HEXAFLUORENIUM EXTENSION OF SUXAMETHONIUM BLOCK

BY

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SUMMARY

Clinical trials of the effectiveness of hexafluorenium (Mylaxen), as an extender of suxamethonium block, have been conducted in 645 administrations of halothane. No serious complications which could be attributed to the drug were encountered. Histamine release after the administration of hexafluorenium was not observed. In view of the extreme efficacy and the apparent safety of the method described, its further application is considered to be justified.

Hexafluorenium was prepared in 1954 by Cavallito, Gray and Spinner, as one of a group of bis-fluorenyl-bis-quaternary ammonium compounds, and a preliminary account of its pharmacological actions was given by Macri (1954). It was shown to produce neuromuscular block in dogs and to possess approximately the same potency as tubocurarine in this species.

The first report of the use of hexafluorenium to provide muscle relaxation during surgical operations was published by Cordaro and Arwood (1955). They employed the drug in 6-9 mg doses once anaesthesia was established and administered additional amounts of 3-6 mg at intervals of 15 to 30 minutes, in order to maintain adequate relaxation. Two important observations emerged from this study: that hexafluorenium was more effective during ether and cyclopropane anaesthesia than during nitrous oxide or thiopentone administration, and was practically ineffective in the unanaesthetized human subject; and that in two patients who received suxamethonium 30 mg, following fractional doses of hexafluorenium, apnoea lasting 20 and 30 minutes respectively occurred.

The influence of anaesthetic agents on the neuromuscular blocking activity of hexafluorenium was discussed by Cavallito, Arrowood and O'Dell (1956). They postulated that the "blanketing" of non-specific lipophilic sites (fat depots, nervous tissue and cell membrane structures) by anaesthetic agents possessing high lipid affinities would lessen the attraction of these receptors for hexafluorenium, and thus enhance its action at the neuromuscular junction. They were able to demonstrate marked potentiation of hexafluorenium block in lightly anaesthetized cats following pretreatment with biologically inactive lipophilic compounds.

Arrowood and Kaplan (1956) reported on the combined use of hexafluorenium and suxamethonium in thirty patients. They utilized a continuous intravenous drip, containing 0.02 per cent hexafluorenium, and intermittent injections of suxamethonium (10-20 mg), to maintain apnoea. They concluded that suxamethonium intensified the neuromuscular block produced by hexafluorenium.

The first report of serious complications resulting from the administration of hexafluorenium, was published by Selvin and Howland (1959). They used a mixture of hexafluorenium and suxamethonium in six patients; bronchospasm was observed in all cases and proved fatal in one.

Foldes et al. (1960b) demonstrated the anticholinesterase activity of hexafluorenium both in vivo and in vitro; an activity practically entirely limited to the inhibition of plasma cholinesterase. No reduction of the red cell acetylcholinesterase could be demonstrated following intravenous injection of hexafluorenium, and it was concluded that the agent was unable to penetrate the intact erythrocyte. It is interesting to note that inhibition was observed in washed erythrocytes suspended in normal saline.

The apparently selective inhibition of plasma cholinesterase by hexafluorenium led Foldes et al. (1960a) to perform clinical trials of the drug,
in combination with suxamethonium, to produce relaxation in lightly anaesthetized patients. They found a five- to sevenfold reduction in the amount of suxamethonium required for adequate relaxation compared with the requirements in a similar series in which hexafluorenium was not used. Several additional advantages were claimed for the combination, among others the absence of such side effects as tachycardia, hypotension and bronchospasm.

When, in September 1962, a small amount of hexafluorenium was made available for clinical trials in Utrecht, the authors decided to investigate the combination with suxamethonium, to provide muscle relaxation during halothane anaesthesia. The lack of reported side effects, when the agents were administered separately, and the possibility of potentiation by the highly lipophilic anaesthetic halothane, were the most important considerations leading to this decision.

