

NEUROMUSCULAR EFFECTS OF ETHER, CYCLOPROPANE, CHLOROFORM AND FLUOTHANE

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THE PERIPHERAL neuromuscular action of ether and its synergism with curare have been fairly well-established (1-9). Gross and Cullen (2) and Poulsen and Secher (4) have shown that neostigmine reverses the peripheral neuromuscular blocking action of ether. Naess (9), on the other hand, using small repeated doses of neostigmine, demonstrated that the effects of curare were reversed while the ether effects were accentuated, indicating a difference in the mode of action of these two agents in depressing neuromuscular transmission.

The action of other anesthetic agents is less well established. Githens and Meltzer (10) could demonstrate no effects from chloroform. Naess (6), however, has shown chloroform to have a relatively strong "curarizing" action, and also a synergism with curare. Nitrous oxide has no apparent action and does not enhance the action of curare (6). Little is known about the neuromuscular effects of cyclopropane and

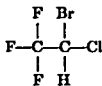


FIG. 1. Fluothane—1,1,1-trifluoro-2-bromo-2-chloroethane.

the newer anesthetic agent, Fluothane (fig. 1). It is the purpose of this investigation to study the peripheral neuromuscular activity of several anesthetic agents and to determine whether or not they potentiate the action of curare.

METHODS

The gastrocnemius muscle-sciatic nerve preparation of the rabbit was used. Most of the surgical preparations were performed under cyclopropane anesthesia; occasionally other agents were used. A tracheostomy was first established and an endotracheal tube inserted. Anesthesia was then continued using an Ayre's T-tube. The gastrocnemius tendon was severed and attached through appropriate pulleys to an isometric lever arm recording on a smoked drum.

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The sciatic nerve was severed and the distal portion connected to the electrodes of a Grass stimulator. The effects of two types of electrical stimulation were studied. A single square wave shock of 3 milliseconds duration was administered every 10 seconds and will be referred to as single shock stimulation. The other stimulus had a frequency of 256 cycles per second and was administered for a duration of 0.3 second every 10 seconds and will be referred to as tetanic stimulation. Supramaximal voltage was used at all times. Time markings shown in the figures are equivalent to one minute intervals.

The femoral artery of the opposite leg was cannulated with polyethylene tubing and the mean blood pressure measured using a mercury manometer.

The animals were then allowed to awaken and remain so for one-half hour or more while nerve stimulation continued and until a steady response of the muscle was obtained. They were then anesthetized with the agent to be tested which was delivered from a Foregger aquameter machine with attached acorn-type vaporizer. Depth of anesthesia was judged by loss of the corneal reflex, loss of response to painful stimulation and by changes in pulse rate and blood pressure. Manually controlled ventilation was performed whenever an anesthetic agent or curare was administered and continued until recovery had occurred. Curare in the form of *d*-tubocurarine chloride (Squibb) was administered into the marginal ear vein.

OBSERVATIONS AND RESULTS

The effect of ether, cyclopropane, chloroform and Fluothane on muscle response to indirect stimulation and their effect on the neuromuscular blocking action of curare were determined. The results are presented for each agent individually.

Ether.—Ether was administered to a total of 14 animals and consistently reduced the height of contractions produced by both single shock and tetanic stimulation. As the depth of anesthesia increased, muscle contraction in response to indirect stimulation progressively diminished and virtually ceased under deep ether anesthesia. Figure 2 is a typical tracing obtained after a short period of light surgical anesthesia with ether during which the height of contractions produced by both types of stimuli were only partially reduced. Curare administered at this time produced a more profound reduction in height of contractions than the same dose, and even twice this dose, produced in the same animal one hour following discontinuance of ether anesthesia.

Blood pressure was lowered during ether anesthesia, but not to the extent seen during chloroform or Fluothane anesthesia. There was approximately a 30–50 per cent reduction in pressure when surgical levels of anesthesia with ether were reached.

