TACHYPHYLAXIS AFTER REPEATED DOSAGE OF DECAMETHONIUM IN ANAESTHETIZED MAN

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- 1 The tetanic and single twitch responses to the adductor pollicis muscle were used to study the neuromuscular effects of repeated dosage of decamethonium in nine anaesthetized patients.
- 2 In two of three patients who received the same total dose of decamethonium in three separate series of injections, blockade of the tetanic response was less after the third administration. In the third patient tachyphylaxis was evident after the second series of injections.
- 3 In three other patients, tachyphylaxis occurred after the second series of injections when the total dose of decamethonium administered was at least twice that given on the first occasion.
- 4 In terms of tachyphylaxis the single twitch response followed a similar pattern to that of the tetanic response.
- 5 Once tachyphylaxis had developed, neuromuscular block of the tetanic response by decamethonium was antagonised by neostigmine (2.5 mg) and enhanced by 2% halothane.
- 6 In contrast, in three patients who were not exposed to more than one series of injections of decamethonium, and presumably therefore before tachyphylaxis had developed, neuromuscular block of the tetanic response was potentiated by neostigmine. Under these circumstances recovery was unaffected by halothane.
- 7 Thus, when tachyphylaxis occurs with decamethonium the characteristics of the block change to resemble those of the competitive neuromuscular blocking agents; these findings could be of importance in clinical anaesthesia.

Introduction

Tachyphylaxis after repeated administration of depolarizing neuromuscular blocking agents is widely known and has been ascribed mainly to a desensitization of the post-synaptic membrane (Thesleff, 1958; Gissen & Nastuk, 1966). In a previous study we used the tetanic and single twitch responses of the adductor pollicis muscles to demonstrate tachyphylaxis with repeated doses of suxamethonium in anaesthetized man (Sugai *et al.*, 1975b). We have now applied this technique to assess the neuromuscular effects of repeated dosage of decamethonium.

Methods

The studies were performed in nine patients about to undergo elective urological surgery after informed consent had been obtained. No premedication was given and anaesthesia was induced with 5% thiopentone (200–500 mg) given intravenously.

Intubation was achieved without the use of a neuromuscular blocking agent after administration of 2–5% halothane and after spraying the larynx with 4% lignocaine. The halothane was then withdrawn and anaesthesia was maintained with 60–66% nitrous oxide in oxygen using intermittent positive pressure ventilation. Supplements of thiopentone (100–200 mg) and pethidine (50–150 mg) were given as required. Simultaneous recordings of tetanic and single twitch contractions of the adductor pollicis muscles were made as described previously (Sugai *et al.*, 1975a). Each ulnar nerve was stimulated supra-maximally at the wrist every 12 s with rectangular pulses of 200 μ s duration, one nerve at 50 Hz for 1 s and the other with single shocks.

Decamethonium was administered intravenously in divided doses to three different groups of patients. In the first group appropriate blocking doses of decamethonium were given to each of three patients and the same doses were given on two further occasions after allowing sufficient time for full recovery from neuromuscular block between each series of injections. Second, three patients received a second series of injections in which the total dose of decame-

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Table 1 Effects of repeated administration of decamethonium on the peak tetanic contraction of the adductor pollicis muscle in six anaesthetized patients. Three patients received the same total dose of decamethonium on three occasions and three patients received a second series of injections when the total dose of the drug was at least doubled.

Patient	First series		Second series		Third series	
	Total dose mg/kg i.v.	% Block tetanus	Total dose mg/kg i.v.	% Block tetanus	Total dose mg/kg i.v.	% Block tetanus
1	0.03	90	0.03	93	0.03	58
2	0.02	68	0.02	75	0.02	24
3	0.03	89	0.03	43	0.03	50
4	0.03	99	0.06	87		
5	0.02	95	0.05	88		
6	0.02	93	0.05	76		

thonium given was at least twice that administered in the first series. Third, a single series of injections of decamethonium were given to three patients.

After tachyphylaxis had developed in the first two groups, the effects of neostigmine 2.5 mg intravenously preceded by atropine 1.2 mg on the neuromuscular blocking action of decamethonium were studied at the stage when recovery of the tetanic response had reached about 50% of the control value.

Four patients in those groups were also exposed to 2% halothane at approximately the same level of recovery from decamethonium block. In the third group of patients in whom tachyphylaxis was not induced, the effects of these drugs were studied at the same stage of recovery from neuromuscular block.

