SPONTANEOUS RECOVERY OF THE THUMB TWITCH FROM NEUROMUSCULAR BLOCK BY SUXAMETHONIUM IN ANAESTHETIZED MAN


SUMMARY

The neuromuscular blocking effect of repeated bolus administration of suxamethonium 1 mg/kg was observed in 10 healthy surgical patients under enflurane-nitrous oxide-oxygen anaesthesia. Tachyphylaxis and slow recovery of the thumb twitch occurred in close dose-relationships with transition of Phase I block to Phase II, using train-of-four fade as an indicator of the transition. Failure of the thumb twitch to recover to 75% of control, and subsequent step-wise depression from additional doses of suxamethonium had a sudden onset shortly after establishment of marked train-of-four fade.

Prolonged exposure to suxamethonium results in a changing pattern and slow recovery of the neuromuscular block (Churchill-Davidson, Christie, and Wise, 1960; Katz, Wolf, and Papper, 1963). Slow recovery of the block presents problems to the anaesthetist because reversibility of the block and completeness of the reversal cannot be ascertained.

This investigation was undertaken to determine, with a new approach, the dose range of suxamethonium likely to result in slow recovery of neuromuscular transmission. The mode of occurrence of slow recovery and its relationships to the changing nature of the block were studied also.

Because a tetanic rate of stimulation affects the post-tetanic twitches, distorts the spontaneous recovery and may have a persisting effect (Katz, 1973; Lee, 1975), it was avoided deliberately. Train-of-four fade appears to be a suitable substitute as an indicator of the changing nature of the block, because it is useful in predicting edrophonium-antagonism of suxamethonium-induced block (Lee, 1974), and in distinguishing Phase II block from Phase I block in anaesthetized man (Lee, 1975). The relationship between the train-of-four fade and the rate of spontaneous recovery of the thumb twitch was explored.

METHODS

Ten healthy adult patients (ASA Class I or II) undergoing general anaesthesia for elective surgery were studied. All were free from neuromuscular disorders and were not receiving antibiotics or other drugs known to affect neuromuscular transmission. The mean body weight was 59.9 (± SD 13.7) kg. Body temperature was normal in all the patients.

Premedication consisted of pentobarbitone 100 mg, pethidine 75 mg and atropine 0.5 mg given i.m. 1 hr before induction. Sleep was induced by thiopentone 200–400 mg i.v. Endotracheal intubation was facilitated by suxamethonium 1 mg/kg or by topical anaesthesia of the larynx and trachea using lignocaine 120–160 mg. No other muscle relaxants were used. Anaesthesia was maintained with enflurane (0.8–1.5%) in nitrous oxide 60% in oxygen. Ventilation was controlled using a mechanical ventilator delivering 10–12 ml/kg 10 times per min.

The ulnar nerve was stimulated at the wrist with 0.1-msec square pulses of supramaximal voltage (Grass Model S4) and the thumb twitch was recorded using a transducer (Grass FT 10C or FT 03, whichever appropriate). Single shocks were repeated every 10 sec. A short train of several twitches 0.5 sec apart was applied each time spontaneous recovery was 50% of the control, for calculation of the train-of-four ratio (fourth-to-first twitch ratio). Tetanic stimulation was avoided. Atropine was given as necessary to maintain the heart rate between 80–100 beats/min. This reduced the risk of bradycardia which might follow repeated bolus injection of suxamethonium.

To provide relaxation, suxamethonium was administered i.v. when indicated. From time to time, the twitches were allowed to recover spontaneously. If full recovery followed, suxamethonium was resumed. If full recovery did not occur shortly, the twitches were allowed to recover until there was
no appreciable progress for 3 min. The magnitude of residual paralysis was assessed before suxamethonium was resumed. If significant residual paralysis warranted its discontinuance, the twitches were observed for an extended period of time to see whether the responses would eventually recover to 100% of control.

