THE SKELETAL MUSCLE RESPONSE TO THE REPEATED ADMINISTRATION OF SUXAMETHONIUM AND ITS INTERACTION WITH EDROPHONIUM IN ANAESTHETISED MAN

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- 1 Tetanic and single twitch contractions of the adductor pollicis muscle in man were recorded during repeated injections of suxamethonium (0.2 mg/kg or 0.1 mg/kg) every 15 minutes.
- 2 Tachyphylaxis to suxamethonium developed rapidly in every patient studied when single twitch contractions were observed but tetanic contractions later showed an increasingly prolonged recovery with repeated injections.
- 3 Edrophonium administered at the point of 50% recovery of the tetanic contractions in patients given suxamethonium (0.2 mg/kg) repeatedly first potentiated the blockade but when the tachyphylaxis had developed fully on the single twitch, usually after the third or fourth injection, the blockade of the tetanic contractions was reversed.
- 4 These findings indicate that the tachyphylaxis and the change in the nature of the blockade produced by suxamethonium in man take place at the same time and might be part of the same phenomenon.

Introduction

If suxamethonium is administered repeatedly or continuously either to man or to animals, its neuromuscular blocking activity is reduced as repeated or continuous administrations proceed (Mohelsky & Ruben, 1953; Hodges & Foldes, 1956; Stenberg & Orndahl, 1956; Poulsen & Hougs, 1958; Iwatsuki, Yamada, Ueda, Nishimura & Kanemaru, 1958; Payne & Holmdahl, 1959; Katz, Wolf & Papper, 1963; Crul, Long, Brunner & Coolen, 1966; Katz & Ryan, 1969). This tachyphylaxis has been most frequently studied by the use of single twitch contractions of skeletal muscle; the response of tetanic contractions of skeletal muscle has been less extensively examined in such studies during the administration of suxamethonium.

In a previous paper (Sugai, Hughes & Payne, 1975) it was demonstrated that tetanic contractions of the thumb in man indirectly evoked by

ulnar nerve stimulation were more sensitive to the effect of suxamethonium than were single twitch contractions and each followed a different time course of recovery. Thus, it seemed important to measure both types of contractions in order to have a more complete understanding of the blockade produced by suxamethonium and of its changing patterns when the drug was administered repeatedly.

In this study measurements were carried out simultaneously both on the tetanic and single twitch contractions of the adductor pollicis muscles during repeated administrations of suxamethonium in order to study how the tachyphylaxis observed with single twitches was manifested with tetanic contractions.

Methods

Eleven patients were studied after their informed consent had been obtained on the previous day. The patients' ages ranged from 59-80 years with a mean age of 68.5 ± 6.5 (s.d.). One patient was

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female and the rest were male. No premedication was given and anaesthesia was induced with halothane, nitrous oxide and oxygen. The trachea was intubated after spraying the larynx with a 4% lignocaine solution without the use of a neuromuscular blocking agent. Anaesthesia was maintained with halothane, nitrous oxide and oxygen. In some patients, pentazocine supplements were used for maintenance instead of halothane.

Ten patients were studied during Helmstein's treatment of carcinoma of the bladder (Helmstein, 1972). One patient was studied before a routine urological procedure. During Helmstein's treatment, the bladder is pressurised hydro-statically by means of a balloon inserted into the bladder. The pressure inside the bladder was kept 10 cm H₂O higher than the diastolic pressure measured at the radial artery. Pressurization of the bladder lasted from 4-6 hours. The inspired halothane concentration was kept as low as possible usually under 0.5%.

Respiration was controlled or assisted in order to maintain the arterial blood gases within normal limits. Statham force transducers were mounted one on each hand to measure the force of the thumb adduction as described in a previous paper (Sugai *et al.*, 1975). The ulnar nerves were stimulated at the wrists; a single square wave pulse of 200 μ s duration was applied to one nerve every 12 s and a tetanic stimulus of 30 pulses each 200 μ s wide was applied for a period of one second every 12 s on the other. The force of the thumb adduction was recorded on a Brush-Clevite pen recorder with a slow chart speed of 5 mm/min and on a Mingograf ink-jet recorder at a fast chart speed of 50 mm/second. The transducers used, the apparatus for nerve stimulation and the techniques for blood gas analysis and the measurement of the temperature of the hands have been described elsewhere (Sugai *et al.*, 1975).

Methods of administration of drugs

After an initial control period of 30-40 min after starting ulnar nerve stimulation, repeated injections of suxamethonium were given at 15 min intervals. Of the eleven patients studied, nine received suxamethonium (0.2 mg/kg) repeatedly by i.v. injections at 15 min intervals; in two patients the dose of suxamethonium was 0.1 mg/kg.

