Studies of Pancuronium in Conscious and Anesthetized Man

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Administration of 22 μg/kg pancuronium to 11 conscious subjects decreased grip strength to 23.6 ± 5.4 per cent of control within 5 minutes. Grip strength returned to 86.0 ± 4.7 per cent of control in 25 minutes and vital capacity to 97.8 ± 2.0 per cent of control in 15 minutes. Exercising at a fast rate during partial block caused rapid fatigue. Administration of edrophonium or neostigmine at the height of the block caused rapid but incomplete return of grip strength. In 11 lightly anesthetized subjects 40 μg/kg pancuronium decreased the twitch tension of the indirectly stimulated adductor pollicis muscle to 11.5 ± 2.8 per cent and tidal volume to 71.4 ± 7.4 per cent of control by 5 minutes. Tidal volume recovered by 15 minutes, but twitch tension was only 66.9 ± 6.0 per cent of control at 60 minutes. The administration of edrophonium or neostigmine at this time had little or no effect on twitch tension. Tetanic stimulation applied 10 to 15 minutes later showed well-maintained tetanus, which was followed by significant posttetanic facilitation and maintenance of the twitch tension above the pre-drug control level for the remainder of the 10- to 15-minute observation period. Moderate elevation of pulse rate was the only significant circulatory change. (Key words: Pancuronium bromide; Grip strength; Vital capacity; Posttetanic facilitation.)

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Pancuronium dibromide (Pavulon) is a bisquaternary nondepolarizing neuromuscular blocking agent (fig. 1). On a weight basis, it is about five times more potent than d-tubocurarine. In man pancuronium-induced neuromuscular block is not accompanied by unwanted side-effects (e.g., significant changes in pulse rate and blood pressure, clinical evidence of histamine release) and is readily reversible by neostigmine. The present study was undertaken to obtain information about the pharmacologic effects of pancuronium in the absence of surgical intervention.

Methods

Eleven conscious and 11 anesthetized subjects were studied. Two of the subjects were included in both conscious and anesthetized groups.

Conscious Subjects

Of the 11 subjects, seven were men and four were women. Ages ranged from 29 to 58 years (mean SE = ± 35.0 ± 2.5). Nonfasting, unmedicated subjects were studied in the supine position. Dextrose, 5 per cent in water, was administered at the rate of 15 to 20 drops/min throughout the experiment. All drugs were injected intravenously.

Control measurements of pulse rate, systolic and diastolic blood pressure, vital capacity, and grip strength were recorded and ergographic tracings were obtained before and 3, 6, 10, 15, 20 and 25 minutes after administration of pancuronium. Blood pressure was measured with a sphygmomanometer, vital capacity with a Wright ventilation meter, and grip strength with a dynamometer (C. H. Stoelting and Co., Chicago, Ill., Model No. 19117). Ergographic tracings were made with an ergograph (F. I. Christensen, physiological Apparatus, Watertown, Mass.).

At 0 minutes subjects were given, in 30
seconds, 22 μg/kg pancuronium, corrected for body weight by the formula \( D = D_i \frac{B}{2 + 35} \), in which \( D \) is dose injected, \( D_i \) is 22 μg/kg, and \( B \) is body weight in kg. Two experiments were done on each subject. On the first occasion the subjects squeezed the bulb of the ergograph, with maximal effort, for a minute, at the rate of 6/min (slow exercise). Grip strength was measured before, during, and after exercise. On the second occasion, 7 to 20 days later, the rate of exercise was 60/min. Grip strength was measured before and immediately after exercise 4, 7, 11, 16, 21 and 26 minutes after pancuronium. In every other respect the experiments were identical. In a third set of experiments four subjects squeezed the bulb of the ergograph at the rate of 6/min throughout the 16- to 20-minute observation period. At the height of the pancuronium block two of these subjects received 0.2 mg/kg edrophonium and the other two 0.05 mg/kg neostigmine, together with 0.4 mg atropine. No other experiments were done on these four subjects.

