Recovery of neuromuscular function after atracurium and pancuronium maintenance of pancuronium block

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The study was undertaken to determine whether a neuromuscular blockade induced with pancuronium but maintained with atracurium was associated with a shorter time to complete recovery after administration of neostigmine than if the blockade was maintained with pancuronium alone. Anaesthesia consisted of thiopentone, N₂O/O₂/enflurane and fentanyl, and the neuromuscular blockade, induced by pancuronium 0.1 mg · kg⁻¹ was monitored by the force of contraction of adductor pollicis during major abdominal surgery lasting 2–5 hr. In 24 patients – Group 1 – atracurium 0.07 mg · kg⁻¹ was repeated when the first twitch of the train-of-four (TOF) returned to 25% of control (T₁/TC 25). In 28 patients – Group 2 – pancuronium 0.015 mg · kg⁻¹ was given at similar recovery of T₁/TC. At the end of surgery, neostigmine 0.07 mg · kg⁻¹ and glycopyrrolate 0.015 mg · kg⁻¹ were given to reverse the residual neuromuscular blockade which was indicated by a T₁/TC of less than 25% in all patients. The time from injection of the reversal drugs to a TOF ratio of 70% was similar in both groups (Group 1, 11.6 ± 7.6 min; Group 2, 10.1 ± 6 min; P = NS), but the recovery index was smaller in Group 2 (Group 1, 4 ± 2.6 min; Group 2, 2.61 ± 1.2 min; P < 0.05). Furthermore, there was no difference between groups in the duration of action of each redose. The study showed that when compared with pancuronium, equipotent doses of atracurium were not associated with (a) a shorter time to complete recovery from a neuromuscular blockade induced with pancuronium or (b) a shorter duration of action.

Key words

MONITORING: neuromuscular function;
NEUROMUSCULAR RELAXANTS: atracurium,
pancuronium.

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Cette étude vise à déterminer si la curarisation initiée par le pancuronium mais maintenue à l'atracurium présente une récupération complète plus rapide après l'administration de néostigmine que lorsque la curarisation est maintenue par le pancuronium seul. L'anesthésie est réalisée avec une association de thiopentone, de N₂O/O₂ avec enflurane et du fentanyl; le bloc neuromusculaire est induit par le pancuronium 0,1 mg · kg⁻¹. Le monitoring consiste à mesurer la force de contraction de l'adducteur du pouce pendant une chirurgie abdominale majeure d'une durée de 2 à 5 h. Chez 24 patients (groupe 1), de l'atracurium 0,07 mg · kg⁻¹ est répété quand le premier twitch du train-de-quatre (TOF) revient à 25% du contrôle (T₁/TC25). Chez 28 patients (groupe 2), du pancuronium 0,015 mg · kg⁻¹ est administré au moment où la récupération atteint le même degré. A la fin de la chirurgie, de la néostigmine 0,07 mg · kg⁻¹ et du glycopyrrolate 0,015 mg · kg⁻¹ sont administrés pour renverser le bloc neuromusculaire tel que démontré par un T₁/TC moindre que 25% chez tous les patients. Le moment de l'injection des antagonistes pour atteindre un TOF de 70% est le même pour les deux groupes (groupe 1, 11,6 ± 7,6 min; groupe 2, 10,1 ± 6 min; P = NS) mais l'index de récupération est moins élevé dans le groupe 2 (groupe 1, 4 ± 2,6 min; groupe 2, 2,61 ± 1,2 min; P < 0.05). On ne note pas non plus de différence entre la durée d'action de chaque dose répétée. Cette étude montre qu'on le compare au pancuronium, l'atracurium à doses équipotentes n'est pas associé a) à une diminution du temps requis pour une récupération complète du bloc induit au pancuronium ou b) à une durée d'action plus courte.

