The dose response effect of long-acting nondepolarizing neuromuscular blocking agents in children

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Cumulative dose-response curves were constructed for pancuronium, metocurine, d-tubocurarine and gallamine in 56 children anaesthetized with thiopentone, N₂O/O₂ and narcotic. The dose response curves of the four relaxants did not deviate significantly from parallelism. The effective dose causing 95 per cent depression of the twitch at 0.1 Hz was: pancuronium 0.08 mg·kg⁻¹, metocurine 0.34 mg·kg⁻¹, d-tubocurarine 0.6 mg·kg⁻¹, and gallamine 3.4 mg·kg⁻¹. Thus, pancuronium is 40 times more potent than gallamine, while metocurine and d-tubocurarine are seven and four times more potent than gallamine. The recovery of twitch height from 5–25 per cent of control for pancuronium (15.6 ± 1.7 min) was significantly faster ($p < 0.01$) than metocurine (27.3 ± 1.9 min), d-tubocurarine (32.2 ± 4.8 min), or gallamine (30 ± 3.3 min). Compared to studies in adults, the present data indicate that children have a tendency (statistically not significant) to require more relaxant and recover more quickly than adults.

Key words

ANAESTHESIA: paediatric; NEUROMUSCULAR RELAXANTS: pancuronium, metocurine, d-tubocurarine, gallamine.

An anaesthetic technique commonly employed in children is nitrous oxide/oxygen and a muscle relaxant supplemented with a narcotic. The most frequently used relaxants are d-tubocurarine and pancuronium. Metocurine is occasionally used and in rare instances gallamine has been used. The dose requirements of these drugs in children were originally assessed on the basis of clinical criteria^{1–3} and from dose response studies during halothane anaesthesia.^{4–6} Notably absent from the literature are data from controlled studies employing evoked (twitch or electromyogram) responses to determine dose response relationships of these relaxants in children during N₂O/O₂ narcotic anaesthesia. In addition, no data on the neuromuscular effects of gallamine in children are available.⁷

In the present study of children anaesthetized with thiopental, N₂O/O₂ and narcotic, we determined the relative potencies and the recovery times for these four nondepolarizing agents by the use of an incremental dose response technique.⁸

Methods

The protocol was approved by the Subcommittee on Human Studies, Committee on Research of the Massachusetts General Hospital.

Fifty-six children 1–15 years of age, ASA physical status Class I and II, requiring neuromuscular relaxation were studied. None of the children were overweight, had neuromuscular disease, received aminoglycoside antibiotics, or had electrolyte abnormalities. They were classified at random into four groups of 14 patients depending on the muscle relaxant used. Premedication consisted of rectal methohexital (25–30 mg·kg⁻¹) in

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TABLE I Muscle relaxant doses and corresponding depression of twitch response in children

<i>Muscle relaxant</i>	<i>Age (yrs)</i>	<i>Weight (kg)</i>	<i>Dose (mg·kg⁻¹)</i>	<i>Per cent depression of twitch response (mean ± SE)</i>
Pancuronium	6.7 ± 1.2	26.3 ± 4.1	0.02	3.8 ± 1.9
			0.04	50.8 ± 8.1
			0.06	83.1 ± 7.7
Metocurine	6.5 ± 1.1	28.1 ± 6.1	0.1	21.4 ± 6.1
			0.15	47.5 ± 7.3
			0.20	69.5 ± 6.5
			0.25	85.1 ± 4.7
d-Tubocurarine	6.6 ± 1.4	28.9 ± 6.1	0.2	23.6 ± 5.6
			0.3	53.3 ± 7.6
			0.4	71.6 ± 7.6
			0.5	88.8 ± 4.9
Gallamine	5.4 ± 1.0	21.3 ± 3.3	1	21.7 ± 4.9
			2	66.7 ± 6.4
			3	94.3 ± 2.1

children less than eight years of age; older children were given diazepam 0.2–0.4 mg·kg⁻¹ p.o. Anaesthesia was induced with thiopentone 5–7 mg·kg⁻¹ and maintained with nitrous oxide and oxygen in a 2:1 ratio. Additional incremental doses of thiopentone 2 mg·kg⁻¹ and meperidine 1 mg·kg⁻¹ or morphine 0.1 mg·kg⁻¹ were administered intravenously when clinically indicated.

The ulnar nerve was supramaximally stimulated at the wrist via surface electrodes. Single twitch stimuli were generated by a Grass S88 stimulator through a stimulus isolation unit (Grass SIU5) at a rate of 0.1 Hz. The duration of each stimulus was 0.2 msec. The evoked thumb adduction was transduced using a Grass FT03 force displacement transducer and recorded on a Grass Polygraph. After the establishment of a stable control twitch response, incremental doses of a given relaxant were used to achieve the desired degree of neuromuscular depression.

When the maximum neuromuscular depression (> 95 per cent) was achieved, an additional dose of thiopentone 2 mg·kg⁻¹ was administered and endotracheal intubation performed. The twitch was allowed to recover spontaneously to at least 25 per cent of the control value. Additional doses of the relaxant were thereafter administered when indicated.

