INTERACTION OF HALOTHANE WITH NON-DEPOLARIZING NEUROMUSCULAR BLOCKING DRUGS IN MAN

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1 Tetanic and single twitch contractions of the adductor pollicis muscles, in response to indirect stimulation of each ulnar nerve, were recorded in patients anaesthetized with thiopentone and nitrous oxide in oxygen.
2 Concentrations of 1 and 2% halothane were administered for 10 min during recovery from neuromuscular paralysis by tubocurarine, dimethyl tubocurarine and gallamine.
3 During exposure to halothane, the peak contraction of the tetanic response was reduced and tetanic fade was increased whereas the single twitch was unaffected.
4 The effects of halothane on the tetanic responses were readily antagonized by intravenous neostigmine preceded by atropine.
5 Halothane could act post-synaptically by a non-depolarizing block or by desensitizing the postsynaptic receptors, but a pre-synaptic action seems more likely since neuromuscular block was only evident when tetanic stimulation was applied. Such an effect could be caused by impairment of the release of acetylcholine.

Introduction

Like other general anaesthetics, halothane in sufficient doses will cause muscular relaxation which results primarily from depression of the central nervous system (Ngai, Hanks & Farhie, 1965; Katz & Gissen, 1967). It is also well established that halothane enhances and prolongs the paralysing effects of non-depolarizing neuromuscular blocking agents (Burns, Mushin, Organe & Robertson, 1957; Katz & Gissen, 1967; Baraka, 1968; Katz, 1971; Miller, Eger, Way, Stevens & Dolan, 1971; Miller, Way, Dolan, Stevens & Eger, 1971; 1972). Consequently, it has been recommended that the doses of these paralysing drugs should be reduced when they are used in combination with halothane (Hughes, 1969).

The aim of the present study was to obtain a quantitative assessment of this drug interaction in man as such information has not yet been published.

Methods

Studies were performed in nine patients who had given their informed consent and were about to undergo elective urological surgery. No premedication was given and anaesthesia was induced with thiopentone (400–600 mg i.v.). Intubation was achieved without the use of a neuromuscular blocking agent after spraying the larynx with 4% lignocaine. Anaesthesia was maintained with a mixture of nitrous oxide and oxygen given by intermittent positive pressure ventilation; supplements of thiopentone (100–200 mg) and either pentazocine (30–60 mg) or pethidine (50–100 mg) were given intravenously as required. Simultaneous measurements of tetanic and single twitch contractions of the adductor pollicis muscles were performed as described previously (Sugai, Hughes & Payne, 1975a). Each ulnar nerve was stimulated supramaximally at the wrist every 12 s with rectangular pulses of 200 μs duration, one nerve at 50 Hz for 1 s and the other with single shocks. Concentrations of 1 and 2% halothane in oxygen were administered for periods of 10 min when tetanic fade had almost disappeared during recovery from neuromuscular blocking doses of tubocurarine (0.25–0.5 mg/kg i.v.), dimethyl tubocurarine (0.1 mg/kg i.v.) and gallamine (0.8–1.6 mg/kg i.v.).

Groups of three patients were used for each drug studied. The effects of neostigmine (2.5 mg i.v.) on this type of block were also investigated.
Figure 1 Tracings from three anaesthetized patients (85, 95, 93 kg males) showing the tetanic responses of the adductor pollicis muscles during recovery from neuromuscular blockade by a) tubocurarine 0.5 mg/kg i.v., b) dimethyl tubocurarine 0.1 mg/kg i.v. and c) gallamine 0.8 mg/kg i.v. Administration of 2% halothane for 10 min (solid bar line) caused an increase in fade (seen as the lighter lines) with a reduction in the peak height of the tetanic contraction. The effects were reversed when the halothane was turned off.

Results

In each group of three patients simultaneous recordings of the tetanic and twitch responses showed that after tubocurarine, dimethyl tubocurarine and gallamine, administration of 2% halothane caused an immediate increase in fade (seen as the lighter lines) with a reduction in the peak height of the tetanic contraction (Figure 1) whereas the single twitch was unaffected (Figure 2). The impairment of the tetanic responses was reversed with the halothane was discontinued. Recordings taken at the same time but at a faster paper speed, show more clearly the increase in tetanic fade on exposure to 2% halothane during recovery from neuromuscular blockade by tubocurarine, dimethyl tubocurarine and gallamine (Figure 3). This increased fade rapidly disappeared when the halothane was withdrawn.

A control tracing, recorded both at slow and fast paper speeds taken in the absence of a neuromuscular blocking agent, showed no consistent reduction in the peak height of the tetanic contraction or the appearance of fade during exposure to 2% halothane for 10 min (Figure 4).

Figure 5 shows an enlarged view of a tetanic contraction and our method of deriving a quantitative assessment of tetanic fade. Fade is defined as the rapid 'fall off' of the tetanus from the peak height to a level at which it 'holds' until the end of the stimulus, i.e. (A−B). Since recording had to be discontinued when the patients underwent surgery it was not always possible to wait until fade had completely disappeared. Thus, the percentage fade before administration of halothane was measured as (A−B)/A × 100 and after halothane (A′−B′)/A′ × 100. Therefore, the increase in percentage fade due to halothane can be expressed as (A′−B′)/A′ × 100 minus (A−B)/A × 100.

