

The Ventilatory Effects of Forane,* a New Inhaled Anesthetic

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The ventilatory effects of Forane were studied in ten volunteers and compared with values obtained in eight volunteers anesthetized with halothane. P_{aCO_2} averaged 60 torr with both 1.9 per cent alveolar Forane (approximately $1.45 \times \text{MAC}$) and 1.6 per cent halothane ($1.9 \times \text{MAC}$). The slopes of the CO_2 response curves were depressed to 30 ± 6 per cent (Mean \pm SE) of awake control values by 1.25 per cent Forane (approximately $1.0 \times \text{MAC}$) and to 45 ± 7 per cent of controls with 1.05 per cent halothane ($1.25 \times \text{MAC}$). Therefore, when equivalent anesthetic doses are considered, less Forane than halothane was needed to increase P_{aCO_2} and depress the slope of the CO_2 response curve. In contrast to halothane, Forane in increasing concentrations did not cause progressive increases in respiratory frequency. At equal multiples of MAC, Forane produces more profound respiratory depression than halothane, and this depression results from a unique failure of respiratory frequency to increase with increasing depth of anesthesia. (Key words: Ventilation; Forane; Carbon dioxide; General anesthesia.)

FORANE (1-chloro, 2,2,2-trifluoroethyl difluoromethyl ether) is a potent, nonexplosive halogenated ether recently introduced for investigative purposes as a general anesthetic agent. Initial observations suggested that it might be a profound respiratory depressant.¹ Accordingly, we have investigated the ventilatory effects of this agent in ten volunteers and compared the results with those obtained in a similar group anesthetized with halothane.

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Received from the Department of Anesthesia, University of California, San Francisco Medical Center, San Francisco, California. Accepted for publication March 10, 1971. Supported in part by USPHS Grants 5T1GM00063-12, 1P01GM15571-02, and a grant from Ohio Medical Products.

Methods

Ten healthy male volunteers 21 to 26 years old were informed about the studies to be performed and their consents obtained. The experimental procedure has been described.²⁻³ Briefly, each subject reported to the study room in the morning after a minimum of eight hours of fasting. No premedicant drugs were given. Using local anesthesia, catheters were placed into a brachial or radial artery and into the right atrium. The position of the atrial catheter was assured by recording right ventricular pressure and then withdrawing the catheter until the ventricular configuration just disappeared. With a nose clip in place, the subject breathed oxygen through a mouthpiece from a conventional anesthetic circle system. A Neff circulator was installed distal to the inspiratory valve to decrease the resistance to breathing.⁴ A recording ventimeter was substituted for the reservoir bag for measuring tidal volume and respiratory frequency.⁵ P_{aCO_2} was measured continuously by means of a Beckman LB-1 CO_2 analyzer. Following denitrogenation, at least three determinations each of P_{aO_2} , P_{aCO_2} , and pH, right atrial P_{O_2} and pH, and minute ventilation were made. Blood oxygen saturations were calculated using the Severinghaus slide rule and converted to content by multiplying 1.34 ml by the hemoglobin concentration and adding $0.0031 \times P_{aO_2}$. Hemoglobin concentration was estimated as a third of the hematocrit, which was determined by the microcapillary technique. Cardiac outputs were determined by the dye-dilution technique. Oxygen consumption (\dot{V}_{O_2}) was calculated by multiplying arteriovenous oxygen content difference by cardiac output. Alveolar ventilation (\dot{V}_A) was calculated by the formula

$$\dot{V}_A = (\dot{V}_{O_2} \times R \times P_B) / P_{A_{CO_2}}$$

where P_B represents barometric pressure, R

(respiratory quotient) was assumed to be 0.8,^{6,7} and PaCO_2 was assumed to equal PaCO_2 . Wasted ventilation (\dot{V}_D) was then calculated by the formula

$$(\dot{V}_E - \dot{V}_A)/\dot{V}_E$$

(where \dot{V}_E is the expired minute ventilation measured from the recording ventilometer) and expressed as per cent of tidal volume (\dot{V}_D/\dot{V}_T per cent). After stable baseline measurements of minute ventilation and cardiac output had been obtained, inspired CO_2 concentration was increased in increments of approximately 2 to 6 torr until PaCO_2 was 8 to 17 torr (mean 11.2 torr) above the resting value. Ventilation and PaCO_2 were measured when PaCO_2 had been held constant for an interval of at least six minutes at each new level.

