

# Clinical Reports

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## Uptake and Biotransformation of Aliflurane (1-Chloro-2-methoxy-1,2,3,3-tetrafluorocyclopropane, Compound 26-P) in Man

DUNCAN A. HOLADAY, M.D.,\* MARIA C. JARDINES, M.D.,† WILLIAM H. GREENWOOD, M.D.†

Extensive tests in laboratory animals have suggested that aliflurane (1-chloro-2-methoxy-1,2,3,3-tetrafluorocyclopropane, Compound 26-P) is potentially a clinically useful inhalational anesthetic. Its physical properties are similar to those of enflurane; the blood-gas partition coefficient at 37 C is 1.7, oil-gas partition coefficient, 117. The MAC in man, predicted from MAC in the dog, as determined by Munson *et al.*,<sup>1</sup> is 1.28 per cent. It is not explosive and does not decompose in soda lime.

Initial trials in healthy volunteers were undertaken to establish the safety and extent of biotransformation of aliflurane.

### METHODS

Ten healthy, informed, young male volunteers, who had histories of no repetitive exposure to drugs for a period of six months, were exposed for one hour to anesthetic concentrations of aliflurane vapors ranging between 0.75 to 3.1 vol per cent.

Aliflurane vapor was delivered by mask in oxygen or, in two instances, in oxygen with 60 and 66 per cent nitrous oxide. Fresh gas inflow was 4.5 l/min into a semiclosed, valves in "Y," partial rebreathing circuit. Subjects were allowed to breathe spontaneously. Polyethylene plastic and nylon breathing tubes were used to minimize the absorption of the agent from the breathing circuit. Arterial blood respiratory gases, expired minute ventilation, and the concentrations of aliflurane in inhaled, mixed exhaled, and end-exhaled

air and in arterial blood were measured at frequent intervals during exposure. Blood pressure, pulse rate, electrocardiogram (ECG) and electroencephalogram (EEG) were monitored.

**Gas Analysis.** Gas samples were collected in glass syringes and analyzed immediately for aliflurane using a gas chromatograph (Hewlett-Packard 7610A) equipped with a hydrogen flame ionization detector. A glass column 2.5 mm × 1 m packed with Chromosorb P®, 60/80 mesh, coated with 10 per cent diisodecylphthalate, was operated at 100 C with a nitrogen carrier gas flow of 25 ml/min. Blood aliflurane concentrations were measured by the method of Fink and Morikawa<sup>2</sup>.

Uptake rate was calculated from the difference of aliflurane concentrations in the inspiratory and expiratory limbs multiplied by the total circuit flow. Total circuit flow equalled fresh gas flow plus expired minute ventilation measured between the mask and "Y" piece with an Ohio Vortex Respiration Monitor®.‡

**Analysis of Urinary Fluorine.** Urine was collected in 24-hour periods beginning 24 hours prior to exposure and for as long as 14 days after exposure. Urine was stored in polyethylene bottles at 4 C until the fluorine content was analyzed. Determination of inorganic fluoride and total nonvolatile fluorine were carried out as previously described.<sup>3</sup> The difference between the fluoride ion concentrations in combusted samples and noncombusted samples represented fluorine excreted as nonvolatile organic compounds (organic fluorine). Excess fluoride excretion was determined as the difference between the amount found after exposure and the amount excreted per day before exposure. Fluoride ion and total nonvolatile fluorine content of blood samples were determined as previously de-

\* Professor.

† Research Trainee.

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Address reprint requests to Dr. Holaday.

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scribed.<sup>4</sup> The sensitivity of the methods for inorganic and total nonvolatile fluorine in urine and total nonvolatile fluorine in blood is 0.5  $\mu\text{g}$  fluorine per ml. The sensitivity of the method for inorganic fluoride in blood is 0.05  $\mu\text{g}$  of excess fluoride per ml. The reproducibility of these methods approximates 5 per cent of the signal.

Electroencephalographic and electrocardiographic outputs were recorded continuously with a Hewlett-Packard Model 8100 polygraph. Blood respiratory gases were measured with an IL Model 113<sup>®</sup> blood-gas analyzer.

### RESULTS

All subjects lost consciousness and later reported complete amnesia during exposures to inspired concentrations ranging from 1 to 3.1 per cent. All subjects had tachypnea, increased motor tone, and continuous eye movements at inspired concentrations between 0.75 and 1.9 per cent (end-expired concentrations 0.73 to 1.6 per cent). In six subjects, inspired concentrations of 1.4–2.8 per cent (end-expired concentrations of 1.0–1.6 per cent) produced periods of anesthesia that resembled light surgical anesthesia, with cessation of eye movements but with only incomplete obtundation of response to pain. Soft-tissue airway obstruction occurred occasionally, but was relieved by positioning the head or insertion of an oral or nasopharyngeal airway.

