

# Relative Ganglion-Blocking Potencies of Cyclopropane, Halothane and Nitrous Oxide, and the Interaction of Nitrous Oxide with Halothane

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The relative effects of halothane, cyclopropane, and nitrous oxide upon transmission in the stellate ganglion were examined in dogs previously given small doses of pentobarbital. The basis for estimating blockade was a comparison of the chronotropic responses to preganglionic and postganglionic nerve stimulation. We found that, while anesthetic actions varied widely in different preparations, there was a consistent relation among the responses to the various anesthetics when compared in the same preparation. Using this method halothane was found to be two to three times as potent in blocking ganglionic transmission as either cyclopropane or nitrous oxide when the agents were compared at equi-narcotic concentrations.

In 1955, Normann and Lufström, when studying the effects of certain anesthetics on ganglionic transmission remarked that the actions of cyclopropane were unpredictable.<sup>1</sup> It occurred to us that this observation might represent nothing more than an inherent variability in the responsiveness of their individual subjects, and that their findings indicated a limited ability of cyclopropane to block ganglia, its actions becoming conspicuous only in the most sensitive preparations. With this in mind, we compared the individual actions of halothane, cyclopropane and (sometimes) nitrous oxide on transmission in the stellate ganglia of 6 dogs. As expected, blocking potency varied widely from one preparation to another, but the animals most sensitive to halothane were also most sensitive to the other two

agents, while the animal least sensitive to halothane was unaffected by either cyclopropane or nitrous oxide. By comparing the relative degree of blockade produced by the three agents at minimal anesthetic concentrations we concluded that halothane has more than twice the ganglion-blocking potency of either cyclopropane or nitrous oxide.

## Methods

Eleven mongrel dogs were studied. Certain data from six of these studies have already been reported.<sup>2</sup> They were anesthetized with pentobarbital (20-40 mg./kg., intravenously), the trachea intubated, artificial respiration (Bird Mark 4 semiclosed; O<sub>2</sub> at 5 liters per minute total flow) instituted, and the femoral artery and vein cannulated. The arterial cannula was advanced (roughly 30 cm.) until it lay in the descending aorta roughly 15 cm. above the bifurcation.

The vagi were divided in the neck. The sternum was split in the mid-line. The sympathetic chains were dissected free bilaterally from T5 to T2-T3, cut at T5, and the white rami divided, with the exception of those connecting with the stellate ganglion, on the side stimulated. On the opposite side, the thoracic chain from T5 to T1 was ablated and the stellate ganglion excised.

Electrical stimuli (5 msec. pulses, 5-11 volts, 2-9 cps., duration 10 seconds) were applied to the sympathetic chain just proximal to the stellate ganglion and to a postganglionic nerve (middle cardiosympathetic) on the same side. Silver bipolar electrodes and a Tektronix pulse generator were used. The voltages employed were supramaximal. The amperage supplied was estimated by

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measuring the voltage drop across a fixed resistance; this voltage decrement was displayed on a Tektronix Model 502 cathode ray oscilloscope. Amperage changes during or between stimulations served to indicate either anatomical displacement of the nerve fibers or electrical shunting caused by an accumulation of blood near the electrodes.

Cardiac rate was transduced by a tachograph activated by the aortic pressure pulses which were in turn transduced by a Statham strain gauge. These variables, together with the stimulus characteristics, were recorded by a Grass polygraph. At the end of each study the tachograph was calibrated using a Tektronix pulse generator.

In most cases gallamine (10 mg., intravenously in repeated doses) was given to prevent movement upon stimulation, and in all cases atropine sulfate (0.4 mg.) was given at half-hourly intervals to prevent cardiac actions caused by stimulation of parasympathetic fibers running with the postganglionic sympathetic fibers.

