BLOOD SERUM FLUORIDE LEVELS WITH ENFLURANE (̄ETHRANE*) AND ISOFLURANE (FORANE*) ANAESTHESIA DURING AND FOLLOWING MAJOR ABDOMINAL SURGERY

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IT IS NOW APPARENT that virtually all inhalation anaesthetics undergo metabolic biodegradation to some degree and are not entirely excreted through the lungs unchanged.¹ There is as yet no evidence that this is brought about by enzyme induction with commonly used premedicant drugs, although it is well known that some barbiturates (phenobarbitone and thiopentone), narcotic analgesics (morphine and meperidine) and even the anaesthetics themselves can stimulate or depress drug metabolism.² There is also evidence that an enzymatic change may occur largely by a common drug-metabolizing system of the hepatic smooth endoplasmic reticulum which is catalyzed by cytochrome P450, reduced by reduced nicotinamide-adenine dinucleotide phosphate (NADPH₂) and oxidized by molecular oxygen.³ Since most of the breakdown products are eliminated through the kidney, this organ is a natural target for toxic substances that may be derived from the metabolic destruction of the parent compound.

In the case of methoxyflurane metabolism in the body, the enzymatic breakdown appears to occur either by cleavage at the ether linkage, allowing liberation of fluoride ion, or the compound liberates chlorine first, then breaks down further to release its fluorine. In either case, after prolonged deep anaesthesia, it appears that sufficient inorganic fluoride ion may accumulate in the blood to cause renal dysfunction.⁴

There is evidence that fluoride ion does not accumulate in the blood during halothane anaesthesia.⁵ However, the combination of a number of factors such as drinking fluorinated water, use of fluorinated toothpaste and repeated halothane anaesthetics may set the stage for the so-called rare allergic-type reaction to this anaesthetic. This may in large part be due to the other sources of fluorine rather than the action of halothane itself.^{6,7}

This study is the continuation of our clinical investigation of fluorinated inhalational anaesthetics in order to determine whether there is appreciable metabolism of enflurane and isoflurane, as evidenced by the accumulation of inorganic fluoride ion in the blood serum.

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METHOD

Patients scheduled for elective major abdominal operations, who gave informed written consent for anaesthesia with enflurane or isoflurane, were subjects for this study. Inorganic fluoride ion was assayed in blood serum with an ion-specific Orion^(TM) electrode, employing the method described by Fry and Taves.⁸

A blood sample was obtained initially just prior to induction of anaesthesia, when a vein was cannulated for infusions; then, after one hour of anaesthesia with enflurane or isoflurane; again, upon arrival of the patient in the recovery room; 24 hours after and, in cases with elevated serum fluoride, again approximately 48 and 72 hours following surgery.

Light premedication consisting of atropine (0.4 to 0.6 mg) and diazepam (5 to 10 mg) or meperidine (25 to 50 mg) was given approximately an hour before induction of anaesthesia. In all patients, anaesthesia was induced with a non-depolarizing muscle relaxant followed immediately by a sleep dose of thiopentone (200 to 500 mg). After hyperventilation with oxygen, intubation and attachment of a semi-closed system and mechanical respirator, anaesthesia was maintained with enflurane or isoflurane with 3:2 nitrous oxide – oxygen. With enflurane, the initial concentration employed was 1.5 to 2.0 per cent, then was gradually reduced to approximately 1.0 per cent, which was usually the lowest concentration that would permit satisfactory operating conditions. With isoflurane, the initial concentration employed was 1.0 per cent with 3:2 nitrous oxide – oxygen and this was usually reduced to 0.7 per cent during maintenance. Muscle relaxants were seldom required during the operations. During abdominal closure, the concentration of enflurane or isoflurane was gradually reduced after the peritoneum was sewn. In the cases managed with isoflurane, it was often possible to discontinue the isoflurane and the nitrous oxide during the skin closure.

Fluid replacement, monitoring of vital signs and ventilatory control were employed in each patient as in our previous case studies.⁵ Disposable inhaler tubing was employed, or tubing sterilized with ethylene oxide and aerated. Enflurane was vapourized from a calibrated temperature- and pressure-compensated enflurane vapourizer made by Cyprane.⁹ Isoflurane was vapourized in a recalibrated Fluotec vapourizer.¹⁰

RESULTS AND DISCUSSION

Studies with Enflurane (Ethrane)

Serial blood samples were analysed for serum inorganic fluoride in 37 of 66 patients who received enflurane. Due to technical problems with the analysing electrode, the values obtained from the first 29 patients were not included in the statistical analysis of the blood data, although the changes observed were of the same order of magnitude throughout. Table I shows the distribution of the patients as to sex, mean age (53 years), age spread (19 to 88) and mean duration of anaesthesia (212 minutes). Table II shows the mean serum inorganic fluoride readings before, during and following anaesthesia. Observe that the fluoride

TABLE I
VITAL STATISTICS ON PATIENTS IN THIS STUDY

	Enflurane	Isoflurane
Number of patients	66	189
male	23	59
female	43	130
Mean age	53 $\pm$ 3	46 $\pm$ 1.3
Age spread	19 – 88	18 – 89
Mean duration of anaesthesia	212 min.	178 min.

TABLE II
COMPARISON OF MEAN SERUM INORGANIC FLUORIDE LEVELS ($\mu\text{M/L}$)*

	Enflurane	Isoflurane
Number of patients	66	189
F ⁻ before anaesthesia	1.54	1.53
F ⁻ one hour anaesthesia	11.1	3.1
F ⁻ end of anaesthesia	15.6	3.6
F ⁻ 24 hours postoperative	7.6	2.9
F ⁻ 48 hours postoperative	3.5	—

*Standard error of means: 0.03 to 2.6.

values rose appreciably during the first hour of anaesthesia, then rose slowly, but usually did not peak until after the end of the administration.

