THE ANESTHETIC POTENCY AND BIOCHEMICAL EFFECTS OF 1 AND 2 CHLOR PROPENE–1 AND 1 AND 2 BROM PROPENE–1 *

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Introduction

The investigation of the comparative anesthetic potency and acute toxicity of a series of saturated and unsaturated halogenated hydrocarbons has been the subject of an extended study which started in 1934 with the preliminary experiments of Peoples and Leake (1). Later studies (2, 3) indicated that certain of the unsaturated monohalogen compounds might be more valuable as general anesthetic agents than their saturated analogues. Other experiments (4) on the relative stability *in vivo* of a number of saturated and unsaturated bromine derivatives demonstrated that certain unsaturated compounds were worthy of further investigation as general anesthetic agents in larger animals.

Four unsaturated compounds were selected for the investigation of their anesthetic potency and biochemical effects in dogs. These included: 1 chlor propene, 2 chlor propene, 1 brom propene, and 2 brom propene.

Experimental

All of the compounds were prepared by dehydrohalogenation of the dihalogen saturated compounds using alcoholic potassium hydroxide. They were redistilled and fractionated in a Lecky column one to two days prior to use and were refrigerated at 5 C. Appreciable decomposition did not occur as evidenced by the constant pharmacological effects obtained.

Blood and bag concentrations were determined manometrically with the Van Slyke-Neill Manometric Apparatus by a method previously described by one of us (S. A. P., 5).

For the investigation of each compound 5 dogs were selected without any regard for sex or weight. The variation in weight was from 5 to 15 Kg. Animals were maintained for five to ten days prior to use on Purina Dog Chow. Food was withheld for twelve hours prior to

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TABLE 1

Concentrations of Halogenated Propenes in Blood and Oxygen Required for Maintenance of 2d Plane, 3d Stage of Anesthesia in Dogs

Compound		Sampling Intervals								
		20 (minutes)			40 (minutes)			60 (minutes)		
		Average	Minimum	Maximum	Average	Minimum	Maximum	Average	Minimum	Maximum
1 chlor propene	Blood	2.4	1.7	4.0	2.6	1.7	3.7	2.6	1.9	3.8
	O_2	2.5	1.6	3.2	3.0	1.9	4.9	3.0	1.6	4.1
2 chlor propene	Blood	2.7	1.9	3.1	2.5	1.8	3.8	2.4	1.9	3.0
	O_2	2.5	1.5	3.9	2.4	1.8	3.3	2.5	0.8	4.0
1 brom propene	Blood	2.7	1.8	3.2	2.8	1.6	3.7	2.4	0.4	3.5
	O_2	2.8	2.0	3.4	2.6	2.0	3.0	2.4	1.6	3.1
2 brom propene	Blood	1.9	0.9	2.9	2.1	1.8	2.6	2.3	1.6	2.9
	O_2	1.5	0.8	2.2	2.0	0.5	3.8	1.6	0.7	2.1

anesthesia. Since preliminary experiments had demonstrated that there was some irritation of mucous membranes by these agents, each dog received 0.5 mg./Kg. of atropine sulfate intraperitoneally thirty minutes prior to anesthesia.

Venous blood samples were withdrawn immediately before anesthesia was induced. Blood glucose was determined by the Hagedorn-Jensen micro method (6, 7), blood lactic acid by the Rappaport and Reifer modification of the Mendel Goldscheider procedure (8), and plasma carbon dioxide combining power by the Van Slyke-Neill manometric method (9). Anesthesia was quickly induced by the Waters' absorption technic using a "to and fro" system. The anesthetic mask was constructed with a side arm, closed with a serum stopper, leading into the soda lime canister (Fig. 1). In this way the volatile liquid

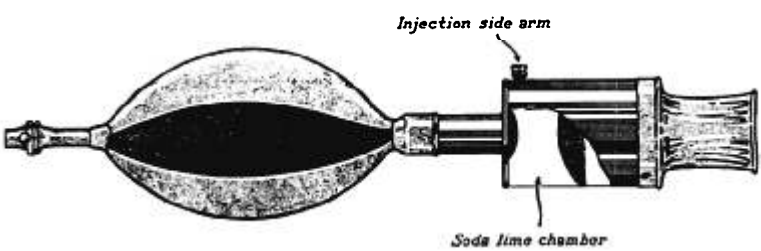

Fig. 1. Anesthetic mask and rebreathing bag.

