Accelerated onset and delayed recovery of d-tubocurarine blockade with pancuronium in infants and children

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The effect of age on the onset and duration of action of a d-tubocurarine (DTC) neuromuscular blockade with and without pancuronium priming in children was examined. Sixty ASA physical status I or II patients in three age ranges (0–1 yr, 1–3 yr and 3–10 yr) were anaesthetized with thiopentone, halothane and nitrous oxide. Each patient received either a single paralyzing dose of DTC 0.4 mg·kg⁻¹, or DTC 0.36 mg·kg⁻¹ preceded three minutes earlier by pancuronium 0.007 mg·kg⁻¹. Evoked force of contraction of the adductor pollicis was measured using train-of-four stimulation applied every 12 sec. Time to 90 per cent first twitch depression after a single dose of DTC increased with increasing age ($r = 0.65$, $p < 0.01$), and was 1.6 min (SEM ± 0.3) in the 0–1 yr group, 1.9 ± 0.3 min (1–3 yr), and 5.2 ± 1.2 min (3–10 yr). Time to ten per cent spontaneous recovery after single dose DTC was shorter in older individuals ($r = 0.40$, $p < 0.05$), being 36.4 ± 5.1 min in infants 0–1 yr, 30.6 ± 4.6 min (1–3 yr), and 24.0 ± 2.7 min (3–10 yr). Priming with pancuronium accelerated the onset significantly in all age groups with 90 per cent T₁ depression occurring at 0.7 ± 0.1 min (0–1 yr), 0.9 ± 0.1 min (1–3 yr), and 2.1 ± 0.6 min (3–10 yr). However, priming delayed recovery, especially in infants. Times to ten per cent spontaneous recovery following DTC with pancuronium priming were 71.0 ± 8.1 (0–1 yr), 42.7 ± 3.8 (1–3 yr), and 29.3 ± 3.9 min (3–10 yr). It is concluded that onset and recovery from a DTC blockade are markedly age-related, and this relationship may be accentuated by pretreatment with pancuronium.

Key words

ANAESTHESIA: paediatric; NEUROMUSCULAR RELAXANTS: tubocurarine, pancuronium; DRUG INTERACTION: tubocurarine, pancuronium; PHARMACODYNAMICS: priming principle.

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The pharmacologic response of paediatric patients to nondepolarizing muscle relaxants is controversial. Early reports suggested that neonates required less d-tubocurarine (DTC) than adults when the drug was administered on a mg per kg basis.¹ However, Goudsouzian *et al.*² demonstrated that the response of children to DTC is similar over a wide range of ages although there was considerable variability in dosage requirement.

The administration of a subparalyzing dose or priming dose of a nondepolarizing relaxant several minutes before the intubating dose is often employed to accelerate the onset of action.³ This acceleration has been demonstrated in adults and children with divided doses^{3–10} or mixtures^{5,8,9} of relaxants. However, giving pancuronium before DTC in adults,⁸ or administering pancuronium in divided doses in children¹¹ did not accelerate onset. Moreover, pancuronium priming significantly prolonged the duration of action of a DTC blockade in adults.⁸

Therefore, this study was designed to examine the effects of age on onset, intensity and duration of a DTC neuromuscular blockade in children. In addition, the effects of pancuronium priming of DTC were evaluated in paediatric patients.

Methods

Studies were performed after institutional approval in 60 ASA physical status class I or II patients undergoing elective surgical procedures. There were 20 patients in each age range: 0–1 yr (infants), 1–3 yr (young children), and 3–10 yr (older children).

Patients with hepatic, renal or neuromuscular disease, or those receiving drugs known or suspected to interfere with neuromuscular transmission were excluded. Infants less than six months old were not premedicated. Those older than six months received intramuscular morphine 0.1 mg·kg⁻¹ and atropine 0.01 mg·kg⁻¹ and occasionally rectal pentobarbitone 3 mg·kg⁻¹. Arterial pressure (DINAMAP), heart rate, electrocardiogram and temperature were monitored continuously. After induction of anaesthesia with thiopentone 3–5 mg·kg⁻¹ IV or halo-

TABLE I Patient data, means $\pm$ SEM (age-months, weight-kg)