Of the nine patients who received repeated injections of suxamethonium (0.2 mg/kg), six patients were given edrophonium (0.1 mg/kg) administered intravenously at the 50% recovery point after the maximal depression of the tetanic contraction on several occasions to test the effect

of edrophonium on the tetanic contractions of the adductor pollicis muscle during recovery from the effects of suxamethonium. Statistical analysis was carried out using the Student's *t*-test.

Results

Effect of repeated i.v. administration of suxamethonium (0.2 mg/kg)

In three patients who received suxamethonium (0.2 mg/kg) without the intervention of edrophonium, the maximal depression of the single twitch decreased rapidly as the repeated injections continued thus demonstrating the rapid development of tachyphylaxis, but in the case of the tetanic contraction tachyphylaxis was less marked. Figure 1 shows a record obtained from one patient who was given repeated injections of suxamethonium (0.2 mg/kg) intravenously. Recovery from the maximal depression of the tetanic contraction changed its pattern as the injections continued, although the maximal depression became less the recovery of the tetanic contraction became more prolonged. The time necessary for both the tetanic and single twitch contractions to reach 10, 20, 50, 80 and 90% of recovery compared with their maximal depressions was determined. This time was measured from the end of the i.v. injection of the drug into the forearm vein. Figure 2 illustrates the time of recovery of the tetanic contractions obtained from the patient whose records are shown in Figure 1. The alteration in the degrees of maximal depression compared with the control is also obvious after each injection of suxamethonium for both tetanic and single twitch contractions. The maximal depression of the tetanic contraction decreased only slightly compared with the single twitch.

When the 10% and 90% recovery points from the maximal depression of the tetanic concentration are compared the 90% recovery time is seen to be shorter for the first four injections in this patient and later gradually becomes prolonged. Thus complete recovery of the tetanic contractions now takes longer. At this time, the tachyphylaxis on the single twitch contraction is far advanced. The 10% recovery time remained relatively unchanged and the 50% recovery time showed a moderate increase.

The 90% recovery time was shortest after the third injection of suxamethonium in the remaining two patients who received suxamethonium (0.2 mg/kg) repeatedly. After this point, the 90% recovery time continued to increase. Ten repeated injections of suxamethonium were given to one of these patients and seventeen injections to the other.

Figure 1 Slow recording of tetanic and single twitch contractions of the adductor pollicis muscles in man during repeated administrations of suxamethonium (0.2 mg/kg) every 15 minutes.

Figure 2 Changes in the time needed for 10 (●), 50 (■) and 90 (▲) % recovery from maximal depression of tetanic contractions and in the extent of the maximal depression of tetanic (○) and single (Δ) twitch contractions with repeated administration of suxamethonium.

Table 1 Maximal depressions and 90% recovery time of tetanic contractions after repeated injections of suxamethonium 0.2 mg/kg in three patients. Depression is expressed as a % of the control taken before each injection.

Patients	First injection						Third injection						Fifth injection						Seventh injection						Ninth injection						Eleventh injection					
	1						2						3						Mean						s.d.						Significance of difference compared with first injection					
90% recovery time of tetanic contraction (s)	444	501	379	441	61		408	418	315	380	57		531	418	396	448	72		662	589	532	549	137		766	698	532	665	120		760	654	689	701	54	
	Significance of difference						0.02 < P < 0.05						0.9 < P						0.2 < P < 0.3						0.02 < P < 0.05						0.02 < P < 0.05					
Maximal depression of tetanic contraction (%)	100.0	100.0	100.0	100.0			100.0	100.0	93.4	97.8	3.8		100.0	100.0	33.1	77.7	38.6		100.0	100.0	58.6	86.2	23.9		100.0	96.2	65.8	87.3	18.7		98.7	95.3	79.6	91.2	10.2	
	Significance of difference						0.5 < P < 0.7						0.5 < P < 0.7						0.5 < P < 0.7						0.5 < P < 0.7						0.3 < P < 0.5					
Maximal depression of single twitch (%)	100.0	100.0	75.9	92.0	13.9		95.0	83.8	30.9	75.3	38.5		90.0	83.8	9.2	61.0	45.0		78.4	73.2	0	50.5	43.8		60.4	46.9	0	35.8	31.7		40.8	39.7	0	26.8	23.2	
	Significance of difference						0.3 < P < 0.4						0.2 < P < 0.3						0.1 < P < 0.2						0.02 < P < 0.05						P < 0.01					

In one patient, tetanic stimulation was stopped intermittently for 15 min in order to eliminate possible fatigue of the thumb muscle. Stimulation was stopped for 15 min after 15 min of continuous stimulation but the repeated injection of suxamethonium (0.2 mg/kg) was continued throughout the study period. A similar tendency for tachyphylaxis especially on single twitch and an increased time of recovery on tetanic contractions was observed in this patient as in the others.

