

## EFFECTS OF HALOTHANE ON GASTROINTESTINAL MOTILITY

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IN 1926, Miller<sup>1</sup> studied the effects of ether, chloroform and ethylene on the motility of the small intestine, colon and stomach in chronic preparations of dogs. He reported that ether or chloroform, in concentrations producing surgical anesthesia, caused almost complete inhibition of the contractions of the small intestine, colon and stomach. By the time the animals recovered sufficiently to show response to whistling or calling, the activity of the gastrointestinal tract had returned approximately to normal. Ethylene produced little or no effect in these preparations.

Weisel and associates<sup>2</sup> in 1938 reported similar effects for cyclopropane on the small intestine in Thiry-Vella dogs. Contractions were inhibited during surgical anesthesia and recovery began 45 seconds to 3 minutes after ceasing administration of the agent and was complete within a few minutes thereafter. It was also reported that in animals premedicated with morphine, tonus was not affected significantly; rhythmic contractions were decreased in rate or in amplitude but were not eliminated by cyclopropane anesthesia.

In the present study, the effects of halothane on the motor activity of various portions of the digestive tract were investigated. Preliminary experiments with ether, chloroform and cyclopropane yielded results which were consistent with those reported for these agents.

### METHODS

Studies were conducted in 10 dogs in which Thiry-Vella loops of jejunal origin had previously been established. The animals also had a portion of cecum fistulized to facilitate the measurement of motor activity of the colon. All measurements were accomplished by the balloon method; recordings were made on kymograph paper. Anesthetic agents were

administered using the Foregger, "copper kettle" apparatus. Halothane was vaporized with oxygen and the mixture administered in a semiclosed, circle, absorption system. In some experiments, only motility in the loop and colon were investigated, but in the majority of cases, a record of gastric motility was made simultaneously via a balloon passed through the esophagus.

The animals were lightly anesthetized with cyclopropane and intubated with endotracheal tubes. After the balloons were inserted, cyclopropane administration was discontinued. The animals usually remained quiescent for a long enough period to allow control recordings of the contractions to be taken. As soon as some limb movements were noted, induction with halothane was started. By this procedure tracings were obtained practically uncomplicated by artifacts due to struggling. Anesthesia was maintained such that the animals did not respond to noxious stimuli but had no serious respiratory depression. Oxygen was administered during emergence from anesthesia.

Several experiments were also conducted in acute preparations. Dogs were anesthetized with cyclopropane and their skulls were trephined. The brain anterior to the tentorium was pithed and cyclopropane administration was discontinued. A small abdominal incision was made and recording balloons placed directly into the lumen of various portions of the gastrointestinal tract. At least 45 minutes elapsed between pithing and drug administration. Control contractions in these preparations were uniformly poor and in some cases, nonexistent. However, these preparations were valuable in studying the antagonism by halothane of contractions elicited by barium chloride and other compounds.

### RESULTS

Figures 1 and 2 show the effect of halothane administration on the motility of the jejunal segment, colon and stomach. It can

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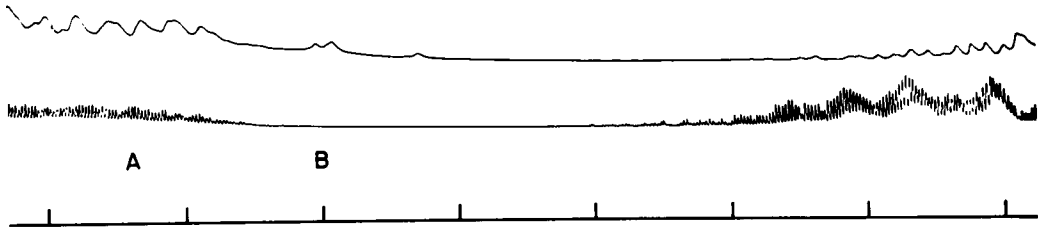


FIG. 1. Effect of halothane on motility of colon (top tracing) and jejunum (bottom tracing). A—halothane on; B—halothane off. Time marker represents 5 minutes.

be seen that the motility of the three structures is inhibited markedly during the administration of the agent and recovery from this effect is quite prompt after the agent is withdrawn. This effect was seen in every experiment performed, which was over twenty in number. In experiments in which the duration of administration of halothane was varied, prolonged administration did not seem to inhibit recovery of motility after the agent was withdrawn. The impression was gained, however, that increasing depth of anesthesia prolongs the recovery time.

Sixteen experiments were performed to determine the ability of halothane to antagonize the effects of drugs producing increased motor activity of the intestinal tract. The first of these compounds investigated was morphine.

The results are shown in figure 3. Even though halothane antagonizes the effects of morphine on the small intestine and colon, it appears that the two drugs are also mutually antagonistic as demonstrated after the second administration of morphine. Halothane is capable of antagonizing the effects of neostigmine on the small intestine and colon. This effect is shown in figure 4. Additional experiments demonstrated that stomach contractions elicited by neostigmine could also be readily antagonized by halothane.