Systolic blood pressures averaged 106 (SEM  $\pm 3.1$ ) torr; a reduction of 5 per cent (SEM  $\pm 3.0$ ), and mean diastolic blood pressure was 65.5 (SEM  $\pm 3.03$ ) torr, an increase of 6 per cent (SEM  $\pm 3.9$ ). Mean pulse rate during exposure was 60.4 (SEM  $\pm 4.2$ )/min, a reduction of 2.9 per cent (SEM  $\pm 9.1$ ). Arterial blood pH values averaged 7.39 (SEM  $\pm 0.012$ ), mean  $\text{Pa}_{\text{CO}_2}$  was 39.0 (SEM  $\pm 1.1$ ) torr, and  $\text{Pa}_{\text{O}_2}$ s averaged 361 (SEM  $\pm 25.3$ ) torr during exposure in those subjects who did not receive  $\text{N}_2\text{O}$ . The intraindividual variances were less than the variances among individuals for all variables except  $\text{Pa}_{\text{O}_2}$ , for which the standard deviation of the group was 71.5 torr and the mean intraindividual standard deviation was 47.0 torr. A nodal rhythm of brief duration occurred in two subjects; other arrhythmias were not observed. The predominant electroencephalographic pattern was 12–60 Hertz. No spike activity or silent periods occurred.

Mean cumulative uptake during one hour of exposure to aliflurane was 17.1 (SEM  $\pm 1.7$ ) g. The average arterial blood content of aliflurane was 28 (SEM  $\pm 3.5$ ) mg/l.

In all cases the peak excretion rate (mg/hr) of

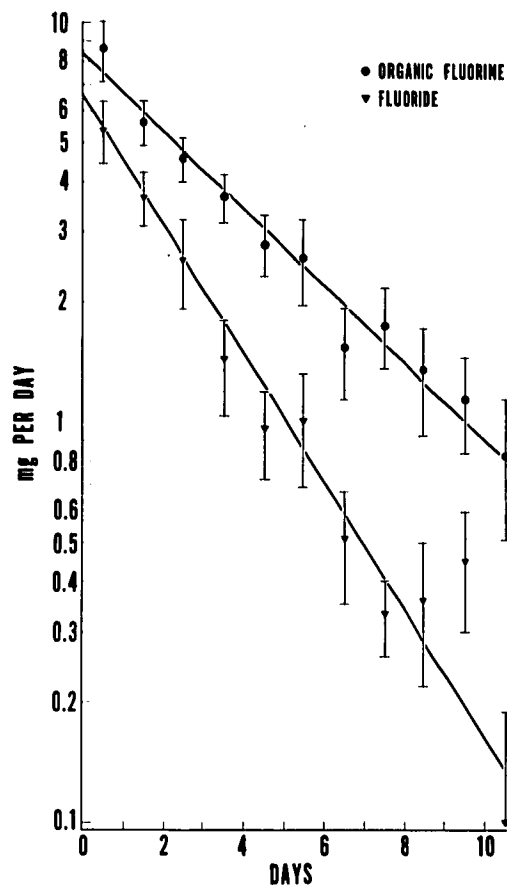


FIG. 1. Urinary excretion of excess fluoride and organic fluorine metabolites following an hour of exposure to aliflurane. For the means of days 0–5,  $n = 10$ ; for the remainder,  $n = 9$ . The vertical lines represent one standard error of the mean.

urinary metabolites occurred in the first 24 hours (fig. 1). The half-time for decay of urinary inorganic fluoride was 45 hours, and that for urinary organic fluorine metabolites was 75 hours. The excess inorganic fluoride excreted in urine averaged 0.20 per cent of uptake; 0.60 per cent of uptake was accounted for as organic fluorine metabolites. No excess fluoride or nonvolatile fluorine metabolites were found in blood samples obtained before exposure or on the day of exposure and the first and fourth days after exposure.

Complete blood counts, serum electrolytes, bilirubin, blood urea nitrogen, creatinine, glucose, total protein, albumin, serum glutamic oxaloacetic transaminase, serum glutamic pyruvic transaminase, lactate dehydrogenase, and alkaline phosphatase determinations and urinalyses on the first, fourth and fourteenth days after exposure showed no consistent change from pre-exposure values or deviation from the normal range of values, except for a slight leukocytosis.

## DISCUSSION

The more ominous, albeit rare, toxic reactions associated with general anesthesia have included hepatic necrosis and renal failure. Evidence that these reactions are associated with biotransformation of the anesthetic and production of toxic metabolites has accumulated<sup>5,6</sup>.