	DTC alone		DTC with pancuronium priming	
	Age	Weight	Age	Weight
Infants	6.4 $\pm$ 1.2	8.4 $\pm$ 0.7	4.4 $\pm$ 0.7	6.6 $\pm$ 0.5
Young children	23.0 $\pm$ 2.2	11.9 $\pm$ 0.8	22.9 $\pm$ 1.9	12.8 $\pm$ 0.7
Older children	55.2 $\pm$ 4.8	17.7 $\pm$ 0.9	54.3 $\pm$ 3.6	18.0 $\pm$ 0.9

n = 10 in each group.

thane, the ulnar nerve was stimulated supramaximally with train-of-four impulses (0.2 ms duration, 2 Hz frequency) delivered every 12 sec by a Grass S48 stimulator and SIU5 isolation unit. The force of contraction of the adductor pollicis was measured with a Grass FT03 force displacement transducer, and recorded on a Grass polygraph. After stabilization of twitch recording, one group (n = 30) received a paralyzing dose of DTC 0.4 mg·kg⁻¹ into a fast-running IV, while the other group received DTC 0.36 mg·kg⁻¹ preceded three minutes earlier by pancuronium 0.007 mg·kg⁻¹. Thus, assuming a six to one potency ratio between pancuronium and DTC,¹² all patients received the equivalent of DTC 0.4 mg·kg⁻¹ which was expected to produce a block of greater than 95 per cent.² Tracheal intubation was accomplished when 90 per cent first twitch depression was reached. Ventilation (with halothane one per cent, nitrous oxide 66 per cent in oxygen) was controlled to maintain normocapnea using the Bain anaesthetic system.¹³ Measurements consisted of: (1) depression of first twitch height (T₁) every 30 seconds following DTC administration, (2) train-of-four ratio (T₄/T₁) at 30, 50, and 70 per cent T₁

TABLE II Onset and recovery times (min) in three paediatric age groups following a paralyzing dose of DTC. Means $\pm$ SEM

	DTC alone	DTC with pancuronium priming
Time to 90% T ₁ depression		
0-1 yr	1.56 $\pm$ 0.34	0.65 $\pm$ 0.06*
1-3 yr	1.91 $\pm$ 0.34	0.93 $\pm$ 0.13*
3-10 yr	5.20 $\pm$ 1.16	2.10 $\pm$ 0.62*
Time to 10% T ₁ recovery		
0-1 yr	36.4 $\pm$ 5.1	71.0 $\pm$ 8.1*
1-3 yr	30.6 $\pm$ 4.6	42.7 $\pm$ 3.8*
3-10 yr	24.0 $\pm$ 2.7	29.3 $\pm$ 3.9*
Maximum T ₁ depression (%)		
0-1 yr	98.7 $\pm$ 0.7	100.0
1-3 yr	98.5 $\pm$ 0.9	99.7 $\pm$ 0.2
3-10 yr	95.7 $\pm$ 1.2	97.7 $\pm$ 1.1

n = 10 in each group.

*p < 0.05 between groups.

FIGURE 1 Relationship between time to 90 per cent first twitch depression and age following d-tubocurarine (DTC) with and without pancuronium (PANC) priming. The linear regression equations are: DTC alone: $y = 0.08x + 0.65$, $r = 0.65$; PANC-DTC: $y = 0.02x + 0.62$, $r = 0.38$.

depression during onset, and (3) time to ten per cent recovery of T₁. Results were expressed as mean $\pm$ standard error of the mean (SEM) and analyzed by unpaired Student's t test and linear regression. A p value < 0.05 was considered significant.

Results

There were no significant differences in age or weight within each subgroup (Table I). The time to 90 per cent T₁ depression following the injection of a single dose of DTC was slower in older children ($r = 0.65$, $p < 0.01$) (Figures 1 and 2). Onset times range from 1.56 ± 0.34 min in the 0-1 yr group to 5.20 ± 1.16 min in the 3-10 yr group (Table II). Priming with pancuronium accelerated onset time significantly in all age groups (Table II). In children receiving a priming dose of pancuronium, the onset of blockade was also age-related, although within a narrower time scale ($r = 0.38$, $p < 0.05$) (Figures 1 and 3). At 30 per cent first twitch height, patients pretreated with pancuronium exhibited significantly less fade compared

TABLE III Train-of-four ratios (per cent) following DTC in three paediatric age groups. Means $\pm$ SEM

