The Neuromuscular Effects of Pancuronium in Infants and Children

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Pancuronium bromide, a bisquaternary muscle relaxant, produces a competitive type of neuromuscular block. In adults it is five to ten times more potent than d-tubocurarine, with a comparable duration of action.1,2

In infants and children pancuronium was found to have a relatively predictable neuromuscular blocking action, with cardiovascular stimulating properties.3,4,5 However, these studies in children concentrated on the drug's cardiovascular effects after a fixed dose. No precise measurement of the duration of action of pancuronium in the pediatric age group has been published, nor has an accurate dose–response curve been drawn.

This study was performed to elucidate the effects of incremental doses of pancuronium bromide on twitch response in lightly anesthetized infants and children in order to construct a dose–response curve and to study the recovery time from neuromuscular blockade.

METHODS

Seventeen infants and children requiring intra-abdominal surgery were studied. Their ages ranged from 5 weeks to 7 years. Premedication consisted of pentobarbital or secobarbital, 4 mg/kg body weight, for infants and children more than 18 months of age. No premedication was given to smaller infants.

Anesthesia was maintained with nitrous oxide and oxygen, followed by halothane. The trachea was intubated without neuromuscular blocking drugs. The electrocardiogram and temperature were monitored. Anesthesia was maintained with halothane (1 or 2 per cent inspired) and nitrous oxide–oxygen 2:1.

Neuromuscular transmission was studied using the method described by Katz and Ryan,6 the only difference being that the ulnar nerve was stimulated with electrical impulses of supramaximal intensity generated by a Block-Aid Monitor at .25 Hz instead of a Grass stimulator. The resultant force of adduction of the thumb was recorded on a Grass polygraph via a Grass model FT-03 force-displacement transducer. When pulse and blood pressure had been stable for more than 5 minutes, and before beginning the operation, a cumulative dose–response curve was constructed in the following manner.

A control twitch height was recorded. Pancuronium was then given intermittently. The first dose was 0.02 mg/kg body weight. At the point of peak response from this dose, a second dose of 0.01 or 0.02 mg/kg was injected. This procedure was repeated until a maximum dose of 0.06 mg/kg had been administered. Onset of action was measured as the time from the injection of the drug to the first depressed twitch. Magnitude of the block was determined as the decrease in twitch height expressed as a percentage of control. Percentage depression of the force of adduction of the thumb was plotted against the log dose of pancuronium on log-probit paper. Recovery time was measured from the time of maximum neuromuscular block after the last dose of pancuronium (i.e., after a total of 0.06 mg/kg) to the return of twitch height to 5, 10, 25, 50, and 90 per cent of control.

If during the course of the surgical procedure relaxation became inadequate, additional pancuronium was given at a dose of 0.02 mg/kg. At the end of the surgical procedure residual neuromuscular blockade was reversed with atropine, 0.02 mg/kg, and prothigmine, 0.06 mg/kg.
TABLE 1. Effects of Incremental Doses of Pancuronium on Depression of Muscle Twitch in Infants and Children

<table>
<thead>
<tr>
<th>Pancuronium (mg/kg)</th>
<th>Per Cent Depression of Twitch</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ± SE</td>
<td></td>
</tr>
<tr>
<td>0.02</td>
<td>21.6 ± 4.5</td>
<td>0–45</td>
</tr>
<tr>
<td>0.03</td>
<td>55.3 ± 9.9</td>
<td>14–88</td>
</tr>
<tr>
<td>0.04</td>
<td>84.4 ± 2.7</td>
<td>70–95</td>
</tr>
<tr>
<td>0.05</td>
<td>92.9 ± 2.0</td>
<td>78–98</td>
</tr>
<tr>
<td>0.06</td>
<td>98.1 ± 0.6</td>
<td>95–100</td>
</tr>
</tbody>
</table>

RESULTS

Onset of Action

The time from injection of the first dose of pancuronium (0.02 mg/kg) to the first detectable effect on the muscle twitch was 1.5 min ± 0.2 (mean ± SE), with a range of 0.5–3 min. However, the onsets of action following the second and succeeding doses were more rapid.

Time to Maximum Effect

The time from injection of the first incremental dose to the maximum effect from the last dose was 7.4 ± 0.5 min. The numbers of doses ranged from 3 to 5.

Dose–Response Curve

The data obtained are summarized in table 1.

Of note is the wide variability (0 to 46 per cent) of responses to the small dose (0.02 mg/kg). As expected, at higher doses the range of twitch depression was much narrower, 0.06 mg/kg always producing 95–100 per cent inhibition of twitch.

A standard dose–response curve was plotted on log probit scales. This type of plot converts the usual sigmoid biological response plot to a straight line. All points were in close proximity to a straight line (fig. 1). The small infants (5–7 weeks) in our series did not have a different dose–response curve when compared with older children (fig. 2).

