Clinical Neuromuscular Pharmacology of Pancuronium

Ronald L. Katz, M.D.*

The neuromuscular effects of pancuronium were studied in 65 patients anesthetized with nitrous oxide supplemented by thiopental and/or meperidine. There was a marked variation among patients in their responses to pancuronium. A dose of 0.02 mg/kg depressed twitch height 44 percent. Recovery to 90 percent of control twitch height took 16 minutes. With repeated doses a cumulative effect was observed. A dose of 0.04 mg/kg produced an 88 percent block. Twitch height recovered to 90 percent of control in 58 minutes. After a dose of 0.08 mg/kg the twitch response was markedly depressed (>98 percent) or abolished, and the trachea could be intubated with ease. Recoveries to 10 and 25 percent of control took 65 and 86 minutes, respectively. During a partial block, tetanus was usually poorly sustained and posttetanic facilitation was observed. (Key words: Pancuronium; Muscle relaxants; Neuromuscular transmission.)

Pancuronium, a new nondepolarizing neuromuscular blocking agent, has recently been made available for clinical trial in the United States. This agent has been used in Europe since 1967, and its advantages over d-tubocurarine are said to be absence of ganglionic blocking action and hypotension, absence of histamine release, and lack of cumulative effect.1-10 The present report focuses on the neuromuscular effects of pancuronium and is concerned with: 1) speed of onset, magnitude and duration of action; 2) variation in responses among patients; 3) possible interactions with other agents used during anesthesia; 4) the effects of repeated doses; 5) the ability of neostigmine to antagonize the block; 6) the dose needed for satisfactory performance of endotracheal intubation.

* Professor of Anesthesiology.

Methods

Sixty-five adult patients were studied during anesthesia and operation. Most received atropine or scopolamine (0.4-0.6 mg), secobarbital or pentobarbital (50-100 mg), and/or meperidine (50-100 mg) for preanesthetic medication. Anesthesia was induced with thiopental or meperidine and maintained with nitrous oxide, thiopental and/or meperidine. Succinylcholine was not used. Ventilation, monitored with a Wright ventilometer, was spontaneous, assisted, or controlled to maintain arterial pH at approximately 7.4. Periodic samples of arterial blood were analyzed by the Astrup technique.

Neuromuscular transmission was studied in a manner previously described.1,11 Briefly, the ulnar nerve was stimulated at the wrist or elbow and adduction of the adductor pollicis measured with a force-displacement transducer. Pancuronium bromide, atropine sulfate, and neostigmine methylsulfate were injected intravenously.

Results

Effects of Thiopental and Meperidine

Studies in the cat suggested that thiopental increased the action of pancuronium.12 In a preliminary study, therefore, we determined the effects of thiopental on the action of pancuronium in seven patients with anesthesia induced with meperidine, 50-200 mg, and maintained with nitrous oxide and oxygen. Administration of thiopental, 50-300 mg, during a partial neuromuscular block produced by pancuronium had no effect on the magnitude of block or the recovery slope. In addition, in six patients anesthetized with thiopental, 125-300 mg, and nitrous oxide and oxygen, the injection of meperidine, 10-100 mg, did not affect the recovery slope or the magnitude of neuromuscular block produced by pancuronium. Finally, there was no difference between the magnitudes and durations of action...
of 0.02 mg/kg of pancuronium in the patients in whom anesthesia was induced with thiopental and those in whom anesthesia was induced with meperidine. Therefore, the data for these patients have been pooled.

**Effects of 0.02 mg/kg of Pancuronium**

Since we previously used 0.1 mg/kg of d-tubocurarine as a test dose, and pancuronium is said to be five times as potent as d-tubocurarine, the first dose of pancuronium studied was 0.02 mg/kg (20 µg/kg). This dose produced a mean decrease in twitch height of 44 per cent. The latency period (time from injection to first depressed twitch) was 81 seconds, and the onset time (from first depressed twitch to peak effect) was 251 seconds. Recoveries to 50, 75 and 90 per cent of control

