NEUROMUSCULAR REFRACTORINESS DURING BLOCKAGE OF TRANSMISSION
A quantitative study
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SUMMARY
The effects of suxamethonium and tubocurarine on the refractoriness of neuromuscular transmission were studied in 21 anaesthetized adult subjects under various levels of neuromuscular block. The ulnar nerve was stimulated every 12 s with twin supramaximal stimuli 4 ms apart. At any level of block, the refractory fraction (the fractional decrement of the compound electromyographic response of the adductor pollicis to the second twin stimulus, relative to the response to the first) was used to quantify neuromuscular refractoriness. The magnitude of block was determined by the response to the first stimulus. Correlation between refractoriness and the degree of block was sought. Without block, neuromuscular transmission averaged 23% (SEM 4) refractory with this twin interval. The refractory fraction was increased markedly by suxamethonium, reaching 0.69 (SEM 0.1) at 50% block. Complete refractoriness occurred during 25–75% block in eight of 11 instances. Tubocurarine did not significantly alter refractoriness, paired responses to the twin stimuli decreasing proportionately during block.

Depolarizing neuromuscular block produced by suxamethonium increased the refractory period of neuromuscular transmission (Epstein and Jackson, 1973) while non-depolarizing block produced by tubocurarine decreased it (Epstein, Jackson and Wyte, 1969). However, these observations were made with sub-paralytic doses of each drug. Since sub-threshold doses might have effects opposite to the therapeutic response (Schuh, 1975), we wondered whether therapeutic doses of these drugs might affect the refractoriness of neuromuscular transmission in a similar manner, and if so, whether this might be useful in the quantitative assessment of neuromuscular block. The present study assessed the effects of suxamethonium and tubocurarine at various levels of block on the refractoriness of neuromuscular transmission. The effect of the induction of anaesthesia was observed also.

METHODS
Twenty-one adult patients were studied during general anaesthesia which was administered for elective surgery. All patients had given informed consent for the study and were classified as A.S.A. grade I or II. They averaged 63 kg (SD 14) in weight and 32 yr (SD 13) of age. All had normal serum electrolyte concentrations and a normal body temperature, and were free from diseases known to affect neuromuscular transmission. Premedication consisted of pentobarbitone 100 mg, pethidine 75 mg and atropine 0.4–0.6 mg given i.m. 1 h before anaesthesia, which was induced with i.v. thiopentone (average 4 mg kg⁻¹) and maintained with nitrous oxide 60% in oxygen. Enflurane, approximately 2% during induction and 1% for the maintenance of anaesthesia, was added as appropriate.

The ulnar nerve was stimulated at the elbow with twin square pulses of 0.2 ms duration generated by a Grass S88 peripheral nerve stimulator, delivered via a Grass SIU5 stimulus isolation unit. The twin stimuli were 4 ms apart and repeated every 12 s. The stimulus voltage required for supramaximal stimulation of the nerve was determined and 50% added to ensure supramaximal stimulation. This was usually of the order of 80–150 V, depending on the skin conductivity. The paired compound electromyographic (e.m.g.) responses of the adductor pollicis muscle, R₁ and R₂, were picked up by a unipolar electrode placed over the belly of the muscle and analysed by a computing neuromuscular transmission monitor designed for clinical use (Lee, Katz et al., 1977). In essence, the compound e.m.g. was amplified, dissected, stored...
temporarily with memory in digital values, discharged with a time expansion and reconverted to the analog signal. This process enabled an oscillographic ink-writing recorder to record with high fidelity the compound e.m.g. response. The fractional decrement in the $R_2$ response relative to the corresponding $R_1$ ($R_1 - R_2)/R_1$ or "the refractory fraction") at any moment was used to quantify refractoriness. The decrement in $R_1$ itself, relative to control, was used to quantify neuromuscular block.