In a typical experiment the cardiac rate response to stimulation of pre- and postganglionic fibers was first observed, and the rate of stimulation adjusted to produce equal and easily measurable effects within the lower part of the range of physiologically occurring frequencies (1-10 impulses/second). Once reproducible responses were obtained, the chest was flooded with mineral oil, and the oil maintained at  $37.5 \pm 0.5^\circ \text{C}$ . by means of an infra-red lamp. Following completion of the control observations (a series of three preganglionic and postganglionic stimulations at two minute intervals), an anesthetic was admitted to the respired gas mixture. Stimulations were then repeated at two-minute intervals until there was no further effect (usually within 20 minutes), and the same observations repeated at another concentration of anesthetic. When halothane was given,\* the concentration sequence was 0.2-1.0-5.0 per cent halothane, but deviations from this order

\* In eight cases end-expired gas samples were obtained and analyzed for halothane. Between 20 and 40 minutes after setting the Fluotax at a given concentration, the alveolar tension of halothane was found to equal  $0.66 \pm 0.025$  (SD) of that inspired.

were occasionally made without discernible effect upon the findings. In calculating the results the findings during the first period of halothane administration were compared with those during the first control period, the last "halothane period" with the second control, and the middle halothane period with the arithmetic mean of the responses during the first and second control periods.

In six studies cyclopropane in oxygen was administered using a flow rate of 1.2 liters per minute. End-expired tensions were monitored by the method of Linde and Price.<sup>2</sup> Nitrous oxide and oxygen were given in 3 cases using conventional flow meters and the concentrations of this anesthetic was estimated by subtraction, using a Beckman oxygen analyzer.

At the end of the experiment hexamethonium (50 mg.) was administered intravenously and the response to pre-ganglionic stimulation immediately repeated. This procedure was used to verify that all of the fibers stimulated were preganglionic and that the stellate ganglion was adequately perfused with blood.

## Results

*Response to Halothane.* Figure 1 shows the variability of the response to halothane encountered in ten preparations studied in this and in the preceding investigation.<sup>2</sup> It can

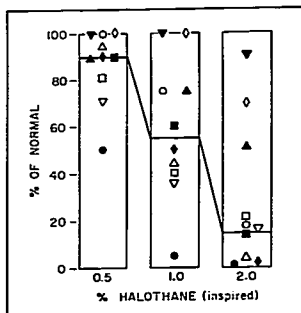


FIG. 1. Effects of 0.5, 1.0, and 2.0 per cent halothane on ganglionic transmission in each of ten different preparations. Ordinate = transmission as per cent of control. Abscissa = per cent halothane inspired. Horizontal lines show the median response.

be seen that inhalation of 0.5 per cent halothane had a significant effect in only three cases, that 1 per cent produced roughly half-inhibition of the response to preganglionic stimulation, and that 2 per cent virtually extinguished the response in seven of the ten preparations. The degree of scatter was particularly large at 1 per cent, ranging from no effect to complete blockade.

**Responses to Cyclopropane.** These are shown in figure 2, where the degree of ganglionic blockade produced in each of six preparations by end-expired concentrations of cyclopropane ranging from 20 to 27 per cent is compared with responses to halothane. The responses to cyclopropane ranged from no effect to half-blockade, with a median level of 18 per cent inhibition. The preparation which was most sensitive to cyclopropane was also most sensitive to halothane, and that least sensitive to cyclopropane was also least sensitive to halothane. One preparation (x) was not exposed to halothane. For comparison, the symbol \*, representing median responses to halothane, has been graphed in place of the missing observation. It can be seen that, while two preparations were too insensitive to permit

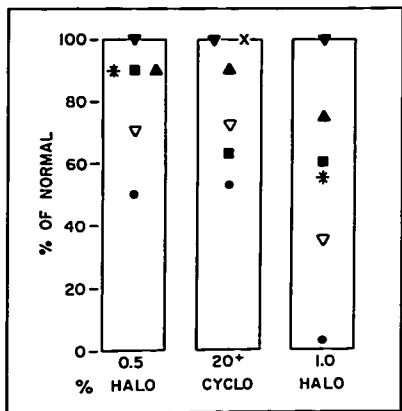


FIG. 2. Effects of 0.5 and 1.0 per cent halothane compared with those to 20-27 per cent cyclopropane in six preparations. See text for explanation.