Aliflurane is chemically stable and apparently more resistant to biotransformation than the inhalational anesthetics in current clinical usage. Urinary fluoride ion represented 0.2 per cent of the absorbed dose. Approximately twice this amount can be assumed to have been released, since it is known that approximately 50 per cent of ingested or injected soluble fluoride salts is deposited in bone<sup>7,8</sup> and the rest is excreted promptly in urine, with a half-life of four to five hours. Organic fluorine metabolites accounted for 0.6 per cent of total uptake. Hence, a total of approximately 1 per cent of absorbed aliflurane was converted to measureable metabolites. This compares favorably with methoxyflurane<sup>4</sup> (41 per cent urinary metabolites), fluoroene<sup>9</sup> (10.0 per cent urinary metabolites), halothane<sup>10,11</sup> (12–25 per cent urinary metabolites) and enflurane<sup>3</sup> (2.4 per cent urinary metabolites).

In summary, the biotransformation of aliflurane was studied in ten healthy young male volunteers. It appears to be highly resistant to biotransformation in man. The maximum excretion of fluoride

and organic fluorine occurred during the first 24 hours following exposure.

## REFERENCES

1. Munson ES, Schick LM, Chapin JC, et al: Determination of the minimum alveolar concentration (MAC) of aliflurane in dogs. *ANESTHESIOLOGY* 71:545–547, 1979
2. Fink BR, Morikawa K: A simplified method for the measurement of volatile anesthetics in blood by gas chromatography. *ANESTHESIOLOGY* 32:451–455, 1970
3. Chase RE, Holaday DA, Fiserova-Bergerova V, et al: The biotransformation of Ethrane in man. *ANESTHESIOLOGY* 35:262–267, 1971
4. Yoshimura N, Holaday DA, Fiserova-Bergerova V: Metabolism of methoxyflurane in man. *ANESTHESIOLOGY* 44:372–378, 1976
5. Brown BR, Sipes IG: Biotransformation and hepatotoxicity of halothane. *Biochem Pharmacol* 16:2091–2094, 1977
6. Cousins MJ, Mazze RI: Methoxyflurane nephrotoxicity: A study of dose response in man. *JAMA* 225:1611–1616, 1973
7. Handbook of Experimental Pharmacology. Volume XX, Pharmacology of Fluorides, Part 1. New York, Springer-Verlag, 1966, pp 117–122, 141–146
8. Fiserova-Bergerova V: Changes of fluoride content in bone. *ANESTHESIOLOGY* 38:345–351, 1973
9. Gion H, Yoshimura N, Holaday DA, et al: Biotransformation of fluoroene in man. *ANESTHESIOLOGY* 40:553–562, 1974
10. Rehder K, Forbes J, Alster H, et al: Halothane biotransformation in man: A quantitative study. *ANESTHESIOLOGY* 28:711–715, 1967
11. Cascorbi HF, Blake DA, Helrich M: Differences in the biotransformation of halothane in man. *ANESTHESIOLOGY* 32:119–123, 1970

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## Intraoperative Obstruction of Endobronchial Tubes

CARLA A. JOB, M.D., F.R.C.P.(C),\* ALBERT M. BETCHER, M.D.,† WARREN T. PEARSON, M.D.,‡  
MANUEL A. FERNANDEZ, M.D.§

Since the introduction of the Carlens catheter, in 1949,<sup>1</sup> the benefits of endobronchial anesthesia have been well documented. As with most technical pro-

cedures, complications, such as malpositioning of the catheter and respiratory obstruction, have been associated with one-lung anesthesia.<sup>2,3</sup> The latter complication may result in dangerous hypoxemia if allowed to persist. Correction of catheter malpositioning, particularly after a surgical procedure has begun, can present the anesthesiologist with a very difficult technical problem.

Two cases of endobronchial catheter obstruction during thoractomy are reported. In the first case, obstruction occurred during closure of bronchoesophageal fistulas, and in the second, during lobectomy for a tuberculous pulmonary abscess.

## REPORT OF TWO CASES

*Patient 1.* A 28-year-old woman was admitted to the hospital because of shortness of breath, persistent cough, and intermittent

\*Attending Anesthesiologist, Beth Israel Medical Center; Assistant Clinical Professor of Anesthesiology, Mount Sinai School of Medicine, City University of New York, New York, New York.

†Director of Anesthesiology, Beth Israel Medical Center; Professor of Anesthesiology, Mount Sinai School of Medicine, City University of New York, New York, New York.

‡Associate Attending in Surgery, Beth Israel Medical Center; Clinical Assistant Professor of Surgery, Mount Sinai School of Medicine, City University of New York, New York, New York.

§Present affiliation; Attending Anesthesiologist, Sydenham Hospital, New York, New York.

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Address reprint requests to Dr. Job.