When tachyphylaxis was suspected, the twitches were allowed to recover until there was no appreciable progress for 3 min, and a bolus of suxamethonium 1 mg/kg was injected. The recovery of the twitches from this bolus was observed similarly. A solution of suxamethonium was prepared for each patient according to the body weight so that each 5 ml of the solution contained exactly 1 mg/kg of the drug. This ensured that two bolus injections administered hours apart contained equal amounts of the drug. Tachyphylaxis was evaluated by comparison of the effects of bolus injections at different times.

The cycle of intermittent paralysis and recovery was repeated at appropriate times. The following were measured whenever available: (1) time from bolus injection of suxamethonium to 25% recovery of the thumb twitch, (2) time from 25% to 75% recovery of the thumb twitch, and (3) the corresponding train-of-four ratio at 50% recovery of the first twitch. The total duration of observation was 2–5 hr. The total quantity of suxamethonium received by the patients varied from 4 to 14 mg/kg (mean = 7 mg/kg).

RESULTS

Figure 1 summarizes the results of all three measurements from all 10 patients. Figure 2 and table I illustrate one patient’s responses.

**Train-of-four ratio** (fig. 1A). In agreement with previous observations, using halothane anaesthesia instead of enflurane, the relation between the train-of-four ratio and the total quantity of suxamethonium a patient had received followed a sigmoid curve. A transitional zone of 2–3 mg/kg divided each curve into two phases, the first phase of minimal fade (train-of-four ratio 0.7–1.0), and the second phase of marked fade (train-of-four ratio approximately 0.3). After an accumulated total of 4–6 mg/kg had been administered, the train-of-four faded markedly in all cases.

**Time from injection of suxamethonium 1 mg/kg to 25% recovery of the thumb twitch** (fig. 1B). This time varied widely from patient to patient. For each patient, it varied randomly and only slightly from bolus to bolus until a total of 4–8 mg/kg of suxamethonium had been administered, when it became shorter. This was observed in five patients. The
NEUROMUSCULAR BLOCK WITH SUXAMETHONIUM

FIG. 2. A 23-year-old Caucasian female weighing 52 kg received the 3rd (A), 4th (B), 5th (C), 6th (D), 7th (E), 8th (F) and 9th (G) bolus of 1 mg/kg of suxamethonium (arrows). Thumb twitches are 10 sec apart (0.1 Hz) or 0.5 sec apart (2 Hz), as indicated. (The record reads from right to left.) The train-of-four fade accelerated from B to D. Failure of the thumb twitch to recover fully had an abrupt onset at end of D and proceeded stepwise through G.

TABLE 1. Further details of the responses of the patient (compare with figure 2)

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The decrease was approximately 25%, from 6.5 min to 5.0 min. Most of the shortening resulted from a selective marked decrease in the 100% block portion, because the time-courses of both the onset (from injection to full effect) and the recovery rate (from beginning of recovery to 25% recovery) were prolonged. In all subjects, doses of suxamethonium 1 mg/kg produced a 100% block for 4–7 min in the beginning. In two patients the same amount of drug failed eventually to produce 100% block for any duration after 7 mg/kg and 8 mg/kg of suxamethonium, respectively. Therefore, the shortening of the duration from injection to 25% recovery was primarily a result of loss of potency (tachyphylaxis) rather than acceleration of recovery. This was not because of spontaneous degradation of the drug at room temperature, since fresh solution made no difference.

Time from 25% to 75% recovery (fig. 1c). During the first 4 mg/kg of suxamethonium, the 25% to 75% recovery time averaged approximately 2.5 min, and remained relatively constant. After this amount had been exceeded, it became prolonged within the next 1–4 mg/kg. The onset of marked prolongation occurred abruptly (shown in six patients in fig. 1c).

