Chronic Exposure to Methoxyflurane:

A Possible Occupational Hazard to Anesthesiologists

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The excretion of methoxyflurane in end-expired air has been studied in patients after methoxyflurane anesthesia and in anesthesiologists after they have administered methoxyflurane anesthsia. Methoxyflurane is detectable in the end-expired air of patients for 10–18 days after anesthesia and in anesthesiologists for as long as 30 hours after exposure. Concentrations in patients' end-expired air could be related to a time-and-concentration measure, methoxyflurane per cent hours (MFPH), for as long as 120 hours after exposure. Samples of air collected in the area in the operating room from which the anesthesiologist inspired air contained 1.3–9.8 ppm methoxyflurane, depending on the concentration of anesthetic being delivered to the patient. A significant decrease in the methoxyflurane concentration in operating room air was obtained using a gas trap. Due to the potential hazards of chronic exposure to anesthetic gases, protection of the anesthesiologist and other operating room personnel seems advisable. (Key words: Methoxyflurane; Anesthesiologists; Operating room; Gas trap.)

RECENT STUDIES [1-3] suggest possible deleterious effects of chronic exposure to certain common anesthetic agents. Linde and Bruce [2] reported 0–49 ppm halothane and 0–428 ppm nitrous oxide in operating room air, while anesthesiologists' end-expired air contained 0–12 ppm halothane. They showed an average concentration of 1.8 ppm in 36 observations of 24 anesthesiologists made within one hour after exposure. They also found slightly increased urinary fluoride ion concentrations in anesthesiologists after administration of halothane.

In 1961, Stewart *et al.*[4, 5] measured concentrations in expired air of two halogenated hydrocarbons similar in structure to halogenated anesthetic agents. Tetrachloroethylene and 1, 1,1-trichloroethane vapor at various concentrations and exposure times had exponential decay curves of more than 40 hours. In 1963, Stewart *et al.*[6] reported a case of carbon tetrachloride ingestion in which carbon tetrachloride concentrations in expired air could be detected by infrared analysis for more than 400 hours after exposure.

These reports and the knowledge that both acute and chronic exposure to agents similar to the halogenated anesthetics may cause deleterious effects prompted us to study the excretion rate of methoxyflurane in the end-expired air of patients and anesthesiologists after various degrees of exposure. Serial urinary fluoride ion concentrations of one patient and one anesthesiologist were determined. Concentrations of methoxyflurane in air inspired by anesthesiologists with and without the use of a gas trap to shunt anesthetic vapors from the area during administration of methoxyflurane were measured.

Methods

The rates of excretion of methoxyflurane were determined by measuring concentrations in the end-expired air of the subjects at intervals following exposure. Samples were collected in Saran plastic bags impermeable to diffusion of methoxyflurane. Only patients who had no discomfort exhaling into the bags were chosen. Subjects were instructed to inhale, exhale about two-thirds of the air, and then breathe into the bag. Samples of air in the operating room were collected using a gastight syringe and injected into Saran bags.

Methoxyflurane concentrations were measured in parts per million, a standard measure of industrial exposure to gases, using a Beckman GC-2A gas chromatograph equipped with a column of 15 per cent Squalane on 50/60 mesh Chromosorb P and a flame ionization de-

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tector. The limit of detection was 0.01 ppm.‡ At low levels care was taken to avoid contamination of the syringe by previous samples injected into the chromatograph.

Under clinical conditions, it was not possible to determine separately the contributions of concentration and length of exposure to the decay curves, as is done in experiments on human volunteers or animals.[4, 5, 7] Although differing exposure times were chosen, concentrations changed during clinical anesthesia. To facilitate comparison of exposures, methoxyflurane per cent hours was calculated by the formula:

$$\text{MFPH} = \sum_{\substack{\text{concentrations} \\ \text{administered}}} \left(\begin{matrix}\text{per cent methoxyflurane} \\ \text{in inspired air}\end{matrix} \times \frac{\text{time administered (min)}}{60} \right)$$

Urinary fluoride ion concentrations were determined using a Beckman *p*H meter with a Beckman fluoride electrode.

Results

Patient Decay Curves

Nine patients who were to have operations of various durations under methoxyflurane anesthesia were selected for study. These patients had no history of cardiovascular, pulmonary, hepatic or renal disease. Preanesthetic samples of end-expired air were collected as controls.

