DUAL NEUROMUSCULAR BLOCK IN MAN

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From time to time reports have appeared in the literature of cases of "prolonged apnoea" following the administration of a depolarising drug to apparently normal subjects which have resulted in a dramatic improvement after the injection of an anti-cholinesterase drug. Such reports gained credence when tidal volume studies revealed an improvement in ventilation in certain cases of depolarisation block following the administration of neostigmine.[1, 2] These studies were not concerned, however, with the precise measurement of neuromuscular transmission, and therefore it remained possible that any improvement in ventilation following the injection of neostigmine (in the presence of a depolarisation block) might be due to its direct action upon the respiratory centre or upon some other part of the central nervous system.

Since the demonstration by Jenden and his co-workers [3] and Zaimis [4] in certain species of animals and by Churchill-Davidson and Richardson [5] in myasthenic patients that a depolarising drug could produce a non-depolarising type of neuromuscular block, the concept of a "dual block" has continued to grow.

Using an electromyographic technique to measure neuromuscular transmission in the hand muscles, Churchill-Davidson and Christie [6] found that a change in the characteristics of the depolarising block occurred after large doses of depolarising drugs. This paper presents further observations on these changes and attempts to relate the changes to the actual doses of such drugs commonly used in clinical practice.

Method

A portable electromyograph was specially constructed for use both in the laboratory and the operating room. It was capable of delivering supramaximal stimuli at rates varying from 1 per second (twitch) to 50 per second (tetanus). The method used for differentiating between a depolarising and a non-depolarising type of neurosmuscular block has already been reported in full elsewhere.[6] In this study the same characteristics were noted; namely, (1) the ability to sustain both twitch and tetanic rates of nerve stimulation, (2) the effect of anti-cholinesterase drugs (neostigmine and edrophonium) upon the neuromuscular block, and (3) the presence or absence of post-tetanic facilitation.

Post-tetanic facilitation is the immediate but short-lived improvement in neurosmuscular transmission that follows a period of tetanic nerve stimulation. It is commonly observed in association with a block due to non-depolarising drugs (fig. 2 c). The sum total of the effect can be likened to a fleeting action of an anti-cholinesterase drug.

The drugs used were decamethonium iodide (C.10) given by intermittent intravenous injection and succinylcholine chloride given both by continuous infusion or by intermittent injection. Neostigmine methylsulphate in doses of 2.5 mg., preceded by 1 mg. of atropine sulphate, was used as the principal anti-cholinesterase drug.

The studies were made during routine surgical procedures in which the use of a relaxant drug was indicated. Apart from the use of either relaxant drug, the basic anaesthetic technique was thiopentone 250–500 mg., meperidine 20–100 mg. and nitrous oxide: oxygen (6:2 litres/minute). In order to ensure adequate removal of alveolar carbon dioxide a high total gas flow was employed together with a carbon dioxide absorption technique utilising controlled respiration with a circle absorber. All anaesthetic drugs used had previously been shown to have no effect upon neuromuscular transmission even when given for two to three hours.

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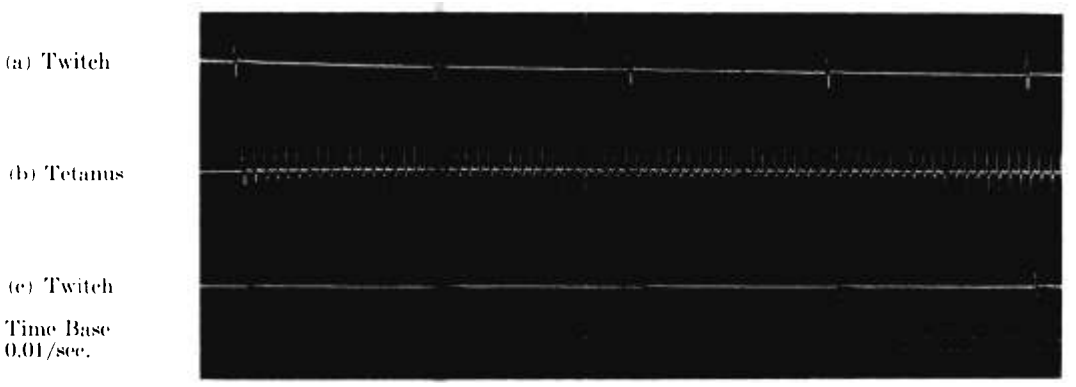
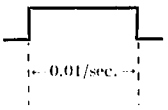


FIG. 1.



