EFFECT OF HALOTHANE ON TUBOCURARINE AND SUXAMETHONIUM BLOCK IN MAN

BY

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SUMMARY

The effect of halothane 2 per cent on neuromuscular transmission and its interaction with both tubocurarine and suxamethonium was investigated in twenty patients undergoing surgery, using the twitch response to ulnar nerve stimulation. Ventilation was constantly controlled throughout the procedure. Halothane did not cause any depression of the twitch response in the absence of tubocurarine; a slight increase was even observed. On the other hand, when halothane was inhaled during tubocurarine block, a marked depression of the twitch was observed. Suxamethonium produced intense fasciculations when injected during halothane anaesthesia, but no significant difference in the degree of block was observed.

The neuromuscular and electromyographic effects of halothane, and its interaction with tubocurarine in man has been investigated by Katz and Gissen (1967). Tubocurarine produced a greater effect when the patients were breathing nitrous oxide, oxygen and halothane, than when breathing nitrous oxide and oxygen only. Ventilation was spontaneous, assisted or manually controlled.

Baraka (1964, 1967) has shown in man that the type of ventilation, with its consequent changes in the arterial carbon dioxide tension, might affect the neuromuscular block produced by muscle relaxants. The purpose of the present investigation is to show the neuromuscular effects of halothane, and its interaction with both tubocurarine and suxamethonium in man, whilst controlled ventilation was constantly maintained throughout the procedure.

METHOD

The method used during this study has been fully described by Baraka (1964). Observations were carried out on twenty healthy adult patients undergoing routine lower abdominal or limb surgery.

Anaesthesia.

Premedication was limited to intramuscular injection of atropine 0.6 mg. Sleep was induced with thiopentone 250 mg intravenously. This was followed by administration of a 50 per cent mixture of cyclopropane with oxygen and by topical laryngeal anaesthesia with 4 per cent lignocaine to facilitate intubation and controlled ventilation. Anaesthesia was then maintained with a mixture of nitrous oxide (3 l./min.) and oxygen (1 l./min), using a Boyle Mark III circuit, including the soda-lime canister.

Ventilation.

Ventilation was continuously controlled throughout the procedure, using a Blease Pulmoflator set to deliver a constant volume of 15 l./min as checked by a Wright anenometer. This technique was adopted so as to avoid any change of ventilation secondary to the inhalation of halothane or the injection of muscle relaxants. Blood drawn for the Pco₂ and pH estimations was “arterialized venous” (Brooks and Wynn, 1959). The values were then estimated following the method described by Robinson and Utting (1961). The average stable blood carbon dioxide tension in the twenty patients was 25.1 mm Hg (21-30), and the average stable pH was 7.51 (7.45-7.55).

Observations on neuromuscular transmission.

The ulnar nerve was supramaximally stimulated at the elbow region, by tetanic bursts at intervals of 10 seconds. The resultant twitch response was recorded by attaching the ring finger to a flat steel spring myograph recording with ink on a rotating drum. It is recognized that this method of recording is rather insensitive and the twitch
amplitude is a function of the lever system. For these reasons qualitative rather than quantitative changes only are considered. Most of the experiments were planned in such a way that each patient acted as his own control.

**General procedure.**

A period of 10–20 minutes was allowed to elapse between the start of anaesthesia and the start of investigation to ensure a steady state of the twitch response and the carbon dioxide tension. The experiments were then planned as follows. In five patients, after a steady twitch was obtained under nitrous oxide with oxygen anaesthesia, halothane 2 per cent was added to the inhaled mixture. Its effect on the twitch response was observed, without the intervention of muscle relaxants.

In a further group of five patients, tubocurarine 1 mg/stone (0.16 mg/kg) was injected intravenously while ventilation continued with nitrous oxide, oxygen and 2 per cent halothane. The degree of block was compared with that obtained when the same dose of tubocurarine was injected in a third group of five patients in whom ventilation was continued with nitrous oxide and oxygen only. Immediately after recovery from tubocurarine neuromuscular block in the latter group, halothane 2 per cent was added to the inhaled nitrous oxide and oxygen mixture, and its effect on the recovering twitch response was observed.

In a fourth group of five patients, suxamethonium 20 mg was injected while the ventilation was maintained using nitrous oxide and oxygen only. The initial fasciculations were clinically observed, and the blocking effect on the twitch response was recorded. When complete recovery of the twitch was reached, halothane 2 per cent was added to the inhaled anaesthetic mixture. After 30 minutes, a second dose of suxamethonium 20 mg was injected and its response was compared with that obtained during nitrous oxide and oxygen only.

**RESULTS**

**Effect of halothane alone.**

Inhalation of halothane 2 per cent by the non-curarized patients under nitrous oxide and oxygen, did not produce depression of the twitch response to ulnar nerve stimulation in any case. On the other hand, a slight increase in the twitch response was observed. This stimulant effect was maintained throughout the whole period of inhalation, and it lasted for 10–30 minutes after the cessation of halothane administration, when the twitch response restored its original level. Figure 1 shows the twitch response in one patient; similar recordings were obtained in the other patients.

**Interaction of halothane with tubocurarine.**

The neuromuscular blocking effect, as estimated by the reduction in the recorded height of the twitch response, of tubocurarine (1 mg/stone*) was much greater and more prolonged in the five patients inhaling nitrous oxide, oxygen and halothane than in the five patients inhaling nitrous oxide and oxygen only. Twenty minutes after injection, recovery was nearly complete when tubocurarine was injected during nitrous oxide and oxygen anaesthesia, while a marked degree of neuromuscular block was still present when

* 1 stone = 6.35 kg; 1 mg/stone = 0.16 mg/kg.

