Neuromuscular and Electromyographic Effects of Halothane and its Interaction with d-Tubocurarine in Man

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The effect of halothane (1–2 per cent) on neuromuscular transmission and the abdominal electromyogram was studied in man. When electromyographic activity was markedly decreased and the abdomen sufficiently relaxed to permit lower abdominal surgery, there was no depression of the indirectly evoked twitch response. However, halothane increased the neuromuscular blocking action of both d-tubocurarine and hexafluorenium. The central nervous system depressant action of halothane and its ability to increase the action of d-tubocurarine are believed to account for the clinical observation that patients anesthetized with halothane require less d-tubocurarine for satisfactory muscle relaxation than do patients receiving nitrous oxide. It was pointed out in the discussion that the neuromuscular blocking action of halothane per se, which can be demonstrated in vitro, is attributable to desensitization of the postjunctional membrane.

Patients anesthetized with halothane appear to require less d-tubocurarine for satisfactory muscle relaxation than do patients receiving nitrous oxide. This may be attributable to a depressant action of halothane on muscle, neuromuscular transmission or the central nervous system. Although studies in animals have demonstrated effects in all of these areas,1–4 comparable studies in man have not yet been reported. The following study was undertaken in man to determine the effects of halothane on the abdominal electromyogram, neuromuscular transmission and on the action of d-tubocurarine.

Methods

Forty-three patients were studied during anesthesia and plastic, urologic or general surgery. Most of them received a belladonna drug, a barbiturate and/or a narcotic for preanesthetic medication. Anesthesia was usually induced with thiopental and maintained with halothane or nitrous oxide-oxygen supplemented by halothane, thiopental or meperidine. The inspired concentration of halothane was usually 1–2 per cent and that of nitrous oxide 60–70 per cent. A Vernitrol Kinet-o-Meter anesthesia machine with either a nonbreathing system or a high flow (7–10 liters) semi-closed circle absorber system was used. Tracheal intubation was accomplished with the aid of 40–100 mg. of intravenous succinylcholine. Ventilation was spontaneous, assisted or manually controlled.

To study neuromuscular transmission the ulnar nerve was stimulated and the adduction of the thumb measured with a force displacement transducer and recorded on a polygraph. To obtain the integrated electromyogram (IEMG) of the oblique-transversus group of abdominal muscles, needle electrodes were inserted into the muscle and the electrical activity measured with an Offner EMG integrator, and recorded on an Invengeneering polygraph (Offner components). These techniques have previously been described in detail.5

Results

Halothane. The effect of halothane on twitch height and IEMG was simultaneously determined in 7 patients. Relaxation sufficient
to permit lower abdominal surgery was produced by the inhalation of 1–2 per cent halothane. The duration of halothane inhalation at the time the abdomen was entered was 60–90 minutes. Although the IEMG of the oblique-transversus group of abdominal muscles was depressed 75 per cent or more, there was no decrease in twitch height in any of these patients.

**Halothane and Hexafluorenium.** In 10 patients anesthetized with nitrous oxide-oxygen supplemented with meperidine or thiopental, the intravenous injection of 0.5–1.0 mg./kg. of hexafluorenium did not decrease twitch height. In another group of patients, anesthetized with 1–2 per cent halothane (5 patients) or nitrous oxide-oxygen plus 1–2 per cent halothane (5 patients), the injection of 0.5–1.0 mg./kg. of hexafluorenium decreased twitch height in 7 of 10 patients. The magnitude of decrease varied from 10 to 55 per cent (fig. 1).

**Halothane and d-Tubocurarine (dTC).** If two doses of dTC (0.1 mg./kg.) are given one hour apart, the second dose will produce a greater effect even though twitch height has returned to the control level in the interim (Katz, R. L., unpublished data). Since preliminary observations suggested that halothane would increase the neuromuscular blocking action of dTC, the initial dose of dTC (0.1 mg./kg.) was given during nitrous oxide-oxygen plus 1–2 per cent halothane (inhaled for 30–60 minutes). After determining the effect of dTC, halothane was discontinued and the same dose of dTC repeated 1–5 hours later, after twitch height had returned to the control level. In all ten patients studied, the action of dTC was greater during halothane inhalation (fig. 2). The magnitude of block was 60–100 per cent (mean of 76 per cent) with halothane, but only 30–70 per cent (mean of 53 per cent) with nitrous oxide. In six patients in whom it was possible to observe the full effect

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**Fig. 1.** Effect of hexafluorenium. Panel A: at ↑ hexafluorenium (0.5 mg./kg.) injected during inhalation of 1 per cent halothane. Panel B: at ↑ hexafluorenium (1.0 mg./kg.) injected during inhalation of 2 per cent halothane. Note decrease in twitch height in both cases.

**Fig. 2.** Comparison of response to d-tubocurarine (dTC) with halothane and with nitrous oxide inhalation. Panel A: at ↑ dTC (0.1 mg./kg.) injected during inhalation of nitrous oxide-oxygen plus halothane (2 per cent). Panel B: three hours after initial injection of dTC, the same dose was repeated at ↑, during inhalation of nitrous oxide-oxygen. Note smaller decrease in twitch height.
of both doses of dTC, the duration of action with halothane was 19–48 minutes (mean of 36 minutes) and with nitrous oxide 10–22 minutes (mean of 16.5 minutes). In three patients the initial dose of dTC was given during nitrous oxide-oxygen-mepiperidine and repeated approximately one hour later during nitrous oxide-oxygen-halothane. Once again a greater magnitude and duration of action of dTC was seen during halothane inhalation. The difference appeared to be greater than that seen in the ten patients discussed above and is probably attributable to the cumulative effect of dTC as well as the action of halothane.

