DIFFERENTIAL EFFECTS OF MYONEURAL BLOCKING DRUGS ON NEUROMUSCULAR TRANSMISSION IN INFANTS

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SUMMARY
Equipment, paralysing doses of pancuronium and tubocurarine were administered to 40 patients, aged from 1 day to 12 months, during nitrous oxide, oxygen and fentanyl anaesthesia. Neuromuscular activity was measured during onset and recovery from paralysis using train-of-four stimulation. At the same depression of the first stimulus of the train, the train-of-four ratio was decreased more during recovery than during onset with each drug and more with tubocurarine than with pancuronium. These results are qualitatively similar to those found in adults, but the decrease in train-of-four ratio was less in infants. Thus, it is concluded that prejunctural neuromuscular activity, recognized as fade in response to train-of-four stimulation, can be detected after administration of pancuronium or tubocurarine to infants, but that it is less marked than in adults.

The classical view that curare-like drugs block the action of acetylcholine at a single receptor site has been challenged recently and pre- and postjunctional recognition sites have been demonstrated in animals (Blaber and Karczmar, 1967; Galindo, 1972; Riker, 1975; Miyamoto, 1978).

In man, monitoring the force of contraction of the adductor pollicis muscle in response to train-of-four stimulation has provided a technique for assessment of neuromuscular transmission which is independent of clinical bias (Ali, Utting and Gray, 1970). Not only can the time-course of action of a neuromuscular blocking drug be measured, but information may also be provided about its sites of action. Bowman (1980) suggested that a decrease in the force of contraction in response to the first stimulus of the train, compared with control, was indicative of the classic postjunctural site of action, whereas the fade of response to train-of-four stimulation occurred because of presynaptic activity.

These relationships may be different in small children because of immaturity of the neuromuscular junction. In the absence of muscle relaxants, neuromuscular transmission was shown to be poorly sustained in infants in response to 50-Hz tetanic stimulation (Churchill-Davidson and Wise, 1964) and train-of-four stimulation (Goudsouzian, 1980). Thus, differences in the response to train-of-four stimulation between adults and children have been recognized. However, the response of the small child to train-of-four stimulation after administration of neuromuscular blocking drugs has not been quantified previously, despite the importance of establishing the normal pattern of response to such stimulation if it is to be used as an index of the intensity of paralysis.

The present study was designed to determine the relationship between first twitch depression and train-of-four fade in full-term neonates and infants younger than 1 year old during the onset of, and recovery from, neuromuscular block induced with paralysing doses of either tubocurarine or pancuronium.

SUBJECTS AND METHODS
The procedure was approved by the Hospital Committee on Medical and Dental Evaluation. Forty neonates and infants were studied during various surgical procedures of at least 1 h duration. Their ages ranged from 1 to 288 days (mean 116) and their weights from 2.7 to 10.1 kg (mean 6.1). None suffered from any condition requiring medical attention or was receiving drugs known to interfere with neuromuscular transmission. They were divided into two groups of 20 patients, of similar ages and weights, and received either tubocurarine or pancuronium on a random basis. Premedication was given to all patients except neonates. Those younger than 6 months old received hyoscine 0.01 mg kg⁻¹ i.m. and those older than 6 months received, in

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addition, pentobarbitone 3 mg kg\(^{-1}\) rectally and morphine 0.1 mg kg\(^{-1}\) i.m. An i.v. cannula was inserted before induction of anaesthesia.

Neuromuscular transmission was monitored according to the method of Ali, Utting and Gray (1970). The ulnar nerve was stimulated supramaximally using silver–silver chloride electrodes applied to the forearm. Trains of four, square pulses of 0.2 ms duration at a frequency of 2 Hz were repeated every 12 s using a Grass S48 stimulator and an SIU5 isolation unit. The hand and forearm were immobilized in a splint and the force of contraction of the adductor pollicis was measured with a force displacement transducer (Grass FT03) and recorded using a pen-and-ink recorder (Grass Polygraph). Thumb skin temperature was maintained at greater than 32 °C. Neuromuscular blockade was expressed as the height of the first twitch (T1) as a percentage of pre-relaxant control values, and as the train-of-four ratio (T4/T1) (the height of the fourth twitch divided by the height of the first in each train).