There have been numerous studies both in adults and children which have documented prolonged neuromuscular blockade that extended into the postanesthesia recovery period despite diligent intraoperative monitoring and seemingly adequate reversal.^{1–4} The incidence of impaired neuromuscular function upon arrival in the recovery room has been shown to be approximately 40% following the use of pancuronium but less than 5% after

vecuronium or atracurium suggesting the greater safety of these intermediate-acting muscle relaxants.^{2,3}

Both vecuronium and atracurium have been used to prolong a neuromuscular blockade induced by a long-acting muscle relaxant in situations where the shorter duration of action of the former drugs might prove to be advantageous, e.g., during a peritoneal closure.⁵⁻⁹ This has resulted in reduced dose requirements and prolongation of action of the intermediate-acting drugs such that the drug first administered appeared to play a dominant role in influencing the duration of action of the subsequent neuromuscular blocker.⁶⁻⁹ Aps and Inglis have suggested that supplementary doses of atracurium 5–10 mg in an adult patient originally paralyzed with pancuronium provide enhanced neuromuscular blockade without the fear of inadequate reversal at the end of surgery.⁵ However, the time to complete recovery after sequential administration of a long- and intermediate-acting nondepolarizing muscle relaxant has not been investigated. The hypothesis of the present study was that a neuromuscular blockade induced with pancuronium but maintained by atracurium is associated with a shorter time to complete recovery after neostigmine than if the blockade is maintained by pancuronium alone. The interaction between the two drugs was subsequently examined.

Methods

With approval of the Institutional Review Board and informed consent, 42 adult patients without hepatic, renal or neuromuscular disease were studied during major colorectal or gynaecological surgery. Each patient received premedication with midazolam 1–3 mg *iv* before surgery, and anaesthesia was induced with thiopentone 3–5 mg · kg⁻¹ and fentanyl 100–200 µg. A control recording of neuromuscular transmission was obtained and pancuronium 0.1 mg · kg⁻¹ was subsequently given. Neuromuscular function was monitored using a Myograph 2000® (Biometer International A/S, Odense, Denmark). The force of contraction of the adductor pollicis muscle was recorded after stimulation of the ulnar nerve at the wrist by four supramaximal square wave impulses of 200 µsec duration delivered at 2 Hz every 12 sec through surface electrodes. The outstretched arm was enveloped in a cotton blanket and plastic bag in an attempt to minimize heat loss. After ablation of the twitch response, the patient's trachea was intubated and anaesthesia maintained with nitrous oxide 60% in oxygen, enflurane to a maximum end tidal concentration of 1%, and additional fentanyl as required.

Patients were randomly allocated to two groups and received either atracurium 0.07 mg · kg⁻¹ or pancuronium 0.015 mg · kg⁻¹ to maintain muscle relaxation

whenever the first twitch (T₁) of the train-of-four (TOF) recovered to 25% of control (T₁/TC 25). Enflurane was discontinued at the end of surgery at which time neostigmine 0.07 mg · kg⁻¹ and glycopyrrolate 0.015 mg · kg⁻¹ were given to reverse the residual neuromuscular block which was indicated by T₁/TC of less than 25% in all patients. Nitrous oxide was discontinued at a TOF ratio of 70% and the patient's trachea was extubated upon restoration of respiration. The patient was subsequently transferred to the post-anaesthesia care unit.

The following data were recorded:

- 1 The time to maximum twitch depression after the initial dose of pancuronium.
- 2 The clinical duration of the initial dose of pancuronium – time from injection to T₁/TC 25 recovery.
- 3 The number of maintenance doses – “redose” – of muscle relaxant.
- 4 The duration of action of each redose – the duration of a complete cycle from one T₁/TC 25 to the T₁/TC 25 immediately following.
- 5 The T₁/TC at which the reversal drugs were given.
- 6 The recovery index – the time from T₁/TC 25 to T₁/TC 75.
- 7 The time taken to reach a TOF ratio of 70% (T₄/T₁ 70) from the injection of the reversal drugs.

Demographic and descriptive data from the two groups were compared using Student's *t* test for continuous variables and chi-square analysis for categorical variables. Further analyses of the relationships between the neuromuscular transmission data obtained from the two groups were performed using analysis of covariance and analysis of variance. Data were considered to be significant at a *P* value of less than 0.05.

Results

Of the 52 patients entered into the study, 24 were randomized to receive atracurium to maintain relaxation – Group 1 – and 28 to receive pancuronium – Group 2. The demographic data for the two groups and the duration of surgery are presented in Table I together with the time to maximum twitch depression and clinical duration of the initial dose of pancuronium. Patients in Group 2 were taller than those in Group 1 but there were no other significant differences between the groups.