Observations began with the induction of anaesthesia. Intubation of the trachea was performed after inhalation anaesthesia and facilitated by the i.v. injection of a neuromuscular blocking agent, either suxamethonium 0.5 mg kg$^{-1}$ or 1 mg kg$^{-1}$ or tubocurarine 0.1-0.3 mg kg$^{-1}$. Data for the present study were collected from recordings made during the first 40 min of anaesthesia, including the first 30 min of exposure to the relaxant drug. In all patients, ventilation of the lungs was spontaneous (assisted or controlled manually as needed) until intubation of the trachea, and controlled with a mechanical ventilator afterwards (12 ml kg$^{-1}$, 10 b.p.m.). During the study, oesophageal or nasopharyngeal temperature did not change more than 0.5 °C from the initial value, and the muscle temperature was assumed to be normal.

**RESULTS**

Patients receiving suxamethonium ($n = 11$) weighed an average 60 kg (SEM 3) and the average age was 30 yr (SEM 5). Those receiving tubocurarine ($n = 10$) weighed 65 kg (SEM 5), and were 33 yr (SEM 4) in age. Before the injection of the muscle relaxant $R_2$ averaged 78% (SEM 4; $n = 11$) of the corresponding $R_1$ in amplitude in the suxamethonium group, and 77% (SEM 5; $n = 10$) in the tubocurarine group. Together ($n = 21$), these gave a control refractory fraction of 0.23 (SEM 0.05). There were no observable changes in the amplitude of $R_1$ and $R_2$ responses during the induction and stabilization of anaesthesia.

The refractory fraction during sub-threshold block, observed before the onset of block and after the recovery from suxamethonium, was not measurably different from control. At the level of 10% block produced by both neuromuscular blocking drugs the refractory fraction decreased slightly. The difference, however, was not statistically significant ($P>0.1$). More profound levels of suxamethonium-induced neuromuscular block increased markedly the refractory fraction; the more marked the block, the more refractory the neuromuscular transmission (fig. 1).

The $R_2$ response became immeasurable at 25% block, 50% block and 75% block of the $R_1$ in one, three and eight instances, respectively.

More profound levels of tubocurarine-induced neuromuscular block slightly increased the refractoriness. However, the effect was variable. A slight increase or decrease in the refractory fraction both occurred. As a group the mean value differed increasing from control as the block increased, but the difference remained statistically not significant ($P>0.1$) up to the level of 75% block of the $R_1$ (fig. 2). Beyond that, both responses became too small for the ratio to be taken with confidence.

**DISCUSSION**

Both the degree of neuromuscular block and the refractoriness of transmission are variables which change with time during the course of block. In addition, the nerve stimulation necessary for their determination may by itself alter both values, particularly in the presence of a non-depolarizing block where stimulus frequency is a critical determinant of the
muscle response. For these reasons, it is desirable to follow the changes dynamically and to make instantaneous assessment of both variables with minimal stimulation. Methodologically, we accomplished this by determination of the $R_1$ and $R_2$ responses, and the ratio. With a twin interval of 4 ms the $R_2$ response was normally sufficiently sub-maximal to allow room for possible growth yet large enough to allow accurate quantification (Epstein and Jackson, 1973; Lee, Barnes et al., 1977).

Our results indicated that at clinical levels of neuromuscular block suxamethonium markedly, and tubocurarine insignificantly, increased the refractoriness of the transmission. Presumably each muscle cell in the muscle contributed to the compound e.m.g. response with either a full-sized action potential or not at all, and the relative amplitude of the compound response reflected the proportion of the muscle cell population excited by each stimulus. An increased refractoriness of transmission during suxamethonium-induced neuromuscular block suggested therefore that a larger fraction of those muscle fibres which had survived the block failed to respond to a closely spaced second stimulus.

Epstein and Jackson (1973) described increased refractoriness with sub-paralytic doses of suxamethonium, decreased refractoriness with minute doses of tubocurarine (Epstein, Jackson and Wyte, 1969) and increased refractoriness with volatile anaesthetics (Epstein and Jackson, 1970). We did not see similar effects during sub-threshold block of the transmission (after recovery from suxamethonium or before the onset of block by tubocurarine), or during increasing depth of anaesthesia (from induction to stabilization of anaesthesia). Suzuki and colleagues (1975) described a slight but significant and consistent increase in $R_2/R_1$ elicited with twin stimuli 7 ms apart, 4–10 min after 0.1 mg kg$^{-1}$ of tubocurarine in patients anaesthetized lightly with pentobarbitone and nitrous oxide. We found inconsistent effects at various levels of block with tubocurarine. Berry (1966) observed that while twin stimuli spaced 1–1.8 ms apart did not augment the thumb twitch over that elicited by single stimulus in the presence of non-depolarizing block. Many methodological differences existed between these studies. The state of neuromuscular transmission immediately before and after a block produced by a relatively large dose of relaxant might not be equated to the state created by injection of minute doses. The enflurane anaesthesia for our patients was probably not deep enough to affect the refractoriness. The rate of nerve stimulation differed also. The twin interval employed by Suzuki and co-workers (1975) was just beyond the refractory period in our experience (Lee, Barnes et al., 1977). Reports by Berry (1966) and by Epstein, Jackson and Wyte (1969) agreed in that tubocurarine in small doses decreased the absolute refractory period of neuromuscular transmission.

