A CLINICAL TRIAL OF HAYATIN METHIODIDE AS A RELAXANT IN 100 CASES

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SUMMARY

Hayatin methiodide has been used as a muscle relaxant during surgery in 100 patients. This drug provided adequate relaxation for endotracheal intubation and surgery. It appeared to be about one-third as potent as tubocurarine. The duration of both these drugs was of equal magnitude in equipotent doses. The neuromuscular block produced by this drug could be completely reversed by neostigmine. It was relatively free from serious side-effects and appears to be a promising muscle relaxant.

Bhattacharji, Sharma and Dhar (1952) isolated an alkaloid, hayatin \( (C_{3}H_{8}N_{2}O_{9}) \) from an Indian indigenous plant \( Cissampelos pareira \) Linn. Its m.p. is 303°C (decomp.) and it is optically inactive. Its methiodide derivative [m.p. 281°C (decomp.)] is also optically inactive and has a chemical structure closely similar to that of tubocurarine chloride with a difference in the relative orientation of the OH and OCH\(_{3}\) groups (Bhattacharji, personal communication, 1964).

Hayatin methiodide has been shown to be a potent neuromuscular blocking agent in several species of animals (Pradhan, Ray and Varadan, 1952; Pradhan and De, 1953, 1959). In mice and rabbits, it was found to be twice as active as tubocurarine chloride, whereas in cats and dogs the two compounds were almost equipotent. The duration of action of their equipotent doses appeared to be approximately the same. The characteristics of neuromuscular block produced by hayatin methiodide and tubocurarine are similar. The neuromuscular block produced by this compound could be completely antagonized by anticholinesterases such as neostigmine.

Hayatin methiodide caused hypotension in cats and dogs that could be prevented by antihistaminic agents indicating thereby a possibility of histamine release by the drug. It showed no direct action on the heart, but caused a brief increase of leg volume indicating its vasodilating effect. The release of histamine by this drug could be further corroborated by its stimulating effect on gastric and bile secretions and formation of weal following its intradermal injection (Pradhan, Ray and Varadan, 1958).

With low doses \((0.2-0.4 \text{ mg/kg})\) no significant effect on the autonomic ganglia has been observed either in experiments on the pressor response to acetylcholine in atropinized cats and dogs, or on contraction of nictitating membrane of cats following preganglionic stimulation (Pradhan, Ray and Varadan, 1958). Recently, however, with doses of 0.8–1 mg/kg blockade of contraction of nictitating membrane up to 30 per cent has been observed (Vohra and Pradhan, 1964, unpublished data).

The drug was not effective when given orally (Pradhan, Ray and Varadan, 1958). Intraventricular administration of hayatin methiodide caused stimulation of the central nervous system (Sur and Pradhan, 1964) like tubocurarine.

Estimation of hayatin methiodide by a spectrophotometric method showed a peak concentration in blood taken within 2 minutes after intravenous administration and virtual disappearance in 15-minute samples. About 4 to 8 per cent of the drug was excreted unchanged in the urine within 3 hours after injection (Basu and Pradhan, 1964).

The \( LD_{50} \) in mice and rabbits was found to be 0.36 and 0.07 mg/kg respectively; the main cause of death was respiratory paralysis (Pradhan...
Hayatin methiodide has recently been subjected to a clinical trial; the observations in the first 100 cases are reported in this paper.

**METHOD**

Hayatin methiodide was used as a muscle relaxant during surgery in 100 patients selected at random (42 males; 58 females), who were considered fit to undergo surgery. The ages ranged from 16 to 75 years (table I) and body weights from 22 to 65 kg. The nature and number of operations, 87 of which were abdominal are given in table II; the duration of these operations ranged from 0.5 to 3 hours.

**Table I**

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>11-20</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td>21-30</td>
<td>9</td>
<td>20</td>
</tr>
<tr>
<td>31-40</td>
<td>11</td>
<td>16</td>
</tr>
<tr>
<td>41-50</td>
<td>8</td>
<td>9</td>
</tr>
<tr>
<td>51-60</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>61-70</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>71-80</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>42</td>
<td>58</td>
</tr>
</tbody>
</table>

The patients were premedicated with atropine sulphate (0.65 mg) half to one hour prior to surgery. Anaesthesia was induced with thiopentone sodium (3–5 mg/kg) usually followed (and in some cases preceded) by hayatin methiodide (0.5–2.5 mg/kg in 0.5 per cent aqueous solution); in some cases ether was used to induce and maintain anaesthesia before injecting hayatin methiodide. The respiration was assisted in the beginning and when apnoea supervened, the lungs were inflated with oxygen, laryngoscopy performed and the trachea intubated under direct vision with a wide-bore cuffed endotracheal tube. After inflation of the cuff ventilation was controlled using nitrous oxide and oxygen (2 l./min; 1 l./min) in a closed circuit with carbon dioxide absorption. Hyperventilation was carried out during the operation.