PRELIMINARY TRIALS

Five young adults, scheduled for elective surgery, were anaesthetized with nitrous oxide, oxygen and 1 per cent halothane. Five minutes after induction was completed a control blood sample was withdrawn and hexafluorenium 40 mg was then injected through the same needle. Further blood samples were taken 5, 10, 30, and 60 minutes after administering hexafluorenium. Serum cholinesterase determinations were performed using the spectrophotometric technique described by Kalow and Lindsay (1955). In vitro estimations of cholinesterase inhibitions were performed in the same control sera, by adding hexafluorenium in a series of dilutions. The results are displayed in tables I and II: it may be observed that the maximum inhibition produced by hexafluorenium 40 mg (in these cases rather more than 0.5 mg/kg) corresponds to 8 \( \mu \text{g/ml} \) in vitro, and further, that 60 minutes after the injection the degree of inhibition (45 per cent) corresponds to 2 \( \mu \text{g/ml} \) in vitro.

In the initial clinical trial the dosage of hexafluorenium was approximately 0.5 mg/kg, and the administration of suxamethonium was based on the need to maintain apnoea during intrathoracic procedures, or to provide adequate relaxation during abdominal operations. The average requirement of suxamethonium in twenty-five thoracic operations was 9.7 \( \mu \text{g/kg/min} \), and in eighty-three abdominal operations 4.8 \( \mu \text{g/kg/min} \).

No serious complications were encountered in these cases. Evidence of muscarinic activity was seen in eight patients, with bradycardia in all, increased salivation in five and mild bronchospasm in one. An immediate reversal of these symptoms was achieved in all cases by the administration of atropine. Neither serious degrees of tachycardia nor large falls of arterial blood pressure were observed; the relaxation was excellent in all cases, and the ease of control most impressive.

EXTENDED CLINICAL USE

Encouraged by the results of the preliminary trials, the authors decided to introduce the combination of hexafluorenium and suxamethonium into routine clinical practice. As soon as regular supplies became available the technique was incorporated in the training programme, and up to the time of writing it has been employed on 645 occasions. The only contraindications stipulated were operative procedures expected to last less than 1 hour and patients with extensive hepatic disease with low cholinesterase levels. Blood pressures and pulse frequency have been moni-
tored in all cases; in rather more than 500 with an automatically-registering combined blood pressure meter and cardiachotometer (Haemotonograph, Godart).

The types of operations performed under halothane anaesthesia with hexafluorenium-suxamethonium relaxation are shown in tables III and IV. All age groups are represented, the youngest patient to date being 8 months old and the eldest 89 years.

**TABLE III**

*Types of abdominal operations performed with the hexafluorenium-suxamethonium combination.*

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrectomy</td>
<td>105</td>
</tr>
<tr>
<td>Biliary tract</td>
<td>144</td>
</tr>
<tr>
<td>Colon and rectum</td>
<td>87</td>
</tr>
<tr>
<td>Major urology</td>
<td>31</td>
</tr>
<tr>
<td>Hiatus hernia</td>
<td>11</td>
</tr>
<tr>
<td>Splenectomy</td>
<td>8</td>
</tr>
<tr>
<td>Pancreatic-duodenectomy</td>
<td>7</td>
</tr>
<tr>
<td>Other</td>
<td>97</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>491</td>
</tr>
</tbody>
</table>

**TABLE IV**

*Types of thoracic operations performed with the hexafluorenium-suxamethonium combination.*

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary resections</td>
<td>95</td>
</tr>
<tr>
<td>Oesophagus resections</td>
<td>18*</td>
</tr>
<tr>
<td>Hiatus hernia</td>
<td>14</td>
</tr>
<tr>
<td>Splenorenal shunt</td>
<td>9†</td>
</tr>
<tr>
<td>Other</td>
<td>18</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>154</td>
</tr>
</tbody>
</table>

* Includes 3 total resections with colon interposition.
† Includes 3 emergency operations.