Data from 20 patients in each group who had received one to four redoses of either atracurium or pancuronium were further analyzed to determine whether the use of atracurium was associated with a shorter time to complete recovery after administration of the reversal drugs (Table II). The mean number of redoses in Group 1 was 2.2 and in Group 2 was 2.4. Patients in both groups were given neostigmine and glycopyrrolate at a similar mean recovery of T₁/TC but the mean time to T₄/T₁ 70, which

TABLE I Demographic data, time to maximum twitch depression and clinical duration of pancuronium 0.1 mg · kg⁻¹

	Group 1	Group 2	P value
Age (yr)	43 ± 14.6	41.7 ± 15.3	0.75
Height (cm)	165.4 ± 9.9	172.2 ± 9.0	0.01*
Weight (kg)	68.4 ± 15.8	72.8 ± 13.6	0.29
BSA (m ²)	1.75 ± 0.22	1.85 ± 0.21	0.09
Sex (M/F)	5/19	11/17	0.15
Duration of surgery (hr)	3.4 ± 0.8	3.9 ± 1.1	0.11
Time to maximum twitch depression (sec)	185.3 ± 72.3	197.8 ± 85.9	0.58
Clinical duration (min) of pancuronium 0.1 mg · kg ⁻¹	114.8 ± 30.8	108.9 ± 39.6	0.58

Data are mean ± SD; P value between groups.

*Significant ($P < 0.05$).

TABLE II Neuromuscular transmission data at recovery

	Group 1	Group 2	P value
T ₁ /TC when reversal drugs given	13.5 ± 10.6	14.4 ± 8.9	NS
Recovery index (min)	4 ± 2.6	2.6 ± 1.2	0.04*
Time to T ₄ /T ₁ 70 (min)	11.6 ± 7.6	10.1 ± 6	NS

Data are mean ± SD; P value between groups.

* $P < 0.05$

was between 10 and 12 min, did not differ between groups. The recovery index was, however, smaller in Group 2. Whereas the mean recovery of T₁/TC at which the reversal drugs were given was similar in both groups, the range of T₁/TC at which reversal was attempted varied between 0% and 25%. There was, however, no difference between groups in the inverse relationship of time to T₄/T₁ 70 and T₁/TC at reversal, which was significant in Group 1 (Figure; Group 1, $r = -0.585$, $P < 0.01$).

A sufficient number of patients received at least three redoses to permit a comparative analysis of the duration of action of successive redoses (Table III). No difference was detected between the groups in the duration of action of the redoses when the results were analyzed by Student's *t* test.

Discussion

The study was designed to determine whether atracurium, given to maintain a neuromuscular blockade induced with pancuronium, is associated with a shorter time to complete recovery. The results suggest that this is not the case and that a maintenance dose of atracurium confers relaxation and recovery characteristics which are indistinguishable from those obtained from an equipotent dose of pancuronium for surgery lasting up to five hours.

The explanation for this observation may lie in the concept of "margin of safety" described by Paton and

FIGURE Relationship between T₁/TC at which the reversal drugs were given and the time to T₄/T₁ 70. Group 1 ●, $r = -0.585$, $P = 0.067$; Group 2 ○, $r = -0.347$, $P = 0.1341$.

TABLE III Neuromuscular transmission data during maintenance of anaesthesia

	Group 1	Group 2	P value
Clinical duration of redose (min)			
1st redose	48.7 ± 16.5 (12)	53.8 ± 19.5 (19)	NS
2nd redose	41.4 ± 9 (6)	42.9 ± 10.7 (11)	NS
3rd redose	30.5 ± 12.2 (6)	36.1 ± 16 (5)	NS

Data are mean ± SD; P value between groups.
(Number of patients).

Waud and invoked by others in discussion of the sequential administration of long- and intermediate-acting muscle relaxants.^{6,7,9,10} Approximately 75% of postjunctional receptors need to be occupied by muscle relaxant before diminution of twitch height can be observed. Administration of additional relaxant at 25% of recovery of T₁ implies receptor occupancy of approximately 94% and consequently the characteristics of the blockade and subsequent recovery will be those of the muscle relaxant already occupying the majority of receptors. For example, when vecuronium is given after pancuronium, the recovery characteristics are those of pancuronium.⁶ In addition, pretreatment with pancuronium 0.007 mg · kg⁻¹ has been shown to potentiate the action of a subsequent bolus of atracurium 0.1 mg · kg⁻¹.¹¹ Our results together with those of Gerber *et al.* reinforce the observations of others that structurally dissimilar substances are likely to produce a potentiating response reflecting their action at pre- and postsynaptic sites at the neuromuscular junction.^{8,11,12}