Blood pressure was recorded using a sphygmomanometer and auscultation before and at desired intervals after the induction of anaesthesia. In 58 cases (table VI, schedule A) recordings were made every 2–5 minutes following injection of hayatin methiodide. In 12 cases (table VI, schedules B and C) the blood pressure was taken every minute for 5 minutes before and 15 minutes after administration of hayatin methiodide. Pulse rate was also noted at frequent intervals before and after the injection of the drug. Electrocardiographic records were made in 6 cases selected at random, using standard limb leads before and at frequent intervals after the initial and supplementary doses of hayatin methiodide.

To study the degree and duration of relaxation, finger movement was recorded in 5 patients following electrical stimulation of a motor nerve in the wrist (Mapleson and Mushin, 1955). The ulnar nerve was stimulated by square wave pulses of 0.3 m.sec duration at 100–130 volts and at the rate of 0.1–1/sec, and the movement of the thumb or the little finger was recorded kymographically.

A suitable dose (5–15 mg) of the relaxant was repeated, wherever required. At the end of the operation the residual effect of the relaxant was
reversed by neostigmine methylsulphate (1.5–2.5 mg) preceded by atropine sulphate (1.3 mg).

RESULTS

Onset of action.

Maximum relaxation was seen within 1 to 2.5 minutes after injection of the drug. In patients to whom ether was being given prior to injection, the onset was more rapid (30–40 sec).

Initial dose.

The patients were given initial doses of hayatin methiodide ranging from 0.5–2.5 mg/kg (total 25–100 mg). The effectiveness of these doses in producing satisfactory conditions for endotracheal intubation is shown in table III. Relaxation of jaw, adequate visualization of the larynx by direct laryngoscopy without resistance from the patient and absence of violent cough or gagging following endotracheal intubation were considered to be the criteria for satisfactory conditions.

<table>
<thead>
<tr>
<th>Dose (mg/kg)</th>
<th>Number of intubations</th>
<th>Duration of relaxation (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5–0.6</td>
<td>0</td>
<td>Easy 44 minutes</td>
</tr>
<tr>
<td>0.8–1.0</td>
<td>0</td>
<td>Difficult 44 minutes</td>
</tr>
<tr>
<td>1.1–1.4</td>
<td>14</td>
<td>Total 44 minutes</td>
</tr>
<tr>
<td>1.5</td>
<td>45</td>
<td></td>
</tr>
<tr>
<td>1.6–2.1</td>
<td>11</td>
<td></td>
</tr>
</tbody>
</table>

An initial dose of 1.5 mg/kg or higher was found to be adequate both for intubation and for producing muscle relaxation for surgery. In some cases a small supplementary dose (5–15 mg) of the relaxant was needed to establish complete control of ventilation and full surgical relaxation.

Duration of action.

In some patients the action of the initial dose persisted long enough to cover the entire duration of operation until termination by neostigmine; in others, further supplementary doses (5–15 mg) were needed.

The duration of action of a particular initial dose was reckoned as the interval between its injection and that of a supplementary dose or that of the terminating dose of neostigmine.

The data on the duration of action of an initial dose of 1.4–1.5 mg/kg given to 50 patients were further analyzed and their distribution has been illustrated in a histogram (fig. 1). The overall mean of the duration of action in this group was 44 minutes.

For an objective estimation of the duration of action, recording of the thumb or little finger movement induced by electrical stimulation over the ulnar nerve in the wrist was made in 5 patients initially anaesthetized with thiopentone, nitrous oxide and oxygen and ether. After intra-
venous injection of hayatin methiodide (1 mg/kg) ether was stopped and controlled hyperventilation was carried out through soda-lime with a fresh gas flow of nitrous oxide and oxygen (2 l/min and 1 l/min). This caused complete abolition of the twitch for a period of 25–60 minutes (fig. 2). In all these cases the amplitude of twitch was completely restored by neostigmine methylsulphate 1.5–2.5 mg within 6–8 minutes.