Based on these and other clinical studies, some generalizations can be made. (1) Immediately after the refractory period the neuromuscular junction is hyperexcitable in the absence of a myoneural blocking drug. Suzuki and colleagues (1975) observed hyperexcitability up to 4 s after a single stimulus. Lee, Barnes and colleagues (1977) noted a similar decrease in refractoriness 20 ms after paired stimuli. Lee, Barnes and colleagues (1977) noted a similar decrease in refractoriness 20 ms after paired stimuli. (2) Sub-paralytic doses of curariform drugs enhance paradoxically the muscle response to nerve stimulation (Schuh, 1975) and decrease the refractoriness (Berry, 1966; Epstein, Jackson and Wyte, 1969). (3) Paralytic doses of curariform drugs not only block the neuromuscular transmission but also cause a fade, namely a further depression of transmission in the period after stimulation (Suzuki et al., 1975; Lee and Katz,
1977). (4) A single stimulus suffices to elicit both post-stimulus effects, “facilitation” and fade. During non-depolarizing block, the time of transition (with overlap) between the short-lasting “facilitation” and long-lasting fade appears to be of the order of 10 ms after the stimulus according to the data of Suzuki and associates (1975), and according to Lee and Katz (1977) who observed that, 20 ms after the stimulus, the fade was compensated for only partially by the facilitation.

In summary, increasing the neuromuscular block produced by suxamethonium increases the refractoriness of transmission in anaesthetized man. Tubocurarine does not significantly alter the refractoriness up to 75% block of the transmission. Although it may be possible to detect the existence of a residual non-depolarizing block with twin stimuli 1-1.8 ms apart (Berry, 1966) it is improbable that the degree of neuromuscular block can be assessed indirectly with accuracy by measuring the refractoriness of transmissions, because of the wide range of individual variability.

REFERENCES


DER NEUROMUSKULÄRE WIDERSTAND WÄHRENDES EINES REIZÜBERTRAGUNGSBLOCKS

Eine quantitative Untersuchung

ZUSAMMENFASSUNG

REFRACCION NEUROMUSCULAR DURANTE BLOQUEO DE LA TRANSMISION

Un estudio cuantitativo

SUMARIO

Se estudiaron los efectos ejercidos por suxametionio y tubocurarina sobre la refracción de la transmisión neuromuscular en 21 sujetos adultos anestesiados a diversos niveles de bloqueo neuromuscular. Se estimuló el nervio cubital cada 12 s, aplicándose estimulos supramaximales gemelos a intervalos de 4 ms. En cualquier nivel de bloqueo, la fracción refractaria (el decrecimiento fraccional de la respuesta electromiográfica compuesta del músculo aductor del pulgar ante el segundo estímulo gemelo, en relación a al respuesta al primero) se empleó para cuantificar la refracción neuromuscular. La magnitud del bloqueo fue determinada por la respuesta al primer estímulo. Se buscó una correlación entre la refracción y el grado de bloqueo. Sin bloqueo la transmisión neuromuscular promedió 23% (SEM 4) de refracción con este intervalo gemelo. La fracción refractaria fue aumentada notablemente por el suxametionio, alcanzando 0,69 (SEM 0,1) con 50% de bloqueo. La refracción completa se produjo durante bloqueo de 25-75% en 8 de 11 casos. La tubocurarina no alteró la refracción significativamente, las respuestas pareadas con los estímulos gemelos disminuyeron proporcionalmente durante el bloqueo.