

Relationship of the Serum Concentration of Pancuronium to Its Neuromuscular Activity in Man

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The relationship between the time course of the decay of serum concentrations of pancuronium and its neuromuscular blocking effect has been investigated after the intravenous administration of 50, 80 and 100 $\mu\text{g}/\text{kg}$ doses to anesthetized patients. Following administration of these doses, maximal neuromuscular block in the adductor pollicis muscle developed in about 7, 2.5, and 2 minutes and lasted about 20, 40, and 60 minutes, respectively. The times from start of recovery to return of twitch tension to 25, 50, and 75 per cent of control were similar in the different dosage groups, but occurred progressively later with increasing doses. At times of 25, 50, and 75 per cent recovery mean serum concentrations (pooled values) were 0.13 ± 0.01 , 0.11 ± 0.01 , and 0.10 ± 0.01 $\mu\text{g}/\text{ml}$ ($\pm\text{SEM}$), respectively. Neuromuscular transmission to the adductor pollicis muscle started to recover at a mean serum pancuronium concentration of 0.21 ± 0.03 $\mu\text{g}/\text{ml}$. The data obtained in this study are in agreement with the experimental and clinical findings of similar studies with *d*-tubocurarine, and indicate that there is a correlation between the serum concentrations of muscle relaxants and the intensity of their neuromuscular activities. (Key words: Neuromuscular relaxants, pancuronium, serum concentrations; Dissociation constant.)

IN SPITE OF the widespread use of muscle relaxants in clinical anesthesia, very little is known about the relationship between their blood levels and their neuromuscular effects in man. It has generally been assumed that the extents of paralysis produced by neuromuscular blocking drugs are determined by their concentrations at their receptor sites, and that these concentrations depend upon the plasma levels of these compounds. This assumption, which had been questioned by Feldman and Tyrrell,¹ was confirmed experimentally by Matteo *et al.*,² who demonstrated a significant positive correlation between serum concentration of *d*-tubocurarine and the intensity of its neuromuscular blockade in man. Waud,³

analyzing the data of Matteo and colleagues,² pointed out that their observations made in man are in good agreement with the experimental data describing the margin of safety of neuromuscular transmission reported by Paton and Waud.⁴ These observations support the original assumption that after equilibration of the receptor sites with the central compartment any factor capable of altering the blood level of a relaxant drug will subsequently influence its neuromuscular activity. The present study was designed to investigate the relationship between courses of the neuromuscular effect and serum concentrations of pancuronium bromide in anesthetized patients, particularly during recovery from paralysis.

Methods

Nine patients, five women and four men, between 15 and 61 years of age, undergoing vascular surgery of the lower extremities, were included in this study. All patients were premedicated with nicomorphine (nicotinic acid ester of morphine), 5 mg, droperidol, 5 mg, and atropine, 0.25 mg, 45 to 60 minutes before induction of anesthesia. Anesthesia was induced with thiopental, 100–150 mg, and gamma-hydroxybutyric acid, 60 mg/kg (but not more than 4.0 g). Endotracheal intubation was performed after topical anesthesia of the larynx with lidocaine, 4 per cent. Anesthesia was maintained with nitrous oxide–oxygen, 4:2 l/min, and repeated small doses of fentanyl lactate and droperidol.

The right forearm and hand of each patient were secured firmly to an armboard and a "boomerang" force-displacement transducer⁵ was attached to the hand. The ulnar nerve was stimulated¶ at the wrist with a needle electrode with square-wave, supra-maximal stimuli of 0.2 msec duration at the rate of 0.2 Hz. The isometric twitch tension of the indirectly stimulated adductor pollicis muscle was continuously recorded.** The control twitch tension of the adductor pollicis muscle was recorded for at least 10 minutes. After it became constant, three groups each consisting of three patients received intravenously in 30 seconds pancuronium bromide 50 (Group I), 80 (Group II), or 100 (Group III) $\mu\text{g}/\text{kg}$. Twitch tension was continuously recorded in all subjects

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¶ Grass S44 stimulator SIU 5 isolation unit.