T ₁ as % control	DTC alone			DTC with pancuronium priming		
	0-1 yr	1-3 yr	3-10 yr	0-1 yr	1-3 yr	3-10 yr
70%	74 $\pm$ 2	71 $\pm$ 2	63 $\pm$ 4	71 $\pm$ 3	72 $\pm$ 3	72 $\pm$ 2*
50%	58 $\pm$ 7	60 $\pm$ 3	47 $\pm$ 4	64 $\pm$ 2	67 $\pm$ 3	62 $\pm$ 3*
30%	44 $\pm$ 3	43 $\pm$ 3	32 $\pm$ 4	53 $\pm$ 3*	56 $\pm$ 3*	45 $\pm$ 3*

*p < 0.5 between groups.

FIGURE 2 First twitch height, expressed as a percentage of control with respect to time following a single dose of d-tubocurarine (DTC) in three paediatric age groups.

FIGURE 3 First twitch height, expressed as a percentage of control with respect to time after injection of d-tubocurarine (DTC) preceded by a sub-paralyzing dose of pancuronium (PANC) in three paediatric age groups.

FIGURE 4 Relationship between time to ten per cent recovery and age following d-tubocurarine (DTC) with and without pancuronium (PANC) priming. The linear regression equations are: DTC alone: $y = -0.25X + 37.6$, $r = -0.40$; PANC-DTC: $y = -0.74X + 69.2$, $r = -0.64$.

with children receiving single dose DTC (Table III). Recovery was delayed significantly in infants (but not children) primed with pancuronium (Table II). Time to ten per cent T_1 recovery decreased with increasing age both with ($r = 0.639$, $p < 0.01$) and without ($r = 0.404$, $p < 0.05$) priming, indicating a prolonged duration of recovery in younger subjects (Figure 4).

Discussion

The present study demonstrated that the onset of a DTC neuromuscular blockade was markedly age-related whether or not pancuronium priming was utilized. Accelerated onset in younger subjects may be due to a greater cardiac output causing more rapid delivery of the drug to muscles, or increased sensitivity of the infant's neuromuscular junction. Using similar anaesthetic techniques, infants were found to be more sensitive to muscle relaxants than adults (e.g., DTC¹⁴ atracurium¹⁵). Fisher *et al.*¹⁶ demonstrated that the plasma concentration associated with 50 per cent neuromuscular blockade (Cpss 50) was age related: Cpss 50 in neonates was about one-third that noted in adults. This may be due to the incomplete structural and function development of the neuromuscular system during infancy as documented by decreased amplitude of frequency sweep electromyogram at frequencies of 50 to 100 Hz.¹⁷ The increased sensitivity of the neonates' junction may be compensated for by the increased volume of distribution of relaxant drugs, so that on a $\text{mg} \cdot \text{kg}^{-1}$ basis, no sensitivity is demonstrated.

The duration of action of neuromuscular blockade with single dose DTC was increased only slightly in infants compared with older children. The rate of disappearance of DTC from blood is characterized by a rapid initial

decline that is then followed by a slower decay.¹⁶ Distribution to tissues is the major cause of the initial decline, whereas the slower decay is due to elimination.¹⁸ Since neonates and infants may exhibit a decreased plasma clearance for DTC,¹⁸ longer recovery times in infants would be expected. However, the differences in recovery times observed between infants and older children were small. Thus it is possible that the presence of a larger volume of distribution in infants compared with older children accentuates the importance of the distribution phase, making recovery earlier than anticipated.

Pretreatment with pancuronium accelerated the onset of block in all paediatric groups studied, but failed to do so in adults.⁸ This may be due to increased potency of the pancuronium-DTC combination, or increased delivery of this mixture to the neuromuscular junction in children compared with adults.

The administration of a subparalyzing dose of a non-depolarizing relaxant has been shown previously to accelerate the onset of action of the same relaxant in adults^{3,4,6,7} and in children.¹⁰ This is probably due to the occupation of a certain number of post-junctional receptors without producing paralysis, thereby reducing the margin of safety.^{19,20} When the second larger dose is given, neuromuscular blockade is accelerated because only a small proportion of the total number of receptors need to be occupied to produce paralysis.

