MAGNITUDE, DOSE-REQUIREMENT AND MODE OF DEVELOPMENT OF TACHYPHYLAXIS TO SUXAMETHONIUM IN MAN

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SUMMARY

Tachyphylaxis to suxamethonium infused at a constant rate was studied in 15 surgical patients under enflurane-nitrous oxide-oxygen anaesthesia. The compound electromyographic response of the adductor pollicis muscle to stimulation of the ulnar nerve was monitored. A short-lasting and a long-lasting nearly steady state were observed in Phase I and in Phase II, respectively, during both of which a constant infusion resulted in a constant block. Tachyphylaxis occurred during the transition of phases, beginning after infusion of 1.4 ± 0.6 (SD) mg kg\(^{-1}\) of suxamethonium, and 36 ± 14 (SD) minutes of exposure. Tachyphylaxis peaked after 2.6 ± 1.3 (SD) mg kg\(^{-1}\), and 72 ± 38 (SD) minutes of exposure. The maximum gain in neuromuscular transmission from the initial maintenance level of block as the result of tachyphylaxis was 53 ± 24 (SD) % of the control. The results are thought to reconcile previously reported conflicting clinical observations on tachyphylaxis.

Repeated bolus doses of suxamethonium in man result in tachyphylaxis (Payne and Holmdahl, 1959; Katz and Ryan, 1969). When the drug is administered by continuous infusion, tachyphylaxis is not always observed. Katz and Ryan (1969) observed no tachyphylaxis when suxamethonium was administered by continuous infusion, a constant level of block being maintained in the human subject by a constant rate of infusion of the drug. In the same patients, tachyphylaxis was observed when suxamethonium was administered by repeated bolus dose. Further, while Churchill-Davidson, Christie and Wise (1960) described tachyphylaxis as one of the five stages in the development of dual block, Crul and others (1966) observed tachyphylaxis to develop independently of the changing pattern of neuromuscular block caused by suxamethonium in man.

Lee (1975) observed that the change of the characteristics of neuromuscular block produced by suxamethonium, in man, from Phase I to Phase II took place in a narrow transitional zone during which a sudden alteration in the dose required to maintain a constant level of block was frequently observed also. This suggested to us the possible existence of two steady states, separated by a transitional period, during which changes in neuromuscular sensitivity might occur. In other words, phasic changes of neuromuscular sensitivity might accompany phasic changes of the characteristics of block. This could also mean that both in Phase I and in Phase II it would be possible to maintain a constant level of neuromuscular block by a constant infusion of suxamethonium, but tachyphylaxis in the form of an increasing resistance to the action of the drug, would occur during the transitional period. The work reported here was undertaken to test this hypothesis, and to study the dose requirement, the time-course and the magnitude of tachyphylaxis. Tachyphylaxis to suxamethonium in man has not been quantified previously.

METHODS

Fifteen adult patients undergoing general anaesthesia for elective surgery were studied. All were classified as ASA I or II and none were receiving previous medication.

Premedication consisted of a barbiturate (secobarbitone or pentobarbitone 100 mg) and atropine (0.4–0.6 mg) injected i.m. 1 h before anaesthesia. Induction of anaesthesia was with thiopentone 200–400 mg i.v., immediately followed by the inhalation of enflurane and nitrous oxide in oxygen. Anaesthesia was maintained with enflurane 1.0–2.0% inspired and nitrous oxide 50% or 66% in oxygen. Intubation of the trachea was facilitated by topical anaesthesia.
of the oropharynx, larynx and trachea with lignocaine (total 160–200 mg). Ventilation was controlled manually and then mechanically after intubation of the trachea with a tidal volume of 12 ml kg\(^{-1}\) at a rate of 10–12 b.p.m.

The ulnar nerve was stimulated at the wrist, once every 10 s, and occasionally with a train of four to eight stimuli at 2 Hz for calculation of the train-of-four ratio (Lee, 1975). Tetanic stimulation was not used. The stimuli came from a Grass Model 4 Peripheral Nerve Stimulator, and passed through a stimulus isolation unit to a pair of stimulating needle electrodes placed subcutaneously near the nerve at the wrist. Supramaximal square electric pulses of 0.15-ms duration were used.

The neuromuscular block was studied with measurements of the compound e.m.g. of the adductor pollicis muscle. This was done using a supramaximal stimulus to pick up the compound e.m.g.; the active one over the middle phalanx of the index finger and the shield in between.

