**PORCINE MALIGNANT HYPERTERMIA IV: NEUROMUSCULAR BLOCKADE**

G. M. HALL, J. N. LUCKE AND D. LISTER

**SUMMARY**

The effect of tubocurarine and pancuronium on the initiation or prevention of porcine malignant hyperthermia (MH) was investigated in Pietrain pigs. Tubocurarine 0.6 mg/kg body weight inhibited a suxamethonium-induced response in three pigs, but failed to prevent a fatal halothane-induced response in a further four pigs. Pancuronium 0.2 mg/kg body weight was given to six pigs before a halothane challenge. Three animals developed MH and died; the remainder succumbed only after reversal of the neuromuscular blockade. The partial protection afforded by large doses of pancuronium is discussed in relation to the ability of previous muscle activity to influence the sensitivity to halothane.

Suxamethonium-induced porcine malignant hyperthermia (MH) (Hall et al., 1966; Lister, 1973) was investigated in detail by Lucke, Hall and Lister (1976). The role of the non-depolarizing neuromuscular blocking agents in the initiation or prevention of MH in pigs is unclear. Harrison (1971) noted that tubocurarine inhibited the onset of suxamethonium-induced MH in one pig but failed to prevent the onset of a halothane-induced response in a second pig. The observations of Hall, Trim and Woolf (1972) suggested that tubocurarine may protect against halothane-induced MH. Chalstrey and Edwards (1972) implicated pancuronium as a triggering agent, although the two pigs studied were anaesthetized with halothane. The purpose of this experiment was to examine the effects of curarization on suxamethonium-induced MH, and the effects of tubocurarine and pancuronium on halothane-induced MH.

**METHODS**

**Suxamethonium-induced MH**

Three Pietrain pigs (mean body weight 66 kg, SEM 4 kg) were anaesthetized and prepared surgically as described previously (Lucke, Hall and Lister, 1976). Approximately 40 min after the induction of anaesthesia arterial and venous blood was sampled. Tubocurarine chloride (BDH Pharmaceuticals Ltd, London) 0.6 mg/kg body weight was then injected i.v. Five minutes later, suxamethonium 50 mg was given (Sux I) and a further 50 mg was administered after 15 min (Sux II). Because there was no MH response to suxamethonium, the pigs were challenged with halothane 20 min after the last dose of suxamethonium to confirm their susceptibility to MH. Two 10-min periods of ventilation with halothane 1.5% (Hal I and II) were separated by an interval of 5 min. The metabolic and physiological measurements made during the experiment are listed in table I. The methods have been described in detail by Lucke, Hall and Lister (1976). The sequence of sample collection following each triggering agent, that is Sux I and II and Hal I and II, is in table II.

**TABLE I. Metabolic and physiological measurements made during suxamethonium and halothane-induced MH**

<table>
<thead>
<tr>
<th>Measurement</th>
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<tbody>
<tr>
<td>Arterial pH and $P_{CO_2}$</td>
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<tr>
<td>Plasma lactate concentration</td>
</tr>
<tr>
<td>Serum potassium concentration</td>
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<tr>
<td>Plasma glucose concentration</td>
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<tr>
<td>Plasma catecholamine concentrations</td>
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<tr>
<td>Heart rate</td>
</tr>
<tr>
<td>Arterial pressure</td>
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<tr>
<td>Muscle temperature</td>
</tr>
</tbody>
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**TABLE II. Sequence of measurements made after each triggering agent (TA)**

<table>
<thead>
<tr>
<th>Time</th>
<th>Measurement</th>
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</thead>
<tbody>
<tr>
<td>TA + 2 min</td>
<td>Arterial gas analysis</td>
</tr>
<tr>
<td>TA + 5 min</td>
<td>Plasma lactate concentration</td>
</tr>
<tr>
<td></td>
<td>Plasma glucose concentration</td>
</tr>
<tr>
<td></td>
<td>Serum potassium concentration</td>
</tr>
<tr>
<td></td>
<td>Plasma catecholamine concentrations</td>
</tr>
<tr>
<td>TA + 10 min</td>
<td>Arterial gas analysis</td>
</tr>
</tbody>
</table>
The results are expressed as means and SEM for the three pigs.