Anesthesia was then induced by mask with Forane and oxygen, the Forane being vaporized from a Fluotec vaporizer. The trachea was intubated without muscle relaxants or topical anesthesia. Breathing continued spontaneously throughout the studies.

Alveolar anesthetic levels were measured with a Beckman infrared analyzer. PaCO_2 , minute ventilation, and tidal volumes were measured in the following sequences. Measurements were first made at three successively higher alveolar concentrations of Forane: 1.26 \pm 0.01 per cent, 1.58 \pm 0.02 per cent, and 1.88 \pm 0.02 per cent. Each concentration was maintained for a minimum of ten minutes prior to making measurements. Subsequently, in each of five subjects the alveolar concentration was maintained at 1.87 \pm 0.03 per cent and in five other subjects it was decreased to 1.28 \pm 0.01 per cent; the ventilatory responses to CO_2 were then determined as in the awake measurements. The alveolar concentrations in the two groups were then reversed: the subjects who had been receiving 1.28 per cent now received 1.87 per cent, and *vice versa*. After at least 30 minutes had elapsed at the new alveolar concentration, ventilatory response to CO_2 was again determined. Following this, the alveolar concentration in both groups was maintained at 1.2 per cent for 30 minutes, after which resting PaCO_2 , minute ventilation and tidal volumes were again measured at alveolar Forane levels of 1.26 \pm 0.02 per cent, 1.56 \pm 0.02 per cent, and 1.90 \pm 0.02 per cent. Again, a minimum of ten min-

utes at a stable alveolar anesthetic concentration preceded each series of measurements. With few exceptions, all subjects followed the above protocol. Where data were not obtained, the resulting reduction in the number of subjects available for analysis is indicated.

For comparison, eight other volunteers underwent similar studies while awake and at two levels of halothane anesthesia. (A portion of these data will be reported later.) The volunteers for the halothane studies were drawn from the same pool of healthy young subjects and did not differ significantly from the Forane subjects in age (22.4 \pm 2.1 vs. 23.6 \pm 1.8 years), height (70 \pm 4 inches for both groups), or weight 158 \pm 21 vs. 165 \pm 32 pounds). Except for the use of halothane anesthesia, the pattern of study was identical to that of the Forane study. Alveolar halothane concentrations were determined by infrared analysis and were maintained at 1.02 \pm 0.02 per cent for 15 minutes, after which minute ventilation, PaCO_2 , and tidal volume were measured. The alveolar halothane concentration was then increased to 1.59 \pm 0.03 per cent for another 15 minutes and the measurements repeated. Alveolar halothane concentration was then decreased to 1.04 \pm 0.01 per cent, and after 116 \pm 8 minutes and 193 \pm 5 minutes the ventilatory responses to inhaled CO_2 were determined. After 30 minutes without elevated inspired CO_2 , ventilation and P_{CO_2} were measured. Then the alveolar halothane concentration was increased to 1.59 \pm 0.02 per cent and, after 15 minutes, measurements of resting ventilation, P_{CO_2} , and ventilatory response to CO_2 were made.

For each subject, a line relating all measurements of minute ventilation and the associated PaCO_2 values was determined by the method of least squares.⁸ The resting point (no imposed increase in inspired CO_2) was included in the line. The slope of the line relating PaCO_2 to \dot{V}_E was expressed in l/min./torr PaCO_2 .

All values were then analyzed for the effect of the anesthetic by Student's paired *t* test, and differences were considered significant when $P < 0.05$.