Figure 1 shows the decay curves of patients A and B, who had short exposures (0.67 and 0.80 MFPH), and patient C, who had the longest exposure (4.16 MFPH). All curves show that the anesthetic is expired most rapidly during the first two days, declining exponentially, then being expired more slowly for the next seven to ten days.

Decay curves for patients C (0.72 MFPH), D (1.86 MFPH), and E (0.91 MFPH) are shown in figure 2. Curves followed to the limits of detection ranged from 12 to 17 days.

‡ One ppm is 1 μl or 6.86 μg methoxyflurane gas per liter.

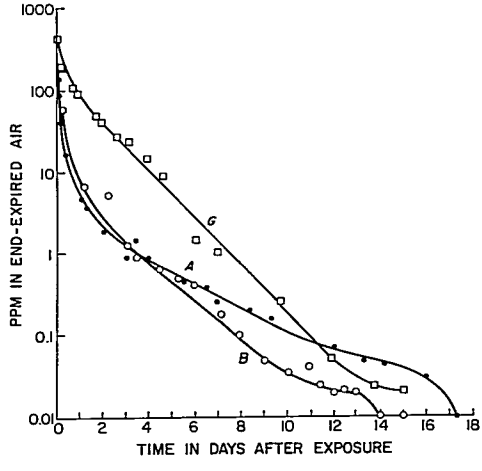

Fig. 1. Methoxyflurane decay curves of patients A (0.67 MFPH), B (0.80 MFPH), and C (4.16 MFPH) following surgical anesthesia.

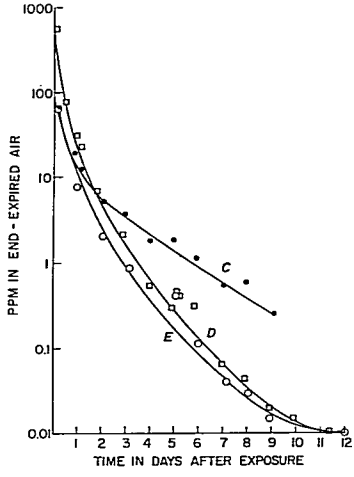

FIG. 2. Methoxyflurane decay curves of patients C (0.72 MFPH), D (1.86 MFPH), and E (0.91 MFPH) following surgical anesthesia. Patient C developed high-output renal failure postoperatively.

Since MFPH is only an approximation of exposure, we were unable to compare the curves accurately in correlation with physical characteristics of the patients.

Near day 5 on curves B, C, D, E, and F, one or more points are above the exponential decay line. This may have been caused by release of the anesthetic by a specific organ. Similar deviations have been found in decay curves for other halogenated compounds[6] and also in recent studies with methoxyflurane.[21]

Parts per million methoxyflurane in the expired air of each patient 24, 48, 72, and 120 hours after termination of exposure are plotted against the patient's exposure in MFPH in figure 3. Correlation of the expired air concentration at a specific time after exposure with exposure is good for the first 72 hours, justifying the use of MFPH for measurement. Experimental deviations include errors in determining MFPH and expired-air concentrations, differences in collecting expired air samples, and indivdual variations in metabolism. After 120 hours individual variation becomes so great that correlation is diminished.

Anesthesiologist Decay Curves

Excretion of methoxyflurane by one anesthesiologist was determined after exposures of 130 and 390 minutes, and excretion by another anesthesiologist after exposure for 300 minutes, as shown in figure 4. Methoxyflurane was dispensed from the same Pentec-2 vaporizer and the flow rate was 5 l/min in every trial. As in the patients, there was an initial rapid decrease in concentration followed by slower excretion. Duration of excretion was related to duration of exposure.

Urinary Fluoride Ion Studies

Figure 5 shows urinary fluoride ion concentrations of patient C (4.16 MFPH) and the anesthesiologist with the 390-minute exposure. Fluoride ion concentrations of patient C were measured before, during, and after exposure. Only post-exposure specimens of the anesthesiologist were examined.