Halothane-induced MH

In the experiment described above all the pigs developed MH when ventilated with halothane, which suggested that tubocurarine did not protect against a halothane-induced response. However, there was an interval of 40 min between the administration of tubocurarine and the first period of ventilation with halothane, so that the degree of neuromuscular blockade present at this time would have been decreased considerably.

Thus, four Pietrain pigs (mean body weight 60 kg, SEM 3 kg) received tubocurarine chloride 0.6 mg/kg 5 min before a halothane challenge. The metabolic and physiological measurements and the halothane challenge were the same as in the suxamethonium experiment, except for an additional set of samples collected 15 min after Hal II.

The effect of the administration of pancuronium bromide 0.2 mg/kg (Organon Laboratories Ltd, Surrey) before halothane stimulation was examined in six Pietrain pigs (mean body weight 57 kg, SEM 3 kg). The protocol was the same as for the tubocurarine-treated pigs. However, some animals survived the halothane challenge and in these the neuromuscular blockade was antagonized with atropine sulphate 1.2 mg and neostigmine methyl sulphate 5.0 mg i.v., the effectiveness of which was assessed initially by the ability of the pig to sustain adequate spontaneous respiration, but in four of the animals a nerve stimulator (Palmer stimulator model 8038) was used to confirm the return of neuromuscular transmission. The halothane challenge was repeated to determine the effects after reversal of the neuromuscular blockade.

The results are given as means and SEM for each metabolic and physiological measurement. In the pancuronium-treated pigs, the mean values for the animals that developed MH during the initial halothane challenge are contrasted with those which became hyperthermic only after the reversal of the neuromuscular blockade.

RESULTS

Suxamethonium-induced MH

The administration of suxamethonium to the three pigs treated with tubocurarine failed to produce muscle fasciculations or metabolic and physiological

Fig. 1. Mean (and SEM) arterial pH, \( P_{\text{aCO}_2} \) (mm Hg), plasma lactate (mmol/litre) and serum potassium (mmol/litre). Suxamethonium 50 mg at Sux I and Sux II, and halothane was started at Hal.

Fig. 2. Mean (and SEM) plasma glucose (mmol/litre), plasma catecholamines (\( \mu g/litre \)), heart rate and muscle temperature (°C). See legend to figure 1.
changes indicative of muscle stimulation. Subsequent ventilation of the animals with halothane 1.5% invoked a fatal episode of MH in all three with typical biochemical and physiological features (figs 1 and 2).

**Halothane-induced MH**

Tubocurarine failed to prevent the development of MH during the halothane challenge and the four pigs died. The changes in arterial pH, \( \text{P}_{a_{\text{CO}_2}} \), plasma lactate and serum potassium concentrations are shown in figure 3 and those in plasma glucose and catecholamine concentrations, heart rate and muscle temperature in figure 4. The metabolic and physiological changes of the established syndrome were similar to those described for suxamethonium-induced MH by Lucke, Hall and Lister (1976).

![Figure 3](image3.png)

**Fig. 3.** Mean (and SEM) arterial pH, \( \text{P}_{a_{\text{CO}_2}} \) (mm Hg), plasma lactate (mmol/litre) and serum potassium (mmol/litre). The 10-min periods of ventilation with halothane started at Hal I and Hal II.

The injection of tubocurarine produced a transient decrease in systolic arterial pressure of 20–30 mm Hg which returned to the control value within 5 min. Subsequent ventilation of the tubocurarine-treated pigs with halothane caused a marked decrease in systolic arterial pressure to 60–70 mm Hg which improved slowly as the hyperthermic response became established.

Of the six pigs treated with pancuronium, three developed MH during the initial halothane challenge, while the remainder succumbed to halothane only after reversal of the neuromuscular blockade. The biochemical, physiological and hormonal changes for these two groups of pigs are compared in figures 5, 6 and 7. The administration of pancuronium had no effect on the arterial pressure and ventilation with halothane did not cause the severe hypotension found in the pigs treated with tubocurarine.