DEPOLARISATION BLOCK. On partial recovery (50%) from complete paralysis 25 minutes after 3.0 mg. decamethonium iodide (recorded consecutively).

Rate of nerve-stimulation: (a) 2.5/second.
(b) 50/second. Note tetanus is well maintained.
(c) 2.5/second. Note absence of post-tetanic facilitation.

RESULTS

Single Dose of a Depolarising Drug. A single paralysing dose (for the hypothenar muscles) of decamethonium (3 mg.) in 20 patients and of succinylcholine (30 mg.) in 20 patients confirmed the presence of the normal characteristics of a depolarisation block: (1) Both twitch and tetanic rates of nerve stimulation are well maintained (fig. 1, *a* and *b*). (2) Post-tetanic facilitation is not present (fig. 1, compare *a* with *c*). (3) Anti-cholinesterase drugs potentiate the block.[6]

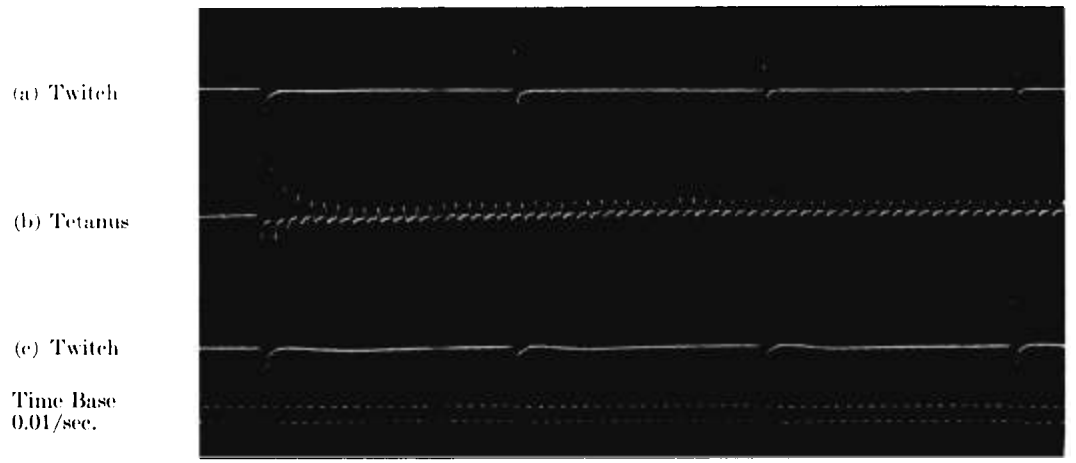


FIG. 2.

NON-DEPOLARISATION BLOCK. On partial recovery from complete paralysis 23 minutes after 12 mg. d-tubocurarine chloride (recorded consecutively).

Rate of nerve-stimulation: (a) 2.5/second. Note characteristic "fade" of potential even at twitch rate of nerve-stimulation.
(b) 50/second. Note characteristic "fade" again.
(c) 2.5/second. Note improvement in neuromuscular transmission, i.e. facilitation brought about by the period of tetanic stimulation. This is post-tetanic facilitation.

TABLE 1

DOSE RESPONSE OF A SERIES OF PATIENTS GIVEN LARGE AMOUNTS OF DECAMETHONIUM AND SUCCINYLCHOLINE

Decamethonium						Succinylcholine					
Case	First Signs of Change of Block		Complete Dual Block*		Reversibility with Anticholinesterase	Case	First Signs of Change of Block		Complete Dual Block*		Reversibility with Anticholinesterase
	Dose (mg.)	Time (minutes)	Dose (mg.)	Time (minutes)			Dose (mg.)	Time (minutes)	Dose (mg.)	Time (minutes)	
1	15	45	18	95	+ (neostigmine)	1	175	40	500	110	? + (edrophonium)
2	8	55	13.75	106	+ (neostigmine)	2	450	75	1,000	150	+ (neostigmine)
3	13	90	20	140	+ (neostigmine)	3	425	75	500	105	+ (neostigmine)
4	6	55	6	57	+ (edrophonium)	4	500	75	—	—	—
5	15	75	21	205	+ (neostigmine)	5	250	45	750	165	+ (neostigmine)
6	11	73	17	140	+ (neostigmine)	6	1,000	80	1,600	196	+ (edrophonium)
7	6	20	—	—	—	7	500	57	1,000	172	+ (edrophonium)
8	11.5	70	15	110	+ (edrophonium)	8	500	70	—	—	—
9	7	42	12	105	+ (neostigmine)	9	250	40	1,000	85	+ (edrophonium)
10	12	96	14	155	+ (neostigmine)	10	400	70	1,200	140	+ (edrophonium)