Cyclopropane.—Cyclopropane produced a consistent increase in the height of contractions in response to single shock stimulation, even during prolonged periods of deep anesthesia, in 12 animals tested. In 4 animals, curare was administered while contractions were enhanced during cyclopropane anesthesia, and in all cases there was a more profound reduction in height of contractions than was produced by an equal dose of curare given to the same animals one hour after termination of anesthesia (fig. 3, bottom tracing).

Height of contractions in response to tetanic stimulation was neither significantly increased or decreased by cyclopropane in 3 animals, but in all 3, contraction height was diminished more by curare during anesthesia than it was by the same dose given in the awake state following anesthesia (fig. 3, top tracing).

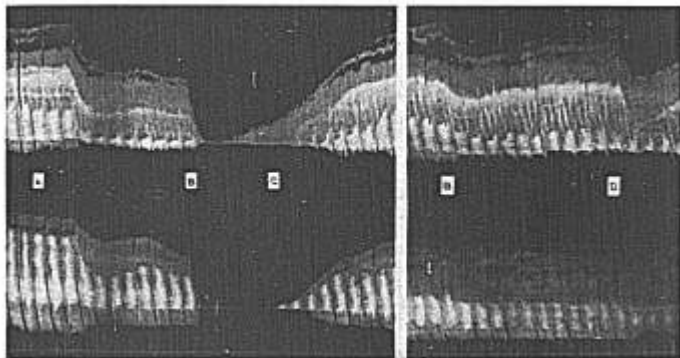


FIG. 2. The effects of ether and curare. Bilateral preparation. Top tracing recorded from right leg using tetanic stimulation. Bottom tracing recorded from left leg of same animal using single shock stimulation. (A) Beginning of ether administration. (B) Curare, 50 $\mu\text{g./kg.}$ (C) Ether discontinued. (D) Curare, 100 $\mu\text{g./kg.}$ Curare administration in right tracing one hour following that in left tracing.

Blood pressure was recorded in 5 animals and there occurred a small to moderate elevation of pressure in every case.

Chloroform.—The height of contractions in response to single shock stimulation was increased with the administration of chloroform in 10 animals studied and remained so during long periods of deep anesthesia. Curare was given to 3 of these animals and in every case the resulting reduction in height of contractions was more profound during the period of chloroform administration than in the awake animal one hour following anesthesia (fig. 4, bottom tracing).

There was no change in height of muscle contractions in one animal and a slight increase in the height of contractions in another animal in

response to tetanic stimulation during chloroform administration. In both of these animals curare produced a more profound reduction in height of contractions during chloroform administration than was produced by the same dose administered one hour following the anesthesia (fig. 4, top tracing).

Blood pressure was lowered by chloroform, the reduction being proportional to the depth of anesthesia and of similar magnitude as during Fluothane anesthesia.

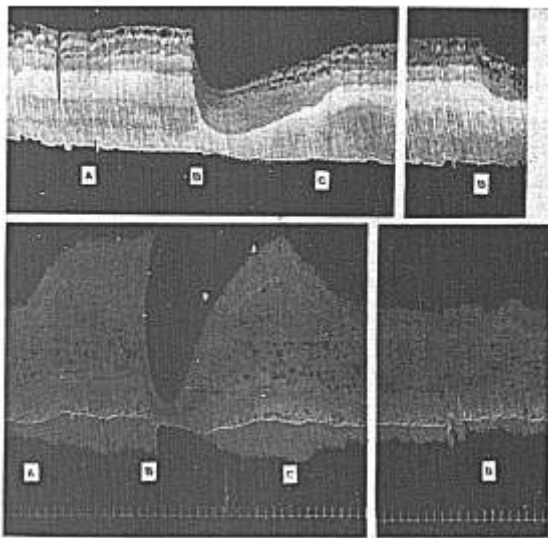


FIG. 3. The effects of cyclopropane and curare. Top tracing, tetanic stimulation. Bottom tracing, single shock stimulation. (A) Beginning of anesthesia with 25 per cent cyclopropane. (B) Curare, 50 $\mu\text{g./kg.}$ (top record); 100 $\mu\text{g./kg.}$ (bottom record). (C) Anesthesia discontinued. Curare administration in right tracing one hour following that in left tracing.