In three patients operated on two or more times, the effect of 0.1 mg./kg. of dTC was determined during nitrous oxide-oxygen-mepiperidine on one occasion and during halothane (1–2 per cent) on another. The magnitude and duration of action of dTC were greater during halothane in all three patients (fig. 3).

Discussion

Previous studies of the effect of halothane on the neurally evoked muscle twitch have produced divergent results. Watland et al. studying the rabbit gastrocnemius and Ngai et al. studying the cat tibialis reported that halothane did not decrease twitch height. In contrast to these studies in vivo, Sabawala and Dillon using human intercostal muscle and Gisen et al., frog sartorius muscle, demonstrated that in vitro, halothane was capable of abolishing the muscle twitch. These discrepancies are not surprising in view of the differences in the species studied and in the experimental design. In a previous study, it was pointed out that (1) diethyl ether depressed the twitch response in the rabbit more easily than in the cat, rat or man; (2) the neuromuscular blocking action of ether was more easily demonstrated in vitro than in vivo. In the present study in man, 1–2 per cent halothane did not depress the twitch response, although higher concentrations might have done so. In a study of diethyl ether, although 5–9 per cent did not decrease twitch height, higher concentrations did produce a 10–30 per cent decrease.

Although halothane did not decrease twitch height, it did increase the action of dTC and hexafluorinum. Clinical observations in patients monitored with a nerve stimulator strongly suggested that the neuromuscular block produced by 0.1 mg./kg. of dTC was greater in patients anesthetized with halothane than in those receiving nitrous oxide. Despite this strong clinical impression, we were unwilling to accept as fact these observations made in 2 different groups of patients, because of the variability of patients’ responses to 0.1 mg./kg. of dTC. We therefore chose to study the effects of dTC during halothane and nitrous oxide anesthesia in the same patient. Injecting dTC during nitrous oxide-halothane inhalation, discontinuing the halothane and repeating the dTC during nitrous oxide inhalation tended to load the experiment against our hypothesis, because of the cumulative effect of dTC. Nevertheless, it was clear that the action of dTC was greater during halothane inhalation than during nitrous oxide. This was supported by the few studies in patients who received halothane and dTC on one occasion and nitrous oxide-oxygen-mepiperidine and dTC on another. These results in man are similar to those of Watland et al. who reported that halothane increased the action of dTC in the rabbit. It has also been demonstrated in man that 5–9 per cent diethyl ether, which does not decrease twitch height, will increase the action of dTC.

The action of hexafluorinum during halothane was compared with its action during nitrous oxide when it was learned that hexafluorinum (0.5–1.0 mg./kg.) was capable un-
der some circumstances of decreasing twitch height (F. F. Foldes, personal communication). In our previous study,7 as well as in the present one, hexafluorourenium did not decrease the twitch height of patients anesthetized with nitrous oxide. However, in the group of patients receiving halothane, hexafluorourenium did decrease twitch height. Do these different results depend upon the presence of halothane or do they represent chance variations in sensitivity to hexafluorourenium in different groups of patients? We accept the former explanation inasmuch as we found not a difference in degree of block, but rather a definite decrease in twitch with halothane, but not with nitrous oxide.

The effect of halothane on neuromuscular transmission was carefully studied by Gissen et al.4 In the in vitro preparation of frog sartorius muscle, the blocking concentration of halothane was 1.5 per cent for the nerve-stimulated twitch, 4 per cent for axonal conduction and 4 per cent for the directly stimulated muscle. Halothane did not change the resting potential at the endplate, but markedly decreased the depolarizing action of carbachol as well as the postjunctional depolarization evoked by iontophoretically applied acetylcholine. In addition, halothane profoundly decreased the amplitude of miniature endplate potentials, an effect attributed to desensitization of the postjunctonal membrane. A prejunctional effect of halothane could not be demonstrated. It was concluded that the postjunctional membrane was the site most sensitive to the neuromuscular blocking action of halothane, with desensitization of this structure the major factor responsible for the block. The junctional effect of halothane was similar to that previously reported by these workers for diethyl ether.8

The decrease in amount of dTC required to produce satisfactory muscle relaxation in patients receiving halothane can be explained only partly by the greater action of dTC during halothane. An additional factor is the decrease in abdominal muscle tone produced by halothane, which was capable of markedly diminishing electromyographic activity of the abdominal muscles without decreasing twitch height. Similar results were observed in the cat by Ngai et al.3 who found that 1–2 per cent halothane did not decrease the twitch response, but 0.4–1 per cent halothane abolished spinal, corneal and masseter reflexes by depression of the central nervous system.

Conclusions

Although halothane (1–2 per cent) does not decrease twitch height in man, it does increase the magnitude and duration of action of d-tubocurarine. Halothane (1–2 per cent) also decreases the integrated electromyographic activity of the abdominal muscles. Both of these effects contribute to the decreased need for d-tubocurarine in patients anesthetized with halothane as compared with those receiving nitrous oxide.

References