**Table 1. Effects of Different Doses of Pancuronium**

<table>
<thead>
<tr>
<th></th>
<th>Dose 0.02 mg/kg</th>
<th>Dose 0.04 mg/kg</th>
<th>Dose 0.08 mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of Patients</strong></td>
<td>16</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td><strong>Time from injection to first depressed twitch</strong></td>
<td>81±7 sec (45–118)</td>
<td>43±6 sec (22–90)</td>
<td>35±3 sec (22–51)</td>
</tr>
<tr>
<td></td>
<td>251±17 sec (147–362)</td>
<td>236±12 sec (174–303)</td>
<td>171±20 sec (122–334)</td>
</tr>
<tr>
<td><strong>Magnitude of twitch depression</strong></td>
<td>44±7 per cent (0–83)</td>
<td>88±4 per cent (50–100)</td>
<td>99.6±0.24 per cent (98–100)</td>
</tr>
<tr>
<td><strong>Recovery time to percentage of control level</strong></td>
<td>—</td>
<td>14±5.7 min (0–46)</td>
<td>65±8.1 min (33–102)</td>
</tr>
<tr>
<td>10 per cent</td>
<td>—</td>
<td>26±6.1 min (0–50)</td>
<td>86±13 min (43–133)</td>
</tr>
<tr>
<td>25 per cent</td>
<td>4±1.7 min (0–18)</td>
<td>37±8 min (0–81)</td>
<td>—</td>
</tr>
<tr>
<td>50 per cent</td>
<td>11±2.4 min (0–27)</td>
<td>50±9.6 min (21–102)</td>
<td>—</td>
</tr>
<tr>
<td>75 per cent</td>
<td>16±2.7 min (0–34)</td>
<td>58±10.7 min (24–116)</td>
<td>—</td>
</tr>
<tr>
<td>90 per cent</td>
<td>—</td>
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</tr>
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*Means ± SE. Ranges are given in parentheses. A dash indicates that the number of patients studied was not large enough to report.*
blocks in three patients. Mean latency period was 36 seconds and onset time, 171 seconds. It was not possible to measure full recovery times in all patients who received this dose, either because of the short durations of their operations or because of the clinical requirements for relaxation. However, in nine patients recoveries of twitch responses to 10 per cent of control values took 65 minutes and in seven patients recoveries to 25 per cent took 86 minutes. In three patients 50 per cent recoveries were seen in 51, 71, and 91 minutes, while 90 per cent recoveries in two patients were observed in 63 and 93 minutes. The results (table 1) probably underestimate the duration of action of 0.08 mg/kg, since the greater the duration of action, the less the likelihood of recording recovery to each level.

In previous studies, we found that in lightly anesthetized patients relaxation was usually considered satisfactory when the twitch response was less than 25 per cent of control, and virtually always satisfactory when the twitch response was less than 10 per cent of control. Similar observations were made with pancuronium. Thus, 0.08 mg/kg of pancuronium provided satisfactory relaxation averaging 65 minutes using the 10 per cent figure or 86 minutes using the 25 per cent figure.

In patients who received thiopental followed by 0.04 or 0.05 mg/kg of pancuronium, intubation of the trachea was attempted. With 0.04 mg/kg we did not obtain conditions comparable to those seen with 1 mg/kg of succinylcholine, i.e., relaxed jaw, fully abducted vocal cords, no coughing after intubation. With 0.08 mg/kg, conditions similar to those seen with succinylcholine were obtained in two patients. In five patients less satisfactory conditions were obtained, but the trachea could be intubated without cough through partially abducted cords. In the remaining three patients the cords were adducted, but the endotracheal tube could easily be passed with only a weak brief cough following intubation.

Effects of Neostigmine

The ability of 2.5 mg of neostigmine (preceded by 1 mg of atropine) to antagonize the effects of pancuronium was determined in 36 patients. In every patient one dose of 2.5 mg of neostigmine was sufficient to restore twitch height to the control level and sustained teta-
nus at 50 Hz. Figure 4 shows the speeds of antagonism at different degrees of spontaneous recovery. In general, the greater the degree of spontaneous recovery, the faster the antagonism. An additional factor of importance was the time elapsed since the initial large dose of pancuronium. In four patients who received pancuronium on two occasions each, neostigmine was injected 10–15 minutes after an initial dose of 0.04 mg/kg of pancuronium which produced 84–95 per cent block. Recovery took 18 to 28 minutes. On another occasion the same initial dose was given; 30–40 minutes later an additional dose of 0.01–0.02 mg/kg was given and neostigmine was injected when the degree of recovery was the same as at the prior operation. Under the circumstances 8 to 11 minutes were needed for antagonism (fig. 4).

