William G. Doherty MB FFARCSI,
Patrick J. Breen MB FFARCSI,
Francois Donati MD PhD,
David R. Bevan MB MRCP FFARCS

Accelerated onset of pancuronium with divided doses

To determine the consequences of administering neuromuscular relaxants in divided doses, pancuronium was given either in a single dose, $0.07 \text{ mg}\cdot\text{kg}^{-1}$, or in an initial dose of $0.007 \text{ mg}\cdot\text{kg}^{-1}$ followed three minutes later with $0.063 \text{ mg}\cdot\text{kg}^{-1}$. When the drug was administered in divided dosage the onset time was reduced, the block was more intense and its duration of action was prolonged. It is suggested that such changes may be advantageous in the provision of rapid intense paralysis.

Key words

NEUROMUSCULAR RELAXANTS: pancuronium;
NEUROMUSCULAR BLOCKADE: onset.

One of the aims in the search for new neuromuscular blocking drugs (NMBDs) is a non-depolarizing relaxant with a rapid onset of action. The goal remains elusive despite the introduction of the shorter-acting NMBDs, atracurium and vecuronium, in the U.S.A. and Europe. In equipotent doses, these agents have a similar onset of action as d-tubocurarine and pancuronium.^{1,2}

Small doses of non-depolarizing relaxants modify the action of succinylcholine given later³ and, recently, it has been observed that such "precurarization" accelerates the onset of subsequent doses of the same drug. Reductions of approximately 25 per cent have been observed in man after divided doses of alcuronium⁴ or atracurium.⁵ Also, intubation can be performed more rapidly when a bolus dose of pancuronium is preceded by a small "priming" dose of metocurine.⁶

The present study was designed to determine

whether the onset of action and duration of effect of pancuronium were modified by its administration in divided doses.

Methods

With appropriate institutional approval, 52 patients undergoing elective general surgical and orthopaedic procedures were studied. All were ASA physical status class I or II and were not known to suffer from renal, hepatic or neuromuscular disease. None had electrolyte abnormalities nor was any taking medication known to interfere with neuromuscular transmission.

Premedication, with meperidine ($1 \text{ mg}\cdot\text{kg}^{-1}$), and atropine ($0.4\text{--}0.6 \text{ mg}$), was given 60–90 minutes before surgery. Anaesthesia was induced with thiopentone ($3\text{--}5 \text{ mg}\cdot\text{kg}^{-1}$), and maintained with nitrous oxide (70 per cent) in oxygen and halothane (0.5–1 per cent inspired). Patients were allowed to breathe spontaneously until the onset of neuromuscular blockade when ventilation was assisted. When full paralysis had been obtained the tracheas were intubated and their lungs were ventilated to maintain normocapnia,⁷ which was checked, in most patients, by measuring end-tidal CO_2 concentration (Hewlett Packard capnograph). Blood pressure and electrocardiogram were recorded.

Neuromuscular transmission was monitored according to the method of Ali *et al.*⁸ The ulnar nerve was stimulated supramaximally with subcutaneous electrodes at the elbow. Four square wave impulses of 0.2 ms duration and 2 Hz frequency were administered every 12 seconds using a Grass S48 stimulator and SIU5 isolation unit. The hand and forearm were immobilized in a splint. The force of contraction of the adductor pollicis muscle was measured with a Grass FT10 force displacement transducer and the response recorded on a Grass Polygraph pen and ink recorder. The skin temperature over the thumb was measured and maintained

From the Departments of Anaesthesia, Royal Victoria Hospital & McGill University, Montreal, Quebec.

Address correspondence to: Dr. D.R. Bevan, Department of Anaesthesia, Royal Victoria Hospital, 687 Pine Avenue West, Montreal, Quebec, H3A 1A1.

FIGURE 1 The development of neuromuscular block after pancuronium given in single ($n = 29$) or divided doses ($n = 23$).

above 32°C by covering the arm and hand with kidney pads.

After stabilization of the twitch recording, pancuronium was injected into a rapidly running intravenous infusion. The same total dose of pancuronium, $0.07\text{ mg}\cdot\text{kg}^{-1}$, was given to all patients. It was administered as a single bolus to patients in group 1, $n = 29$, and as an initial dose of $0.007\text{ mg}\cdot\text{kg}^{-1}$ followed three minutes later by the remainder in group 2, $n = 23$.

Depression of first twitch height (T1) was measured every 30 seconds after the large dose of pancuronium until maximum twitch depression was obtained. In addition, the train-of-four ratio (T4/T1) was determined by interpolation at ten per cent decrements of T1. Also, the time to ten per cent

recovery of T1 was measured. Mean values are presented with the standard error of the mean (SEM) as the index of dispersion. Unpaired Student's *t* tests were used for analysis of the data. The null hypothesis was rejected when $p < 0.05$.