**ANESTHETIZED SUBJECTS**

Of the 11 subjects, ten were men and one was a woman. Ages ranged from 17 to 38 (29.1 ± 1.7) years.

The subjects were given 1.5 mg/kg diphenhydramine, 1.5 mg/kg meperidine, and 0.006 mg/kg atropine intramuscularly about 60 minutes before the start of anesthesia. The mouth and pharynx were topically anesthetized with 1 per cent tetracaine. Infusion of 5 per cent dextrose in water was started and a radial artery was cannulated. A blood pressure cuff and a stethoscope were attached to the other arm. Anesthesia was induced with 2.5 per cent thiopental administered in 25-mg increments every 15 seconds until disappearance of the lid reflex. At this time an oropharyngeal airway was inserted and administration of nitrous oxide-oxygen (2-1 liters/min) was started through a tight-fitting face mask. When a subject showed signs of awakening, 25-mg to 50-mg increments of thiopental were injected.

After induction of anesthesia, the hand and forearm were firmly fixed, needle electrodes were secured close to the ulnar nerve at the wrist, and the proximal phalanx of the thumb was attached to a spring-loaded Grass Model FT 10C force-displacement transducer (sensitivity range 500 mg to 10 kg). The isometric tension of the adductor pollicis muscle elicited by supramaximal (50 to 80 mV) square-wave

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**Fig. 1.** The structural formula of pancuronium dibromide (mol wt 73).

**Fig. 2.** The effect of 22 μg/kg pancuronium, injected at 0 min, on vital capacity and grip strength of conscious subjects. The means and two standard errors are shown for each period of testing.
stimuli of 0.2-msec duration applied to the ulnar nerve was recorded on a Grass Model 50 polygraph. Except for 10-sec periods when tetanic stimulation was applied at the rate of 50 Hz, the ulnar nerve was continuously stimulated at the rate of 0.1 Hz from before administration of pancuronium to the conclusion of the study.

Pulse rates, systolic and diastolic blood pressures, respiratory rates and minute volumes of all subjects were recorded. Arterial pH, $P_{O_2}$, and $P_{O_2}$ values of eight of the subjects were

**Fig. 3.** Ergographic tracings indicating the influence of rate of voluntary exercise (top tracing 6/min, bottom tracing 60/min) on fatigue during partial pancuronium block. Note the absence of fatigue during slow exercise and the rapid fatigue during fast exercise.

**Fig. 4.** Ergographic tracing demonstrating the antagonistic effect of edrophonium on pancuronium block. Rate of exercise 6/min. Note the rapid onset of action of edrophonium.
measured. Base deficits of five subjects were determined after 10 minutes of nitrous oxide-oxygen inhalation (control measurements), 3, 6, and 10 minutes after administration of 40 μg/kg pancuronium, corrected for body weight, and at 5-minute intervals thereafter until the conclusion of the study. Blood pressures were measured as in the conscious subjects. Respiratory rate was calculated by measuring the duration (t) of nine respiratory cycles (the time elapsed from the start of the first to the start of tenth expiration). From this, the respiratory rate per minute (R) was calculated by the formula \( R = \frac{540}{t} \). The total volume of ten expirations was also measured with a Wright ventilation meter. Dividing this volume by 10 gave mean tidal volume, and multiplying mean tidal volume by the calculated respiratory rate gave the minute volume. pH, \( P_{CO_2} \), \( P_{O_2} \) and base deficit were measured with an Astrup apparatus. Each subject's spontaneous respiration was manually assisted throughout the experiment except for 30 seconds before and during the respiratory measurements. Nitrous oxide and oxygen flows were reduced to 500 ml each during this period.

Ten to 20 minutes after twitch tension had reached an apparently steady state during recovery from the pancuronium block, tetanic stimulation was applied for 10 seconds. Neostigmine, 0.02 mg/kg, was administered to six subjects and edrophonium, 0.2 mg/kg, to two others, together with 0.4 mg atropine, 10 to 15 minutes before tetanic stimulation.