**Other Observations**

In each of five patients who received 0.02 mg/kg of pancuronium the same dose was repeated an hour later, after twitch height had returned to the control level and tetanus was well sustained. The magnitudes of blocks after the second doses were somewhat greater (14–42 per cent), but the durations of action were greatly increased (105–187 per cent).

During partial neuromuscular block, the response to tetanic stimulation at 50 Hz was usually poorly sustained and there was posttetanic facilitation. However, in seven patients tetanic stimulation at 50 Hz was well sustained, a response also occasionally seen with d-tubocurarine.1

**Discussion**

Pancuronium was synthesized in 196410 as one of a series of bisquaternary ammonium derivatives of 5 L-androstanes. Results of animal studies suggested that the neuromuscular block produced by pancuronium was nondepolarizing. In the frog rectus abdominis it did not produce a contracture but did abolish contractures produced by acetylcholine.11 In extracutaneous muscles of the cat it did not produce a contracture and abolished contractures produced by succinylcholine.15 Also in the cat, the block was antagonized by cholinesterase inhibitors and succinylcholine but increased by a dose of d-tubocurarine insufficient to depress the twitch by itself.12,13,15 The block was also antagonized by potassium chloride and epinephrine.14 A decrease in temperature decreased its action.11 During partial neuromuscular block tetanus was poorly sustained and posttetanic potentiation was observed.7,12,14,15
The potency of pancuronium in the cat was approximately ten times that of d-tubocurarine, with equieffective doses producing similar durations of action. The effects of hexamethonium, d-tubocurarine, and pancuronium on ganglionic transmission were studied in vitro (guinea pig ileum response to nicotine) and in vivo (cat nictitating membrane response to preganglionic stimulation of the cervical sympathetic trunk). In vitro, pancuronium had half the ganglionic-blocking effect of d-tubocurarine and a fourth the ganglionic-blocking effect of hexamethonium, while in vivo, it had an eighth the action of hexamethonium. Although both hexamethonium and d-tubocurarine lowered the arterial pressure in the cat, pancuronium did not. Studies in the guinea pig demonstrated that pancuronium, unlike d-tubocurarine, did not release histamine and produce bronchoconstriction. Although an atropine-like effect was not observed, pancuronium did block the decrease in arterial pressure produced by vagal stimulation. The decrease in arterial pressure produced by acetylcholine was not blocked by pancuronium.

The first clinical trials with pancuronium were reported in 1967 by Baird and Reid. They studied its effects in six patients during halothane anesthesia and found that it was approximately five times as potent as d-tubocurarine. There were no changes in pulse rate or systolic blood pressure. The block was characterized by poorly sustained tetanus, and post-tetanic facilitation and could be antagonized by neostigmine. Similar effects were described in subsequent reports, most of which were clinical appraisals of the drug without objective measurements or dose–response curves of neuromuscular effects.

To study pancuronium per se quantitatively, it was necessary initially to find an anesthetic technique which did not modify the action of pancuronium. Preliminary studies showed that the action of pancuronium was increased by halothane and also by the prior administration of succinylcholine. Similar observations have been made previously with d-tubocurarine. Thipental and meperidine, previously found not to modify the action of d-tubocurarine, did not modify the action of pancuronium, either. Therefore, the present studies were carried out using nitrous oxide supplemented by thipental and meperidine.
With 0.02 mg/kg of pancuronium the peak effect was reached 332 seconds after injection and 251 seconds from the time of the first depressed twitch. Other workers \(^6,\) \(^4,\) \(^8\) reported a more rapid onset of action of pancuronium, faster than that of d-tubocurarine. However, it is not clear which dose they are referring to. Furthermore, these reports were subjective clinical impressions. In none of these studies was the effect of pancuronium objectively assessed by recording the muscle response to nerve stimulation. The speed of onset of pancuronium in the present study is similar to that reported by Norman et al.\(^9\) and Lund and Stovner.\(^6\) In both these studies the action of pancuronium was assessed objectively, by measuring either twitch response\(^9\) or grip strength.\(^6\)