Antagonism of contractions elicited by acetyl- $\beta$ -methylcholine and barium chloride was studied in acute preparations. Halothane antagonizes contractions produced by either of the two compounds at all of the three sites investigated.

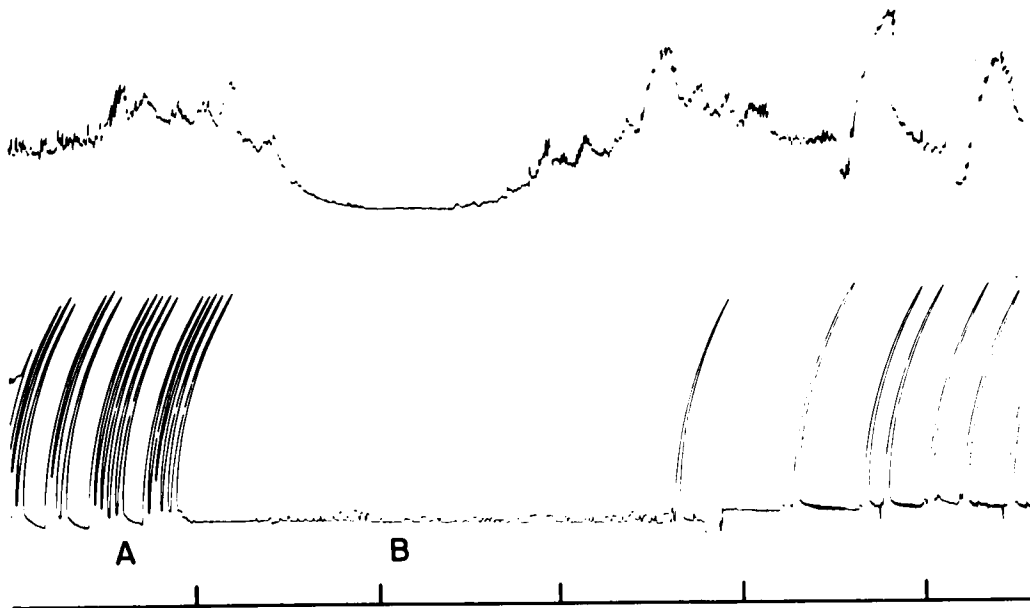


FIG. 2. Effect of halothane on motility of jejunum (top tracing) and stomach (bottom tracing). A—halothane on; B—halothane off. Time marker represents 5 minutes.

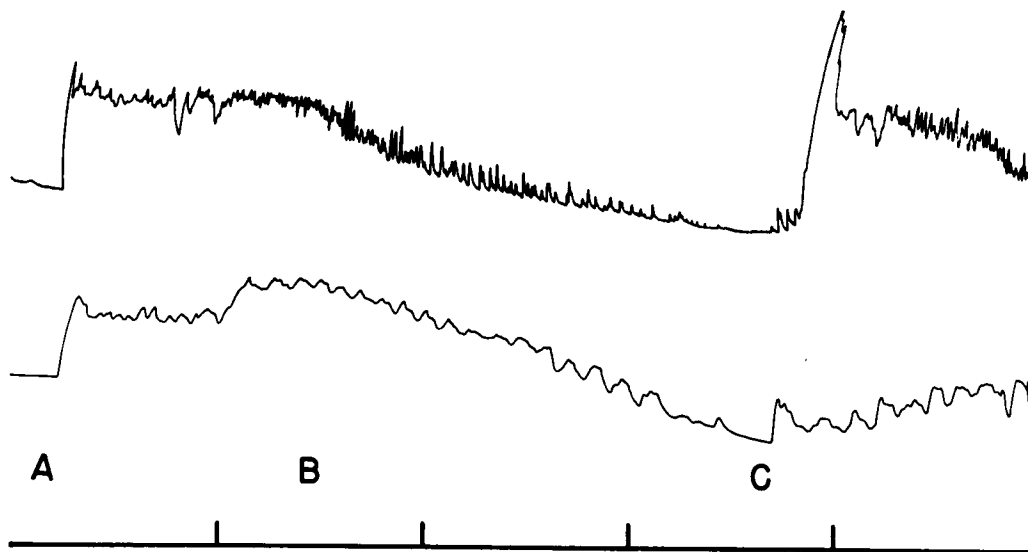


FIG. 3. The effects of morphine and halothane on the motility of jejunum (top tracing) and colon (bottom tracing). A—morphine, 200  $\mu\text{g./kg.}$  B—halothane on; C—morphine, 200  $\mu\text{g./kg.}$  Time marker represents 5 minutes.