**Dose requirement.**

An estimation of the dose requirement during operations of varying durations was made in 57 patients; these cases needed one or more small supplementary doses to maintain adequate relaxation and therefore had a minimum residual amount of the relaxant at the end of the operation. The dose requirement in these cases ranged from 0.6 to 2.5 mg/kg/hr. The distribution of this

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**Fig. 2**

Recording of thumb movement in response to electrical stimulation over the ulnar nerve in the wrist in a patient (C.M.N., male, 50 yrs, 55 kg) undergoing prostatectomy.
Marked falls (more than 40 mm Hg) of mean blood pressure occurred in 6 out of these 58 cases; the pre-operative blood pressure of 2 of these was about 179/90 mm Hg. However, only 3 of these patients needed a small dose of a vasopressor agent for restoration of blood pressure. The speed of restoration varied in different patients; in some it was quick (3–5 minutes), while in others it took about 10 minutes. In some cases the blood pressure rose higher than the initial level before settling down to normal.

To study the hypotensive effect of hayatin methiodide alone, 8 patients were anaesthetized with ether. When the blood pressure recorded every minute showed a steady level, hayatin methiodide (1 mg/kg) was given intravenously. All these cases showed hypotension of various magnitudes (table VI). Preadministration of an antihistaminic agent (promethazine hydrochloride, 25–50 mg) in 4 other cases similarly treated, appeared to reduce the hypotension to some extent (table VI).

The changes in pulse rate occurring within 15 minutes of the injection of hayatin methiodide in 50 patients are shown in table VII. An increase in pulse rate was seen in 40 per cent, a decrease in 46 per cent and no change in 14 per cent of these cases.

Electrocardiographic studies in 6 cases did not show any change attributable to this drug.

Other effects.

In 8 cases of Caesarean section, the relaxant did not produce any untoward effect on the foetus or the uterine tone.

In 3 patients a generalized urticarial rash was observed after administration of the relaxant, but disappeared spontaneously in about half an hour.

**Table V**

*Dose requirements of hayatin methiodide and tubocurarine.*

<table>
<thead>
<tr>
<th>Duration of anaesthesia (hr)</th>
<th>Hayatin methiodide</th>
<th>Tubocurarine chloride*</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of cases</td>
<td>mg</td>
<td>mg/kg</td>
</tr>
<tr>
<td>1</td>
<td>72.32 ± 1.86</td>
<td>1.64 ± 0.04</td>
</tr>
<tr>
<td>1½</td>
<td>81.52 ± 3.90</td>
<td>1.97 ± 0.07</td>
</tr>
<tr>
<td>2</td>
<td>88.22 ± 6.55</td>
<td>2.11 ± 0.12</td>
</tr>
</tbody>
</table>

*Data of Dundee, Gray and Riding (1954) on tubocurarine in 100 patients are given for comparison.
TABLE VI
Changes in mean blood pressure due to hayatin methiodide under different schedules of treatment.

<table>
<thead>
<tr>
<th>Schedule of treatment*</th>
<th>Nature of pressure change</th>
<th>No. of cases showing intensity of change (mm Hg)</th>
<th>Total number of cases</th>
<th>Percentage of the total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>1–10</td>
<td>11–20</td>
<td>21–30</td>
</tr>
<tr>
<td>A. Thiopentone and hayatin methiodide (58 cases)</td>
<td>Rise</td>
<td>4</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Fall</td>
<td>16</td>
<td>8</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>None</td>
<td>6</td>
<td>0</td>
<td>7</td>
</tr>
<tr>
<td>B. Hayatin methiodide (58 cases)</td>
<td>Fall</td>
<td>0</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>C. Antihistaminics and hayatin methiodide (4 cases)</td>
<td>Rise</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Fall</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

Schedule A. Hayatin methiodide was injected immediately following or preceding thiopentone.
Schedule B. Hayatin methiodide was injected when the blood pressure level became steady after anaesthesia (as detailed in the text).
Schedule C. Same as in schedule B, except that an antihistaminic was used in premedication.