Failure of spontaneous recovery. Failure of the thumb twitch to recover to 100% of control (observation time: 30–120 min) occurred also with a sudden onset, and each additional bolus thereafter depressed further the immediate final level of recovery in a stepwise manner (fig. 2). In three patients, the recovery failed to achieve 75% of control, remaining in the 50–75% range, with marked train-of-four fade, for over 30 min. This occurred after a total of 5 mg/kg, 6 mg/kg and 8 mg/kg of suxamethonium respectively. Ninety minutes later, however, the twitches gradually approached 90% of control, while the train-of-four ratio approached 0.8. This demonstrated the potential of the neuromuscular transmission to recover fully, although slowly. In all cases,
as long as the train-of-four still faded, the twitch improved with time. The abrupt onset of failure to recover fully occurred in or followed shortly after the establishment of marked train-of-four fade, within the next 0–5 mg/kg.

**Reversal of the residual block.** Edrophonium 10 mg was injected in five patients, all of whom demonstrated marked train-of-four fade and failure to make a full spontaneous recovery. Immediate reversal, without return of the block to the preceding level during the next 15–30 min, was observed in all five cases. The amplitude of antagonism was not analysed.

**DISCUSSION**

In anaesthetized man, slow recovery of residual block and failure to recover fully occur abruptly during the course of prolonged exposure to suxamethonium. Once the train-of-four fades markedly (that is, the block becomes Phase II) the abrupt onset of slow recovery and incomplete recovery may follow rapidly. Previously these close dose-relationships were not appreciated fully, because of the use of tachyphylaxis as an indicator of Phase II block. Tachyphylaxis was not compatible with these observations because its prolonged and pronounced post-tachyphylaxis effects distort the twitch height, leave no time for observation of recovery, and do not permit observation of the effect of anticholinesterases on the twitches free from its influence.

The results confirm also the close dose-relationships between tachyphylaxis and Phase II block (Wylie and Churchill-Davidson, 1972; Lee, 1975). Tachyphylaxis may occur during and immediately following the transition from Phase I to Phase II block, as indicated by train-of-four fade (fig. 1A and B compared). This is slightly different from the generalized statement that tachyphylaxis precedes Phase II block (Wylie and Churchill-Davidson, 1972), where Phase II is defined differently.

It is understood that different results may come from different methods of observation. For example, one of us has observed previously the absence of tachyphylaxis when suxamethonium was infused at a constant rate, a constant degree of block being maintained for 2–3 hr. But tachyphylaxis was observed in the same study when repeated bolus doses of suxamethonium were injected, each bolus becoming less effective (Katz and Ryan, 1969).

That the duration of action may increase while the potency decreases may seem confusing, unless these two phenomena are observed separately. For example, the sixth dose of 1 mg/kg may have less peak effect (tachyphylaxis), but more residual block (slow recovery) than the first dose.

Failure of recovery and its sudden onset may not be appreciated fully unless artefacts are excluded specifically. For example, the thumb twitch may recover from a bolus to 85% of control in 20 min with no further progress during the next 10 min. One could attribute the 15% residual block to non-specific factors like a drifting recorder, an altered thumb–transducer relationship or changes in temperature and perfusion, and fail to recognize its true nature. Demonstration of a train-of-four fade, however, will confirm immediately that the neuromuscular transmission is still blocked; therefore, lack of progress within a reasonable period of time indicates a failure to recover. Avoidance of tetanic stimulation permits the prolonged observation necessary to confirm that the failure is a spontaneously reversible pharmacological phenomenon, not an artefact. The abrupt onset, the step-wise depression from each additional bolus and antagonism with edrophonium confirm the observations further.

Is failure of recovery of this magnitude significant clinically? Since the thumb twitch is a relatively insensitive indicator of neuromuscular block by tubocurarine, its incomplete recovery in Phase II block probably represents a significant residual block also. Unfortunately, tetanic force, vital capacity, ability to cough and other indices were not measured in this study.

The effect, if any, of enflurane on the development of Phase II and on the recovery of the twitches is not clear.

Although antagonism of Phase II block seems predictable by the train-of-four ratio (Lee, 1974), the reversal may not be complete. The authors suggest that clinical use of suxamethonium should be restricted judiciously and the spontaneous recovery should be monitored closely once the train-of-four fade becomes marked. This is because suxamethonium may lose, with a narrow margin of safety, its advantages of fast onset, potent block and rapid and complete recovery, if its administration is continued. Tachyphylaxis further complicates the problems, and the necessity of rapid administration of large doses may perpetuate a vicious cycle.