**METHODS**

*Abdominal surgery.*

Anaesthesia is induced with a sleep dose of thiopentone, or in elderly patients methohexitone, followed by suxamethonium 20–40 mg. The lungs are now rhythmically inflated with nitrous oxide, oxygen and 1 per cent halothane, until maximal relaxation permitting endotracheal intubation is attained. The anaesthesia is maintained with oxygen and halothane in a completely closed system (Dräger or Loosco circle absorber), with the halothane vaporizer (Loosco (Pearce, 1962)) outside the circle. When adequate spontaneous respiration is re-established, the initial dose of halothane is administered intravenously, followed 3–5 minutes later by suxamethonium. The approximate doses used are 0.5 mg/kg of halothane and 0.15 mg/kg of suxamethonium. Repeat doses of suxamethonium are usually required at 20–30-minute intervals and when, during the course of the anaesthesia, the effect of such a repeat dose wears off within 10 minutes, further administration of hexafluorenium (0.25–0.3 mg/kg) is indicated. Respiration is assisted during the operation, although in lower abdominal surgery, when a rule less suxamethonium is needed, spontaneous respiration may be permitted. After closure of the peritoneum the halothane is discontinued, the circuit is opened, and the respiration assisted with nitrous oxide and oxygen until the spontaneous respiration is adequate.

*Intrathoracic surgery.*

The same closed-circuit technique is employed as for abdominal operations, but in tuberculous patients the Waters system is preferred, sterilization of this unit being relatively simple. The initial dose of suxamethonium (0.3 mg/kg) is administered shortly before the pleura is opened, and supplementary doses (0.15–0.20 mg/kg) at 20–30-minute intervals. When the pleura is incised, the circuit is opened, and the lung allowed to collapse. It is then reinfated with a mixture of 70 per cent helium and 30 per cent oxygen, and after flushing the system a few times with this mixture the circuit is closed and anaesthesia continued with oxygen and halothane. The administration of halothane is discontinued as soon as the pleura is closed, and the respiration is supported with nitrous oxide and oxygen, until adequate respiratory efforts render further assistance unnecessary.

**RESULTS**

*Relaxation.*

This was excellent in all but one case. The patient in question, a young Spaniard, was apparently capable of hydrolyzing (?) suxamethonium rapidly, even after the administration of 80 mg of hexafluorenium. Two weeks after the anaesthetic his serum cholinesterase was found to be abnormally high (201 μmol/ml/hour), although in vitro estimations revealed normal inhibition by hexafluorenium (75 per cent inhibition at the 8 μg/ml level).

A consistent finding in this clinical trial was the rapid return to normal of neuromuscular activity when the administration of halothane was discontinued.
Cardiovascular effects.

Transient falls of arterial pressure (up to 20 mm Hg) were frequently observed in the first few minutes following the injection of hexafluorenum. Serious hypotension, with systolic pressures at or below the pre-operative diastolic level, and not related to blood loss, occurred on twelve occasions, and in every case rapid improvement took place when the halothane concentration was reduced.

The pulse rate was usually slightly increased during the first few minutes following the injection of hexafluorenum. Significant tachycardia, with pulse rates exceeding control values by at least 30 per cent, was encountered on twenty-two occasions. The intravenous administration of 1–3 mg propranolol (I.C.I. 45,520) in the last eight patients demonstrating tachycardia proved effective: the pulse rate diminished rapidly, reaching normal levels in all cases within 10 minutes.

Bradycardia, necessitating the use of atropine, was seen in a further sixteen cases.

Bronchospasm.

With the exception of the case reported in the preliminary trials, no respiratory complications have been encountered, either during or after anaesthesia.

During the course of these trials Mostert and Kündig (1964) reported a case of fatal bronchospasm following the administration of hexafluorenum. They suggested, largely on the basis of reactions to intradermal injections, that hexafluorenum caused histamine release and, as a result, bronchospasm.

The possibility of histamine release by hexafluorenum had not previously occurred to the present authors, and although their clinical experience with hexafluorenum was at variance with the observations of Mostert and Kündig (1964), further investigation was clearly indicated.

ADDITIONAL STUDY

Blood samples were taken from ten adult patients selected at random, before and at various intervals after the intravenous injection of 40 mg hexafluorenum. The histamine concentration was determined by biological assay using a guinea-pig ileum preparation. The results, presented in table V, reveal no significant change in blood histamine levels at any time up to 1 hour after the administration of hexafluorenum.