* The dose stated is the total given throughout the operation, immediately prior to attempted reversal with anticholinesterase drugs. No attempt was made to determine the exact time and dose at which dual block first became established.

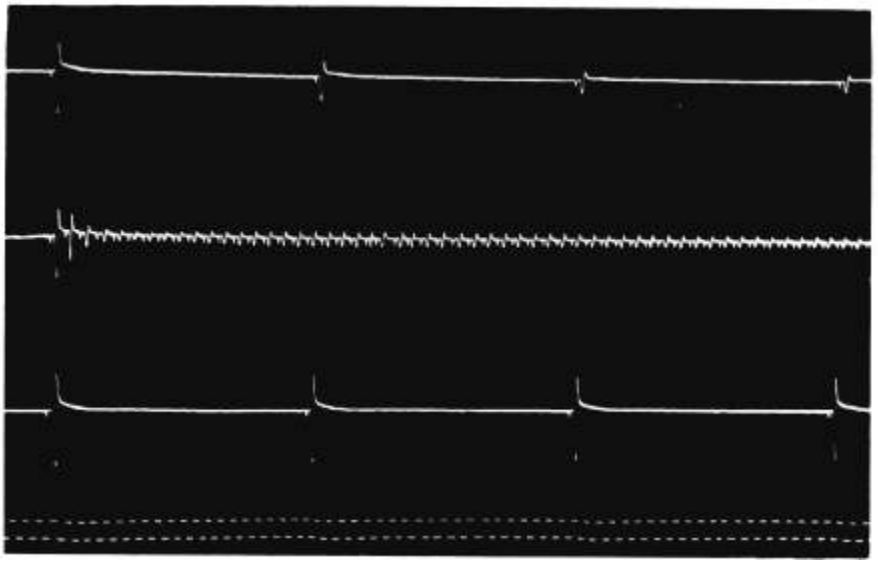


FIG. 3.

DUAL BLOCK after 18.0 mg. decamethonium iodide given intermittently over 2 hours 10 minutes. Pictures taken 10 minutes after last dose.

Rate of nerve-stimulation: (a) 2.5/second. Note the presence of marked "fade" even with twitch rate of stimulation.

(b) 50/second. Note presence of "fade" resembling block due to non-depolarising drug.

(c) 2.5/second. Post-tetanic facilitation is present as in non-depolarising block.

These results are best compared with those following a single paralysing dose (for the hypothenar muscles) of *d*-tubocurarine (12 mg.) showing the characteristics of a non-depolarisation block: (1) There is inability to maintain both twitch and tetanic rates of nerve stimulation (fig. 2, *a* and *b*). (2) Post-tetanic facilitation is present (fig. 2, compare *a* with *c*). (3) Anti-cholinesterase drugs reverse the block.[6]

Large Total Dose of a Depolarising Drug. Following large doses of either decamethonium (10 patients) or succinylcholine (10 patients) a gradual but constant change in the characteristics of the neuromuscular block can be observed (table 1). At first, the change is merely a lessening of the response after a constant dose of the drug. This alteration in the dose-response relationship can be described as tachyphylaxis. As the total dose mounts so a "fade" in the responses to a successive train of stimuli gradually appears, but, at first, only at very fast rates of nerve stimulation (*i.e.*, 50 per second). Finally, a dose is reached where this "fade" of successive responses can be recognised even with very slow rates of nerve stimulation (*i.e.*, 2–3 per second). Post-tetanic facilitation can also be observed (fig. 3, compare *a* with *c*). At this stage the characteristics of the neuromuscular block strongly resemble those seen after a single dose of *d*-tubocurarine, and a dramatic improvement in the neuromuscular block follows an injection of an anti-cholinesterase drug (fig. 4). A similar response to neostigmine after a large dose of succinylcholine (1,500 mg.) has already been demonstrated.[6]