**FIG. 1**

Kymograph showing the effect of halothane 2 per cent on the twitch response to ulnar nerve stimulation without the intervention of muscle relaxants. A slight increase in the twitch is observed throughout the whole period of inhalation. When halothane is excluded, the original twitch is restored after about 20 minutes.
it was injected during nitrous oxide, oxygen and halothane anaesthesia. Figure 2 is typical of the response under both conditions. The degree of tubocurarine neuromuscular block was strikingly different between the two series and closely similar within each group. There was no doubt as to the qualitative significance.

Immediately after complete recovery from tubocurarine block in patients inhaling nitrous oxide with oxygen only, the addition of halothane 2 per cent produced marked depression of the twitch response. Cessation of halothane inhalation was followed by recovery. Figure 3 is typical of the response observed.

**Interaction of halothane with suxamethonium.**

Following the injection of suxamethonium, the twitch was not initially enhanced before depression

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**Fig. 2**

Kymographs obtained in patients during nitrous oxide and oxygen anaesthesia (upper tracing) and nitrous oxide, oxygen and halothane anaesthesia (lower tracing) after injection of tubocurarine 1 mg/stone (0.16 mg/kg). It can be seen that halothane potentiated the neuromuscular block.

**Fig. 3**

Kymograph showing the effect of tubocurarine 1 mg/stone (0.16 mg/kg) when injected during nitrous oxide and oxygen anaesthesia. After apparent complete recovery from block, the addition of halothane 2 per cent (B–C) produced a marked depression of the twitch.
ensued. The same observation has been shown by Payne and Holmdahl (1959). The clinical impression was that fasciculations were more marked when suxamethonium was injected during nitrous oxide, oxygen and halothane anaesthesia, than during nitrous oxide with oxygen only. No important difference in the degree or duration of suxamethonium block could be observed under both conditions. A typical example is illustrated in figure 4.

**FIG. 4**
Kymograph showing the blocking effect of suxamethonium 20 mg when injected during nitrous oxide and oxygen anaesthesia. The response is compared to that obtained when the same dose is injected during nitrous oxide, oxygen and halothane 2 per cent. No marked difference in the degree or duration of the block is observed.

**DISCUSSION**
The present investigation shows that the inhalation of halothane 2 per cent in man did not depress the twitch response to ulnar nerve stimulation. On the other hand, a slight increase in the twitch was observed during inhalation, and was maintained for 10–30 minutes after cessation of inhalation. Sabawala and Dillon (1958) in an in-vitro study of human intercostal muscles, observed that halothane 4 per cent produced a rise in the twitch response to direct muscle stimulation. Halothane might have a direct positive inotropic effect on the human muscle fibre both in vitro and in vivo. This effect might be one of the factors which increase the incidence and intensity of shivering during recovery from halothane anaesthesia.

Although the inhalation of halothane 2 per cent did not depress the twitch response to nerve stimulation in non-curarized patients, it produced a marked depression of the twitch when inhaled by patients given tubocurarine. Gissen, Karis and Nastuck (1966) have shown, using in-vitro preparations of frog, that halothane depresses the postjunctional depolarization evoked by iontophoretically applied acetylcholine. Normally, a nerve impulse produces a synchronous release of about 10\(^6\) molecules of acetylcholine at a single motor nerve ending (Wright, 1965). This might still be enough to produce an adequate endplate potential despite the desensitizing effect of halothane. However, if the cholinergic endplate receptors are partially occupied with tubocurarine molecules, the depressant effect of halothane on the endplate might manifest itself as neuromuscular block.

In contrast with tubocurarine neuromuscular block which is markedly potentiated with halothane, the blocking effect of suxamethonium did not show any important difference whether the patient was inhaling nitrous oxide and oxygen only, or nitrous oxide, oxygen and halothane. The only difference observed was the more marked initial fasciculations which followed the injection of suxamethonium during halothane inhalation.

It is probable that the inhalation of halothane 2 per cent by man, might produce two different effects peripherally; a depressant effect on the endplate which is manifest as potentiation of the tubocurarine neuromuscular block, and a direct positive inotropic effect on the muscle fibre which might magnify the fasciculations after suxamethonium.

**REFERENCES**


**TUBOCURARINE ET SUXAMETHONIUM CHEZ L’HOMME**

**SOMMAIRE**

L’effet d’halothane deux pourcent sur la transmission neuromusculaire et son interaction aussi bien avec tubocurarine que suxamethonium a été étudié chez vingt patients opérés, à l’aide de la crispation consécutif à une stimulation du nerf ulnaire. Durant l’intervention entière, la respiration était assiée. Halothane n’inhibit pas les contractions en absence de tubocurarine; il y avait même une légère intensifica
dation de la réaction. Mais d’autre part, les contractions étaient considérablement inhibées lorsque l’halothane était inspiré pendant un block par tubocurarine. Le suxamethonium provoquait des fasciculations intenses lorsqu’il était injecté durant une anesthésie par halothane, mais une différence significative du degré de blocage n’a pas été observé.

**DE R EINFLUSS VON HALOTHAN AUF DIE TUBOCURARIN- UND SUXAMETHONIUM-BLOCKADE BEIM MENSCHEN**

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