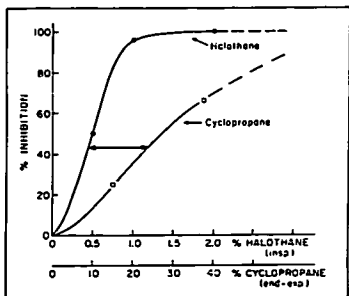


FIG. 3. Dose-response curves for halothane and cyclopropane obtained in a single preparation. See text for further explanation.

comparisons, in three of the remaining four cases the responses to cyclopropane were almost identical with those to 0.5 per cent halothane. In the remaining case the response to cyclopropane was intermediate between that to 0.5 and 1.0 per cent halothane.

Figure 3 shows dose-response curves for both halothane and cyclopropane in the most sensitive preparation studied. The arrow indicates that the same degree of inhibition (42 per cent) would have been produced by 23 per cent cyclopropane and 0.4 per cent halothane (inspired). Applying the same method to the other three preparations gave a mean value of  $0.60 \pm 0.11$  (S.E.) per cent halothane (inspired) as equivalent to 23 per cent cyclopropane in terms of ganglion-blocking potency.

**Response to Nitrous Oxide.** Although three preparations were exposed to nitrous oxide (75 per cent), in only one was there a measurable effect. This animal was also exposed to several concentrations of halothane, to cyclopropane, and to halothane and nitrous oxide, both singly and in combination. Fortunately, the responses were extraordinarily stable, so that the three anesthetic agents could be directly compared in terms of potency.

Figure 4 shows the dose-response curve to halothane. The individual effects of 75 per cent nitrous oxide and 20 per cent cyclopropane (lower left) are graphed on the abscissa.

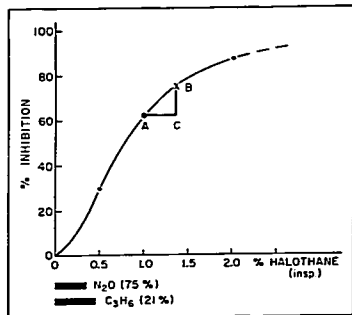


FIG. 4. Dose-response curve for halothane in oxygen, and the additional effect produced by nitrous oxide. Details are given in the text.

These effects are equivalent, respectively, to 0.35 and 0.45 per cent halothane (inspired). If the effects of halothane and nitrous oxide were merely additive, then the combined effect of these drugs would be the same as if 0.35 per cent halothane were added, instead of 75 per cent nitrous oxide. Points A and B in the figure are, respectively, the measured degrees of inhibition produced by the inhalation of 1 per cent halothane in oxygen and in 75 per cent nitrous oxide/25 per cent oxygen. Point B can also be obtained theoretically by laying off the horizontal distance equivalent to 0.35 per cent halothane (A-C), then erecting the perpendicular C-B which intersects the dose-response curve exactly at B. Thus, the interaction of nitrous oxide with halothane in this preparation was not a true potentiation but a simple addition of individual effects.

**Response to Pentobarbital.** The effects of this anesthetic in doses of 5 mg./kg. were examined in three preparations and found to be negligible.