In several animals to which chloroform was administered, after all demonstrable effects of curare given to the unanesthetized animal had disappeared, there was a reduction rather than an enhancement of the height of contractions produced by single shock stimulation, indicating that chloroform may make evident the presence of small residual amounts of curare.

Fluothane.—The height of contractions produced by single shock stimulation was unaltered or slightly increased in 5 animals and was

slightly decreased in 2 animals tested during various depths of Fluothane anesthesia. These changes were not significant nor was there any correlation with depth of anesthesia. Curare produced a more profound reduction in the height of contractions after only a short period of Fluothane administration than was produced by a similar dose of curare in the awake animal one hour following anesthesia (fig. 5, bottom tracing).

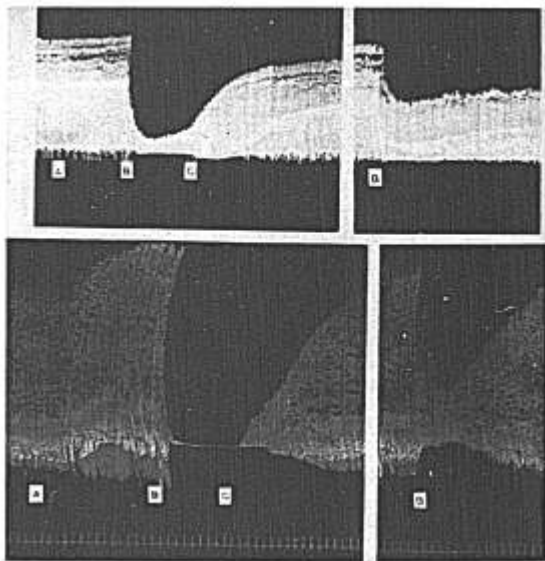


FIG. 4. The effects of chloroform and curare. Top tracing, tetanic stimulation. Bottom tracing, single shock stimulation. (A) Beginning of anesthesia. (B) Curare, 50 $\mu\text{g./kg.}$ (top record); 100 $\mu\text{g./kg.}$ (bottom record). (C) Anesthesia discontinued. Curare administration in right tracing one hour following that in left tracing.

The height of contractions in response to tetanic stimulation was also little affected by Fluothane in 3 animals tested, but as in single shock stimulation, curare produced a more profound reduction in the height of contractions in all of these animals than the same dose of curare produced one hour following anesthesia (fig. 5, top tracing).

Fluothane consistently produced a fall in blood pressure that was proportional to the depth of anesthesia. Hypotension began almost simultaneously with administration of the agent and continued until a 60-80 per cent reduction of pressure was obtained in deep anesthesia.

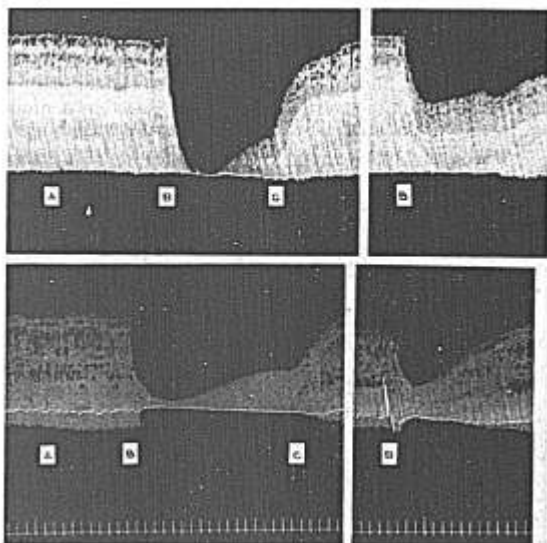


FIG. 5. The effects of Fluothane and curare. Top tracing, tetanic stimulation. Bottom tracing, single shock stimulation. (A) Beginning of anesthesia. (B) Curare, 50 $\mu\text{g./kg.}$ (top record); 100 $\mu\text{g./kg.}$ (bottom record). (C) Anesthesia discontinued. Curare administration in right tracing one hour following that in left tracing.