An i.v. infusion was established, and a steady flow of lactated Ringer's solution, approximately 10 ml kg\(^{-1}\) h\(^{-1}\), was maintained to prompt and steady delivery of the muscle relaxant infused into the line. The arterial pressure cuff was positioned on the other arm, to avoid interference of the steady flow of solution. A large syringe charged with suxamethonium solution was prepared for each patient according to the body weight so that each 5 ml of the solution contained 1 mg kg\(^{-1}\) of the drug. An infusion pump was used in each case to infuse suxamethonium into the i.v. line at a port as close to the patient as possible. Prior exposure to muscle relaxants was avoided. The study was begun only after an initial period when the block was 10% less than, but leaving, the maintenance level because of tachyphylaxis (fig. 1). This first, nearly steady, state took 5–15 min to be established and lasted 21 ± 11 (SD) min.

Tachyphylaxis began 36 ± 14 (SD) min and peaked 72 ± 38 (SD) min after the beginning of the infusion (fig. 2). In terms of drug requirement, tachyphylaxis began after infusion of 1.4 ± 0.6 (SD) mg kg\(^{-1}\) of suxamethonium and peaked after 2.6 ± 1.3 (SD) mg kg\(^{-1}\). The figures given above included the block induction time of 5–15 min when the infusion rate was less than the maintenance level. The maximum gain in twitch response from the first steady state level was 53 ± 24 (SD) % of the unblocked control (fig. 2). In one patient, a 97% block recovered totally.

After tachyphylaxis had peaked, the compound e.m.g. response first became level, then decreased
SUXAMETHONIUM TACHYPHYLAXIS

Fig. 1. Tachyphylaxis to suxamethonium. A patient weighing 68 kg received a total of 384 mg of suxamethonium by continuous infusion. Continuous tracings of neurally elicited compound e.m.g. of the adductor pollicis muscle. The 2-Hz responses were recorded with increased paper speed. The first steady state lasted 29 min, from A to B. Peak tachyphylaxis, observed at C, occurred 57 min from initiation of infusion. The magnitude of tachyphylaxis was 32% of unblocked control. Train-of-four faded increasingly as tachyphylaxis developed and as the block returned. The infusion rate was constant until D, when it was decreased to two-thirds; E when it was decreased to one-half the initial maintenance rate; and F when it was discontinued. The first steady state was disturbed easily by factors which affected the delivery of the drug. The second steady state could be maintained with ease, despite changes in the infusion rate, from D to F. Marked train-of-four predicted edrophonium reversal (G: 15 mg; H: 10 mg, edrophonium chloride i.v.), as shown.

Gradually if the same infusion rate was maintained (fig. 1). This was followed by a new long-lasting "steady" state when the compound e.m.g. response could be maintained nearly constant, with ease, at any suitable infusion rate. Figure 3 summarizes the time-course and the magnitude of tachyphylaxis observed.

Qualitatively, the mode of onset and the characteristics of neuromuscular block showed phasic changes also, those occurring before tachyphylaxis being distinctly different from those occurring after. Before tachyphylaxis, the neuromuscular block was characterized by rapid response to changes in the rate at which suxamethonium was infused. It was impossible to adjust the infusion rate to achieve and maintain a predetermined level of block. Either recovery beyond the desired level or a block more profound than the desired level always resulted before the adjustment became effective. The block was not cumulative. After tachyphylaxis, by contrast, the neuromuscular block was characteristically indifferent to changes in the rate of infusion. A constant level of block was maintained. A prolonged steady residual block was encountered occasionally after the infusion was discontinued (fig. 1); this recovered slowly. During the slow spontaneous recovery, minutes rather than seconds of rapid infusion were required to stop the recovery and increase the block. The block was then cumulative.

Before tachyphylaxis, the train-of-four ratio was more than 0.7. After tachyphylaxis had peaked, the ratio was less than 0.4 in every patient. The block
Fig. 2. Magnitude, time to peak tachyphylaxis, and dose requirement of peak tachyphylaxis to suxamethonium in man. Patients are numbered individually. In parentheses are corresponding pairs of time since initiation of infusion (min) and amount of suxamethonium already infused (mg kg⁻¹). Mean values quoted in the text were obtained without patients 9 and 11 because 9 had a total block and 11 had a total recovery. Solid circle: muscle response before tachyphylaxis as percentage of unblocked control. Open circle: muscle response at peak tachyphylaxis. Bars: gain in muscle response as a result of tachyphylaxis.

Fig. 3. Magnitude and time course of tachyphylaxis to suxamethonium infused at a constant rate: mean values. Compare figure with similar figures reported by Jenden, Kamijo and Taylor (1954) and Gissen and Nastuk (1966, 1970). Standard deviations are omitted for graphic clarity and for ease of comparison. For these values, see text and figure 2.

was reversible with edrophonium, in all five patients tested. In between, the train-of-four faded increasingly (fig. 1), taking into consideration that the train-of-four ratio was also dependent on the level of neuromuscular block which decreased during tachyphylaxis. These qualitative observations were made on numerous additional occasions during the preliminary observations.