Patient C had a detectable increase in urinary fluoride ion two hours after induction of anesthesia; urinary fluoride ion continued to increase to a peak 16 hours after induction. The anesthesiologist also had an increase in urinary fluoride ion, with a peak five hours after exposure. It was not known whether the anesthesiologist's control specimen was affected by exposure to methoxyflurane on the previous day. Four urine specimens were collected from the anesthesiologist in a 24-hour period after his return from a one-week vacation, during which fluoride intake from drinking water did not change. The concentrations of fluoride ion in these specimens ranged from 1.7 to 3.0×10^{-5} molar. Using the highest value from these specimens as a control, there was a fivefold increase in fluoride ion concentration in the anesthesiologist's urine six hours after a 390-minute exposure to methoxyflurane under his usual working conditions.

Operating Room Air Levels

Sixteen determinations of methoxyflurane levels in operating room air were made at different concentrations delivered by the same Pentec-2 vaporizer with the gas flow at 5 l/min. All specimens were collected in the

area in which the anesthesiologist inspired air. The levels ranged from 1.3 ppm at the 0.2 per cent setting to 9.8 ppm at the 1.0 per cent setting.

Several factors influence the concentration of methoxyflurane in air in the operating room. The rate of air turnover is a major factor. Methoxyflurane is absorbed by both the patient and the rubber components of the anesthesia machine. The highest concentrations in room air at each vaporizer setting were found after the first hour and when the anesthesiologist and anesthesia machine were partially surrounded or enclosed in a tent of surgical drapes.

Operating Room Air Levels With Gas Trap

Ten determinations of methoxyflurane concentrations in operating room air were made during use of a gas trap over the pop-off valve to shunt anesthetic vapors from the room. The gas trap, devised by Corbett,[8] consisted of a balloon fitted over the valve, with the vapors shunted to wall suction via a system of connectors and tubing. The gas flow rate was again 5 l/min in every case. All samples were collected in the area in which the anesthesiologist inspired air. With the gas trap in use, concentrations in operating room air ranged from 0.015 to 0.095 ppm, representing a significant decrease from the 1.3 to 9.8 ppm found without it.

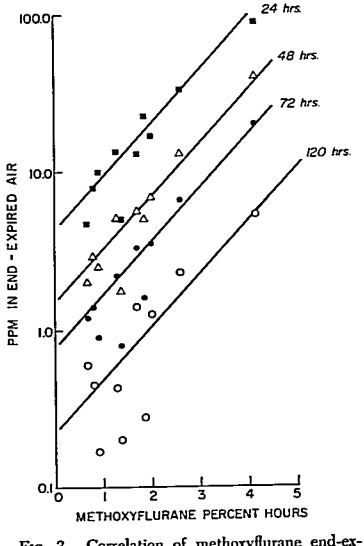

Fig. 3. Correlation of methoxyflurane end-expired air concentrations with exposure in MFPH at specific times after termination of exposure.

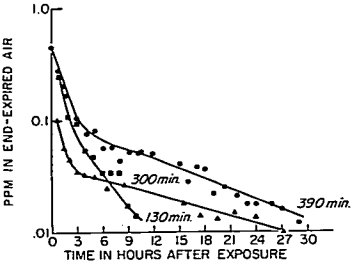

Fig. 4. Methoxyflurane decay curves of anesthesiologists following administration of anesthesia.

Discussion

Van Dyke and Chenoweth[9] concluded that the C-F bond in methoxyflurane is unstable and is metabolized to fluoride ion in the human body. They also found increased inorganic fluoride levels in the long bones of rabbits chronically exposed to low concentrations of methoxyflurane.

Chronic fluorosis has been reported as an occupational disease in persons exposed to fluoride compounds such as fluor-spar (CaF_2) and cryolite ($NaF \cdot AlF_3$), and also in persons exposed to fluoride-containing gases. Fluoride intake above tolerance levels over a sufficient period of time can lead to cumulative absorption and may prove harmful to man.[10]

Taylor *et al.*,[11] working with rats, found that sodium fluoride in acutely toxic doses produces necrosis of the renal tubular cells and, in a small proportion of the test animals, dilation of the tubules. Renal lesions have also been found after prolonged ingestion of fluorides.[12] The most common alteration in renal function in chronic fluoride ingestion was an increased