An attempt was made to duplicate the experiment reported by Mostert and Kündig (1964), using intradermal injection of hexafluorenum to demonstrate histamine release. It was felt that the solvent used in the commercial preparation may have been responsible for the weals produced, containing as it does 20 per cent polyethylene glycol, a hygroscopic substance. A comparison was made: between the weals produced by the intradermal injection of Mylaxen (the commercial preparation of hexafluorenum, an aqueous solution of hexafluorenum and the solvent used in Mylaxen). All three substances produced urticarial weals (fig. 1), the smallest being that caused by the solvent. In contrast to the experience of Mostert and Kündig, all weals disappeared rapidly and no residual pigmentation was observed.

DISCUSSION

The rapid resumption of normal neuromuscular activity which followed the withdrawal of halothane supports the theory advanced by Cavallito, Arrowood and O'Dell (1956), but extended trials now in progress are required to determine whether halothane anaesthesia prolongs the anticholinesterase activity of hexafluorenum.

The incidence and degree of tachycardia which follows hexafluorenum administration is a point of disagreement in some recent publications. Mostert (1963) reported a constant slight increase in twenty-five cases when hexafluorenum was administered to patients anaesthetized with methohexitone ("Incidenten après l'hexafluorenum on a observé, de façon constante, une légère accélération du pouls: de 10 à 30 par minute"). More serious degrees of tachycardia were noted when hexafluorenum was given during anaesthesia with halothane, or trichloroethylene (Mostert and Kündig, 1964). They noted that the heart rate was increased in all but one of sixty-two patients receiving hexafluorenum. The heart rate increased by 6 to 90 beats/min; average 38 beats/min. This tachycardia was ascribed to a sympathomimetic activity of hexafluorenum, and the prompt return to normal pulse rates in the present series following the administration of a specific adrenergic beta-
receptor blocking agent tends to support this assumption. At this stage no explanation can be offered for the fact that excessive tachycardia was so rarely encountered during these trials. The muscarinic action of suxamethonium may have played a role in the few cases in which this drug was injected less than 3 minutes after the administration of hexafluorenium, although it is noteworthy that repeat doses of suxamethonium were never followed by significant reductions in the pulse rate.

Histamine has been shown to antagonize suxamethonium-induced neuromuscular block (Bovet-Nitti et al., 1964) when injected in the dose 0.5 mg/kg 7 to 10 minutes before the injection of suxamethonium. The administration of hexafluorenium in the same dosage produces potentiation and prolongation of the block. These facts and the unequivocal results of blood levels (table V) lead to the conclusion that the reported cases of bronchospasm and the (variable) response to intradermal injections were not caused by released histamine.

The excellent relaxation and the relative lack of side effects encountered in the present study justify the continued clinical application of the hexafluorenium-suxamethonium combination.

ACKNOWLEDGMENTS

We are indebted to Professor W. Lammers for granting facilities for the determination of blood histamine levels in the Pharmacological Department of the National Institute for Public Health (Utrecht).

Pure crystalline hexafluorenium, needed for intradermal testing, was obtained through the good offices of Mr. P. B. v.d. Lande of Nourypharm.
REFERENCES


L'EXTENSION DU BLOC AU SUXAMETHONIUM PAR L'HEXAFLUORENIUM

SOMMAIRE
Des essais cliniques sur l'efficacité de l'hexafluorenium (Mylaxen) pour étendre le bloc du suxaméthonium ont été effectués au cours de 645 administrations d'halothane. On n'a pas rencontré de complications sérieuses qui seraient à attribuer à la drogue. On n'a pas observé de libération d'histamine après l'administration d'hexafluorenium. Vu l'extrême efficacité et l'innocuité apparente de la méthode décrite, on considère qu'il est justifié de continuer à l'employer.

DIE VERSTÄRKUNG DES SUXAMETHONIUM- BLOCKS DURCH HEXAFLUOREN

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