Results

During Forane anesthesia, tidal volume decreased with increasing depth of anesthesia

TABLE 1. Effects of Doses and Duration of Fentanyl and Halothane Anesthesia on Resting Ventilation*

	No. Subjects	Time (Min)	Alveolar Concentration (Per Cent)	PACO ₂ (mm)	\dot{V}_E (l/Min)	f (1/Min)	V _T (ml)	Oxygen Consumption (ml/Min)	Alveolar Ventilation (l/Min)	V _D /V _T (Per Cent)	$\Delta V_D/V_T$ (Per Cent)
Fentanyl	10	—	Awake	38.0 ± 0.8	7.0 ± 0.3	14 ± 1	534 ± 40	244 ± 14	3.8 ± 0.2	48 ± 3	—
	10	35	1.20 ± 0.01	48.5 ± 1.7 [†]	5.0 ± 0.4 [†]	24 ± 1 [†]	240 ± 13 [†]	106 ± 12 [†]	2.4 ± 0.2 [†]	57 ± 4	23 ± 12
	6	46	1.58 ± 0.02	55.0 ± 2.8 [†]	4.0 ± 0.3 [†]	22 ± 1 [†]	212 ± 14 [†]	175 ± 12 [†]	1.9 ± 0.2 [†]	57 ± 5	21 ± 13
	9	72	1.88 ± 0.02	61.0 ± 4.0 [†]	4.0 ± 0.3 [†]	22 ± 2 [†]	184 ± 14 [†]	164 ± 15 [†]	1.6 ± 0.2 [†]	58 ± 4 [†]	28 ± 14
	10	282	1.20 ± 0.02	48.0 ± 1.0 [†]	7.5 ± 0.0 [†]	24 ± 1 [†]	308 ± 25 [†]	187 ± 11 [†]	2.3 ± 0.1 [†]	68 ± 2 [†]	40 ± 8
	6	301	1.50 ± 0.02	55.3 ± 1.0 [†]	6.3 ± 0.5 [†]	24 ± 1 [†]	277 ± 10 [†]	190 ± 17 [†]	2.2 ± 0.2 [†]	65 ± 2 [†]	33 ± 9
Halothane	6	318	1.00 ± 0.02	58.5 ± 1.4 [†]	5.8 ± 0.5 [†]	25 ± 1 [†]	230 ± 12 [†]	188 ± 12 [†]	2.0 ± 0.2 [†]	65 ± 2 [†]	42 ± 9
	8	—	Awake	36.5 ± 1.0	7.4 ± 0.5	16 ± 1	480 ± 31	107 ± 23	3.0 ± 0.4	61 ± 4	—
	8	23	1.02 ± 0.02	46.6 ± 1.3 [†]	7.3 ± 0.4 [†]	32 ± 2 [†]	220 ± 0 [†]	151 ± 11	2.0 ± 0.2 [†]	72 ± 3 [†]	22 ± 8
	8	45	1.50 ± 0.03	50.7 ± 1.7 [†]	6.2 ± 0.3 [†]	41 ± 3 [†]	154 ± 4 [†]	143 ± 13	1.5 ± 0.2 [†]	70 ± 3 [†]	27 ± 7
	8	262	1.04 ± 0.01	53.2 ± 2.0 [†]	7.3 ± 0.2	33 ± 2 [†]	210 ± 14 [†]	173 ± 11	2.0 ± 0.2 [†]	72 ± 2 [†]	22 ± 11
	8	283	1.55 ± 0.03	60.6 ± 2.4 [†]	7.0 ± 0.7 [†]	42 ± 3 [†]	180 ± 7 [†]	170 ± 14	1.7 ± 0.2 [†]	77 ± 3 [†]	21 ± 20 ± 8

* All values given as means ± standard error when $P < 0.05$.

† Differs from awake value.

‡ Differs from awake value and all other concentrations at similar time.

§ Differs from awake value and one other concentration at similar time.

¶ Differs from awake value at same concentration.

** Differs from both other concentrations at similar time, and †.

*** Both ‡ and †.

†† Differs from other concentrations at similar time.