Results

Conscious Subjects

With the subjects exercising at a slow rate, 22 μg/kg pancuronium decreased grip strength to 23.6 ± 6.6 (range 0–69) per cent of control in 6 minutes (fig. 2). Grip strength returned to 86.0 ± 4.7 (47–103) per cent of control in 25 minutes. Rapid exercise decreased grip strength to 81.4 ± 2.5 (70–91) per cent of control before administration of pancuronium, and to 8.9 ± 2.1 (0–22) per cent of control 4 minutes after its administration. After fast exercise the recovery of grip strength was slower, 59.7 ± 5.4 (43–76) per cent at 26 minutes, than after slow exercise.

Fig. 5. The antagonistic effect of neostigmine on pancuronium block. Rate of exercise 6/min. Note the slow onset of action of neostigmine.

The ergographic tracings (fig. 3) indicate that there was little or no decrease of the grip strength (fatigue) during partial pancuronium block with slow exercise, but with fast exercise in contrast to slow exercise, there was considerable fatigue.

The pancuronium block could be antagonized promptly by edrophonium (fig. 4) or more slowly with neostigmine (fig. 5).

Pancuronium, 22 μg/kg, decreased vital capacity to 83.6 ± 5.4 (48–100) per cent of control in 3 minutes, but by 15 minutes it had recovered to 97.0 ± 2.0 (85–105) per cent of control. Ptosis and weakness of extraocular and pharyngeal muscles developed more rapidly than weakness of the hand muscles. While ptosis and difficulty in swallowing disappeared in about 15 minutes, diplopia usually persisted for 40 to 45 minutes after pancuronium.

There were moderate but significant (P < 0.05) increases in pulse rates 6, 10, and 15 minutes after pancuronium (table 1). The changes in systolic and diastolic blood pressure and respiratory rate were insignificant. All subjects had recovered fully objectively.
and subjectively, 60 to 90 minutes after administration of pancuronium.

**ANESTHETIZED SUBJ ECTS**

Administration of 40 µg/kg pancuronium decreased the indirectly elicited twitch tension of the adductor pollicis muscle to 11.5 ± 2.8 (0–25) per cent of control within 5 minutes (fig. 6). Twitch tension returned to 66.9 ± 6.0 per cent of control (range 42–90 per cent) in 60 minutes. The administration of 20 µg/kg neostigmine and 0.4 mg atropine (six subjects) or 0.2 mg/kg edrophonium (two subjects) at this time caused no significant change in twitch tension. When recovery of twitch tension reached a steady state (in about 60 to 90 minutes) the tetanic tension was comparable to the pre-pancuronium control value and was well maintained (fig. 7). The mean posttetanic twitch tension was 169.1 ± 8.5 per cent of control ($P < 0.001$). The twitch tension did not decrease below the control value in any of the 11 subjects for the remainder of the 10–15-minute observation period. Neostigmine or edrophonium given 10 to 15 minutes before tetanic stimulation had no significant effect on either tetanic tension or posttetanic facilitation.

The mean tidal volume was 71.4 ± 7.5 (range 28–151) per cent of control at 5 minutes and 107.3 ± 8.3 (range 69–165) per cent at 15 minutes. The changes in minute volume were very similar (fig. 6). Except for a moderate decrease in arterial pH (7.31 ± 0.0) and an increase in $P_{CO_2}$ (49.4 ± 1.9 torr) ($P < 0.05$) at 5 minutes the mean pH and $P_{CO_2}$ values ranged from the preanesthetic values of 7.36 ± 0.01 and 41.1 ± 2.4 torr to 7.33 ± 0.01 and 45.5 ± 1.3 torr, respectively. Arterial $P_{O_2}$ ranged from a preanesthetic value of 94.4 ± 4.0 torr to 193.6 ± 15.8 torr, commensurate with the concentration of oxygen inhaled.

There was no clinical evidence of histamine release (e.g., wheals or reddening along the veins through which pancuronium was injected, bronchiolar constriction) in any subject.

Changes in blood pressure and respiratory rate were not significant (table 2).