As with d-tubocurarine,\(^1^8\) both the magnitude and duration of action of pancuronium varied markedly from patient to patient. Thus, the use of a test dose, preferably assessed with a nerve stimulator and by the effect on respiration, would seem wise. One of the claims for pancuronium is that there is no cumulative effect.\(^5,\) \(^10,\) \(^12\) In the present study a cumulative effect was observed, even with doses as small as 0.02 mg/kg given an hour apart, and after twitch height had returned to the control level and remained stable for as long as 48 minutes. With repeated doses the magnitude of action did not increase as much as the duration of action. Similar results were observed by Norman et al.\(^9\) A cumulative effect is not surprising, since it is known that the margin of safety of neuromuscular transmission is such that twitch height may be at the control level at a time when neuromuscular transmission is only better than 25 per cent of normal capacity.\(^1^9\)

Pancuronium, 0.08 mg/kg, produced profound blocks (>98 per cent) in ten patients studied. This effect occurred rapidly, and endotracheal intubation was possible in each patient after two to three minutes. The duration of action of this dose is long, with recovery to 10 per cent of control requiring 65 minutes and recovery to 25 per cent, 86 minutes. By our previously reported criteria (see results), this indicates that 0.08 mg/kg provides 65 or 86 minutes of satisfactory relaxation. Both of these figures are greater than the 45-minute period of effective action claimed by the manufacturer\(^1^0\) for 6 mg (0.86 mg-kg in a 70-kg patient). Subsequently, doses of 2 mg are recommended.\(^1^0\) On the basis of our studies such a dosage schedule would represent an overdose of relaxant.

The neuromuscular blocking action of pancuronium could easily be reversed by 2.5 mg of neostigmine (fig. 4). In patients whose twitch height were 20 per cent of control or greater, reversal usually occurred in less than ten minutes, and always in less than 15 minutes. With twitch height below 20 per cent of control, reversal took as long as 29 minutes. These recovery times are not as rapid as those reported by Komesaroff and Field\(^3\) or McDowell and Clark,\(^4\) who reported recovery within five minutes. The differences in results are probably due to their recovery times' being based on clinical impressions, while in the present study our criteria were recovery of twitch height to the control level and ability to sustain tetanus at 50 Hz.\(^2^0,\) \(^2^1\)

References

10. Brochure on pancuronium published by Organon Laboratories Limited
15. Katz RL: Unpublished data

Drugs

ATROPINE AND SYMPTOMS
Six healthy subjects were exposed to three periods of negative pressure applied to the lower body until vasodepressor syncope developed. Three forms of treatment were administered randomly to each patient and the results compared. The treatments were: saline solution, given intravenously; pretreatment with atropine sulfate, 2 mg intravenously; atropine sulfate, 2 mg intravenously after vasodepressor syncope had developed. Heart rate, auscultatory blood pressure, and forearm blood flow were measured. When saline solution alone was used, heart rate and diastolic blood pressure increased, systolic blood pressure and forearm blood flow decreased as negative pressure was applied. With syncope, heart rate and blood pressure decreased while forearm blood flow remained unchanged. Pretreatment with atropine did not change blood pressure or forearm blood flow responses from those seen following solution of saline administration. However, heart rate increased and, with syncope, increased further. Pretreatment with atropine may have delayed the onset of syncope. When syncope occurred, atropine increased heart rate, with no significant changes in blood pressure, forearm blood flow or the symptoms associated with vasodepressor syncope. (Murray, R. H., and Shropshire, S.: Effect of Atropine on Circulatory Responses to Lower Body Negative Pressure and Vasodepressor Syncope, Aerospace Med. 41: 717 (July) 1970.)

DDT AND DRUG METABOLISM
Occupational exposure to DDT increases the metabolism of phenylbutazone and the urinary excretion of 6-beta hydroxy cortisone in man. Considerable variation in phenylbutazone half-life was found in different people; there was no correlation between DDT levels in factory workers and phenylbutazone half-life. (Poland, A., and others: Effect of Intensive Occupational Exposure to DDT on Phenylbutazone and Cortisol Metabolism in HumanSubjects, Clin. Pharmacol. Ther. 11: 724 (Sept.) 1970.)