Mixtures of two different relaxants may potentiate each other,^{20,21} due to differences in pre- and post-synaptic activity among relaxants, or because of different affinities of relaxants for the two subunits of the acetylcholine receptor.²² This synergism may explain the delayed recovery observed following pancuronium priming in infants 0–1 yr, although the younger age of infants who received priming (4.4 vs 6.4 months) might have played a role. Potentiation of DTC by pancuronium priming has also been demonstrated in adults⁸ where similar doses of the mixture increased time to ten per cent recovery from 39 to 57 min.

More train-of-four fade at the same level of T_1 depression was observed when DTC was administered as the sole relaxant compared with pancuronium pretreatment, especially at deeper levels of blockade ($T_1 = 30$ per cent of control) and in older children. It is known that DTC exhibits more fade than pancuronium because of its greater pre-junctional activity,²² and that fade requires time to develop.²³ Thus it is not surprising that patients receiving DTC as the sole relaxant showed more fade. They required a larger dose of DTC compared with pancuronium pretreated patients (0.4 vs 0.36 mg·kg⁻¹) and neuromuscular block took longer to develop. This confirms earlier studies in adults,^{8,20} and children.²⁴

In paediatric anaesthesia, arterial oxygen tension

diminishes rapidly during apnoea, secondary to decreased functional residual capacity relative to tidal volume, and increased oxygen consumption.²⁵ In addition, pre-oxygenation may be difficult in these patients. Therefore, a shorter onset time of relaxants may be of considerable benefit when a rapid-sequence induction and intubation are necessary. Although reductions of onset time by pancuronium priming are smaller in infants as in older children and adults,⁸ even a small decrease might be advantageous because of the reduced reserve in these patients. However, pancuronium priming of DTC may be associated with a prolonged duration of neuromuscular blockade in infants, which can exceed the duration of surgery.

In summary, onset of and recovery from a DTC blockade were significantly age-related. Time to 90 per cent T_1 depression increased with increasing age, whereas time to ten per cent spontaneous recovery was inversely related to age. Pretreatment with pancuronium accelerated onset in all age groups, but delayed recovery.

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Résumé

On a examiné l'effet de l'âge sur le début et la durée d'action de la d-tubocurarine (DTC) dans un blocage neuromusculaire avec et sans amorce au pancuronium chez les enfants. Soixante patients, de status physique ASA I ou II, de trois échelles d'âge différentes (0–1 an, 1–3 ans et 3–10 ans) ont été anesthésiés avec du thiopental de l'halothane et du protoxyde d'azote. Chaque patient a reçu une seule dose paralysante de 0.4 mg·kg⁻¹ de DTC, ou de 0.36 mg·kg⁻¹ de DTC précédé de 0.007 mg·kg⁻¹ de pancuronium donné trois min. auparavant. On a mesuré la force de la contraction évoquée de l'adducteur du pouce en utilisant une stimulation train-de-quatre appliquée à toutes les douze secondes. A 90 pour cent de la dépression de la première contraction après une dose unique de DTC, le temps augmentait avec l'âge ($r = 0.65$, $p < 0.01$); il était de 1.6 min. (SEM ± 0.3) chez le groupe de 0–1 an, 1.9 ± 0.3 min. dans le groupe de 1–3 ans, et de 5.2 ± 1.2 min. dans le groupe de 3–10 ans. A dix pour cent du rétablissement spontané après une dose unique de DTC le temps était plus court chez les individus plus âgés ($r = 0.40$, $p < 0.05$); il était de 36.4 ± 5.1 min. chez les nourrissons de 0–1 an, 30.6 ± 4.6 min. chez les enfants de 1–3 ans, et de 24.0 ± 2.7 min. chez les enfants de 3–10 ans. L'amorce au pancuronium accélérât le début d'action de façon significative dans tous les groupes d'âge avec 90 pour cent de dépression T₁ se produisant à 0.7 ± 0.1 min. (0–1 an), 0.9 ± 0.1 min. (1–3 ans), et 2.1 ± 0.6 min. (3–10 ans). Cependant, l'amorce retardait le rétablissement, particulièrement chez les nourrissons. A dix pour cent du rétablissement spontané à la suite du DTC avec amorce au pancuronium, les temps étaient de 71.0 ± 8.1 (0–1 an), 42.7 ± 3.8 (1–3 ans), et 29.3 ± 3.9 min. (3–10 ans). On conclut que le début d'action et le temps de rétablissement d'un blocage DTC sont reliés à l'âge de façon marquée, et cette relation peut être accentuée par un prétraitement avec du pancuronium.