**DISCUSSION**

The ability of tubocurarine to inhibit suxamethonium-induced MH but not halothane-induced MH confirmed the findings of Harrison (1971) and showed that depolarization of the motor end-plate was necessary for the triggering action of suxamethonium. The coarse, prolonged fasciculations observed after the administration of suxamethonium to untreated, control pigs may be the result of two mechanisms. First, the binding of suxamethonium to the receptor sites and subsequent depolarization may occur at normal motor end-plates, but there is then an
excessive release of calcium from the sarcolemma or sarcoplasmic reticulum, or both (Harrison, 1973a). Second, the number or size of the receptor sites on the sarcolemma may be increased so that suxamethonium causes a greater muscle stimulation through a normal excitation–contraction coupling mechanism. The present study does not permit these two possibilities to be distinguished, but Swatland and Cassens (1972) found an increased number of structural abnormalities in the end-plate region of MH-susceptible pigs. Moulds and Denborough (1974) studied muscle biopsies from MH-susceptible patients and found that an abnormal, prolonged contracture was produced when suxamethonium was added to the water bath. Although they did not comment on the mechanism by which suxamethonium produced this response, Moulds (personal communication) considered that the presence of extra-junctional acetylcholine receptors could not be excluded.
The inability of tubocurarine to prevent halothane-induced MH indicated that the inhalation agent was acting primarily at a site beyond the motor end-plate. Thus, the mode of action of pancuronium in affording some protection against a halothane response was not evident. One possibility was that a high level of neuromuscular blockade led to a totally inactive muscle with a very low concentration of free ionized calcium. The administration of halothane was then unable to increase this calcium concentration sufficiently to stimulate muscle metabolism. Support for this concept of previous muscle activity modifying the susceptibility to triggering agents in MH has been provided by the observations of Berman (1973) and Mogensen, Misfeldt and Hanel (1974) in man, and Van den Hende and others (1976) in the pig. Lucke (1975) found that deep barbiturate anaesthesia reduced the sensitivity to halothane-induced MH in the Pietrain pig.

It is possible that the beneficial effects of pancuronium are unrelated to its neuromuscular blocking properties, but linked to the amino-steroid configuration of the compound. Ellis and others (1974) recommended glucocorticoids for the treatment of human MH on an empirical basis, and Hall, Trim and Woolf (1972) and Harrison (1973b) found that high doses of Althesin protected against MH in the Landrace pig. Lucke and Lister (1975) were unable to confirm these results in the Pietrain pig, although the dose of Althesin used was less than that reported by Harrison (1973b). Although preliminary work by Child and others (1971) indicated that the hormonal activity of Althesin was only slightly less than that of hydrocorrisone, this was not confirmed in a further study (Child et al., 1972). Buckett and Bonta (1966) showed that pancuronium has no hormonal activity; thus a steroid-like effect of these two protective agents can be excluded.

The dose ratio of pancuronium to tubocurarine in this study was only 1 : 3, whereas in man equipotent ratios varying from 1 : 5.5 (Lund and Stovner, 1970) to 1 : 7.4 (Monks, 1972) have been found. In other animals values as high as 1 : 11.5 were recorded by Buckett and others (1968), but no information was available on equivalent doses in the pig. It is conceivable that a higher dose of tubocurarine may produce an effect similar to that of pancuronium, but this was not attempted because of the hypotension that occurred when the tubocurarine-treated animals were ventilated with halothane. The use of a non-depolarizing neuromuscular blocking drug, such as gallamine, would overcome the problem of hypotenstion and enable the specificity of the pancuronium-induced protection to be assessed.

Pancuronium was totally ineffective in reversing established MH on several occasions. Successful prevention but unsuccessful treatment is analogous to the effect of an a-adrenergic blockade in porcine MH (Lister, Hall and Lucke, 1976). We have postulated that one effect of the large increase in plasma catecholamine concentration in MH may be to induce an increase in acetylcholine release at the neuromuscular junction and stimulate muscle metabolism even further (Lister, Hall and Lucke, 1976). However, the inability of pancuronium even to modify an established hyperthermic response suggests that this mechanism cannot contribute greatly to the hyperthermic response.

Halothane-induced MH produced biochemical, physiological and endocrine changes very similar to those in suxamethonium-induced MH (Lucke, Hall and Lister, 1976), but there was a considerable difference in the time of onset of the syndrome. After halothane exposure, the 2-min sample for blood-gas analysis and the 5-min sample for general biochemical analysis showed no significant difference from the control values (figs 3 and 4), and it was not until after 10 min of ventilation with halothane 1.5% that biochemical signs of MH were present. The blood-gas changes recorded at this time (figs 3 and 5) were similar to those found 2 min after the commencement of a suxamethonium-induced response (Lucke, Hall and Lister, 1976).