Table 1 shows the time necessary for 90% recovery after maximal depression of tetanic contractions and the maximal depression of the tetanic and single twitch contractions compared with their controls before each injection. The values presented for the three patients were obtained after the first, third, fifth, seventh, ninth and eleventh injections of suxamethonium. Means and standard deviations and the statistical significance of the differences compared with the first injection are also tabulated.

The time for 90% recovery of the tetanic contraction is significantly longer for the ninth and eleventh injections compared with the first injection although the single twitch contractions demonstrate significantly less depression after these injections compared with the first injection.

The time for the recovery of the tetanic contractions after the third injection is significantly shorter than that for the first injection which demonstrates the development of a tetanic-contraction tachyphylaxis at this stage.

The effect of repeated administration of suxamethonium (0.1 mg/kg)

The two patients who received suxamethonium (0.1 mg/kg) repeatedly, showed marked tachyphylaxis of the single twitch contractions. The depression of the single twitch contraction in these patients was less marked from the beginning compared with the patients who received the higher dose of suxamethonium. Tachyphylaxis of the tetanic contraction was also observed to a lesser degree. In one patient, the 90% recovery time became increased after the fourth injection of suxamethonium. In the other patient, the 90% recovery time showed no significant change.

The effect of edrophonium on the recovery pattern of tetanic contractions

During recovery from repeated injections of suxamethonium (0.2 mg/kg) in six patients edrophonium (0.1 mg/kg) was administered at the 50% recovery point of the tetanic contractions. In these patients the recovery pattern was basically similar

to that in the patients who were not given edrophonium. When edrophonium was administered during the recovery stage of the tetanic contractions after the first injection of suxamethonium, potentiation of the tetanic blockade was observed in all six patients studied. However the potentiation became less marked when edrophonium was tested after subsequent injections of suxamethonium, until a point was reached when the injection of edrophonium reversed the block and hastened the recovery of the tetanic contractions. At this point the depression of the single twitch contraction was very small and showed marked tachyphylaxis compared with the initial effect. The reversal of the block became increasingly marked beyond this point on tetanic contractions but no marked effect of edrophonium on the single twitch contractions was observed.

Figure 3 is a record from one patient who was given edrophonium during recovery from repeated injections of suxamethonium (0.2 mg/kg). At the fourth injection of suxamethonium, edrophonium is seen to reverse the block. In this patient gallamine (0.4 mg/kg) was administered after nine repeated injections of suxamethonium and during the recovery period from the blockade induced by gallamine, suxamethonium (0.2 mg/kg) was administered. Even though a clear reversal of the block had been demonstrated by edrophonium after the ninth injection of suxamethonium, suxamethonium given during the recovery from gallamine antagonized the depression of the single twitch and tetanic contractions. The antagonism of the tetanic block however only lasted for about 1 min and thereafter, a slight potentiation of the block was observed.

The effect of edrophonium on the recovery pattern of the tetanic contractions was evaluated by determining the percentage change of the tetanic contractions after edrophonium compared with the height of the tetanic contractions immediately before the injection of edrophonium. When there was no abrupt change, this was taken as zero.

When the block was potentiated the percentage change was taken as negative and when the block was reversed this was taken as positive. Figure 4 illustrates the percentage change in tetanic contractions caused by edrophonium intervention. The percentage change was plotted on the ordinate against the number of doses of suxamethonium plotted in sequence on the abscissa. In five patients this line crossed the zero level between the third and fourth injection and in one patient between the second and third injections and demonstrated that the change in response to edrophonium first occurs around the third and

Figure 3 Slow recording of tetanic and single twitch contractions of the adductor pollicis muscles in man with repeated administration of suxamethonium (S, 0.2 mg/kg) every 15 min followed by edrophonium (E, 0.1 mg/kg) at the 50% recovery point of the tetanic contractions. G gallamine (0.4 mg/kg).

Figure 4 Alteration in the % change of tetanic contractions produced by edrophonium (0.1 mg/kg) in six patients during repeated administration of suxamethonium (0.2 mg/kg) every 15 minutes.

fourth injection of suxamethonium in most patients.

Discussion

Repeated injections of suxamethonium caused tachyphylaxis in every patient studied when the effect was measured by the indirectly elicited single twitch contraction. The effect on the tetanic contraction, however, was two-fold. When the effect was judged by the maximal depression of the height of the contractions tachyphylaxis was less obvious compared with the single twitch contractions. Moreover, complete recovery of the tetanic contractions took increasingly more time with successive injections whereas the single twitch contractions not only showed a marked tachyphylaxis in terms of the maximal depression but also a faster recovery.