Recovery Time

The times of recovery from maximal neuromuscular blockade to 5, 10, 25, and 90 per cent of control twitch height are summarized in table 2. Recovery of the twitch to 25 per cent of control required a mean of 23.6 min. Relaxation for abdominal surgery usually became unsatisfactory at this point.

Recovery from Repeated Doses of Pancuronium

There appears to be a tendency for the action of pancuronium to cumulate with repeated doses. For example, in two patients who received further increments of pancuronium (0.02 mg/kg) after the initial dose–response study was completed, the mean recovery time from 5 to 25 per cent of the control twitch height was 15 min, in contrast to 12.6 min after the initial dosage.
Also, the mean time for recovery from 5 to 50 per cent was 28 min, in contrast to 22.1 min after the initial dose.

Reversal of Neuromuscular Blockade

All neuromuscular blockades were adequately reversed with atropine and prostigmine (0.02 and 0.06 mg/kg, respectively) as determined by return of muscle twitch to control height and well-sustained tetanus. Clinical evidence included return of abdominal muscle tone, free movements of the limbs, and a strong cry in infants.

DISCUSSION

Norman and Katz\(^8\) found that in adults anesthetized with halothane 0.02 mg/kg pancuronium gave 68 per cent depression of twitch height, and later, Katz\(^9\) observed that 0.02 mg/kg pancuronium caused an average of 44 per cent depression of twitch height in adults anesthetized with thiopental, nitrous oxide and oxygen. However, when succinylcholine had been given half an hour prior to injection of pancuronium, the same dose caused 77 per cent depression of twitch height. Also, when halothane (0.5–1 per cent) was incorporated in the anesthetic technique, the depression of twitch height was 77 per cent. However, the same dose in our study of children (pancuronium and halothane) produced only 21 per cent depression of twitch height. The difference between the two means (77 ± 4.9 and 21 ± 4.6) was significant (\(P < 0.001\)).

Miller et al.\(^1\) found in adult subjects that the ED\(_{50}\)'s of pancuronium for depression of thumb adduction were 0.82, 0.49, and 0.35 mg/m\(^2\) during 0.4, 0.8 and 1.2 per cent end-expired halothane anesthesia. Transforming these results to mg/kg, the ED\(_{50}\)'s were 0.02, 0.012, and 0.009 mg/kg with these concentrations of halothane. In the present study, the ED\(_{50}\) was 0.025 mg/kg with a mean inspired halothane concentration of 1.5 per cent.

Despite the difference in methodologies, our results indicate that children may require more pancuronium than adults to achieve the same degree of muscle relaxation.

Norman\(^8\) found that in adults the recovery time from 0.05 mg/kg (99 per cent depression of muscle twitch) to 50 per cent of normal twitch was 36.8 min with halothane anesthesia. In our study the recovery time from incremental doses of 0.06 mg of pancuronium (98 per cent depression of muscle twitch) was 32.9 min, a comparable figure, suggesting that adults and children may re-
cover from the same degree of paralysis at similar rates.

In the usual clinical situation, 95 per cent depression of thumb twitch is associated with effective abdominal-muscle relaxation. We found that a dose of 0.06 mg/kg in children produces very satisfactory muscle relaxation with halothane-\(N_2O/O_2\) anesthesia. This dose regularly produces 95 per cent depression of the twitch response or more, and relaxation lasts for about 25 min when twitch height has recovered to 25 per cent of normal. This compares favorably with the work of Yamamoto, who found that the duration of respiratory paralysis in infants and children under light halothane anesthesia was 37.5 min after 0.08 mg/kg pancuronium.

We preferred to use the dose of pancuronium based on body weight rather than surface area because it is more practical and there is lack of accuracy in calculation of surface area from weight and height. Our results indicate that the dose–response curve of small infants (less than 7 weeks of age) does not differ markedly from that of older children (fig. 2). For example, at a dose of 0.06 mg/kg, a 70-kg adult with a body surface area of 1.7 sq m would have received 4.2 mg (2.5 mg/sq m). In a baby weighing 3 kg (0.2 sq m surface area), the dose based on surface area would be 0.5 mg instead of 0.18 mg based on body weight. Consequently, dosage based on surface area will be excessive for infants.

CONCLUSION

A cumulative dose–response study of pancuronium bromide in infants and children has demonstrated that a dose of 0.06 mg/kg produces 95–100 per cent depression of adduction of the thumb. The ED\(50\) in this study was 0.028 mg/kg. No difference between the requirements for pancuronium of infants and children was found.

The mean twitch recovery time to 25 per cent of control from 98 per cent depression after 0.06 mg/kg of pancuronium in children is 25 minutes. This recovery time is approximately the same as that after 0.05 mg/kg in adults. Twitch depressions produced by these doses were approximately equal in the two groups.

There was wide variability in the responses to smaller doses of pancuronium in infants and children.

It is preferable to use body weight rather than surface area in determining the dosage requirement for pancuronium.

REFERENCES