**Discussion**

Qualitatively, the neuromuscular effect of pancuronium was similar to the effects of d-tubocurarine$^5,6$ and diallylnortoxiferine dichloride (Alloferin)$^7$. In conscious subjects, at the dose level (mg/kg) that produced a decrease of grip strength of about 75 per cent pancuronium was about 4.6 and 2.8 times greater than that of $d$-tubocurarine$^5,6$ and diallylnortoxiferine,$^7$ respectively. Of all the muscle relaxants investigated in human subjects only toxiferine dichloride has been more potent than pancuronium. Toxiferine, 15 µg/kg, caused a 92.5 per cent decrease of grip strength.$^5,6$ Pancuronium had the same relative sparing effect on ventilatory muscles as $d$-tubocurarine$^5,6$ or diallylnortoxiferine.$^7$ This was also evident at the 40 µg/kg dose level in anesthetized subjects, in whom twitch tension of the indirectly stimulated adductor pollicis decreased by almost 90 per cent, but tidal volume by only 30 per cent.

As with other nondepolarizing agents$^5,6$ the rate of voluntary exercise had a marked

### Table 1. Changes of Pulse Rate, Blood Pressure and Respiratory Rate in Conscious Subjects

<table>
<thead>
<tr>
<th>Time (Min)</th>
<th>Pulse Rate</th>
<th>Blood Pressure</th>
<th>Respiratory Rate</th>
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</thead>
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<tr>
<td></td>
<td></td>
<td>Systolic</td>
<td>Diastolic</td>
</tr>
<tr>
<td>3</td>
<td>109.6 ± 5.9†</td>
<td>103.0 ± 1.9</td>
<td>104.3 ± 3.4</td>
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<tr>
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<td>104.3 ± 4.3</td>
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<tr>
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<td>107.9 ± 4.3</td>
<td>97.5 ± 2.2</td>
<td>99.9 ± 3.5</td>
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</table>

* From the administration of pancuronium.
† Mean and standard error expressed as per cent of control values.
Fig. 6. The effect of 40 µg/kg pancuronium, injected at 0 min, on the minute volume, respiratory rate and twitch tension of the indirectly stimulated (0.1 Hz) adductor pollicis muscle. Explanation of symbols as in figure 2.

effect on the development of fatigue during partial pancuronium block (fig. 3).

It is difficult to reconcile the effects of anticholinesterases on the course of the residual block observed after administration of 40 µg/kg pancuronium to anesthetized subjects, on the one hand, with the effect of tetanic stimulation, on the other. That the twitch tension recovered to only about 65 per cent of control in 60 minutes indicates partial pancuronium block. Under these circumstances the block should be significantly antagonized by anticholinesterases. This was not the case. A possible explanation for the failure of the more

Fig. 7. The influence of tetanic stimulation on the twitch tension of the indirectly stimulated adductor pollicis muscle before and after administration of 40 µg/kg pancuronium. Between a and d, sensitivity of the preamplifier was reduced by a factor of 5; between b and c, paper speed was 5 mm/sec; between 1 and 2 the stimulation rate was 50 Hz. Note the significant and well sustained posttetanic facilitation during residual pancuronium block.
**Table 2. Changes of Pulse Rate, Blood Pressure and Respiratory Rate in Anesthetized Subjects**

<table>
<thead>
<tr>
<th>Time* (Min)</th>
<th>Pulse Rate</th>
<th>Blood Pressure</th>
<th>Respiratory Rate</th>
</tr>
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<td>Diastolic</td>
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<td>94.2 ± 2.4</td>
<td>98.1 ± 4.1</td>
</tr>
<tr>
<td>10</td>
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<td>98.2 ± 3.8</td>
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<tr>
<td>15</td>
<td>112.2 ± 7.3</td>
<td>99.1 ± 3.7</td>
<td>97.9 ± 3.5</td>
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<td>20</td>
<td>112.2 ± 7.4</td>
<td>96.1 ± 2.7</td>
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<td>107.8 ± 4.7</td>
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<tr>
<td>50</td>
<td>112.9 ± 5.2</td>
<td>99.5 ± 3.6</td>
<td>103.4 ± 4.3</td>
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<tr>
<td>60</td>
<td>110.4 ± 6.4</td>
<td>98.9 ± 3.8</td>
<td>105.1 ± 4.0</td>
</tr>
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</table>

* From the administration of pancuronium.
† Mean and standard error expressed as percent of control values.