**DISCUSSION**

Tachyphylaxis to suxamethonium occurs in man during the transitional zone of phasic change of the characteristics of neuromuscular block; the block in each of our patients was in Phase I before tachyphylaxis and in Phase II after tachyphylaxis had peaked. This conclusion is supported by the fact that peak tachyphylaxis was observed after approximately 3.0 mg kg⁻¹ of suxamethonium, which was the dose requirement for the transitional zone of the phasic change of the train-of-four ratio reported previously (Lee, 1975). Therefore, qualitatively and quantitatively, our data supported our hypothesis and confirmed the original observation of Churchill-Davidson, Christie and Wise (1960) that tachyphylaxis occurred with the changing phases of suxamethonium-induced neuromuscular block in man. Using train-of-four fade as indicator of the phasic change, we were able to leave the neuromuscular transmission undisturbed by the tetanus. This permitted quantification of the tachyphylaxis with the continuous infusion technique. Differences in criteria for delineation of Phases I and II might explain the finding by Crul and others (1966) that tachyphylaxis occurred independent of phasic changes.

Since the dose requirement for Phase I block to begin transition to Phase II is small (Lee, 1975), it is not surprising that the first steady state of drug sensitivity to suxamethonium is short-lasting, and tachyphylaxis begins soon after exposure. We realized only after the preliminary observations that in some patients the first steady state could be demonstrated and tachyphylaxis could be quantified only if observation began with infusion. This required avoiding confusion between tachyphylaxis and recovery, and avoidance of tetanic stimulation during neuromuscular blockade, changing rate of drug infusion, and complete block of transmission at any time during the quantitative study.

While a constant level of neuromuscular block would result from infusion of suxamethonium at a constant rate in Phase I and Phase II, it is impossible to obtain and maintain a predetermined level of block in Phase I. The recovery is too rapid. In addition, the sensitivity varies from subject to subject and changes with time. The circulation time (the transit time) is therefore too long. A small difference in the infusion rate may make a large difference in the magnitude of block produced. Once spontaneous
recovery has begun, one cannot deliver the right amount of drug to the site of action in time to hold the block at the desired level. Overshooting is difficult to avoid because spontaneous recovery can be as rapid as 10% twitch increase in 10 s. Once spontaneous recovery has been arrested, on the other hand, sufficient drug for a profound block would probably have been infused into the blood stream. By the time one has learned by trial-and-error the fine adjustment of the infusion rate required for a predetermined level of block for a patient, the block is too often no longer in Phase I.

By contrast, decreased potency, delayed onset of block and delayed recovery in Phase II (Churchill-Davidson, Christie and Wise, 1960; Lee, 1976) would have predicted diminution of immediate responsiveness to changes in the infusion rate and hence ease of maintenance of any predetermined level of neuromuscular block by adjusting the infusion of suxamethonium. Naturally, it requires a different rate of infusion from that required in Phase I, for the same level of block. Presumably, the conditions under which Katz and Ryan (1969) made their observation of absence of tachyphylaxis to suxamethonium infused at a constant rate correspond to the second steady state we described here.

One might speculate from our results that if a bolus injection of suxamethonium were repeated many times, its effect would be found to remain relatively constant in Phase I and again in Phase II, with changes occurring in between. Given as a bolus, a certain amount of drug effective in Phase I may lose all its effect in Phase II (Payne and Holmdahl, 1959; Lee, 1976). Given as a constant infusion, the block will go through a period of tachyphylaxis because of loss of its Phase I potency and reach a new state of block as the Phase II effect accumulates.

If tachyphylaxis is associated with the phasic change of block and is at least partially a result of "self-antagonism" between the Phase I and Phase II effects of suxamethonium (Lee, 1976), why does it peak during the transitional period, instead of after Phase II block has become established as one of us has observed previously (Lee, 1975)? This is explicable if one assumes that the neuromuscular block produced by constant infusion of suxamethonium in Phase II is primarily the result of its residual non-depolarizing blocking effect, which is cumulative. Accumulation of this residual block as it develops may interrupt and prevent full tachyphylaxis, to result in a return of some of the block if the same infusion rate is maintained. Consequently, tachyphylaxis observed with the constant infusion technique may be underestimated. It may also have peaked earlier than would be observed by the bolus technique. Variability in individual sensitivity, metabolism, dose requirement for phasic change, the level of block maintained and other factors may all affect the magnitude and the time course of tachyphylaxis observed.

Simultaneous occurrence of tachyphylaxis and phasic change, in vivo, is reminiscent of the observation made previously by Jenden, Kamijo and Taylor (1954), and Gissen and Nastuk (1966, 1970), in vitro, that during continuous exposure to a constant concentration of a depolarizing agent the neuromuscular block occurred in two phases separated by a period of partial recovery. Our results were similar to theirs not only in time-course, but also in magnitude. In general, when the initial block is in the order of 90% of control, a maximal recovery of approximately 50% occurs after approximately 50 min of continuous exposure. With continuous infusion at a constant rate, the blood concentration of suxamethonium probably remains relatively constant for some time, or at least does not undergo phasic changes to be responsible for the changing level of block. Therefore, phasic changes observed clinically probably correspond to similar phasic changes observed intracellularly.