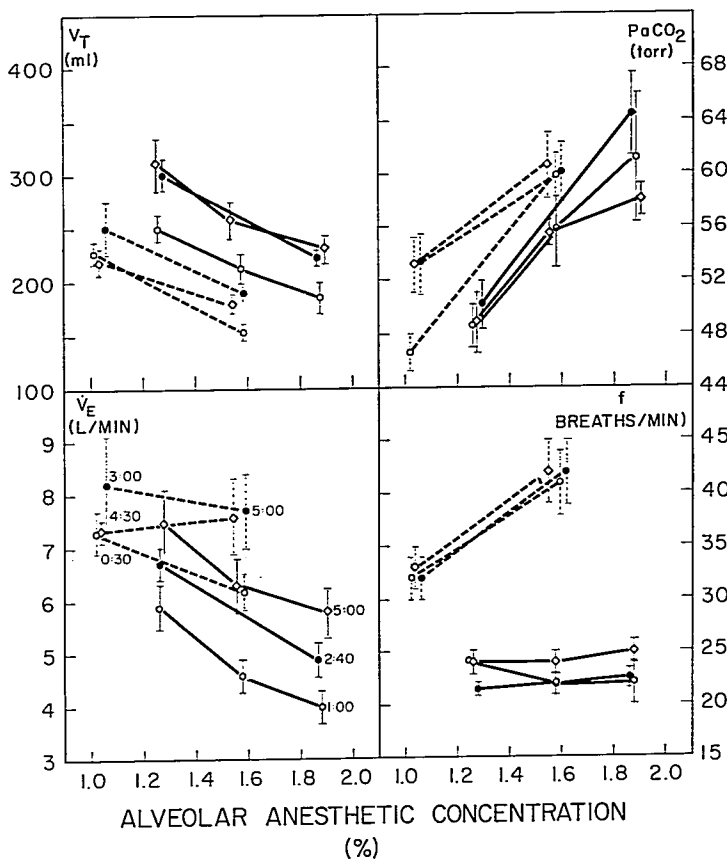


FIG. 1. Responses of resting P_{aCO_2} (torr), V_E (l/min), f (breaths/min) and V_T (ml) at various alveolar concentrations (per cent) of Forane and halothane. Numerals in graph of V_E refer to hours after start of anesthesia. Solid line = Forane; dashed line = halothane; circle = early dose-response relationship; square = late dose-response relationship; solid dot = dose-response relationship immediately before CO_2 challenges, i.e., in the midportion of the study.

(table 1; fig. 1). Minute ventilation also decreased, not only because of the decrease in tidal volume but also because there was no compensatory increase in the frequency of breathing. In contrast, tidal volume decreased

with increasing depth of halothane anesthesia, but minute ventilation changed little at any depth of halothane anesthesia because of a compensatory increase in respiratory rate.

P_{aCO_2} increased with increasing depth of

TABLE 2. Effects of Doses of Forane and Halothane Anesthesia on the Ventilatory Response to CO₂*

	No. Subjects	Time (Min)	Alveolar Concentration (Per Cent)	PaCO ₂ (torr)	\dot{V}_E (l./N.in)	Slope (l./N.in/torr PaCO ₂)	CO ₂ Response Slope as Per Cent of Awake Slope
Forane	1G	—	Awake	38.9 ± 0.8	7.0 ± 0.3	2.89 ± 0.22	100
	10	157 ± 14	1.28 ± 0.01	50.2 ± 1.7 ¹	6.7 ± 0.3	0.83 ± 0.39 ¹	30 ± 6
	8	159 ± 22	1.87 ± 0.03	64.7 ± 3.4 ²	4.9 ± 0.3 ²	0.40 ± 0.25 ²	14 ± 3 ³
Halothane	8	—	Awake	36.5 ± 1.0	7.4 ± 0.5	2.69 ± 0.40	100
	8	116 ± 8	1.02 ± 0.02	51.1 ± 1.5 ¹	7.1 ± 0.7	0.99 ± 0.13 ¹	46 ± 6
	8	193 ± 5	1.06 ± 0.01	53.0 ± 2.3 ¹	8.2 ± 0.9	1.08 ± 0.14 ¹	45 ± 7
	4	310 ± 22	1.59 ± 0.02	59.9 ± 2.3 ²	7.7 ± 0.7	0.27 ± 0.01 ²	13 ± 2 ³

* Slope = slope of ventilatory response to CO₂.

¹ Value significantly different from awake value.

² Value significantly different from awake value or preceding value in column.

³ Value significantly different from preceding value in column.

anesthesia with both agents, despite a decrease in oxygen consumption during Forane anesthesia. PaCO₂ averaged 60 torr with both 1.9 per cent alveolar Forane and 1.6 per cent halothane. The calculated V_D/V_T increased with increasing depth of anesthesia, especially after prolonged Forane anesthesia.

During CO₂ challenge, the slopes of the CO₂ response curves decreased with increasing depths of both Forane and halothane anesthesia (table 2; fig. 2).