...complete recovery of neuromuscular transmission could be dislocation of the stimulating needle electrode. It is unlikely that this would occur in all subjects, however. Furthermore, increasing the stimulating voltage did not increase the twitch tension, as it would if the stimulating electrode had been displaced. Another possibility is that, like d-tubocurarine pancuronium in concentrations much below those necessary for inhibition of the depolarization of the postsynaptic membrane decreases acetylcholine release at the presynaptic membrane of the motor nerve terminal. It is conceivable that the effect of pancuronium on presynaptic acetylcholine release is greater than that of d-tubocurarine and that the slow recovery of neuromuscular transmission after pancuronium is caused by this mechanism. This assumption, together with the marked augmentation of presynaptic acetylcholine release during and after tetanic stimulation,* would also explain the sustained elevation of the twitch tension to above the control value after tetanus. The increased amount of acetylcholine released by tetanic stimulation may competitively displace pancuronium from presynaptic receptors. Since the increase of presynaptic acetylcholine release outlasts the duration of the tetanus,* prolonged posttetanic facilitation will ensue. The posttetanic restoration of neuromuscular transmission of partially curarized muscle was also described by Hutter.10

In view of the above, why did anticholinesterases, which also cause accumulation of acetylcholine at the neuromuscular junction, fail to antagonize the residual pancuronium block? The different mechanisms of acetylcholine accumulation caused by tetanic stimulation and by anticholinesterases may be the answer to this question. During tetanic stimulation larger amounts of acetylcholine released within the terminal nerve fiber diffuse through the presynaptic membrane into the subneural space. After anticholinesterases the higher acetylcholine concentration in the subneural space is due primarily to inhibition of its hydrolysis. It is conceivable that although acetylcholine diffusing through the presynaptic membrane is capable of displacing pancuronium from its presynaptic receptors, the acetylcholine accumulated in the subneural space because of the inhibition of its breakdown cannot do so.

The well sustained tetanus observed in the presence of partial pancuronium block in this study is in contradistinction to the generally accepted view that tetanus is poorly maintained during partial depolarization block.10,11 Katz,12 however, also observed that in man tetanus was well maintained during 40 to 50 per cent d-tubocurarine block. It is probable that the maintenance of tetanus depends on the degree of the block. In agreement with this, in both our experiments and those of Katz,12 where tetanus was well maintained, there was 35 to 50 per cent block. In Hutter’s10 experiments, in which tetanus was not maintained, there was a 90 per cent block.

At first, the higher pulse rates observed in...
conscious volunteers were attributed to psychological factors. The moderate but consistent elevation of the pulse rate in anesthetized volunteers, in whom these factors had been eliminated, indicate that it is caused by pancuronium itself. The mechanism of the elevated pulse rate could not be determined in this study.

Our observations confirm the findings of other investigators\(^1\)\(^-\)\(^2\) that pancuronium is a nondepolarizing neuromuscular blocking agent. Like other nondepolarizing relaxants,\(^5\)\(^-\)\(^7\) it has a relative sparing effect on the respiratory muscles in conscious subjects, and probably in anesthetized subjects also. It causes a moderate increase in pulse rate which is more marked in conscious than in anesthetized subjects. Its effect on systolic and diastolic blood pressure is insignificant. There was no clinical evidence of histamine release after pancuronium. In agreement with this, no elevation of the plasma histamine levels was found after 120 \(\mu\)g/kg pancuronium in anesthetized subjects.\(^12\) For these reasons, the continued investigation of pancuronium for the production of surgical relaxation seems justified.

References

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