As with chloroform, Fluothane reduced the height of contractions during single shock stimulation after the effect of a blocking dose of curare had completely disappeared in the awake animal.

DISCUSSION

The ability of certain anesthetic agents to produce muscle relaxation is a well known clinical fact. The manner by which this relaxation is produced has not been completely explained. Either apparently first inhibits neuromuscular transmission following which there is depression of response to direct stimulation (6). How much of a role the "central effects" of ether contribute is difficult to determine. The potent combination of ether and curare has been thought to represent a potentiation of one drug by the other and the findings presented here confirm that fact.

Naess (6), using various frequencies of stimulation ranging from 2-300 per second, has reported a rather potent "curare-like" effect from chloroform. This finding would correlate well with the profound

relaxation obtainable clinically during chloroform anesthesia. However, chloroform had no such action on muscle response to indirect stimulation using the two types of stimuli chosen in this investigation. There was actually an increase in the height of contractions with single shock stimulation during chloroform anesthesia, a phenomenon which is difficult to explain at this time. In spite of this increased height of contractions, there was a potentiation of the neuromuscular effects of curare.

Deep cyclopropane anesthesia does yield some degree of muscle relaxation clinically but not the profound relaxation obtained with even lighter planes of chloroform anesthesia. However, the effects of cyclopropane on muscle response to the two types of stimuli used in this investigation were very similar to those of chloroform, as was the potentiation of the effects of curare. Again, the increased height of contraction with single shock stimulation is difficult to explain, especially when one considers that during this period of apparent increased excitability there is simultaneously present a condition in which the neuromuscular effects of curare are accentuated.

Clinical investigations of Fluothane have indicated that profound relaxation is obtainable with this agent. Johnstone (11) has indicated it unwise to combine the use of curare and Fluothane. There was little apparent alteration in muscle response to indirect stimulation during Fluothane anesthesia under conditions of our experiments. As with the other three anesthetic agents studied, there was a potentiation of the neuromuscular effects of curare by Fluothane. This potentiation was not so profoundly different from that seen with the other agents that there would appear to be any more danger to the use of curare during Fluothane anesthesia than to its use with other anesthetic agents from the standpoint of the neuromuscular system. With anesthetic agents such as ether, chloroform and Fluothane, which by themselves are capable of producing excellent muscle relaxation, it seems logical that only small doses of curare need be used as an adjunct.

SUMMARY

The neuromuscular effects of ether, cyclopropane, chloroform and, Fluothane have been studied in rabbits, using the response of the gastrocnemius muscle to single shock and tetanic stimulation of the sciatic nerve. Ether was the only agent that had any depressant effect on the response of voluntary muscle to indirect stimulation. Cyclopropane, chloroform, and Fluothane produced no demonstrable depression of muscle response to indirect stimulation. In fact, cyclopropane and chloroform enhanced muscle contraction produced by single shock stimulation. These findings would tend to indicate that the muscle relaxation produced by these anesthetic agents, with the exception of ether, is not due to a peripheral action but rather to "central effects."

The mechanisms by which these agents potentiate the neuromuscular effects of curare can only be a matter of speculation until further information is obtained.

This study was supported by grants from Imperial Chemical (Pharmaceuticals) Limited, Cheshire, England, and the Medical Trust Fund of the State University of Iowa. Fluothane was supplied by Ayerst Laboratories.

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