** Brush Clevite recorder.

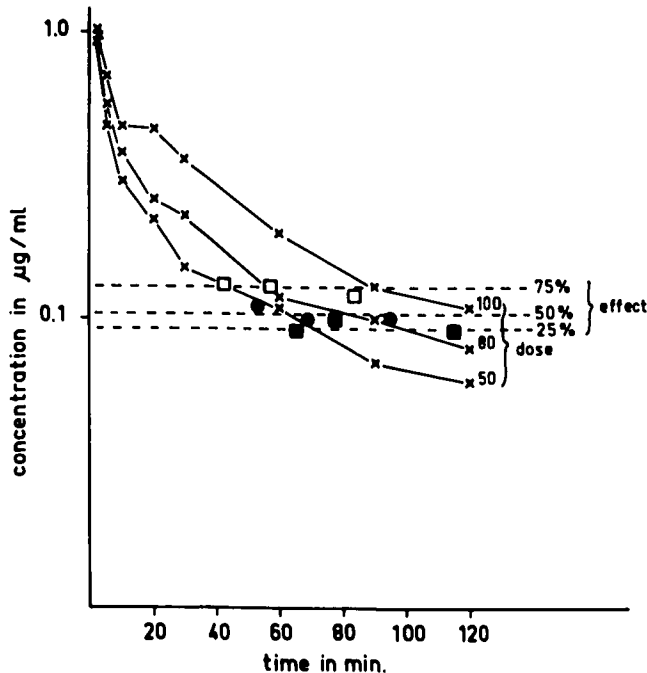


FIG. 1. Time courses of decay of serum concentrations of pancuronium after intravenous administration of 50, 80, and 100 $\mu\text{g}/\text{kg}$ doses to anesthetized subjects. The horizontal broken lines indicate the serum levels found in the presence of 75 (\square), 50 (\bullet), and 25 (\blacksquare) per cent neuromuscular block.

until the end of anesthesia or until the twitch tension returned to 75 per cent of control, whichever occurred later.

Time of development and duration of maximal effect of pancuronium and times at which twitch tension returned to 25, 50, and 75 per cent of the control value were recorded. Duration of maximum effect was defined as the time during which the twitch contractions were 10 per cent of the control value.

Blood samples were obtained 2, 5, 10, 20, 30, 60, 80, and 120 minutes after the start of pancuronium administration and also when twitch tension had returned to 25, 50, and 75 per cent of the control value. The concentrations of pancuronium were determined by an analytic method described elsewhere.⁶ Since the fluorimetric assay for the estimation of pancuronium does not discriminate between the unchanged drug and its bisquaternary metabolites, the total concentrations of these bisquaternary ammonium compounds were determined throughout.

In calculating the K_b it was assumed that at the start of recovery 91 per cent of the cholinergic receptors of the postjunctional membrane were occupied by the blocking drug.⁴ It was also assumed that 91 per cent receptor occupancy coincided with the end of maximum effect. After correcting the serum

concentration values for protein binding of the drug, reported to be 20 per cent for pancuronium in human plasma,⁷ the K_b and the proportions of the receptors occupied were calculated by substituting the free serum pancuronium concentrations into the equation used by Waud.³

$$Y = \frac{[\text{pancuronium}]}{[\text{pancuronium}] + K_b} \quad (1)$$

Where Y = receptor occupancy at the start of recovery; $[\text{pancuronium}]$ = molar concentration of pancuronium; K_b = dissociation constant of pancuronium/receptor complex.

We used the Wilcoxon's matched-pairs signed-ranks test for comparing the means (pooled values) of serum pancuronium concentrations measured at different degrees of recovery of neuromuscular block.

Results

The maximal effects (90 per cent or more block) from pancuronium 50, 80, and 100 $\mu\text{g}/\text{kg}$ occurred in 7, 2.5, and 2 minutes, and the durations of the maximal effects averaged about 20, 40, and 60 minutes, in Groups I, II and III, respectively.

Recovery of twitch to 25, 50, and 75 per cent of control occurred progressively later with increasing doses of pancuronium (fig. 1). The times necessary for recovery of twitch tensions from 25 to 75 per cent of control, however, were approximately the same in the three groups. The serum concentrations of pancuronium at the times when twitch tensions returned to 25, 50 and 75 per cent of control were very similar in the three groups. Neuromuscular transmission of the adductor pollicis muscle started to recover at a mean (pooled values) serum pancuronium concentration of $0.21 \pm 0.03 \mu\text{g}/\text{ml}$, which after correction for protein binding appeared to be $0.17 \mu\text{g}/\text{ml} = 231 \text{ nM}$. Because of the small number of patients, no statistically significant difference could be demonstrated between the serum concentrations of pancuronium at the time of recovery within each group. When, however, the serum concentrations measured at the times of recovery for each group were pooled, the mean value at 25 per cent recovery (0.13 ± 0.01) was significantly greater ($P < 0.01$) than the mean values at 50 (0.11 ± 0.01) and 75 per cent (0.10 ± 0.01) recovery, indicating the correlation between serum pancuronium concentrations and neuromuscular blockade. The difference between the serum concentrations obtained at 50 and 75 per cent recovery was not statistically significant.

From equation 1, the calculated K_b value for pan-

curonium is 22.9 (table 1). Using this value, receptor occupancies at the times when twitch contractions were 25, 50, and 75 per cent of control were 85, 84, and 83 per cent, respectively.