The present study is unique inasmuch as we have demonstrated that, in the peculiar circumstances of sequential administration of different muscle relaxants, the characteristics of the initial blockade extend not only to the duration of action, but also to the time to complete recovery. Investigators from several centres have documented, both in adults and children, prolonged neuromuscular blockade despite the administration of reversal drugs that has extended well into the postanesthesia recovery period.¹⁻⁴ This protracted impairment of neuromuscular function has been observed more commonly after blockade induced by long-acting muscle relaxants whereas atracurium was associated with a more complete recovery.¹⁻³ The hypothesis of the present study was that atracurium would confer more favourable recovery characteristics than if the blockade was continued with repeated pancuronium administration. However, there was no difference between the groups, not only in the depth and duration of relaxation, but also in the time from injection of the reversal drugs to T_4/T_1 70, which suggests that, in contrast to the proposal by Aps and Inglis,⁵ substituting an intermediate-acting muscle relaxant for a long-acting one confers no benefit.

Considerable variation exists in the literature as to the comparative potency of atracurium and pancuronium depending on whether the dose-response curves were generated from bolus or cumulative administration of the drugs, the age of the patients, and the simultaneous administration of volatile anaesthesia. We felt, however, that the ED_{95} obtained from single dose injections of muscle relaxant during balanced anaesthesia as described by Donlon *et al.* for pancuronium – $0.053 \text{ mg} \cdot \text{kg}^{-1}$, and Sokoll *et al.* for atracurium – $0.27 \text{ mg} \cdot \text{kg}^{-1}$, provided the most accurate assessment of potency.^{13,14} We consequently chose an atracurium:pancuronium potency ratio of 5:1.

The study was unable to demonstrate cumulation with repeated doses of muscle relaxant in either group. Cumulation does not occur with atracurium, which has a very rapid distribution half-life, and is unlikely to occur when spontaneous recovery occurs after the distribution phase following a large initial dose of pancuronium.¹⁵⁻¹⁸

The study was undertaken during surgery lasting between 2–5 hr. It is possible that with surgery of increasing duration the initial muscle relaxant will be removed progressively from the neuromuscular end plate and be replaced by the drug used to maintain muscle relaxation. One might expect in such circumstances that, as the initial drug is eliminated, the characteristics of the clinical duration and the recovery will become typical of the maintenance drug. Our data support such a conclusion with respect to Group 1. Within group analysis of the duration of action of up to three redoses of atra-

curium, shows a trend towards a shorter duration with successive redoses (Table III). Kay *et al.* and Middleton *et al.* observed a similar decrease in the clinical duration of each redose when small increments of atracurium or vecuronium were given repeatedly after recovery to T_1/TC 10 from a neuromuscular blockade induced by pancuronium or *d*-tubocurarine.^{7,9} In their similar publications, the same team of investigators reported that the intensity and duration of the neuromuscular blockade following the first increment was always greater than that of subsequent increments, and ascribed a pharmacokinetic explanation to these observations based on the exponential decrease of the long-acting muscle relaxant at the neuromuscular junction and its replacement by the intermediate-acting drug. They further reported that the clinical duration of atracurium and vecuronium became constant after the third increment, and commented that despite this, a considerable proportion of receptors must still have been occupied by the long-acting muscle relaxant for such a small dose of the intermediate-acting drug to have produced a neuromuscular blockade in excess of 90%.

What is harder to explain is the decreasing duration of action of successive redoses of pancuronium in Group 2. It is difficult to understand why repeated doses of the same muscle relaxant given at the same index of recovery should not result in a similar duration of action. It is possible, however, that the fluid requirements and blood loss of our patients altered the distribution and elimination of pancuronium. Agoston *et al.* have suggested that the time to recovery after pancuronium is influenced not only by the drug-receptor dissociation rate constant, but also that it is directly related to the rate of change of the plasma concentration of the drug.¹⁹ These workers demonstrated that when pancuronium is administered into the isolated arm, or systemically by bolus intravenous injection or continuous infusion, the recovery index increased from 10 min to 23 min and 46 min respectively. The recovery index in our patients in Group 2 was smaller than that in Group 1, suggesting a lower plasma concentration for a given degree of block, and supporting a pharmacokinetic explanation for a shorter duration of action of pancuronium with repeated doses.

In summary, we investigated the time to complete recovery after reversal from a neuromuscular blockade induced with pancuronium but maintained with atracurium during surgery lasting up to five hours. The time to complete recovery was no shorter than if the blockade was maintained with pancuronium alone.

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