With 1.28 per cent alveolar Forane, the slopes were depressed to 30 ± 6 per cent of the awake control values, whereas with 1.05 per cent alveolar halothane they were depressed to 45 ± 7 per cent of controls. At the levels of halothane and Forane studied, tidal volume and frequency were similar to the values in table 1.

Discussion

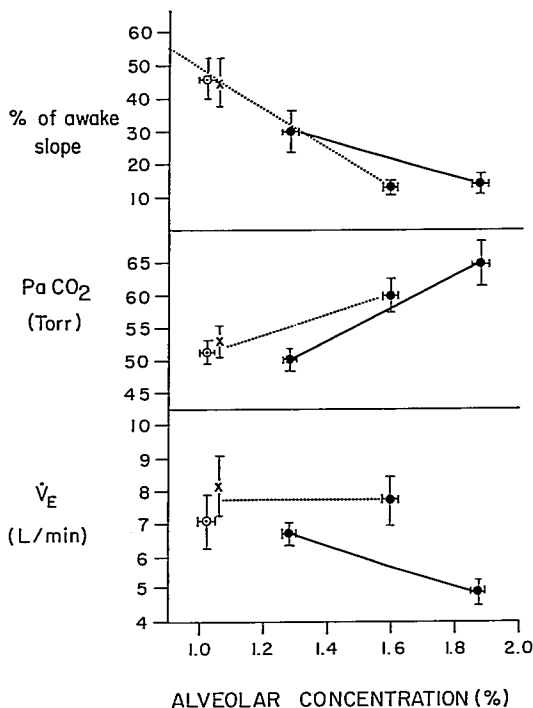
Forane is a profound respiratory depressant, as evidenced by the increasing PaCO₂, decreasing \dot{V}_E , and decreasing ventilatory response to CO₂ as depth of anesthesia is increased. The effects of halothane anesthesia on respiration were consistent with those previously reported by Munson *et al.*² Comparisons of the findings with Forane with those obtained with halothane are limited by the lack of an exact measurement of Forane's potency in man. However, preliminary determinations in our laboratory suggest that the MAC of Forane in man lies between 1.2 and 1.4 per cent, compared with a MAC for halothane of 0.84 per cent.³ If we assume a MAC of 1.3 per cent,

then at equal multiples of MAC, Forane produces more profound respiratory depression than halothane, or, for that matter, any other commonly used inhalation anesthetic.¹⁰ This appears to be the result of a minimal increase in respiratory frequency during Forane anesthesia and a failure of frequency to increase further with increasing depth of anesthesia. This failure of respiratory frequency to increase is unique among the inhalation anesthetics previously studied.¹⁰ The absence of dose-related changes in respiratory frequency suggests that frequency will not be a useful sign of depth of anesthesia with Forane. On the other hand, changes in tidal volume correlate with dose and therefore could be used as a guide to depth of anesthesia.

During halothane and early Forane anesthesia, V_D/V_T increased by an average of 25 per cent over awake values. During prolonged Forane anesthesia, V_D/V_T increased even more, resulting in an unchanged PaCO₂ despite the increase in minute ventilation later in each study. The absolute values of V_D/V_T are less meaningful than per cent changes from awake V_D/V_T for each individual because of the inaccuracies of the dye-dilution method of determining cardiac output and the incomplete mixing of the venous blood obtained from the right atrial catheters.

The results of our studies suggest that respiration must be controlled to avoid respiratory acidosis during Forane anesthesia. To what extent surgical stimulation may antagonize the respiratory depressant effects of Forane is not yet known, nor how adjuvants

FIG. 2. Response of resting \dot{V}_E (l/min), P_{aCO_2} (torr), and per cent of awake slope at various alveolar concentrations (per cent) of Forane and halothane. Values shown are mean \pm SE. Solid line = Forane; dashed line = halothane; circled dot = early halothane anesthesia; X = late halothane anesthesia.



such as opiates, muscle relaxants, and nitrous oxide may modify the respiratory effects of this new agent.

The authors gratefully acknowledge the capable technical assistance of Mrs. Anne White, Mr. Richard Shargel, Miss Dianne Impelman, and Miss Eddie Von Gal.

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