THE SCREENING OF ATRACURIUM IN MHS SWINE

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The non-depolarizing neuromuscular blocking drugs tubocurarine (Britt, Webb and Le Duc, 1974), gallamine (Ryan, 1979) and pancuronium (Chalstrey and Edwards, 1972; Waterman, Albin and Smith, 1980) have all been incriminated at some time as triggers of the malignant hyperthermia syndrome (MH) in susceptible individuals or swine. Although these original claims are now a matter of contention (Short et al., 1976; Denborough, 1979; Harrison, 1980) they do provide the raison d'être for the screening of all newly-developed non-depolarizing neuromuscular blockers for MH triggering potential.

We report the outcome of such an assessment of the recently developed non-depolarizing agent, atracurium besylate, in MHS Landrace swine. The design of the study differs from that of a previous study (Lucke, 1983) in that our animals were challenged (a) when atracurium-induced neuromuscular blockade was maximal and neither clinically waning nor reversed, and (b) with halothane alone, avoiding suxamethonium with its associated interaction with non-depolarizing agents at the neuromuscular junction (Harrison, 1973).

MATERIALS AND METHODS

Six MHS Landrace swine were selected on a positive MH response to a brief "barnyard" exposure to mask-administered halothane, the syndrome being reversed with dantrolene (Harrison, 1975). Weights ranged from 22 to 35 kg.

For all investigations, anaesthesia was induced in the pen with thiopentone administered via an ear vein on the first and via an internal jugular cather on subsequent occasions. Following endotracheal intubation, anaesthesia was maintained with 70% nitrous oxide in oxygen administered via a volume preset ventilator set to maintain normocarbia (as assessed by arterial gas analysis) supplemented by intermittent thiopentone.

Catheters were inserted to an internal jugular vein and carotid artery via a cut-down in the neck to provide: a source for samples of blood for the measurement of blood-gas tensions and acid-base balance, a continuous waveform display and digital read-out of arterial and venous pressures (Statham P23 strain gauges), and a route for the infusion of drugs and fluids. ECG monitoring (Hellige Servomed) was maintained using chest wall electrodes.

Temperature was recorded from an i.m. thermistor needle probe deep in the thigh muscle mass (ELLAB).

The atracurium challenge consisted of a 1.0-mg kg⁻¹ i.v. bolus in all instances except one, when 0.8 mg kg⁻¹ was administered inadvertently. The halothane challenge was by way of introduction of 2% halothane (Fluotec Mark 2 vaporizer) to the fresh gas supply.

Established malignant hyperpyrexia was identified by 20% increases in resting heart rate and mean arterial pressure, a stiffening of the hind quarters and the development of a combined metabolic and respiratory acidosis. Those animals which were destined for subsequent challenges were salvaged with titrated amounts of i.v. dantrolene, i.v. sodium bicarbonate and hyperventilation with 100% oxygen.
Before the challenge all animals were homeostatically stable, particular attention being paid to indices of cardiovascular function, and acid–base balance.

The design of the study was such that it could test the MH triggering potential of atracurium, and the modification of the triggering potential of halothane by atracurium.

Two animals (Nos 1 and 2) were challenged de novo with atracurium and then 1 h later with halothane and a second bolus dose of atracurium. The remaining four animals were challenged initially with halothane in order to provide control times for the onset of the syndrome, and 2 days later were rechallenged with atracurium. The last two (Nos 5 and 6) were given a third challenge of simultaneously-administered halothane and atracurium 1 h after the second.

RESULTS

The results are set out in table I.

Table I. Time (min) to trigger MH syndrome. Hal. = 2% halothane; Atra. = atracurium; CPK = Creatine phosphokinase measured before and 24 h after initial halothane challenge (normal: 10-75 u litre⁻¹); Neg. = MH not triggered; — = Investigation not performed; d = Death from untreated MH.

<table>
<thead>
<tr>
<th>Pig No.</th>
<th>Hal.</th>
<th>Atra.</th>
<th>CPK (u litre⁻¹)</th>
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<td>Before</td>
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<tr>
<td>1</td>
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<td>Neg</td>
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<td>5</td>
<td>15</td>
<td>Neg</td>
<td>20</td>
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<tr>
<td>6</td>
<td>15</td>
<td>Neg</td>
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Atracurium failed to trigger the syndrome when given alone but, despite a slight increase in the time required (from 15 to 20 min), the syndrome appeared on cue when animals Nos 5 and 6 were given their third challenge with halothane (plus atracurium) 1 h later.

Creatinine phosphokinase concentrations in those animals which survived were markedly increased on the day following the manifestation of MH. No attempt was made to compare the increase following halothane alone with that following halothane administered concomitantly with atracurium.

DISCUSSION

Our study demonstrated that atracurium neither initiated nor attenuated the MH syndrome in MHS swine in response to the inhalation of halothane, an action similar to that of other non-depolarizing neuromuscular blockers when studied in the same model (Harrison, 1979). Although there is inherent danger in extrapolating from animal data, it would seem that the drug is safe for use in the human MHS subject.

An aspect of the action of atracurium in the circumstances of MH that still needs to be addressed is whether its action would be prolonged by the very severe acidosis or shortened by the hyperthermia of the established MH syndrome. However, such action per se is unlikely to affect prognosis.

A side issue perhaps worthy of comment concerns the uselessness of resting serum creatinine phosphokinase (CPK) concentrations in swine as a diagnostic criterion of MH (Mitchell and Heffron, 1975), or as a correlate of rapidity of response to halothane exposure. This is well exemplified by examination of the resting (before) concentrations of CPK in our animals (table I), in particular that of animal No. 2, in which a virtually normal CPK concentration accompanied one of the most rapid reactions to halothane and actual death from halothane-induced MH.

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REFERENCES


