EXPERIMENTAL STUDIES WITH PRESTONAL, A NEW SHORT-ACTING MUSCLE RELAXANT

BY

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Many anaesthetists feel that a nondepolarizing relaxant combining brief duration of action with easy reversibility by neostigmine or edrophonium (Tensilon) would be a most useful drug (Foldes, 1956). The first clinical observations (Frey, 1955) suggested that Prestonal (N,N,N',N'-tetramethyl-N,N'-bis(carbopropoxymethyl)-1,16-dioxahexadecane-1,16-diammonium bromide) might fulfil these requirements.

Prestonal (see figure 1) is chemically related to decamethonium. It differs from the latter by the lengthening of the decamethylene chain with two oxyethyl groups and by the substitution of a carbopropoxy group into one of the methyl groups on both quaternary nitrogens. It has been shown previously that both lengthening the distance between the two quaternary nitrogens (Zaimis et al., 1952), and substitution of larger radicals in place of the methyl groups attached to the quaternary nitrogens (Ginzel et al., 1951; Randall, 1952; Hoppe et al., 1953) tend to reduce the depolarizing effect of muscle relaxants. It was anticipated that as a result of these structural changes Prestonal would produce a short and easily reversible nondepolarizing block. Consequently, experiments were designed to obtain information on the potency and duration of action as well as the type of myoneural block produced by Prestonal in man.

MATERIAL AND METHODS

The investigations to be described were carried out on 51 patients undergoing various surgical procedures under spinal analgesia not extending above the level of the tenth dorsal segment. This method of anaesthesia itself has little effect on respiration, and, at the same time, excludes the influence of surgical stimuli on respiration. For the patient's comfort and to eliminate the effects of emotional influences on respiration, light general anaesthesia was maintained throughout. After spraying the patient's mouth and pharynx with 1 per cent amethocaine hydrochloride solution, a sleeping dose of thiopentone was administered and an oral airway inserted. Anaesthesia with nitrous oxide and oxygen was started at a flow rate of 4 litres and 2 litres per minute respectively. The flow rate was reduced to a maintenance level of 500 ml of each gas when most of the patient's nitrogen had been eliminated. Sufficient pethidine (25-50 mg) was then given intravenously to maintain a stable plane of anaesthesia. For the same reason, additional small doses of thiopentone were also given in the course of the experiment as required. When general anaesthesia became stabilized, control values for tidal volume, respiratory rate, pulse rate and blood pressure were obtained. Tidal volumes were measured with a Bennett ventilation meter incorporated into the CO$_2$ circle absorption system. Whenever necessary for the patient's welfare, assisted or controlled respiration was used. In representative experiments, tidal volume changes were also recorded graphically by connecting a spirometer in place of the breathing bag of the anaesthesia apparatus. The presence or absence of flushing after the administration of Prestonal was also noted.

The drugs used and their doses were:

- Prestonal 1.5 or 0.75 mg/kg.
- Edrophonium (Tensilon) 0.3 mg/kg.
- Pyridostigmine (Mestinon) 0.15 mg/kg.
- Neostigmine (Prostigmine) 0.02 mg/kg.
The influence of edrophonium (Tensilon) on the respiratory effect of Prestonal.

Note that 0.3 mg/kg edrophonium has no effect on tidal volume. The same dose of edrophonium given when tidal volume recovered to 50 per cent of control caused apnoea.
All drugs were injected into the tubing of the intravenous infusion. The doses of Prestonal were injected in 30 seconds; all other drugs were injected as rapidly as feasible through a No. 22 s.w.g. needle. The duration of respiratory depression was defined as the time elapsed between the start of apnoea and the return of the tidal volume to the control value.

Experimental Procedure.

(A) 1.5 mg/kg of Prestonal was administered intravenously to 31 patients. Twenty-six of these received an additional 0.75 mg/kg dose of Prestonal when the tidal volume returned to control value. Twenty-one of the 26 patients were given a second 0.75 mg/kg dose of Prestonal when the tidal volume returned to normal after the first 0.75 mg/kg dose.

(B) Ten patients were given an initial 0.75 mg/kg dose of Prestonal followed 30 minutes later by a second identical dose. Another 10 patients in this group were given 0.3 mg/kg of edrophonium one minute before the initial 0.75 mg/kg dose of Prestonal. In these patients a second identical dose of Prestonal was given 30 minutes later, this time not preceded by edrophonium.

(C) Of the 21 patients in group A, who were given a second 0.75 mg/kg of Prestonal, 13 received 0.3 mg/kg of edrophonium and 8 received 0.15 mg/kg of pyridostigmine at the time when their tidal volumes had recovered to 50 per cent of the control values.

(D) Seven patients from groups A and B received 0.3 mg/kg of edrophonium when their tidal volumes reached the control values after the administration of the last dose of Prestonal.