Results

The patients in the two groups were comparable with respect to weight and sex distribution (Table I). However, the mean age was significantly greater in patients who received the single dose (group 1), ($p < 0.05$).

The onset of neuromuscular block was quicker in the group who received pancuronium in divided doses (Table II, Figure 1). This acceleration of onset was associated with a small, but significant increase in the duration of neuromuscular block, as assessed by time to ten per cent recovery of T1 (Table II).

The block was more intense in the group after divided doses in which all patients achieved 100 per cent paralysis. After single doses, 11 of 29 patients did not achieve 100 per cent block and the mean T1 block was 98.6 ± 0.5 per cent ($p < 0.01$).

There was no difference in the relationship of T1 and T4/T1 between the groups during the onset of neuromuscular blockade (Figure 2).

Discussion

The neuromuscular blockade achieved with divided doses of pancuronium has a more rapid onset, is more intense and lasts for longer than that after a single bolus of the same total dose. These differences could be detected at total doses within the clinical range and using a "priming" dose similar to that used for "precurarization" which produces minimal detectable weakness.³ These results are similar to previous reports using different non-depolarizing relaxants.⁴⁻⁶ The reason for the acceleration and intensification of the block is uncertain although several factors should be considered.

The mean age of the patients receiving the divided dose was lower than in those receiving the bolus dose. Although it has been observed that the onset of action of other non-depolarizing relaxants is more rapid in small children,⁹ it is unlikely that the delivery of relaxant to the neuromuscular junction in these two groups of middle-aged patients could be explained by differences in circulation time as has been proposed for infants. Also,

TABLE I Demographic data

		Age (yrs)	Weight (kg)
Group 1	Single dose 15 M, 14 F	59.4 ± 2.7	68.1 ± 3.0
Group 2	Divided dose 14 M, 9 F	44.9 ± 2.9	74.6 ± 3.1

FIGURE 2 The relationship between train-of-four ratio and first twitch tension during the onset of pancuronium induced neuromuscular blockade.

the effect of aging is to decrease the clearance and, hence, to prolong the duration of action of curare-like compounds.¹⁰ In the present study the duration was prolonged in group 2, consisting of younger patients, which suggests that the differences observed are related more to changes at the neuromuscular junction than in alterations of drug delivery or clearance.

The initial priming dose of pancuronium produced no alteration of twitch activity. Nevertheless, it may have reduced the margin of safety¹¹ of the neuromuscular junction so that a second larger dose produced rapid paralysis by occupying only a

small proportion of the remaining vacant receptors. The extent of the neuromuscular block at any time is dependent upon the concentration of pancuronium at the receptor and this can be estimated by adding a hypothetical "effect" compartment (biophase) to a simple two compartment pharmacokinetic model.¹² The pharmacokinetic data for pancuronium obtained by Hull *et al.*¹³ were applied to the conditions of the present study and calculations of predicted pancuronium concentration at the neuromuscular junction were performed on an IBM personal computer. These calculations demonstrated that the concentration of pancuronium sufficient to produce paralysis did occur earlier after divided dose administration. However, the differences were too small to account for more than about 20 per cent of the acceleration in onset which was observed. Furthermore, the pharmacokinetic model does not explain the deeper block and the prolonged duration of action observed with divided doses. Therefore, one must postulate that the preconditioning dose somehow alters the sensitivity of the neuromuscular junction.

It has been suggested that train-of-four fade represents pre-junctional effects whereas first twitch depression represents post-junctional activity of the NMBDs.¹⁴ Combinations of non-depolarizing relaxants which have different pre- and post-junctional actions are synergistic.¹⁵ In the present study the relationship between train-of-four fade and first twitch depression was examined in an attempt to detect an alteration of the pre-synaptic to post-synaptic balance. There were no differences between the groups. Thus, there was no evidence that pre-junctional activity was responsible for the different neuromuscular effects.

In the unparalyzed patient the production of an end-plate potential requires the activation of a polymeric acetylcholine receptor comprising five glycoprotein subunits and an ion channel. A positive co-operativity between this complex and a number of acetylcholine molecules, analogous to the interaction between haemoglobin and oxygen, has been suggested to explain the sigmoid dose-response relationship between acetylcholine and end-plate response.¹⁶ If a similar process occurs with the antagonists, then the small "pre-treatment" dose of pancuronium might have been sufficient for subsequent doses to produce a more marked and rapid effect.