So far, slow recovery from suxamethonium block has not been observed in man without a marked train-of-four fade. This applies also in the case of prolonged block as a result of atypical plasma cholinesterases (Savarese et al., 1975). Therefore, the
train-of-four ratio during suxamethonium block is not only of academic interest in indicating the changing nature of the block, but also of potential practical use because it may warn of slow recovery before it occurs. A device capable of digital display of the ratio has been described by Ali and Kitz (1973), who used the train-of-four ratio in the quantitative assessment of the residual non-depolarizing neuromuscular block. Such a device may be of value for those using large amounts of suxamethonium.

Because the train-of-four fade during Phase II varies also with the (per cent of) block, as does tetanic fade (Katz, 1973), and becomes observable at any frequency above 0.1 Hz (Lee, 1975), it is suggested that the train-of-four be applied not more often than every 10 sec, and the fourth-to-first ratio be calculated at the level of 30–50% recovery of the first twitch.

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REFERENCES


REPRISE SPONTANEE DES CONTRACTIONS DU POUCE PROVENANT D’UN BLOCAGE NEUROMUSCULAIRE PAR LE SUXAMETHONIUM SUR UN HOMME ANESTHESIE

RESUME

Après administration orale répétée de suxaméthonium à raison de 1 mg/kg, on a observé, sous anesthésie par enfurane/oxyde azoteux/oxygène, l’effet du blocage neuromusculaire sur 10 patients en bonne santé ayant subi une intervention chirurgicale. Il s’est produit une tachyphylaxie et une lente reprise des contractions du pouce, en rapport étroit avec les doses, avec transition du blocage de la phase I à la phase II et avec des étendrements en séries de quatre pour indiquer la transition. Il y a eu subitement, peu après l’établissement des étendrements marquées en séries de quatre, un manque de reprise à 75% du contrôle des contractions du pouce, suivi d’une dépression progressive provenant des doses supplémentaires de suxaméthonium.

SPONTANER RÜCKGANG VON DAUMENZUCKUNGEN NACH NEUROMUSKULAR BLOCK MITTLES SUXAMETONIUMGABE BEI NARKOTISIERTEN PATIENTEN

ZUSAMMENFASSUNG

Wiederholte Bolusverabreichung von Suxamethonium 1 mg/kg ergab eine Wirkung von Neuromuskularblock in 10 gesunden postoperativen Patienten, die mit Enfluran Nitro-Oxyd narkotisiert worden waren. Tachyphylaxie und langsamer Rückgang der Daumenzuckungen standen im nahen Zusammenhang mit den vorübergehenden Stadien Block I bis II, unter der Voraussetzung, dass die Übergangsstadien als “vierfach-seriell” bezeichnet werden. In 75% der Fälle, in denen die Daumenzuckungen nicht weichten, war das Resultat bei stufenweiser Zufuhr von weiteren Dosierungen von Suxamethonium ganz plötzlich, nach der “vierfach-seriellen” Phase erreicht.

RECUERACION ESPONTANEA DE LA CONTRACCION DEL PULGAR DEL BLOQUEO NEUROMUSCULAR PRODUCIDO POR EL SUXAMETIONIO EN EL HOMBRE ANESTESIADO

SUMARIO

Se observó el efecto del bloqueo neuromuscular de la administración de repetidos bolos de 1 m/kg de suxametionio en 10 pacientes quirúrgicos sanos bajo anestesia enfurano-óxido nitroso-oxygène. Se produjo taquifilaxia y recuperación lenta de la contracción del pulgar en íntimas dosis-relaciones con transición en el bloqueo Fase I a la Fase II, mediante el uso del morir de serie de cuatro como un indicador de la transición. La imposibilidad de recuperación de la contracción del pulgar al 75% del control y la subsiguiente depresión gradual de dosis adicionales de suxametionio tuvo un repentino comienzo después del establecimiento del morir de serie de cuatro.