The hyperglycaemia that was a constant feature of suxamethonium-induced MH (Lucke, Hall and Lister, 1976) was more variable in the halothane-triggered pigs. Those animals which developed MH rapidly showed a typical hyperglycaemia (figs 4 and 6), but there was no change in plasma glucose when hyperthermia occurred after successful blockade with either tubocurarine or pancuronium (figs 2 and 6). An association between the plasma catecholamine concentrations and the presence of either a normal or increased plasma glucose concentration was not evident and, in the absence of other hormonal data relevant to glucose homeostasis, such as plasma insulin, glucagon, cortisol and growth hormone concentrations, the reason for this variation remains unresolved.

In conclusion, neither tubocurarine nor pancuronium triggered MH in the Pietrain pig. On the contrary, tubocurarine prevented a fatal response to suxamethonium and large doses of pancuronium afforded some protection against halothane. The
beneficial effects of pancuronium suggest that the occurrence of MH in an individual animal may be influenced by several factors, one of which is the state of muscle activity when the triggering agent is administered.

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REFERENCES


HYPERTERMIE MALIGNE DES PORCS: IV. BLOCAGE NEUROMUSCULAIRE

RESUME

L’effet de la tubocurarine et du pancuronium sur le déclenchement ou la prévention de l’hypertension maligne des porcs (MH) a été étudié sur des porcs piétrains. Une dose de tubocurarine de 0,6 mg/kg de poids du corps a modéré la réaction provoquée par le suxaméthonium sur trois porcs, mais n’a pas réussi à prévenir une réaction fatale provoquée par l’halothane sur quatre autres porcs. On a administré à six porcs, 0,2 mg de pancuronium par kg de poids du corps avant un essai à l’halothane, trois animaux ont été atteints par la MH et en moururent; les autres n’ont succombé qu’après l’inversion du blocage neuromusculaire. On traite dans cet article de la protection partielle assurée par de fortes doses de pancuronium par rapport à la capacité de l’activité musculaire antérieure susceptible d’influencer la sensibilité à l’halothane.

MALIGNE SCHWEINE-HYPERTERMIE, IV: NEUROMUSKULARE BLOCKIERUNG

ZUSAMMENFASSUNG

Die Wirkung von Tubocurarine und Pancuronium auf Entstehung oder Verhütung maligner Schweine-Hyperthermie (MH) wurde bei Pietrain-Schweinen untersucht. Eine Dosis von 0,6 mg Tubocurarine per kg Körperfektgewicht unterdrückte eine durch Suxamethonium ausgelöste Reaktion bei drei Schweinen, konnte aber eine tödlich verlaufende, durch Halothan ausgelöste Reaktion bei vier weiteren Schweinen nicht verhindern. Sechs Schweine erhielten vor einer Halothan-Verabreichung eine Dosis von
0,2 mg Pancuronium/kg Körpergewicht. Drei Tiere entwickelten darauf eine tödlich verlaufende MH, während der Rest erst nach Umkehrung der neuromuskulären Blockierung einging. Der durch grosse Dosen von Pancuronium gewährte, teilweise Schutz wird im Zusammenhang mit der Empfindlichkeit der vorherigen Muskelaktivität diskutiert, die Fähigkeit der vorherigen Muskelaktivität diskutiert, die Empfindlichkeit auf Halothan zu beeinflussen.

HIPERTERMIA MALIGNA PORCINA. IV:
BLOQUEO NEUROMUSCULAR

Se investigó con cerdos Pietrain el efecto de tubocurarina y pancuronio sobre la iniciación o prevención de la hipertermia maligna (HM) porcina. Tubocurarina 0,6 mg/kg de peso corporal inhibió la respuesta inducida con suxametonio en tres cerdos, pero no impidió una respuesta fatal inducida por el halotano en otros cuatro cerdos. Pancuronio 0,2 mg/kg de peso corporal fue administrado a seis cerdos antes de una provocación con halotano. Tres animales desarrollaron HM y fallecieron; el resto sucumbió solamente tras inversión del bloqueo neuromuscular. La protección parcial proporcionada por grandes dosis de pancuronio es comentada en relación con la facultad de la previa actividad muscular para influenciar la sensibilidad al halotano.