TABLE VII
Changes in pulse rate (beats/min)

<table>
<thead>
<tr>
<th>Nature of change</th>
<th>Number of cases showing change in pulse rate</th>
<th>Total number of cases</th>
<th>Percentage of the total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1–10</td>
<td>11–20</td>
<td>21–30</td>
</tr>
<tr>
<td>Increase</td>
<td>12</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Decrease</td>
<td>16</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>None</td>
<td>7</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

A transient rash was observed in another patient along the course of the vein through which the drug was injected.

Reversal of the relaxant effect.

At the end of the operation the residual effect of the relaxant could be completely reversed by neostigmine 1.5–2.5 mg preceded by atropine (1.3 mg). The reversal was complete and rapid in all cases, except in one in whom a gastrojejunostomy was performed for an inoperable carcinoma of the pyloric antrum. Even after injection of neostigmine 2.5 mg at the end of the operation, a persistent weakness of the muscles of the jaw and the tongue was observed in this case, though his respiratory excursions were adequate. Complete recovery took place in about 3 hours during which the patient breathed through a nasotracheal tube.

DISCUSSION

In the present series of 100 cases, hayatin methiodide has proved to be an effective and safe neuromuscular blocking agent for clinical use. It was found to resemble tubocurarine in many respects.

The dose requirement of hayatin methiodide for the first 2 hours of operation ranged from 0.6–2.5 mg/kg/hr. Such a wide variation in its dose requirement could be expected in a series of patients selected at random because of variations in the condition of patients and the nature of operations.

Doughty and Wylie (1951) found that 20 mg of tubocurarine and 80 mg of gallamine when given along with thiopentone produced good muscular relaxation for endotracheal intubation in 76 and 80 per cent of cases respectively. However, the
dosage of thiopentone (250–1000 mg, i.e. twice the sleeping dose) used by these workers was higher than is now usual. In this series, using a much smaller dose of thiopentone (100–250 mg) together with 1.5 mg/kg of hayatin methiodide, it was possible to perform intubation easily in 94 per cent of cases (table III). Since, with the decrease in the depth of anaesthesia, higher doses of a relaxant become necessary to achieve ideal conditions for intubation, our data may not be properly comparable with those of Doughty and Wylie. However, if it is to be compared at all, hayatin methiodide would appear to be at least one-third as potent as tubocurarine and at least 1.5 times more than gallamine, although in earlier animal experiments its potency appeared to be equal to or greater than that of tubocurarine (Pradhan and De, 1953). The average dose requirements of hayatin methiodide for durations of 60, 90 and 120 minutes again reveal that the relative potency of hayatin methiodide is about one-third of that of tubocurarine (table V).

The average duration of relaxation after an effective dose (0.8–2.5 mg/kg) of hayatin methiodide has been found to vary from 32 to 44 minutes (table IV). The method of assessing the duration of action may have some fallacies, because the selected end-point of action of a particular dose was not precise. For example, repetition of a supplementary dose was usually made on subjective impressions of the anaesthetists and the surgeon. The termination of relaxation by neostigmine did not also indicate the end-point of drug action. More precise determination of duration of action of hayatin methiodide by experiments on conscious volunteers (Macfarlane et al., 1950) has not been done. A more objective assessment of the duration of action has been possible, however, by recording the thumb movements before and after injection of hayatin methiodide in 5 cases of this series. Preadministration of ether in these cases influenced the results to some extent. The duration of action of tubocurarine has been stated to be 25–40 minutes (Evans and Gray, 1959; Goodman and Gilman, 1955); as shown by animal as well as the clinical data, the duration of action of hayatin methiodide when given in equipotent doses appears to be at least of the same magnitude.

Hayatin methiodide when given alone or in combination with thiopentone produced a transient fall of blood pressure of varying intensity, but this was seldom sufficient to need treatment. Hypotension may be due partly to histamine release, since preadministration of an antihistaminic agent appeared to reduce the intensity of such hypotension to some extent; this may also be due to a ganglion blocking action which has been demonstrated in high doses (loc. cit.). Similar effects on blood pressure have been described also in patients receiving tubocurarine (Thomas, 1957; Prime and Gray, 1952; Goodman and Gilman, 1955). Both increase and decrease in pulse rate following administration of hayatin methiodide have been observed in this series. Similar changes have been reported in the case of tubocurarine (Doughty and Wylie, 1951).

ACKNOWLEDGMENTS

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REFERENCES