Anaesthesia was induced with thiopentone 3–5 mg kg\(^{-1}\) and fentanyl 2–3 \(\mu\)g kg\(^{-1}\) i.v., followed by incremental doses as required to provide satisfactory clinical conditions up to maximum total doses of thiopentone 5 mg kg\(^{-1}\) and fentanyl 10 \(\mu\)g kg\(^{-1}\). Intubation was performed, in infants, after induction of anaesthesia and after rapid administration of bolus doses of tubocurarine or pancuronium sufficient to produce a T1 of 10% or less. The tracheae of neonates were intubated whilst the subject was conscious, and a similar dose of one of the neuromuscular blockers was administered immediately afterward. Ventilation was controlled to maintain normocarbia with a mixture of 66% nitrous oxide in oxygen.

The initial dose of neuromuscular blocking drug was based on dose–response data for tubocurarine and pancuronium in children (Goudsouzian, Ryan and Savarese, 1974; Goudsouzian et al., 1975). Thus, the first 10 children in the pancuronium group received 0.04 mg kg\(^{-1}\) but, as four of them required additional doses to achieve 90% block, this dose was subsequently increased to 0.05 mg kg\(^{-1}\) and an equipotent dose of 0.3 mg kg\(^{-1}\) was used in the tubocurarine group. When necessary, incremental doses of 25% of the initial dose were given to achieve 90% depression of the height of the first twitch (T1) compared with control. Then, T1 was allowed to recover spontaneously to at least 50% of control. If further doses of neuromuscular blocker were required, the study was terminated.

The speed of onset of neuromuscular blockade was estimated from the time from injection to maximum block and the rate of spontaneous recovery was assessed for the 10–25% and 10–50% recovery times. Train-of-four ratios were measured at 10% increments of T1 during onset and recovery.

The patients were divided into sub-groups according to age (birth to 3 months and 3–12 months) to allow comparison of the responses to relaxants at different ages. Twenty patients received each neuromuscular blocker: eight were aged birth–3 months and 12 were aged 3–12 months in each relaxant group.

Where applicable, unpaired Student’s t-tests were used and the null hypothesis was rejected when \(P<0.05\).

**RESULTS**

Mean values are presented, with SEM as the index of dispersion.

The two groups of children were comparable with respect to age (means 119±17 days in the group receiving pancuronium and 113 ± 22 days for those receiving tubocurarine) and weight (6.2 ± 0.4 kg and 6.0 ± 0.5 kg, respectively) (table I).

The pharmacodynamic responses to pancuronium and tubocurarine are shown in table II. The onset times and the mean maximum depression of T1 achieved after pancuronium and tubocurarine were similar, although the results for pancuronium represent 10 patients (six aged from 1 day to
3 months) who had received 0.04 mg kg⁻¹ and 10 who had received 0.05 mg kg⁻¹. The onset data were collected before administration of additional relaxant and were not significantly different between different age groups.

Recovery of T1 to 10% of the initial control value was significantly slower after tubocurarine than after pancuronium at all ages (P < 0.05). However, subsequent recoveries from 10 to 25% and 25 to 50% were similar for each drug at all ages.

Data from three patients who had been given tubocurarine have been omitted from some comparisons, as shown in table II, because T1 failed to reach 50% within 1 h of spontaneous recovery.

The mean values of T4/T1 at 10% increments of T1 during onset and recovery of the block are shown in figure 1 and the values of T4/T1 at 50% depression of T1 are shown in table II. The T4/T1 ratio was less during recovery than during the onset of neuromuscular block in every patient with each relaxant. During onset and recovery, the mean values for tubocurarine were less than for pancuronium. At 50% T1 depression, mean T4/T1 was significantly less during recovery than during onset for each relaxant (P < 0.001) and was significantly less during recovery after tubocurarine than after pancuronium (P < 0.001). However, there were no differences between the younger and older infants during onset or recovery after either drug.

**DISCUSSION**

The intensity and duration of neuromuscular block-
ade achieved in the present study were similar to those described in young subjects by Goudsouzian, Ryan and Savarese (1974) and Goudsouzian and colleagues (1975). Too few patients were studied with too wide a scatter in individual results to detect pharmacodynamic differences between those younger than 3 months and those aged 3–12 months. In particular, there were no significant differences in the recovery rates between the younger and older children. Fisher and his colleagues (1982) predicted that, as a result of the prolonged terminal half-life in plasma of pancuronium in neonates, recovery may be prolonged in the very young, particularly after repeated administration.