Results

A quantitative assessment of the results obtained in the first two groups of patients studied is shown in Table 1. In the first group, two patients who were given three separate series of injections of decamethonium showed a diminished paralysis of both the tetanic and single twitch responses of the adductor pollicis muscles after the third series of injections (Figure 1). In the third patient tachyphylaxis occurred after the second series of injections and the response was not significantly altered by the third series. Although the tetanic block was always less with successive series of injections the rate of recovery was variable and in some instances was more prolonged even when the extent of the block was less (Figure 1).

In the second group of three patients tachyphylaxis developed after the second series of injections in which the total dose administered was at least twice that given in the first series. An example is shown in Figure 2 in which it is seen that the block of the tetanic response was slightly less after the second series of injections despite the fact that the dose of decamethonium had been doubled. Whether or not tachy-

phylaxis had developed, neuromuscular block by decamethonium was always accompanied by tetanic fade both during onset and recovery. Furthermore, once tachyphylaxis had been established exposure to halothane during the recovery phase slows the process and re-establishes fade of the tetanic contraction (Figures 2 and 3). Although the effect on the single twitch was slightly greater after the second

Figure 1 Tracings from an anaesthetized patient who had received the same total dose of 0.03 mg/kg decamethonium on three occasions. Paralysis of both the tetanic and single twitch responses of the adductor pollicis muscle was less after the third series than the first series of injections indicating that tachyphylaxis had developed.

Figure 2 Tracings from an anaesthetized patient who received a total dose of 0.03 mg/kg decamethonium in the first series of injections. On the second occasion, when the total dose was increased to 0.06 mg/kg, tachyphylaxis was evident because paralysis of the tetanic response of the adductor pollicis muscle was somewhat less. Furthermore a dose of 0.05 mg/kg was now required to produce paralysis of the single twitch equal to that on the first occasion. Administration of 2% halothane delayed recovery of the tetanic response and increased tetanic fade.

series of injections the difference in dose establishes that tachyphylaxis had also occurred with the single twitch response.

Of the six patients in whom tachyphylaxis had developed with decamethonium, four were given intravenous neostigmine (2.5 mg) when recovery of the tetanic response had reached about 50% of the control values and all four responses showed a rapid reversal to complete recovery (Figure 4). The single twitch responses were fully recovered at the time of the injection of neostigmine and were unaffected by the drug. Four of the 6 patients were also given 2% halothane during recovery from the decamethonium block which was immediately enhanced and tetanic fade reappeared; these effects were reversed when the halothane was withdrawn (Figure 5).

In the group of three patients who were given not more than one series of injections of decamethonium, neostigmine enhanced the block of the tetanic response but again the recovery of the single twitch response was not affected (Figure 6). Of the nine patients studied, three were exposed to halothane in a 2% concentration during recovery from the first

Enhancement of fade by halothane

- a Tetanic fade during recovery from decamethonium block.
- b After 5 min exposure to 2% halothane.
- c After 10 min exposure.
- d 1 min after halothane withdrawn.

Figure 3 Individual tetanic contractions (50 Hz for 1 s) recorded at a fast paper speed to show the pattern of fade that developed during the study illustrated in Figure 2.

series of injections of decamethonium. In none of these patients did halothane have any discernible effect either on the tetanic or on the single twitch response (Figure 7).

Discussion

This study has confirmed the observations of Freund (1969) that tachyphylaxis develops in anaesthetized man after repeated doses of decamethonium. Similar

Figure 4 Tracings from an anaesthetized patient when tachyphylaxis had developed after a third administration of 0.04 mg/kg decamethonium. Neostigmine 2.5 mg, preceded by 1.2 mg atropine, antagonised the blockade of the tetanic response of the adductor pollicis muscle; the single twitch had already recovered.

Figure 5 Tracing from an anesthetized patient when tachyphylaxis had developed after 0.04 mg/kg decamethonium was given on a second occasion. Administration of 2% halothane depressed the tetanic response of the adductor pollicis muscle which recovered when the halothane was withdrawn. Recovery of the single twitch was unaffected by halothane.

Figure 7 Tracings from an anesthetized patient who had received 0.01 mg/kg decamethonium only on one occasion. Administration of 2% halothane during recovery from blockade had no effect on the tetanic or single twitch response of the adductor pollicis muscle.

observations were reported after repeated doses of suxamethonium by Payne & Holmdahl (1959) and by Sugai *et al.* (1975b). The present study has also shown that the tachyphylaxis is accompanied by a change in the mode of action of the drug.