In conclusion, tachyphylaxis to suxamethonium is a reproducible phenomenon, whether the drug is injected as repeated bolus or as a continuous infusion. Clinically, the occurrence and its peak effect correspond to the transition of Phase I neuromuscular block to Phase II, in both time course and in dose requirement.

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REFERENCES


GROSSE, DOSIS-ERFORDERNIS UND ART DER ENTWICKLUNG VON MENSCHLICHER TACHYPHYLAXIE AUF SUXAMETHONIUM

ZUSAMMENFASSUNG

Tachyphylaxie auf mit konstanter Geschwindigkeit verabreichtes Suxamethonium wurde bei 15 Operationspatienten unter Narkose mit Enfluran-N₂O-O₂ untersucht. Die zusammengesetzte elektromyographische Reaktion des Adductor pollicis-Muskels bei Stimulierung des Ulnarnervs wurde aufgezeichnet. Ein nahezu Gleichgewichtszustand von kurzer Dauer in Phase I und von langer Dauer in Phase II wurde beobachtet, wobei während beider Phasen eine konstante Infusion bei einer konstanten Blockierung führte. Tachyphylaxie trat während des Phasenübergangs ein, beginnend nach einer Infusion von 1,4 ± 0,6 (SD) mg/kg Suxamethonium nach 36 ± 14 (SD) min. Die maximale Gewinn in neuromuskulärer Übertragung als Resultat der Tachyphylaxie betrug 53 ± 24 (SD) % des Kontrollwertes, gemessen nach dem anfänglichen Einhaltungswert der Blockierung. Diese Ergebnisse sieht man als Übereinstimmung früher berichteter, widersprüchlicher klinischer Beobachtungen über Tachyphylaxie an.

PORTEE, DOSE ET MODE DE DEVELOPPEMENT DE LA TACHYPHYLAXIE QUE PROCURE, CHEZ L'HOMME, LE SUXAMETHONIUM

RESUME

La tachyphylaxie que procure le suxaméthonium injecté à un débit constant a été étudiée sur 15 malades subissant des interventions chirurgicales sous anesthésie à l’enflurane-N₂O-O₂. On a surveillé la réaction électromyographique composée du muscle adducteur du pouce à la stimulation du nerf ulnaire. On a observé respectivement dans la phase I et dans la phase II un équilibre presque cinétique de courte et de longue durée, pendant lequel l’injection constante a entraîné un blocage constant. La tachyphylaxie s’est manifestée pendant la transition des phases, commençant après l’infusion de 1,4 ± 0,6 (étac type) mg/kg de suxaméthonium et 36 ± 14 (étac type) min d’exposition. La tachyphylaxie a atteint son maximum après 2,6 ± 1,3 (étac type) mg/kg et 72 ± 38 (étac type) min d’exposition. Le gain maximal dans la transmission neuromusculaire résultant de la tachyphylaxie a été de 53 ± 24 (étac type) % des valeurs témoins, mesuré en termes de niveau d’entretien initial du blocage. On estime que les résultats réconcilient les observations cliniques contradictoires signalées précédemment sur la tachyphylaxie.

MAGNITUD, DOSIS NECESARIA Y MODO DE DESARROLLO DE TAQUIFILAXIS ANTE SUXAMETONIO EN EL HOMBRE

SUMARIO

Se estudió la taquifilaxis ante suxametonio infundido a paso constante en 15 pacientes quirúrgicos sometidos a anestesia de enflurano-N₂O-O₂. La respuesta electromiográfica compuesta del músculo aductor fue observada ante el estímulo del nervio cubital. Se observaron un estado casi estable de corta duración y uno de larga duración en la fase I y en la fase II, respectivamente, durante las cuales una infusión constante dio como resultado un bloqueo constante. Se produjo taquifilaxis durante las fases de transición, que comenzó después de la infusión de 1,4 ± 0,6 (SD) mg kg⁻¹ de suxametonio, y 36 ± 14 min de exposición. La taquifilaxis alcanzó su ápice al cabo de 2,6 ± 1,3 (SD) mg kg⁻¹ y 72 ± 38 min de exposición. El aumento máximo de transmisión neuromuscular como resultado de la taquifilaxis fue de 53 ± 24 (SD) % del control, medido en términos del nivel de mantenimiento inicial del bloqueo. Se piensa que los resultados reconcilian observaciones clínicas conflictivas anunciadas anteriormente sobre taquifilaxis.