RESULTS

The observations made on the subjects of group A are summarized in table I. All subjects in this group developed apnoea after both the initial 1.5 mg and the subsequent 0.75 mg/kg doses. The onset of apnoea was more rapid after the fractional doses than after the initial dose. In contrast to this, both the duration of apnoea and the duration of respiratory depression were shorter after the fractional doses than after the initial dose. The differences between the onset and duration of

<table>
<thead>
<tr>
<th>Table I</th>
<th>The respiratory effects of Prestonal</th>
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</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>Dose of Prestonal (mg/kg)</td>
</tr>
<tr>
<td>31</td>
<td>1.5</td>
</tr>
<tr>
<td>26</td>
<td>0.75†</td>
</tr>
<tr>
<td>21</td>
<td>0.75†</td>
</tr>
</tbody>
</table>

* Standard error. † Given when tidal volume returned to normal value after previous dose.

<table>
<thead>
<tr>
<th>Table II</th>
<th>Comparison of the respiratory effects of Prestonal alone and when preceded by edrophonium.</th>
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<tr>
<td>Group</td>
<td>Drug (mg/kg)</td>
</tr>
<tr>
<td>I.</td>
<td>Prestonal 0.75</td>
</tr>
<tr>
<td>II.</td>
<td>Prestonal 0.75</td>
</tr>
<tr>
<td></td>
<td>Edrophonium 0.30†</td>
</tr>
</tbody>
</table>

Repeat dose of Prestonal given 30 minutes after first dose.

| Group    | Drug (mg/kg) | No. of patients | Frequency of apnoea | Onset of apnoea (sec) | Duration of apnoea (sec) | Duration of respiratory depression (sec) |
| I.       | Prestonal 0.75 | 10 | 5 | 67 ± 5 | 266 ± 63 | 508 ± 63 |
| II.      | Prestonal 0.75 | 9 | 6 | 75 ± 10 | 225 ± 22 | 516 ± 96 |

* Standard error. † Given 1 minute before Prestonal.
The influence of pyridostigmine (Mestinon) on the respiratory effect of Prestonal.

Note that 0.15 mg/kg of pyridostigmine given when tidal volume recovered to 50 per cent of control had no appreciable effect.

apnoea and the duration of respiratory depression after the first dose on one hand, and the second and third doses on the other were statistically significant. There was no significant difference between these values after the second and third doses.

The observations made on the patients in group B are summarized in table II. There was no significant difference in the incidence or onset of apnoea when 0.75 mg/kg Prestonal was administered alone (subgroup I), or preceded by 0.3 mg/kg edrophonium (subgroup II). The duration of apnoea and respiratory depression was more prolonged in the edrophonium group, but the differences were not statistically significant. The effects of a second dose of Prestonal given 30 minutes later were more marked in the group which received the first dose of Prestonal alone than in the group in which Prestonal and edrophonium were given together. Thus in subgroup I, the onset of apnoea was faster and the duration of apnoea and respiratory depression was longer than after the first dose of Prestonal. In contrast to this in subgroup II, the effects of the second dose were very similar to the first. These differences, however, were again not statistically significant.

The results obtained with the patients in group C are presented in table III. The figures in table III indicate that 0.3 mg/kg edrophonium or 0.15 mg/kg pyridostigmine administered when the respiratory tidal volume returned to 50 per cent of the control value following 0.75 mg/kg Prestonal, prolonged the respiratory depression. This prolongation was more marked (statistically significant) with edrophonium than with pyridostigmine (not statistically significant). The greater potentiating effect of edrophonium is also evident from the fact that apnoea developed in 11 of the 13 patients who received edrophonium at the...
TABLE III

The influence of anticholinesterases on the respiratory effects of Prestonal

<table>
<thead>
<tr>
<th>Drug (mg/kg)</th>
<th>No. of patients</th>
<th>Duration of respiratory depression (sec)</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prestonal 0.75</td>
<td>26</td>
<td>540 ± 30*</td>
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</tr>
<tr>
<td>Prestonal 0.75</td>
<td>13</td>
<td>842 ± 110</td>
<td>Apnoea developed in 11 patients</td>
</tr>
<tr>
<td>Edrophonium 0.30†</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Prestonal 0.75</td>
<td>8</td>
<td>695 ± 59</td>
<td>No apnoea or appreciable decrease of tidal volume</td>
</tr>
<tr>
<td>Pyridostigmine 0.15†</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Standard error.
† Administered when tidal volume returned to 50 per cent of control value.

Fig. 4

The influence of neostigmine (Prostigmine) on the respiratory effect of Prestonal.
Note that 0.02 mg/kg of neostigmine given when tidal volume recovered to 50 per cent of control had no appreciable effect.
time of 50 per cent recovery. No apnoea or visible diminution of the tidal volume occurred in the pyridostigmine group. The difference in the effect of edrophonium and pyridostigmine on tidal volume after 50 per cent recovery following Prestonal is also evident in figures 2 and 3.

The effect of 0.02 mg/kg neostigmine given after 0.75 mg/kg doses of Prestonal at the time of 50 per cent recovery of tidal volume was observed on 2 patients. Here again, though no immediate diminution of tidal volume could be observed after neostigmine (fig. 4), the duration of respiratory depression was somewhat prolonged in both patients.