When the action of edrophonium was superimposed at the time of the occurrence of 50% recovery of the tetanic contractions edrophonium first potentiated the blockade. After the third or fourth injection of suxamethonium, however,

edrophonium antagonized the block observed on the tetanic contraction. At this time, tachyphylaxis of the single twitch contraction was far advanced. The finding, which was consistent in every patient given edrophonium, suggests that the mode of action of suxamethonium changes fairly rapidly. The finding could also indicate that the phenomenon of tachyphylaxis and the alteration in the mode of action of suxamethonium might be closely related.

It has been reported in man that tachyphylaxis develops after repeated or continuous injection of suxamethonium (Poulsen & Hougs, 1958; Payne & Holmdahl, 1959; Katz *et al.*, 1963; Crul *et al.*, 1966; Katz & Ryan, 1969). These reports differ, however, in the percentage of patients who developed tachyphylaxis. Poulsen & Hougs (1958) used a continuous infusion in conscious subjects and reported that 73.3% of the patients studied developed a tachyphylaxis. Payne & Holmdahl (1959) used an intermittent dose of 10 mg and reported that 73.9% of the patients developed tachyphylaxis under light trichloroethylene and nitrous oxide anaesthesia. Katz *et al.* (1963) administered an intermittent dose of suxamethonium (0.3 mg/kg) every 10 min under anaesthesia using halothane, trichloroethylene, methoxyflurane, halopropane, nitrous oxide or cyclopropane and found that 30% of the patients developed tachyphylaxis. Crul *et al.* (1966) used an intermittent dose of suxamethonium (0.125 mg/kg-10 mg/kg) during anaesthesia with nitrous oxide with or without halothane. They found that 28.4% of the patients developed tachyphylaxis.

These differences in the percentage of patients who developed tachyphylaxis might result from different experimental conditions. In general a large intermittent dose of suxamethonium combined with an inhalational anaesthetic seems to be associated with less tachyphylaxis. In the present study under light halothane anaesthesia with an intermittent dose of suxamethonium (0.2 mg/kg) every 15 min, all patients developed tachyphylaxis.

The mode of action of suxamethonium in man can change after its prolonged or repeated administration (Churchill-Davidson & Christie, 1959; Katz *et al.*, 1963; Crul *et al.*, 1966; Katz & Ryan, 1969). Katz *et al.* (1963) reported that the development of the change in the type of blockade is dependent on dose but not on time. Crul *et al.* (1966) suggested that this effect is both time and dose dependent and later Katz & Ryan (1966) showed that it is dependent on both increasing time and dose. The present results indicate that the change in the pattern of blockade can occur early and after repeated injections of a relatively

small amount of suxamethonium and suggest that tachyphylaxis is associated with a change in the pattern of the block. Repeated administrations of decamethonium have also been shown to lead to tachyphylaxis and simultaneously to a change of the type of blockade as demonstrated by the reversal of the block by edrophonium (Freund, 1969).

It could be argued that the prolonged recovery of the tetanic contractions might be the result of decreased metabolism of suxamethonium after its prolonged administration. However if the change in the pattern of recovery demonstrated in the present study is the result of delayed metabolism of the drug alone, both the single twitch and tetanic contractions might be expected to be affected similarly. The results suggest therefore that the change is most likely to be the result of a change in the mode of action of suxamethonium. The reversal of the blockade by edrophonium at a later stage tends to support this reasoning.

Another aspect to be considered is the fact that even beyond the point where the tetanic contractions were markedly reversed by edrophonium the interaction between suxamethonium and gallamine remained basically antagonistic although after the reversal a brief potentiation of the gallamine block by suxamethonium occurred.

One possibility is that neuromuscular blockade by suxamethonium might involve several different processes and the relative importance of these processes might change with time and with the dose of the drug administered.

These possible processes include depolarization of the end-plate, desensitization of the end-plate (Thesleff, 1958, and an action on the nerve terminal (Galindo, 1971). At the beginning of the application of the drug, the membrane depolarization might play a dominant role in the genesis of the blockade but the relative importance of desensitization might increase as the application continues (Gissen & Nastuk, 1966). The involvement of the action of suxamethonium on the motor-nerve terminal might also have an important action (Galindo, 1971) especially in the later stage when the blockade can be reversed by edrophonium which is known to have a facilitatory action on the motor-nerve terminal (Riker & Standaert, 1966).

In conclusion, the repeated injections of suxamethonium caused a different response in the tetanic and single twitch contraction of the thumb in man. Tachyphylaxis for the single twitch contractions rapidly developed, but the tetanic contractions showed an increasingly prolonged recovery with repeated injections. Edrophonium first potentiated the block, but at about the time when the tachyphylaxis was fully developed on

the single twitch, it reversed the block of the tetanic contractions.

These findings suggest that tachyphylaxis and the change in the nature of the block caused by suxamethonium take place simultaneously in man and might be part of the same phenomenon.

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