TABLE 2

BIOCHEMICAL EFFECTS IN DOGS OF HALOGENATED PROPENES DURING AND AFTER RECOVERY FROM ANESTHESIA

Compound	Biochem. Constituents	Anesthesia (Minutes)				Recovery (Minutes)		
		0	20	40	60	30	60	120
1 chlor propene	Plasma CO_2 Combining Power (Vol. %)	49.7* (47.1–53.4)†	41.4 (33.8–49.7)	47.1 (38.8–57.8)	52.5 (44.3–61.0)	43.5 (32.4–52.3)	46.2 (29.3–62.4)	45.4 (31.8–52.0)
	Blood Glucose (mg. %)	79 (66–88)	126 (88–175)	131 (99–180)	135 (112–164)	102 (83–130)	102 (81–116)	93 (80–116)
	Blood Lactic Acid (mg. %)	24.5 (11.1–41.3)	34.5 (16.1–73.8)	27.3 (17.9–51.7)	28.8 (16.4–40.0)	42.8 (19.2–60.0)	31.4 (19.0–49.6)	28.3 (16.5–50.0)
2 chlor propene	Plasma CO_2 Combining Power (Vol. %)	44.1 (30.4–48.0)	41.9 (37.8–46.0)	38.9 (24.1–46.3)	41.4 (31.5–48.0)	40.2 (28.5–50.8)	42.3 (31.7–47.2)	48.2 (36.9–52.6)
	Blood Glucose (mg. %)	77 (72–86)	118 (84–164)	132 (91–168)	138 (86–159)	134 (89–183)	136 (82–203)	112 (79–158)
	Blood Lactic Acid (mg %)	23.1 (19.9–30.0)	29.6 (7.5–47.5)	40.3 (19.0–65.8)	37.6 (19.6–68.2)	35.8 (12.2–50.0)	27.1 (22.2–30.0)	27.1 (22.2–30.0)
1 brom propene	Plasma CO_2 Combining Power (Vol. %)	46.7 (41.1–50.2)	43.6 (39.3–46.0)	44.5 (38.8–50.0)	44.5 (38.8–49.0)	44.3 (34.1–49.0)	44.8 (39.5–51.8)	49.1 (40.8–57.0)
	Blood Glucose (mg. %)	78 (63–94)	108 (94–120)	126 (103–154)	120 (105–136)	98 (74–113)	97 (83–110)	85 (58–99)
	Blood Lactic Acid (mg. %)	27.2 (13.3–45.9)	36.6 (22.2–57.7)	38.2 (27.0–52.1)	41.4 (20.0–52.1)	55.9 (35.7–68.2)	30.6 (13.5–54.5)	30.6 (13.5–54.5)
2 brom propene	Plasma CO_2 Combining Power (Vol. %)	44.6 (34.7–52.0)	47.4 (41.2–64.7)	46.4 (37.6–60.8)	38.9 (27.6–46.9)	34.6 (31.7–37.3)	36.7 (31.8–39.0)	41.6 (31.8–46.7)
	Blood Glucose (mg. %)	79 (66–98)	105 (80–146)	125 (97–164)	134 (105–177)	128 (98–155)	121 (97–150)	100 (79–130)
	Blood Lactic Acid (mg. %)	27.0 (23.4–35.4)	36.7 (24.5–67.6)	36.8 (29.7–45.1)	35.5 (23.2–47.9)	53.3 (40.8–67.7)	51.2 (42.5–61.0)	32.8 (16.0–44.1)

* Average results. † Ranges of concentration.

could be injected and quickly vaporized in the warm chamber. Within one to two minutes after the introduction of 0.5 to 2 cc. of the agents, the second plane of the third stage of anesthesia (Guedel, 10) was reached. Anesthesia was maintained at this level for sixty minutes.