Sequence of Events in the Formation of a Dual Block. Electromyographic studies revealed the following pattern in the change from a depolarisation to a non-depolarisation type of block: (1) Typical depolarisation block with maintenance of both fast (tetanic) and slow rates of stimulation. The absence of any post-tetanic facilitation.* Anti-cholinesterase drugs increase the degree of neuromuscular

* Minute scrutiny of the pattern of potentials obtained after even a single small dose of a depolarising drug (decamethonium or succinylcholine) often revealed the first traces of a "fade" and very slight facilitation. The precise incidence of this change in a random sample of the population is under investigation.

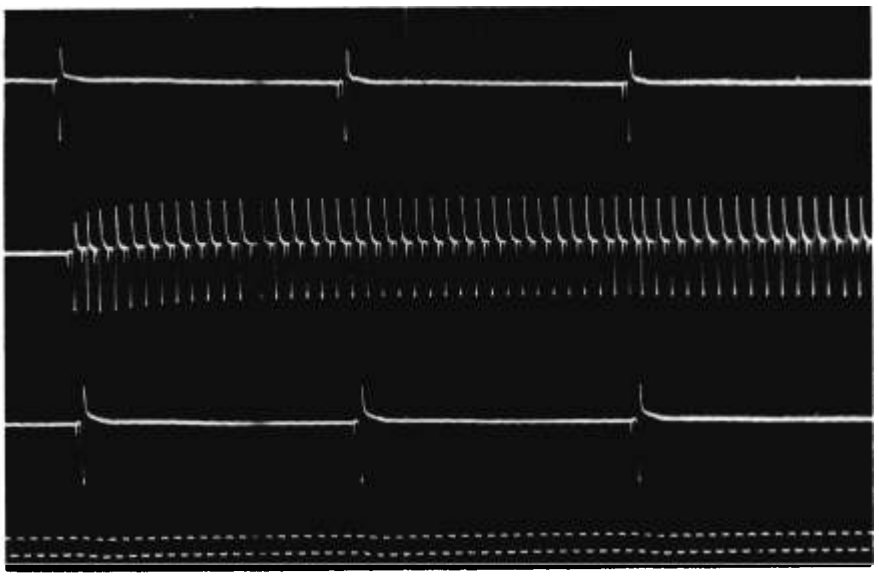


FIG. 4.

REVERSAL OF DUAL BLOCK by neostigmine (2.5 mg.) (Taken five minutes after Fig. 3). Marked improvement in tidal volume.

Rate of nerve-stimulation: (a) 2.5/second. Potential now well maintained.
(b) 50/second. Potential now well maintained.
(c) 2.5/second. Potential now well maintained.

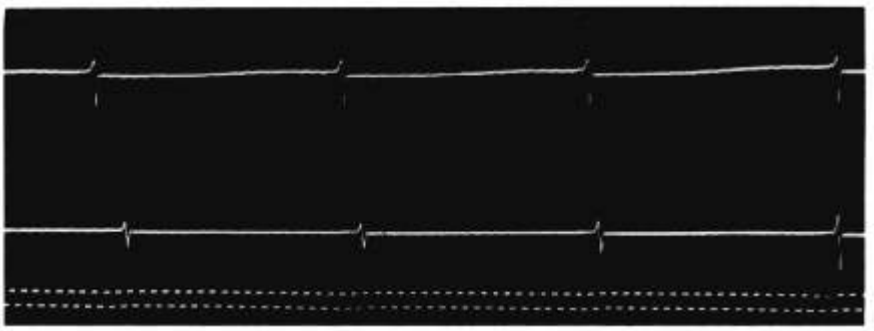


FIG. 5.

(a) 7 minutes after 50 mg. succinylcholine (2.5/stimuli/sec and). 70% recovery.
(b) After 1600 mg. succinylcholine given intermittently over 2 hours. Last dose given 20 minutes before recording.

block. (2) Tachyphylaxis, *i.e.*, a gradually diminishing paralysant action in response to the same dose of the drug. (3) An inability to sustain very fast rates of stimulation, with a resultant "fade" in successive responses and the presence of post-tetanic facilitation. (4) A "fade" of successive potentials even with slow (twitch) rates of stimulation. (5) Reversibility of varying degrees following the injection of an anti-cholinesterase drug.

