 1952; Mohelsky and Ruben, 1953; Foldes et al., 1961). As a consequence, rapid shallow breathing following inadequate reversal of non-depolarizing block might lead to apnoea due to recurarization of the muscles involved; Gissen and Katz (1969) suggested that the response to a tetanus may be used as a measure of adequate dosage of anticholinesterases.

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REFERENCES


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