Blood and bag samples were withdrawn at twenty minute intervals during the anesthetic period and the concentration of each compound employed was determined. Blood biochemical constituents were determined at the same time intervals during this period. Blood samples were withdrawn at thirty, sixty, and one hundred twenty minute intervals after removal of the mask and were analyzed as were the control samples.

Results

All of the compounds studied were effective as general anesthetic agents at blood concentrations varying from 0.4 to 3.8 mM./L. and concentrations in oxygen varying from 0.5 to 4.0 mM./L. One compound, 2 brom propene, appears to be slightly more potent.

Changes in blood constituents all reflected a mild degree of sympathetic stimulation. This is in all probability a manifestation of the mild irritating properties of the compounds. Emerson and co-workers (11) have shown that sympathetic stimulation comparable to that produced by dosages of 0.5 mg./Kg. of epinephrine results from maintenance of animals in surgical anesthesia (Stage III, Plane 2–3) with ether. They also found that comparable effects could not be produced with divinyl oxide. Guedel (12) believes that any anesthetic agent will produce sympathetic effects if the second stage is not passed through rapidly. Even with cyclopropane a sympathetic effect on the heart leading to ventricular fibrillation may occur.

The changes in blood sugar, lactic acid and plasma carbon dioxide combining power, produced by the halogenated propenes, indicate that only slight sympathetic stimulation occurred. The recovery determinations of these blood constituents are suggestive evidence that this may have occurred as the result of the sympathetic stimulation which necessarily is produced during the induction of anesthesia. This is borne out by the fact that during the recovery period of two hours the values for blood glucose returned to normal, whereas with comparable periods of anesthesia using ether, Emerson et al. and Phatak (13) have found a much greater delay in return to normal.

Discussion

All of the halogenated propenes investigated are more potent than the two most commonly used general anesthetic agents, cyclopropane and ether. A comparison of the blood levels necessary to maintain anesthesia at Stage III, Plane 2 demonstrates that these agents are all approximately seven times and twice as potent as ether and cyclopro-

pane, respectively. Table 3 contains the blood anesthetic levels of the common general inhalation anesthetics, and of the 4 compounds studied at the sixty minute period of anesthesia. Chloroform, the most powerful of the general inhalation anesthetic agents, is about equal in potency to the compounds investigated.

TABLE 3

BLOOD CONCENTRATIONS OF THE COMMON INHALATION ANESTHETICS AND HALOGENATED PROPENES NECESSARY FOR THE MAINTENANCE OF ANESTHESIA

Compound	mM./L.	Stage or Degree of Anesthesia
Ether (Haggard, 1924) (15)	16.8	Stage III, Plane 2
Cyclopropane (Robbins, 1935) (16)	4.0	Stage III, Plane 2
Chloroform (Buckmaster & Gardner, 1907) (17)	2.5	Surgical anesthesia
Ethyl Chloride (Beecher, 1938) (18)	4.7	Surgical anesthesia
1 Chlor Propene (60 minutes)	2.6	Stage III, Plane 2
2 Chlor Propene (60 minutes)	2.4	Stage III, Plane 2
1 Brom Propene (60 minutes)	2.4	Stage III, Plane 2
2 Brom Propene (60 minutes)	2.3	Stage III, Plane 2

Halogenation and unsaturation have markedly increased the potency of the parent hydrocarbon propane. However, contrary to findings with other types of halogenated compounds, the brom and chlor propenes are approximately equal in potency. Attempts to make other generalizations (14) with respect to the increase in potency by unsaturation in the halogenated saturated hydrocarbons are inconclusive.

SUMMARY

There is suggestive evidence from this and other studies that the 1 and 2 brom and 1 and 2 chlor propenes possess some value as general inhalation anesthetic agents. Studies on the chemical stability and chronic toxicity of these compounds are indicated prior to the institution of any clinical trial.