Dose Relationship in the Formation of a Dual Block. In this series a fully established dual block could be first recognised in the hand muscles with doses of succinylcholine varying from 500–1,500 mg. and decamethonium from 6 mg.–20 mg. given over a period of 1–2 hours. Figure 5 is an example of the change seen after both a small and a large dose of succinylcholine.

None of the 20 patients investigated with a large total dose of depolarising drug failed to show some signs of a dual block, though the degree of reversibility varied in relation to the completeness of the establishment of this condition. In all patients in whom there was a marked improvement in neuromuscular transmission following anti-cholinesterase therapy (as measured electromyographically) there was also a corresponding improvement in the minute volume of respiration.

DISCUSSION

The results presented in this paper demonstrate that the injection of a depolarising drug in a normal anaesthetised patient will lead ultimately to a dual type of neuromuscular block in the hand muscles provided a sufficiently large dose is used. In this study the dose of succinylcholine required to produce a dual block varied in different patients from 500–1,500 mg. and for decamethonium from 6–20 mg. The first trace of a non-depolarising type of block could sometimes be recognised even after a single small dose of the depolarising drug–*i.e.*, 40 mg. of succinylcholine and 2.0 mg. of decamethonium. It may well be that a wider survey of the population might reveal that a complete dual block does sometimes occur even with very small doses of the depolarising drugs. In fact, in one case not included in this series which was investigated for a prolonged response to succinylcholine, evidence for the presence of a dual block was obtained after only 100 mg. of the drug had been given.

In each instance in which the block changed its characteristics completely from one of depolarisation to one of non-depolarisation, the injection of an anti-cholinesterase drug (neostigmine) led to a marked improvement in neuromuscular transmission. At the same time the respiratory minute volume was also improved. These findings lend support to the suggestion that a similar type of dual neuromuscular block also affects the respiratory muscles. Furthermore, it is supported by the work of Creese and his co-workers,[7] Dillon [8] and Taylor,[9] showing that a two-phased block can be recognised with *in vitro* preparations of human intercostal muscles.

The majority of the electromyographic changes described in this paper can also be observed as alterations in the crude mechanical contractions of the hand muscles on stimulation of the ulnar nerve. Thus, with a simple peripheral nerve stimulator [10] it is now possible for the anesthesiologist to diagnose the precise type of neuromuscular block that is present at any given moment.

Summary

Evidence is presented to show that whereas a single small dose of a depolarising drug (succinylcholine or decamethonium) is usually followed by a depolarising type of neuromuscular block, successive doses finally produce a dual type of block in the hand muscles of normal anaesthetised patients. The sequence of events in this changeover is described. The dose level at which this change may be anticipated is also mentioned, together with a practical suggestion for the diagnosis of neuromuscular block in man.

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CARBON MONOXIDE Dogs were exposed to air containing 0.2–0.3 per cent carbon monoxide until they appeared to be near respiratory failure. They then breathed air, 100 per cent oxygen, or 5 per cent carbon dioxide in oxygen. Loss of carbon monoxide from the blood, and its elimination in expired air were markedly slower when air was breathed. The loss of carbon monoxide was significantly faster when oxygen and carbon dioxide was breathed than with oxygen alone. This difference was related to a greater volume of ventilation due to the carbon dioxide. (*Killick, E. M., and Marchant, J. V.: Resuscitation of Dogs From Severe Acute Carbon Monoxide Poisoning, J. Physiol. 147: 274 (Sept.) 1959.*)

ANTIEMETIC The antiemetic properties of trimethobenzamide hydrochloride (Tigan) have been investigated in dogs and compared to the effects of chlorpromazine. Tigan was found to resemble chlorpromazine in its antiemetic effects, both having their primary effect on the chemoreceptive trigger zone. Tigan produced less hypotension than did chlorpromazine, showed no antagonism to the blood pressure effects of epinephrine as did chlorpromazine, showed no antagonism to the bronchoconstrictor action of histamine in cats, and appeared to lack the sedative properties of chlorpromazine. (*Schallek, W., and others: Anti-Emetic Activity of 4-(Dimethylaminoethoxy)-N-(3,4,5-Trimethoxybenzoyl) Benzylamine Hydrochloride, J. Pharmacol. & Exper. Therap. 126: 270 (July) 1959.*)