Dose response curves were plotted on log-probit coordinates for each drug. The curves were tested for parallelism and potency was determined using

the method of Litchfield and Wilcoxon.⁹ Differences were considered significant when $p < 0.05$.

Recovery time was determined from injection of the last dose of relaxant to the return of twitch height to five and 25 per cent of control. The recovery times of the four relaxants were compared using analysis of variance.

At the end of the surgical procedure residual neuromuscular blockade was antagonized by intravenous administration of atropine 0.02 mg·kg⁻¹ and neostigmine 0.06 mg·kg⁻¹.

Results

The age and weight of the patients, the incremental doses of the four relaxants, and the per cent depression of the twitch after each dose are summarized in Table I. The time from injection of the first dose to the peak effect of the last incremental dose did not differ significantly from group to group, and averaged 10 ± 0.3 min. The dose response curves of pancuronium, metocurine, d-tubocurarine and gallamine did not deviate significantly from parallelism (Figure 1). The doses which produce 50 per cent and 95 per cent depression of the twitch (ED₅₀ and ED₉₅) were derived from the dose response curves, and are summarized in Table II. Of the four relaxants, pancuronium was the most potent. Metocurine was one fourth as potent as pancuronium, i.e., four times more metocurine than pancuronium was required to achieve the same degree of neuromuscular depression. d-Tubo-

TABLE II Effective doses for 50% and 95% twitch depression of children and adults anaesthetized with N_2O/O_2 relaxant

	Children		Adults	
	$ED_{50} mg \cdot kg^{-1}$	$ED_{95} mg \cdot kg^{-1}$	$ED_{50} mg \cdot kg^{-1}$	$ED_{95} mg \cdot kg^{-1}$
Pancuronium	0.04 (0.03–0.05)	0.081 (0.05–0.125)	0.36 (0.025–0.052)	0.070 (0.039–0.124)
Metocurine	0.15 (0.11–0.21)	0.34 (0.22–0.64)	0.13 (0.10–0.17)	0.28 (0.16–0.49)
d-Tubocurarine	0.28 (0.2–0.38)	0.6 (0.34–1.05)	0.26 (0.17–0.32)	0.51 (0.31–0.83)
Gallamine	1.5 (1.09–2.05)	3.4 (1.94–3.95)		

The adult data are from Savarese *et al.*¹² The 95% confidence limits are in parenthesis.

FIGURE 1 The dose response curves of pancuronium, metocurine, d-tubocurarine and gallamine in children anaesthetized with thiopental, N_2O/O_2 and narcotic, at a frequency of stimulation 0.1 Hz.

curarine had one-seventh the potency of pancuronium, whereas gallamine had one-fortieth the potency of pancuronium.

Table III summarizes the recovery times after administration of the relaxants. There was no significant difference in recovery times from 5–25 per cent of control between d-tubocurarine, metocurine and gallamine. However, this time was significantly longer after metocurine ($p < 0.01$), d-tubocurarine ($p < 0.02$), and gallamine ($p < 0.001$), than after pancuronium.

In all four groups, endotracheal intubation was always possible at a mean twitch depression 99.2 ± 0.2 per cent of control. Although the vocal cords were abducted for endotracheal intubation, in some patients there was a slight cough indicating diaphragmatic movement.

Discussion

Comparative analysis of the dose response data in children shows that pancuronium is the most potent of the four relaxants studied. The relative requirements for pancuronium, metocurine, d-tubocurarine and gallamine are 1:4:7:40 respectively. These compare favourably with those obtained from adult patients.¹⁰

The 5–25 per cent recovery time from pancuronium was significantly shorter than from d-tubocurarine, metocurine or gallamine; the 5–25 per cent recovery times for the latter three relaxants did not significantly differ from each other. In a previous comparative study in children¹¹ this faster

TABLE III 5–25% of recovery times of the twitch height after muscle relaxants in children and adults

Relaxants	Children min (mean $\pm$ SE)	Adults† min (mean $\pm$ SE)
Pancuronium	15.6 $\pm$ 1.7*	24.0 $\pm$ 2.1*
Metocurine	27.3 $\pm$ 1.9†	39.9 $\pm$ 4.4†
d-Tubocurarine	32.2 $\pm$ 4.8	37.6 $\pm$ 3.8
Gallamine	30 $\pm$ 3.3	

* $p < 0.01$ adults vs children.

† $p < 0.02$ adults vs children.

‡The adult data are from Ali HH, Savarese JF, personal communication.

recovery time from pancuronium was not demonstrated while in other studies^{5,6} such a difference was noted. Several adult studies have also shown this conflicting data.¹⁰ Our impression is that the recovery time is shorter with pancuronium than with other long-acting relaxants. Because the difference is relatively small, however, and the individual variation is large, and because most studies are performed in a limited number of patients, this tendency might appear in some instances but not in others.