Of the 7 patients in group D who received 0.3 mg/kg edrophonium when their tidal volumes returned to the control value following the Prestonal, 2 developed apnoea (fig. 3) and in the remaining 5, there was a 70 to 95 per cent reduction of the tidal volume within 30 to 60 seconds. Their tidal volumes returned to the control values in an average of 235 seconds.

**Side Effects.**

A moderate fall in blood pressure, often accompanied by a rise in pulse rate, was seen in some of the patients who received the 1.5 mg/kg dose of Prestonal. These changes were of short duration and never serious enough to give cause for anxiety. A few patients also showed marked flushing of the skin of the head, neck, and arms after the 1.5 mg/kg dose of Prestonal. This was also noted by earlier workers who recommended that Prestonal should not be administered faster than 2.0 mg per second (Frey, 1955).

**DISCUSSION**

The mg/kg potency of Prestonal is of the same order as that of gallamine. Its duration of action is relatively short, and lies between those of suxamethonium and decamethonium. The duration of apnoea after moderate (0.75 mg/kg) doses is about 3 minutes and the duration of respiratory depression is about 7 minutes. Doubling the size of the dose increases the duration of apnoea to about 5 minutes, and the duration of the respiratory depression to about 12 minutes.

Prestonal has less cumulative effect than the nondepolarizing muscle relaxants, e.g. d-tubocurarine or gallamine. The administration of a second 0.75 mg/kg dose of Prestonal, 30 minutes after the first dose, has only slightly greater effect on the tidal volume than the first dose (see table II). It is not known whether this relatively low cumulative effect is due to rapid excretion, breakdown or some other factor. Although Prestonal is a fairly potent inhibitor of both human plasma cholinesterase ($K_{i0} = 7.3 \times 10^{-4}$ mol/l.) and red cell cholinesterase ($K_{i0} = 10^{-5}$ mol/l.) (Foldes et al., 1956) it is not hydrolyzed by either of these enzymes.

The finding that a 0.75 mg/kg dose of Prestonal given immediately after recovery from the effects of a 1.5 mg/kg dose has the same effect as the second of two 0.75 mg/kg doses given 30 minutes apart (see tables I and II) suggests the possibility of desensitization or "tachyphylaxis" which is more marked after the larger initial dose. This phenomenon has been described previously with decamethonium (Pelikan et al., 1950; Unna et al., 1950) and demonstrated with suxamethonium both in laboratory animals (Foldes et al., 1956) and in man (Poulsen and Hougs, 1956).

The advantages of relatively short duration of action and moderate cumulative effect offered by Prestonal are partially offset by the fall in blood pressure and other signs of histamine release observed during its use. A further disadvantage is that when endotracheal intubation is attempted after apnoeic doses of Prestonal have been given the muscles of the jaw and larynx are frequently found to be incompletely relaxed.

The marked potentiating effect of edrophonium, and the absence of any antagonism by pyridostigmine or neostigmine on its neuromuscular action, indicate that contrary to expectations, Prestonal is a depolarizing and not a nondepolarizing muscle relaxant. The lengthening of the distance between the two quaternary nitrogen atoms and the substitution of one of the methyl groups on both quaternary nitrogen atoms by methylcarbopropoxy groups has only resulted in a marked increase in the concentration of Prestonal required at the myoneural junction as compared with decamethonium and has failed to convert it from a depolarizing to a nondepolarizing agent.

The findings of the present study also furnished some information on the duration of action of
edrophonium. The observation that the respiratory depression produced by the intravenous administration of 0.3 mg/kg edrophonium after full recovery from the respiratory effect of Prestonal was less than 4 minutes (fig. 2) emphasizes again the relatively short duration of action of edrophonium. This short duration of action was also shown by the finding that when administered one minute before Prestonal (see table II) its potentiating effect was only moderate. The lack of greater potentiation under these circumstances was undoubtedly due to the fact that the effect of edrophonium wore off before the effect of Prestonal, and consequently its activity was disguised by that of the latter.

SUMMARY

(1) The effects of Prestonal on the tidal volume of 51 patients were investigated.
(2) The duration of action of Prestonal was found to be between those of suxamethonium and decamethonium. 0.75 mg/kg Prestonal caused apnoea lasting about 3 minutes in most subjects. The duration of respiratory depression after this dose was about 7 minutes. 1.5 mg/kg Prestonal caused apnoea of 5 minutes and respiratory depression of about 12 minutes duration.
(3) Prestonal was found to have relatively little cumulative effect.
(4) A transient fall of blood pressure and flushing of the skin were occasionally seen following intravenous administration of 1.5 mg/kg Prestonal.
(5) The respiratory effects of Prestonal were markedly potentiated by the subsequent intravenous administration of 0.3 mg/kg edrophonium. The potentiating effects of neostigmine and pyridostigmine were less marked.
(6) The effect of edrophonium, pyridostigmine and neostigmine on the myoneural effects of Prestonal indicated that this compound produced a depolarization block in man.

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REFERENCES