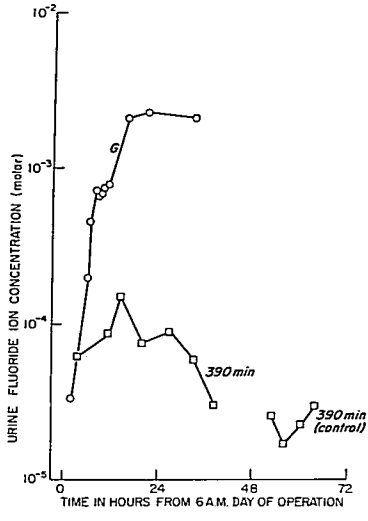

FIG. 5. Urinary fluoride ion concentration of patient G and the anesthesiologist with the 390-minute exposure.

urinary volume. Bond and Murray[12] also found that rats given 2–7.5 mg fluoride per day for 18–48 weeks developed polyuria, polydipsia, increased urinary nitrogen, and a lowered renal threshold for glucose. The urine had a low specific gravity.

Impaired renal function manifested by decreased blood urea clearances and filtration rates has been found in individuals drinking water containing 5–11 ppm fluoride (Shortt *et al.*,[13] Siddiqui[14]). Cases of polyuria associated with chronic fluoride intoxication in human beings have been described.[15] Roholm found acute nephritis at autopsy in eight of 32 persons who died of acute fluoride intoxication.

In most persons who develop acute or chronic fluoride intoxication renal function is not impaired. There is an individual susceptibility, the mechanism of which is unknown.

Fluoride ion is known to inhibit certain enzymes. Weber and Reid[16] demonstrated significant decreases in the activities of cytochrome oxidase and isocitric dehydrogenase in mice maintained on high-fluoride diets. Inhibition of other enzymes by fluoride ion has been reported, and may account for the polyuria and lowered renal threshold for glucose in patients with fluoride toxicity.

Polyuria and renal failure following methoxyflurane anesthesia have been well documented in case reports.[17] If enzyme inhibition were the mechanism involved in high-output renal failure, either an unusually rapid rate of metabolism of methoxyflurane with greater-than-usual fluoride ion production or enzyme systems unusually sensitive to fluoride ion would be expected. We know of no reports of high-output renal failure in anesthesiologists. However, it is interesting that Bruce *et al.*[1] reported a twofold increase in chronic renal disease as a cause of death among anesthesiologists in the period from 1957 to 1966 over the period from 1947 to 1956. It was during the later ten-year period that the fluorinated anesthetic agents were introduced.

Chronic exposure to methoxyflurane, halothane, nitrous oxide, and diethyl ether stimulates microsomal enzyme induction, which affects the metabolism of not only the inducing agent itself, but also numerous other substances, both exogenous and endogenous.[18-21] Whether the concentrations of anesthetic agents in anesthesiologists are sufficient to produce microsomal enzyme induction has not been studied. However, enzyme induction by subanesthetic doses of methoxyflurane has been demonstrated in the rat.[22]

Since methoxyflurane remains in storage depots for a remarkably long time, it is conceivable that anesthesiologists may have measurable levels of methoxyflurane or metabolites for months or even years at a time. Thus, there is reasonable cause for concern that chronic exposure to methoxyflurane may be harmful because it increases the possibility of development of chronic fluoride intoxication, microsomal enzyme induction, and teratogenic or carcinogenic effects.

Protection of the anesthesiologist and other operating room personnel from chronic exposure to anesthetic vapors seems advisable. Effective exhaust systems should become standard equipment on all new anesthesia machines, and adaptive devices should be made

available for presently existing machines as soon as possible.

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Drugs

DIAZEPAM AND MUSCLE RELAXANTS The effect of intravenous diazepam, 0.15 to 0.2 mg/kg, on neuromuscular block was studied in surgical patients during thiopentone–halothane–nitrous oxide anesthesia using the twitch response of the adductor pollicis longus muscle. Diazepam produced a twofold increase in the intensity and a threefold increase in the duration of neuromuscular block after 40 to 60 mg gallamine. Conversely, the duration of paralysis produced by 25 mg succinylcholine was reduced by 20 per cent following the administration of diazepam. Preliminary studies suggest that the site of action is at the presynaptic area. (*Feldman, S. A., and Crawley, B. E.: Interaction of Diazepam with the Muscle-relaxant Drugs, Brit. Med J. 2: 336 (May) 1970.*)