### Discussion

A comparison of the ganglion-blocking activity of various anesthetics is meaningful only when related to general anesthetic potency. Minimal alveolar anesthetic concentrations for halothane, cyclopropane, and nitrous oxide are, approximately 0.01, 0.20, and 1.5 atmospheres, respectively.<sup>4,5</sup> In the case of halothane, the inspired tension producing the

minimal alveolar anesthetic concentration was approximately 1.5 per cent. An anesthetic tension was not attainable with nitrous oxide in this study because ambient pressure was merely atmospheric. However, the additive nature of the interaction between nitrous oxide and halothane makes it possible to estimate the effect which would have been produced by 1.5 atmospheres of nitrous oxide in the one preparation which was sufficiently sensitive to permit measurement of the inhibition caused by 75 per cent nitrous oxide (fig. 4). In this preparation 1.5 atmospheres of nitrous oxide apparently would have produced the same effect as 0.67 per cent halothane (inspired), and it was therefore less than one-half as potent in blocking the ganglion as was halothane. Cyclopropane at minimal anesthetic concentration was also less than half as potent as halothane, since it was equivalent to an inspired tension of 0.60 per cent  $\pm 0.11$  (S.E.) of the latter agent.

The additive nature of the blocking actions of nitrous oxide and halothane may have clinical significance, because the combined effect of 0.5 per cent halothane and 75 per cent nitrous oxide may produce the same degree of blockade as 1.0 per cent halothane, thus greatly increasing the inhibition of ganglionic transmission (*cf.* fig. 1). It goes without saying that this prediction requires that human and canine ganglia behave similarly.

The degree of inhibition caused by cyclopropane at high concentrations in some preparations was unexpected in view of the apparently linear relation between alveolar tensions of cyclopropane and plasma norepinephrine concentrations in man.<sup>6</sup> We had supposed that this relation indicated a progressively greater impulse traffic in post-ganglionic sympathetic fibers with increasing anesthetic depth, at least in man, but this would be impossible if the sympathetic ganglia became blocked at the same time. On the other hand, it has been found<sup>7</sup> that the canine response to cyclopropane does not resemble that observed in man: epinephrine (not norepinephrine) is the predominant catechol, and the catecholamine concentrations do not continue to rise as anesthetic depth increases. A possible explanation of this difference in response would be that canine sympathetic ganglia are

more sensitive to cyclopropane than are those in man. Another important possibility is that the basal anesthetic used (pentobarbital) has some ganglion blocking activity in high doses and may have summated with that caused by cyclopropane.

An interesting aspect of the present study is the finding that cyclopropane can potentiate the chronotropic response to post-ganglionic stimulation. It was mentioned previously<sup>2</sup> that when halothane reduced the resting heart rate, the standard stimulus often produced an augmented effect. However, this was so only because the standard stimulus tended to increase heart rate to a constant level, irrespective of the initial rate, and it therefore did not represent a "true" or direct pharmacological potentiation. With cyclopropane, true potentiation occurred; *i.e.*, the response increased irrespective of changes in initial heart rate. The degree of potentiation found at minimal anesthetic concentration was usually small (about 8 per cent), but sometimes large. Potentiation of responses to catecholamines seems to be characteristic of cyclopropane<sup>3</sup> and may account for an unsuspectedly large part of the resistance to circulatory depression which is so conspicuous a feature of cyclopropane anesthesia.

A completely unexpected result of this study was the absence of arrhythmic cardiac contractions during sympathetic stimulation. We had been led to believe that ventricular rhythms, including fibrillation, were to be expected when sympathetic nervous activity was increased during an exposure to "hydrocarbon" anesthetics which "sensitized the myocardium" to the effects of catecholamines.<sup>3, 10, 11</sup> The failure of such rhythms to occur in this study casts doubt on the importance of such a mechanism in the dog, at least under the conditions of the present study.

### Summary and Conclusions

The relative blocking abilities of cyclopropane, halothane, and nitrous oxide have been compared, using the stellate ganglion of the dog. Halothane produced a negligible effect when administered at an inspired concentration of 0.5 per cent. One per cent caused half-inhibition and two per cent essentially

complete blockade. Both cyclopropane and nitrous oxide were less than half as potent as halothane, when compared at equianesthetic concentrations. Nitrous oxide added non-specifically to the block produced by halothane.

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