Discussion

The magnitudes of neuromuscular blocking effects of the various doses were similar to those observed by other investigators⁸⁻¹⁰ with identical doses of pancuronium. In all the above-cited clinical studies, wide individual variations were seen, especially after larger doses of pancuronium. Similar individual variations were seen after tubocurarine, 0.3 and 0.6 mg/kg, in the studies of Matteo.² Luñd and Stovner¹⁰ found that on a weight basis the potency of pancuronium compared with *d*-tubocurarine increased with increasing doses of the former compound, but at the level of 50 per cent block pancuronium was found to be four times more potent than *d*-tubocurarine. In the study with *d*-tubocurarine by Matteo *et al.*, the serum concentrations at the time twitch contraction started to recover were not influenced by anesthetics,² nor were they dose-dependent, although they occurred progressively later with increasing doses. At the start of recovery the serum concentration of *d*-tubocurarine was reported to be 0.70 $\mu\text{g/ml}$ by Matteo *et al.*² Correcting this value for protein binding, which has been found to be 44 per cent,¹¹ and substituting this corrected value into equation 1 at an assumed receptor occupancy of 0.91, a calculated K_b value of 63.4 nM is obtained (table 1). This value and the K_b value for pancuronium, 22.9 nM, are similar in relationship to those measured directly from the lumbrical muscle of the guinea pig, which were 25.1 and 110.0 nM for pancuronium and *d*-tubocurarine, respectively.¹²

The limited number of experiments in this study and the inherent variability in the relationship between indirect twitch response and both concentration of antagonist and receptor occupancy do not allow us to determine an accurate K_b (dissociation constant of drug/receptor complex) for pancuronium. Nevertheless, we attempted to calculate K_b using the measured serum pancuronium concentrations, as it was interesting to see whether the K_b values from clinical studies obtained in this way would approach those measured directly from the lumbrical muscle of the guinea pig¹² and whether receptor occupancy, which can be calculated from the K_b values and serum concentrations of the antagonist, would be similar in relation to experimental observations elsewhere. From the calculated K_b values, receptor occupancies

TABLE 1. Relationship of Relative Potencies, Corrected Serum Concentrations, and Calculated and Measured K_b 's of Pancuronium and *d*-Tubocurarine

	Pancuronium	<i>d</i> -Tubocurarine	Approx. Ratio
Doses producing* 50 per cent block (mg/kg)	0.014	0.055	1:4
Free serum concentration ($\mu\text{g/ml}$) at start of recovery	0.17‡	0.40†	1:2
Free serum concentration ($\mu\text{g/ml}$) at 50 per cent block	0.09‡	0.27†	1:3
Measured K_b (nM)	25.1§	110.0§	1:4
Calculated K_b (nM)	22.9‡	63.4†	1:3
Receptor occupancy at 50 per cent block	0.84‡	0.87†	1:1

* In man (Lund and Stovner, 1970¹⁰).

† In man (Matteo *et al.*, 1974²).

‡ In man, present study.

§ In guinea pig (Waud *et al.*, 1973¹²).

at 50 per cent block after pancuronium and *d*-tubocurarine were 0.84 and 0.87, respectively. It is interesting that substitution of the mean *d*-tubocurarine concentrations corrected for protein binding obtained at the times of 25 and 75 per cent recovery from figure 2 of Matteo *et al.*² into equation 1 gives values of receptor occupancy of 0.89 and 0.82, respectively. These values are very close to the receptor occupancy values for pancuronium, 0.85 and 0.83, found in our study.

The serum pancuronium concentrations at which neuromuscular transmission started to recover in the present study are practically identical to those reported by Somogyi and associates,¹³ *i.e.*, $0.21 \pm 0.03 \mu\text{g/ml}$ ($\pm\text{SEM}$) and $0.218 \pm 0.069 \mu\text{g/ml}$ ($\pm\text{SD}$), respectively. The analytic assay used in these studies measures a mixture of pancuronium and metabolites, which could have influenced the results. The pharmacologic effects of the metabolites, however, can be neglected, since only one metabolite, *i.e.*, the 3-OH compound, is known to occur in man¹⁴; it appeared in small quantities a few hours after administration of the drug. Human volunteer and animal (cat and monkey) studies revealed that the 3-OH compound is about three to six times less potent than pancuronium, while the other two metabolites, 17-OH and 3,17-OH pancuronium, are 80 and 130 times less potent, respectively (unpublished data). All three metabolites had half-lives similar to that of pancuronium in the animal species investigated.

The findings of Matteo *et al.*,² Somogyi *et al.*,¹³ and the present study support the assumption that there is a correlation between plasma concentrations and magnitudes of neuromuscular block under condi-

tions prevailing in these studies. The validity of the above assumption is further strengthened by the agreement between our calculated K_p values and those directly measured by Waud *et al.*¹²

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