The mean results obtained in the three groups of three patients are summarized in Table 1. No
Figure 3  Tracings from three anaesthetized patients (70 kg female, 95, 93 kg males) recorded at a faster paper speed clearly show the increase in tetanic fade on exposure to 2% halothane for 10 min (solid bar line) during recovery from neuromuscular blockade by a) tubocurarine 0.25 mg/kg i.v. b) dimethyl tubocurarine 0.1 mg/kg i.v. and c) gallamine 0.8 mg/kg i.v.

Figure 4  Control tracings from an anaesthetized patient (60 kg male) of the tetanic responses of the adductor pollicis muscle recorded at both slow (a) and fast (b) paper speeds. In the absence of a neuromuscular blocking agent there was no consistent reduction in the peak height of the tetanic contraction or the appearance of fade during exposure to 2% halothane for 10 min (solid bar line).
significant differences in their interaction with halothane were observed among the three neuromuscular blocking agents studied. However, after each drug, administration of 1% halothane for 10 min caused some reduction in the peak contraction and an increase in the percentage fade. These effects were significantly greater after exposure to 2% halothane; the P value approximated 0.01 for the increase in percentage fade.

It was also shown that the neuromuscular effects of 2% halothane, administered during recovery from neuromuscular blockade, were readily antagonised by intravenous neostigmine (2.5 mg) preceded by atropine (1.2 mg) and given while the administration of halothane continued (Figure 6).

Discussion

We have demonstrated that concentrations of 1 and 2% halothane, administered during recovery from neuromuscular paralysis by non-depolarizing agents, considerably reduced the peak contraction of the tetanus and increased the tetanic fade. Since recovery of the twitches of the adductor pollicis muscle was unimpaired, this observation highlights the genuine differences between the single twitch and the tetanic responses. Thus, as shown previously the tetanic response is a more sensitive and a more reliable index than the single twitch for the accurate assessment of recovery from neuromuscular blockade (Sugai, Hughes & Payne, 1976).

### Table 1

<table>
<thead>
<tr>
<th>Drug</th>
<th>1% halothane (10 min)</th>
<th>2% halothane (10 min)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dose (mg/kg i.v.)</td>
<td>Total number of exposures</td>
</tr>
<tr>
<td>Tubocurarine</td>
<td>0.25–0.5</td>
<td>3</td>
</tr>
<tr>
<td>Dimethyl tubocurarine</td>
<td>0.1</td>
<td>3</td>
</tr>
<tr>
<td>Gallamine</td>
<td>0.8–1.6</td>
<td>2</td>
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HALOTHANE AND NEUROMUSCULAR BLOCKADE 489

Our findings agree well with previous reports that anaesthetic concentrations of halothane potentiate paralysis by non-depolarizing agents in animals and in man (Burn, Epstein, Feigan & Paton, 1957; Katz & Gissen, 1967; Baraka, 1968; Hughes, 1970; Miller, Eger et al., 1971; Miller, Way et al., 1971; Miller, Way, Dolan, Stevens & Eger, 1972).

The neuromuscular blocking action of halothane was weak in magnitude since it could be demonstrated only in the presence of partial blockade by a non-depolarizing neuromuscular blocking agent and even then only the tetanic response was affected. Halothane reduced tetanic transmission with the reappearance of tetanic fade and in the absence of any depression of the single twitch it would seem that insufficient acetylcholine was available to maintain a sustained contraction. Presumably, the twitch was unaffected by halothane because 70–80% occupancy of the receptors was not achieved; it has been shown by Paton & Waud (1967) that this degree of occupancy is necessary before neuromuscular block becomes evident.

The mechanism of action of halothane at the neuromuscular junction is complex. An effect on nerve conduction was unlikely since both tetanic and single twitch responses would have been affected equally whereas in fact the twitches were unimpaired. A postsynaptic non-depolarizing block by halothane is a possibility since neostigmine was antagonistic. Alternatively, halothane may desensitize the post-junctional membrane to acetylcholine as shown by Karis, Gissen & Nastuk (1967) in electrophysiological studies in vitro. Such an effect has also been ascribed to suxamethonium after repeated administration when anticholinesterase drugs were shown to be antagonistic (Sugai, Hughes & Payne, 1975b).

The possibility of a presynaptic action of halothane cannot be excluded, and in fact, such a mechanism is supported by some of our evidence. For instance, neuromuscular block with halothane was manifested only when tetanic stimulation was applied. It is likely that prejunctional events would be more evident when the motor nerve terminals are fully activated and when the acetylcholine reserves are fully mobilized as during tetanic stimulation. It is possible that halothane causes a weak depressant action on the release of the transmitter from the motor-nerve terminals. This explanation is supported by the fact that neostigmine was antagonistic and that anticholinesterase drugs are known to have a facilitatory action on the motor-nerve terminal (Riker & Standaert, 1966).

The principal effect of halothane is uncertain; since we cannot verify in man that halothane impairs transmitter release, further study employing in vitro preparations from animal tissues may provide the answer.

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References


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