TABLE II Onset and recovery of neuromuscular block

		Onset times (min)		Recovery times 10% Recovery of T1
		50% Block	90% Block	
Group 1	Single dose	1.9 ± 0.1	3.4 ± 0.4	45.9 ± 2.9
Group 2	Divided dose	1.2 ± 0.1	2.1 ± 0.1	57.1 ± 4.3
p		< 0.001	< 0.01	< 0.05

In clinical practice the ability to accelerate the onset of paralysis produced by non-depolarizing relaxants would be advantageous. If the accelerated depression of muscle twitch activity is accompanied by easier intubating conditions, then curare-like relaxants could be used in emergency situations when succinylcholine is contraindicated. The newer shorter acting relaxants also allow acceleration by increasing the dose without producing excessively prolonged paralysis so that the combination of "precurarization" and increased dosage may produce good conditions rapidly. Further investigation will be required to determine the best drug combinations and doses and the optimal precurarization intervals.

References

- 1 Ali HH, Savarese JJ, Basta SJ, Sunder N, Gionfriddo M, Lineberry C. Clinical pharmacology of atracurium: a new intermediate acting nondepolarizing relaxant. *Seminars in Anesthesia* 1981; 1: 57-62.
- 2 Durant NN. Norcuron, a new nondepolarizing neuromuscular blocking agent. *Seminars in Anesthesia* 1982; 1: 47-56.
- 3 Ferguson A, Bevan DR. Mixed neuromuscular block. The effect of precurarization. *Anaesthesia* 1981; 36: 661-6.
- 4 Hutton P, Morgan G, El-Hassan K, Black AMS. Speeding the onset of neuromuscular block by alcuronium. *Br J Anaesth* 1983; 55: 918P.
- 5 Gergis SD, Sokoll MD, Mehta M, Kemmotsu O, Rudd GD. Intubation conditions after atracurium and suxamethonium. *Br J Anaesth* 1983; 55: 83S-86S.
- 6 Nagashima H, Stoll M, Nguyen H, Duncalf D, Foldes F. Surgical relaxation with metocurarine-pancuronium combinations. *Anesth Analg* 1984; 63: 254.
- 7 Bain JA, Spoerel WE. Flow requirements for a modified Mapleson D system during controlled ventilation. *Can Anaesth Soc J* 1974; 20: 629-36.
- 8 Ali HH, Utting JE, Gray C. Stimulus frequency in the detection of neuromuscular block in humans. *Br J Anaesth* 1970; 42: 967-78.
- 9 Donati F, Bevan JC, Bevan DR. Neuro muscular blocking drugs in anaesthesia. *Can Anaesth Soc J* 1984; 31: 324-35.
- 10 Duvaldestin P, Saada J, Berger JL, D'Hollander A, Desmonts JM. Pharmacokinetics, pharmacodynamics, and dose-response relationships of pancuronium in control and elderly subjects. *Anesthesiology* 1982; 56: 36-40.
- 11 Paton WDM, Waud DR. The margin of safety of neuromuscular transmission. *J Physiol* 1967; 191: 59-90.
- 12 Sheiner LB, Stanski DR, Vozeh S, Miller RD, Ham J. Simultaneous modeling of pharmacokinetics and pharmacodynamics: application to d-tubocurarine. *Clin Pharm Ther* 1979; 25: 358-71.
- 13 Hull CJ, Van Beem HBH, McLeod K, Sibbald A, Watson MJ. A pharmacodynamic model for pancuronium. *Br J Anaesth* 1978; 50: 1113-23.
- 14 Bowman WC. Prejunctional and postjunctional cholinergic receptors at the neuromuscular junction. *Anesth Analg* 1980; 59: 935-43.
- 15 Lebowitz PW, Ramsey FM, Savarese JJ, Ali HH. Potentiation of neuromuscular blockade in man produced by combinations of pancuronium and metocurine or pancuronium and d-tubocurarine. *Anesth Analg* 1980; 59: 604-9.
- 16 Dreyer F. Acetylcholine receptor. *Br J Anaesth* 1982; 54: 115-30.

Résumé

Afin de déterminer les conséquences de l'administration d'un bloqueur neuro-musculaire en doses fractionnées, on a injecté du pancuronium de deux façons différentes: 1) en dose unique $0.07 \text{ mg} \cdot \text{kg}^{-1}$ et 2) en dose initiale $0.007 \text{ mg} \cdot \text{kg}^{-1}$ suivie après trois minutes de $0.063 \text{ mg} \cdot \text{kg}^{-1}$. A la suite de l'administration du médicament en doses fractionnées, l'action est plus rapide, le bloc est plus intense et sa durée plus prolongée. Ceci suggère qu'il y a lieu de prendre avantage de ces phénomènes quand on recherche une paralysie intense et rapide.