When the present data were compared with adult data¹² performed with the same technique and at a similar rate of stimulation we found that the ED50 and ED95 are consistently higher in children than in adults (Table I); however, the difference is not statistically significant. Although the adult data was obtained from employing bolus doses of relaxants and we used incremental doses, differences in the method of administration of long acting relaxants have not been shown to cause a difference in the dose response curves.⁸ A higher dose requirement in infants and children can be explained by the higher vascular and extracellular volumes of these patients compared to adults.¹³ The same tendency has been seen by Fisher *et al.*¹⁴ in a pharmacokinetic study of d-tubocurarine in children. They found that the volume of the central compartment and the steady state distribution volume of d-tubocurarine is higher in children than in adults. Previously we observed that children anaesthetized with halothane N₂O/O₂ required the same amount of relaxant as adults anaesthetized with N₂O/O₂ narcotic.⁴⁻⁶ Considering the potentiating effect of halothane on relaxants,¹⁵ it appears that children are more resistant to non-depolarizing relaxants than adults.

The 5-25 per cent recovery times of children receiving pancuronium and metocurine were significantly faster than those of adults ($p < 0.01$ and $p < 0.02$ respectively). With d-tubocurarine the same tendency was present but this was not statistically significant, probably because of the large individual variation in this group of patients. The faster recovery from pancuronium and metocurine in children may be related to the increased metabolic clearance or excretion of drugs by children compared to adults.¹⁶

The onset and duration of action of d-tubocurarine, gallamine and metocurine are comparable

when equipotent doses of the drugs are used. However, in certain clinical circumstances, one agent may have an advantage over the others. For example, if the planned anaesthetic technique is N₂O/O₂ relaxant in a healthy child, then d-tubocurarine is a good choice since it tends to lower pulse rate and the blood pressure,² tachycardia and mild hypertension being a common problem of this technique. If a change in pulse and blood pressure will be detrimental to the patient, then metocurine may be a better choice. If tachycardia is desired, gallamine may be the desired agent because of its vagolytic properties. However, this agent has been popular with only a limited number of paediatric anaesthetists because of the suggestion that its vagolytic properties last longer than its neuromuscular effects.⁷ Pancuronium is slightly different from the other agents studied. Its duration of action is moderately shorter and the mild tachycardia and rise in blood pressure which is frequently seen after the drug is administered² may help to counteract the hypotensive effects of halothane.

In conclusion, we recommend that children receive 0.08 mg·kg⁻¹ pancuronium, 0.35 mg·kg⁻¹ metocurine, 0.6 mg·kg⁻¹ d-tubocurarine or 3.5 mg·kg⁻¹ gallamine to achieve satisfactory neuromuscular relaxation during N₂O/O₂ narcotic anaesthesia. These doses will produce 95 per cent depression of twitch, with recovery of the twitch height of 25 per cent of control 15 min after pancuronium and 30 minutes after metocurine, d-tubocurarine, and gallamine. Since clinical relaxation is frequently unsatisfactory when the twitch height is greater than 25 per cent of control,¹⁰ additional doses will be required 15 min after the initial dose of pancuronium and 30 min after the initial dose of the other relaxants if satisfactory surgical relaxation is to be maintained. Since there is a wide variation in the neuromuscular response, this should be followed by a twitch monitor. However, the dose which we recommend is for adequately anaesthetized children and the clinician may elect to use higher doses for endotracheal intubation during the induction of anaesthesia, as has been previously suggested.¹¹

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Résumé

On a établi les courbes de réponses à des doses croissantes de pancuronium, métocurine, d-tubocurarine et gallamine chez 56 enfants anesthésiés du thiopental, N_2O/O_2 et morphinique. Les courbes pour ces quatre relaxants ne se sont pas écartées du parallélisme. La dose effective capable de causer 95 pour cent de dépression de la contraction musculaire à une stimulation de 0.1 Hz était de: pancuronium $0.081 \text{ mg} \cdot \text{kg}^{-1}$, métocurine $0.34 \text{ mg} \cdot \text{kg}^{-1}$, d-tubocurarine $0.6 \text{ mg} \cdot \text{kg}^{-1}$, et la gallamine $3.4 \text{ mg} \cdot \text{kg}^{-1}$. Ainsi, le pancuronium s'avère être 40 fois plus puissant que la gallamine alors que la métocurine et le d-tubocurarine sont respectivement sept et quatre fois plus puissants que la gallamine. La récupération de l'amplitude de contraction à 25 pour cent de la valeur contrôle s'est effectuée pour le pancuronium et $15.6 \pm 1.7 \text{ min}$ ce qui était plus rapide ($p < 0.01$) que pour la métocurine ($27.3 \pm 1.9 \text{ min}$), le d-tubocurarine ($32.2 \pm 4.8 \text{ min}$) ou la gallamine ($30 \pm 3.3 \text{ min}$). Si on les compare à des études semblables chez l'adulte, ces données semblent indiquer que l'enfant nécessite des doses plus élevées de relaxants et qu'il récupère sa fonction musculaire plus rapidement. Cependant ces données ne permettent de voir qu'une tendance sans confirmation statistique.