Tachyphylaxis was demonstrated in two ways. First, when the same amount of drug was administered by divided doses on up to three occasions, substantially less block of the tetanic and single twitch responses was obtained after the second and third series of injections. Second, when an attempt was made to keep the degree of block constant with successive series of injections the total dose needed for this purpose in a second series was at least twice that required for the same degree of block in the first series. Thus, the results also indicate that tachyphylaxis

after decamethonium can occur after only a few injections of relatively small amounts of the drug.

Although easy to demonstrate, the phenomenon of tachyphylaxis is more difficult to explain. Initially decamethonium causes neuromuscular block by a persistent depolarisation of the motor end-plate but a desensitization also develops at this region (Thesleff, 1958). It is claimed that membrane depolarisation plays the dominant role in the early stage of block but the relative importance of the desensitization of the post-synaptic membrane to decamethonium is thought to increase after repeated exposure (Gissen & Nastuk, 1966). If this hypothesis proves to be correct then it could explain the apparent resistance to decamethonium after repeated administration of the drug. But an alternative explanation exists. As long ago as 1951 Burns & Paton postulated that membrane penetration by acetylcholine and related substances was an essential component of the process of depolarisation which in turn was critically dependent on the concentration gradient across the end-plate membrane. In the case of acetylcholine its rapid destruction by cholinesterase normally preserves the concentration gradient across the membrane and maintains a consistent response during neuromuscular transmission. However decamethonium is not destroyed by cholinesterase and repeated application of the drug could lead to accumulation and the reduction of the concentration gradient with the consequent development of tachyphylaxis.

The change in the nature of the block after the development of tachyphylaxis was demonstrated by the response to neostigmine and to halothane. Neostigmine is said to enhance neuromuscular blockade by decamethonium and other depolarising agents and we found this to be so initially but after tachyphylaxis

Figure 6 Tracings from an anesthetized patient who had received only one administration of 0.03 mg/kg decamethonium. Neostigmine 2.5 mg, preceded by 1.2 mg atropine given during recovery from paralysis enhanced blockade of the tetanic response of the adductor pollicis muscle; recovery of the single twitch was unaffected.

had developed the block was antagonised by neostigmine as is the block induced by non-depolarising drugs. The initial neuromuscular block produced by decamethonium is not normally affected by halothane but after the development of tachyphylaxis exposure to halothane increased the block and re-established fade, characteristics of the interaction between halothane and competitive blocking agents (Miller, *et al.*, 1972; Hughes & Payne, 1979).

On the question of fade it has previously been claimed by Zaimis & Head (1976) that a tetanus is well maintained during partial blockade by suxamethonium in anaesthetised man. In contrast it was found in this study that neuromuscular block by decamethonium, as in a previous study with suxamethonium (Sugai *et al.*, 1975b), was accompanied by tetanic fade even before tachyphylaxis had developed. However, this difference may be more apparent than real because examination of the data of Zaimis & Head (1976) shows that while the response of the anterior tibialis muscle to a single tetanic stimulus during suxamethonium block was essentially a square wave the corresponding response of the adductor pollicis showed some evidence of fade. Thus any apparent difference may be related not only to the specificity of individual muscle responses but also to the pattern of the applied stimuli.

It may also be of importance that the change in the nature of the block was more evident in the tetanic response than in the single twitch response. This observation may reflect the fact that during tetanic stimulation the motor nerve terminals are more fully

activated and the acetylcholine reserves more completely mobilised. Thus any effects due to an interference with the action of acetylcholine would be more evident during tetanic stimulation. A pre-junctional effect on the output of acetylcholine has been ascribed to suxamethonium (Galindo, 1971) and such an effect for decamethonium cannot be excluded. For instance, if repeated dosage of decamethonium gradually reduced the output of the transmitter the administration of neostigmine would tend to preserve the limited amount of acetylcholine released and thus lead to antagonism of the block (Bowman, 1980). Furthermore the synergistic blocking effect of halothane and decamethonium gives support to this interpretation since the weak neuromuscular blocking action of halothane is likely to be due to a depressant action of the drug on the release of the transmitter from the motor nerve terminals (Hughes & Payne, 1979).

Finally, the ease with which the tachyphylaxis and the change in the pattern of response occur after repeated doses of decamethonium described in this study provides sound experimental evidence to justify the reluctance of most anaesthetists to continue to use decamethonium as a neuromuscular blocking agent in clinical practice.

We are indebted to Miss V.A. Bishop, SRN, and to Mr A.J. Harman for skilled technical assistance, to our surgical and nursing colleagues for their tolerance and patience and to our volunteers without whom this study would not have been possible.

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(Received April 22, 1981)