#### DISCUSSION

We have demonstrated that halothane is capable of profoundly affecting gastrointestinal motility in dogs. Also, we have described the results obtained from both the acute and the chronic preparations involving the antagonism of various substances causing increased motor activity, by halothane. Since the toxic effects of barium chloride are well recognized, it was not reasonable to risk the loss of our chronic preparations to demonstrate the effects of halothane on contractions elicited by this compound. Hence, the acute

preparation was utilized for this purpose. The technique of pithing allowed these acute experiments to be carried out without the presence of anesthetic agents which might have influenced the results obtained. Although control contractions were quite poor in these preparations, the response to barium chloride injections was classical. Moreover, the primary effects of barium chloride on the gastrointestinal tract are thought to be peripheral in origin and therefore an intact central nervous system was not essential to demonstrate the halothane antagonism of barium chloride induced contractions.

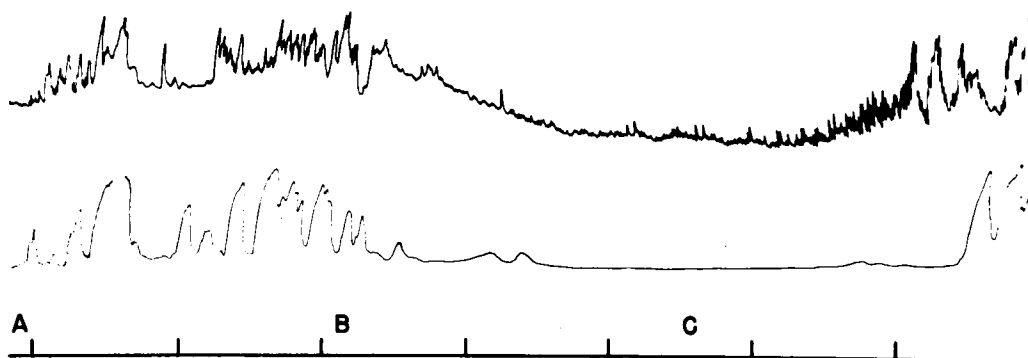


FIG. 4. The effects of neostigmine and halothane on the motility of jejunum (top tracing) and colon (bottom tracing). A—neostigmine, 50  $\mu\text{g./kg.}$  B—halothane on; C—halothane off. Time marker represents 5 minutes.

We routinely used cyclopropane in our chronic preparations only as a means of passing recording balloons down the esophagus into the stomach without causing struggling. We feel certain that this procedure had little influence on the results obtained, since control contractions were quite good before the halothane was administered. Three experiments were conducted in a similar fashion using halothane instead of cyclopropane and the results were identical.

Neostigmine methylsulfate, at least in part, increases intestinal activity by cholinesterase inhibition. This increased activity of the intestinal movements is readily antagonized by atropine sulfate. Since halothane readily antagonized the neostigmine-induced contractions, it was necessary to study halothane with smooth muscle stimulating agents such as morphine sulfate and barium chloride. Atropine sulfate does antagonize the stimulating action of morphine and barium to some extent, but apparently the major site of action is beyond the cholinergic receptor at the postganglionic parasympathetic neuroeffector junction. The mechanism of the musculotropic action of these two agents is not understood. Although these studies do not prove or disprove an anticholinergic action for halothane, they do demonstrate some musculotropic effect. The mechanism by which halothane depresses gastrointestinal motility is unknown, but these

studies do suggest, at least in part, a peripheral mechanism.

#### SUMMARY

Halothane, in concentrations capable of producing anesthesia, depresses motility of the jejunum, colon and stomach of dogs; and activity returns promptly after the agent is withdrawn. Contractions return approximately to preanesthetic levels before any limb movements can be detected. Also, this agent is capable of antagonizing the contractions produced by the parenteral administration of morphine, acetyl- $\beta$ -methylcholine, neostigmine and barium chloride.

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#### REFERENCES

1. Miller, G. H.: Effects of general anesthesia on muscular activity of gastrointestinal tract, *J. Pharmacol. Exp. Ther.* **27**: 41, 1926.
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**ANESTHETIC UTILIZATION** Anesthesia of over three-hours duration was induced and maintained with nitrous oxide and intravenous doses of either meperidine or oxymorphone. Data was compared to a previous study in which thiopental was used as the intravenous anesthetic agent. The cumulative dose of each drug per square meter body surface was determined and time/dose curves plotted. The curves for the 3 drugs were found to be superimposable. The apparent transformation rate of each drug was found to be roughly 0.5 per cent per minute of the drug pool. The apparent distribution space

was the same for all three drugs which would suggest that under the experimental conditions uptake by fat depots was not important. There was no correlation between time/dose curve of succinylcholine and that of the anesthetic agents. The common factor for the latter may be the effective blood flow through the liver or the permeability of the hepatic cell membrane. (*Keeri-Szanto, M.: Anesthetic Time/Dose Curves. II. Limiting Factor in Utilization of Intravenous Anesthetics During Surgical Operations, Clin. Pharmacol. Ther.* **2**: 45 (Jan.-Feb.) 1961.)