REFERENCES

1. Peoples, S. A., and Leake, C. D.: Anesthetic Action of Vinyl Chloride, Proc. Am. Soc. Pharmacol. & Exper. Therap., J. Pharmacol. & Exper. Therap. 48: 284 (July) 1933.
2. Abreu, B. E.; Peoples, S. A., and Emerson, G. A.: A Preliminary Survey of the Anesthetic Properties of Certain Halogenated Hydrocarbons, Anesth. & Analg. 18: 156–161 (May–June) 1939.
3. Silverman, M., and Abreu, B. E.: The Toxic and Anesthetic Properties of Certain Mono-Chlor Propenes, Univ. California Publ., Pharmacol. 1: 119–128 (Dec.) 1938.
4. Abreu, B. E., and Emerson, G. A.: Difference in Inorganic Bromide Content of Liver after Anesthesia with Saturated and Unsaturated Brominated Hydrocarbons, Univ. California Publ., Pharmacol. 1: 313–320 (Aug.) 1940.

5. Peoples, S. A.: A Method for Determining the Solubility of Gases and Vapors in Liquids by Means of the Van Slyke-Neill Apparatus, Proc. Am. Soc. Pharmacol. & Exper. Therap., J. Pharmacol. & Exper. Therap. 72: 31–32 (May) 1941.
6. Hagedorn, H. C., and Jensen, B. N.: Zur Mikrobestimmung des Blutzuckers mittels Ferricyanide, Biochem. Ztschr. 135: 46–58, 1923.
7. Hagedorn, H. C., and Jensen, B. N.: Die Ferricyanidmethode zur Blutzuckerbestimmung, Biochem. Ztschr. 137: 92–95, 1923.
8. Rappaport, F., and Reifer, I.: Determination of Lactic Acid. I. Determination of Lactic Acid in Blood with Physiological Sugar Values, Mikrochim. Acta 2: 62–64, 1937.
9. Van Slyke, D. D., and Neill, J. M.: The Determination of Gases in Blood and other Solutions by Vacuum Extraction and Manometric Measurement, J. Biol. Chem. 61: 523–574 (Sept.) 1924.
10. Guedel, A. E.: Inhalation Anesthesia, The MacMillan Company, 1937.
11. Emerson, G. A.; Klyza, S. J.; Abreu, B. E., and Phatak, N. M.: Hyperglycemia and Ketonemia with Ether and Divinyl Oxid, Anesth. & Analg. 16: 85–89 (Mar.–Apr.) 1937.
12. Guedel, A. E.: Personal communication.
13. Phatak, N. M.: Carbohydrate Metabolism in Ether Anesthesia: I. Fate of Injected d-Lactic Acid in the Dog, the Rabbit and the Rat, Anesth. & Analg. 19: 18–26 (Jan.–Feb.) 1940.
14. Abreu, B. E.: Unsaturated Mono Halogenated Hydrocarbons as General Anesthetic Agents, Anesthesiology 2: 393–397 (July) 1941.
15. Haggard, H. W.: The Absorption, Distribution and Elimination of Ethyl Ether. IV. The Anesthetic Tension of Ether and the Physiological Response to Various Concentrations, J. Biol. Chem. 59: 783–793 (Apr.) 1924.
16. Robbins, B. H.: Studies of Cyclopropane. II. Concentrations of Cyclopropane Required in the Air and Blood for Anesthesia, Loss of Reflexes and Respiratory Arrest, J. Pharmacol. & Exper. Therap. 58: 251–259 (Nov.) 1936.
17. Buckmaster, G. A., and Gardner, J. A.: The Rate of the Assumption of Chloroform by the Blood during Anesthesia, Proc. Roy. Soc., series B, 79: 555, 1907.
18. Beecher, H. K.: The Physiology of Anesthesia, The Oxford University Press, 1938.

COMBINED MEETING OF THE SECTION ON ANESTHESIA OF THE CONNECTICUT STATE MEDICAL SOCIETY AND THE CLINICAL CONGRESS

BRADY AUDITORIUM, NEW HAVEN, CONN.

September 17, 1941—8:00 P.M.

1. Two case reports.
   By Mario Garofalo, M.D., St. Raphael Hospital, New Haven, Conn.
2. Anesthesia in the Aged.
   By R. J. Forastiere, M.D., Bellevue Hospital, New York City.
3. Anesthesia and Liver Function.
   By Lester M. Morrison, M.D., Philadelphia, Pa.