In one patient, the peak fluoride level exceeded 40 $\mu\text{M/L}$. This occurred in a 39-year-old male who underwent abdominal surgery for 310 minutes. The inorganic fluoride rose in the serum from 1.0 $\mu\text{M/L}$ (control) to 12 (at one hour), 10 (after anaesthesia), 44 (24 hours after surgery), 29 (48 hours after) and 4.1 (72 hours after). Recovery from anaesthesia and surgery was uneventful. Two other patients had inorganic fluoride levels over 25 $\mu\text{M/L}$ at the end of the operation – one with 29 $\mu\text{M/L}$ (a 52-year-old female whose operation lasted 200 minutes) and one with 30 $\mu\text{M/L}$ (a 38-year-old female whose operation lasted 105 minutes). In both of these, the inorganic fluoride level in the serum was less than 10 $\mu\text{M/L}$ (or < 0.2 ppm) at 24 hours.

Studies with Isoflurane (Forane)

A similar analysis was done in 189 patients who received isoflurane. The data from these patients are also summarized in Table I and Table II. The mean age was 46 years, with an age spread of 18 to 89 years. Mean duration of anaesthesia was 178 minutes. There was no appreciable elevation in the serum inorganic fluoride assays. The highest level observed in this large series was 12 $\mu\text{M/L}$ (or < 0.25 ppm) which occurred at the end of anaesthesia in two patients. In both, the assay showed less than 4 $\mu\text{M/L}$ at 24 hours after anaesthesia.

On the basis of these data, it appears as if only a small amount of biodegradation of isoflurane occurs, causing free inorganic fluoride in the blood, with a peak effect appearing shortly after the end of the administration and followed by an exponential decline during the following 24 to 48 hours.

There does not appear to be any accumulation of inorganic fluoride ion with isoflurane. As with halothane, there is a very small rise, that may be attributed

to mobilization of body stores rather than to biodegradation of the anaesthetic molecule.⁵

It is important to realize that the duration of action of parenteral anaesthetics is generally dependent and limited by the conversion of the drugs to inactive metabolites before their excretion occurs, primarily in the urine and bile. Otherwise, many compounds such as thiopentone and methotrimeprazine would act for months.^{11,12} On the other hand, the inhalational anaesthetics depend mainly on excretion through the lungs to the air, without appreciable metabolism in the liver and other tissues. Thus, another indication that enflurane and isoflurane probably do not undergo extensive metabolism in the body is the rapid recovery from anaesthesia, although the early postanaesthetic awakening is undoubtedly due in large part to their relatively low partition coefficients in fat and blood.^{9,10}

In order to avoid an unexpected substantial rise in the serum inorganic fluoride ion with enflurane, we recommend that this anaesthetic agent should be used in an accurately calibrated vapourizer (temperature- and pressure-compensated) with nitrous oxide, following induction with a barbiturate and a muscle relaxant whenever a major or prolonged operation is expected.⁹ It would be wise also to avoid administering anaesthesia with enflurane for major operative procedures more frequently than at biweekly intervals. Although biodegradation and elevation of inorganic fluoride ion in the blood appear to be unlikely with isoflurane, it is probably wise to adhere to the same precautions.

SUMMARY AND CONCLUSIONS

Blood serum inorganic fluoride was measured serially with a fluoride-specific electrode before, during and after major abdominal operations performed under anaesthesia with enflurane (Ethrane) in 66 patients and with isoflurane (Forane) in 189 patients. The fluoride levels observed indicated that enflurane is probably metabolically biodegraded slightly, while isoflurane is free from enzymatic degradation that releases fluoride ion into the blood. With these anaesthetics, the highest blood levels of serum inorganic fluoride observed were lower than those seen with well-controlled administration of methoxyflurane. Nevertheless, we recommend that if one of these new agents is chosen for a prolonged major operation it should be used only after induction with another anaesthetic (such as thiopentone) and a non-depolarizing muscle relaxant; maintenance may then be carried on with approximately 60 per cent nitrous oxide, 40 per cent oxygen, and 1 per cent or less of one of these agents, as was done in this study. There would then be only a very remote possibility that toxicity could develop through accumulation of fluoride ion in the blood and, subsequently, in the kidney. Administration of enflurane at more than biweekly intervals is not recommended.

RÉSUMÉ

Nous avons mesuré le fluorure inorganique du sérum sanguin en séries avec une électrode spécifique pour le fluorure, avant et après des opérations abdominales majeures pratiquées sous anesthésie à l'enflurane (Ethrane) chez 66 malades et avec

l'isoflurane (Forane) chez 189 malades. Les taux de fluorure observés indiquent que l'enflurane subit probablement une biodégradation métabolique légère, alors que l'isoflurane est dépourvu de toute dégradation enzymatique qui libère des ions fluorures dans le sang. En employant ces agents anesthésiques, les taux les plus élevés de fluorure inorganique sérique observés demeuraient inférieurs aux taux observés au cours d'une anesthésie bien contrôlée au méthoxyflurane. Néanmoins, nous conseillons, si l'un de ces nouveaux agents est choisi pour une opération majeure prolongée, de l'utiliser pour l'induction seulement avec un autre anesthésique (tel le thiopentone) et un myorésolutif non dépolarisant; le maintien peut alors être continué avec environ 60 pour cent de protoxyde d'azote et 40 pour cent d'oxygène et 1 pour cent ou moins de l'un de ces agents, comme nous l'avons fait au cours de cette étude. A ce moment là, il y aurait très peu de possibilité qu'il puisse se faire une accumulation toxique de fluorure dans le sang et, subséquemment, dans le rein. Nous ne conseillons pas l'usage de l'enflurane en deça d'un intervalle de deux semaines.

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