The most striking findings of the present study were the differences in the relationship between the T4/T1 ratio and T1 depression between groups receiving different neuromuscular blocking drugs. After the introduction of train-of-four monitoring to clinical anaesthetic practice by Ali, Utting and Gray (1970) it was assumed that the fade of T4/T1 was characteristic of non-depolarizing neuromuscular blockade, and differences between relaxants or those induced by time were not recognized (Ali, Utting and Gray, 1971a, b; Lee and Katz, 1980). However, Williams, Webb and Calvey (1980) observed, during the onset of neuromuscular blockade, assessed by electromyography in adults, that, for the same depression of T1, the T4/T1 ratio was smaller for tubocurarine than for pancuronium. We found similar differences between tubocurarine and pancuronium in infants during both onset and recovery.

It has been suggested that, if a single receptor and a single mechanism were involved for all non-depolarizing neuromuscular blocking drugs and their antagonists, then it would be expected that T4/T1–T1 relationships would be similar for all drugs (Donati, Ferguson and Bevan, 1983). The differences seen between each agent and with time with the same agent in the present study are incompatible with that hypothesis. From studies with neuromuscular blocking drugs including alpha-bungarotoxin, and the ganglion blocking agent hexamethonium, Bowman (1980) concluded that depression of T1 and decrease of T4/T1 were independent effects of acetylcholine antagonists: the former is a consequence of postjunctural block, whereas the latter arises from an action at prejunctural receptors. Thus, the differences seen in the present study suggest that, in children as in adults, tubocurarine has more powerful prejunctural activity than pancuronium and that greater prejunctural activity is observed with time with both pancuronium and tubocurarine.

In conclusion, this study demonstrates that train-of-four stimulation is appropriate for neuromuscular monitoring in children. Similar qualitative differences are seen with time and with different neuromuscular blocking drugs as in adults. The small quantitative differences between adults and infants in the relationship between T1 depression and T4/T1 fade are unlikely to be of serious clinical importance.

REFERENCES
EFFETS COMPARÉS DES AGENTS CURARISANTS SUR LA TRANSMISSION NEUROMUSCULAIRE CHEZ LE JEUNE ENFANT

RESUME
Des doses équipotentes et curarisantes de pancuronium et de tubocurarine ont été administrées à 40 patients, âgés de 1 jour à 12 mois, au cours d'une anesthésie au fentanyl et protoxyde d'azote dans l'oxygène. L'activité neuromusculaire était mesurée lors de l'établissement et de la disparition de la curarisation grâce au stimuli en train de quatre. Pour une même dépression du premier stimulus du train, le rapport du train de quatre était plus bas lors de la décuration que lors de la curarisation avec les deux agents, cet effet étant plus marqué avec la tubocurarine qu'avec le pancuronium. Ces résultats sont qualitativement les mêmes que ceux retrouvés chez l'adulte mais l'affaiblissement du rapport du train de quatre était moindre chez le nourrisson. Ceci permet de conclure que l'activité neuromusculaire préjonctionnelle, reconnue par l'affaiblissement de la réponse à la stimulation en train de quatre, peut être détectée après administration de pancuronium et de tubocurarine chez le nourrisson sans qu'elle soit toutefois aussi marquée que chez l'adulte.

UNTERSCHIEDLICHE WIRKUNG VON MUSKELRELAXANTIEN AUF DIE NEUROMUSKULäre ÜBERLEITUNG BEI SÄUGLINGEN

ZUSAMMENFASSUNG

EFECTOS DIFERENCIALES DE LAS SUBSTANCIAS BLOQUEADORAS MIONEURALES SOBRE LA TRANSMISION NEUROMUSCULAR EN INFANTES

SUMARIO
Se administraron dosis paralizantes de pancuronio y de tubocurarina a 40 pacientes de 1 día hasta 12 meses de edad, en el curso de una anestesia por fentanilo, oxígeno y óxido nitroso. Se midió la actividad neuromuscular durante el inicio de la anestesia y la recuperación de la parálisis mediante estimulación por el tren-de-cuatro. En la misma depresión del primer efecto del tren, la tasa del tren-de-cuatro se redujo mucho más durante la recuperación que al momento de iniciarse la anestesia con cada una de las substancias y más aún con la tubocurarina que con el pancuronio. Dichos resultados son similares desde el punto de vista cualitativo a los observados en adultos, pero el descenso de la tasa del tren-de-cuatro era menor en los infantes. Entonces, se concluye que la actividad neuromuscular prejunctional que se reconoce por la atenuación en la respuesta del estímulo del tren-de-cuatro, puede detectarse después de la administración del pancuronio o de la tubocurarina en infantes, pero que es menos marcada que en los adultos.