ENFLURANE (ETHRANE) ANAESTHESIA IN MAN
Metabolism and effects on biochemical and haematological variables

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SUMMARY
In 10 patients serum inorganic fluoride increased to a mean peak value of 16 μmol litre⁻¹ after 2 h of enflurane anaesthesia. Four days after anaesthesia, serum inorganic fluoride had decreased to the values before operation. The maximum daily inorganic fluoride excretion in urine (U_F) did not exceed 200 μmol litre⁻¹. In a group of 20 patients routine biochemical and haematological variables were measured before and after enflurane anaesthesia. There were only minor changes in these variables, attributable to the surgical procedure. It is concluded that renal dysfunction is unlikely to follow enflurane anaesthesia in patients with previously normal hepatic and renal function.

Enflurane (Ethrane), 2-chloro-1,1,2-trifluoroethyl- trifluoromethylether (CHF₂-O-CF₂CHFCI), a potent non-flammable volatile general anaesthetic agent, has been in general use in North America since 1971 and has been introduced in Europe more recently. It is now on limited clinical trial in the United Kingdom, and we report our initial experience.

Renal damage associated with prolonged use of a related agent, methoxyflurane, is probably a result of inorganic fluoride produced during metabolism of this compound (Cousins and Mazze, 1973). Although inorganic fluoride is a product of the metabolism of enflurane also, the serum concentrations are less than in the case of methoxyflurane (Cousins et al., 1976).

We have administered enflurane to 10 patients in whom metabolism of enflurane to inorganic fluoride was studied (group 1), and to 20 patients in whom haematological and biochemical variables were studied before and after anaesthesia (group 2).

PATIENTS AND METHODS
Patients with normal renal function before operation, physical status grades I—III (American Society of Anesthesiologists (1963) classification), requiring general anaesthesia for various surgical procedures, gave written consent for the administration of enflurane and the collection of appropriate blood and urine samples. The protocol of the study was approved by the Ethics Subcommittee of King's College Hospital.

Group 1
Central venous blood samples were analysed, before operation and for 4 h after operation, for inorganic fluoride concentration using a fluoride-specific electrode (Fry and Taves, 1970).

Anaesthesia was induced with thiopentone; pancuronium was used for muscle relaxation and after intubation of the trachea anaesthesia was maintained with nitrous oxide in oxygen and enflurane 0.5–2.5%. IPPV was provided by a Manley ventilator; enflurane was delivered from an Enfluratec vaporizer (Cyprane Limited). Blood concentrations of enflurane were estimated in central venous blood samples using a silicone oil extraction technique (Jones et al., 1978). For 4 days after operation peripheral venous blood samples and urine were analysed for inorganic fluoride.

Group 2
In 20 patients, undergoing abdominal surgery, anaesthesia was induced with thiopentone and maintained with nitrous oxide in oxygen and enflurane 0.5–2.5%. Where appropriate, the trachea was intubated after administration of pancuronium. A Magill circuit was used for spontaneous ventilation, and a Manley ventilator for IPPV. Enflurane was delivered from an Enfluratec vaporizer.

Before operation and at 24 h and 5 days after operation, peripheral venous blood samples were taken for analysis of the following: serum bilirubin, total proteins, albumin, aspartate aminotransferase (AST), hydroxybutyrate dehydrogenase (HBD), calcium, phosphate, sodium, potassium, alkaline phosphatase (ALP), magnesium, calcium, creatinine,
uric acid, urea and blood glucose. All measurements were carried out by the Biochemistry Laboratory, King's College Hospital, using standard methods employing the Auto Analyser SMA 6/60 and 12/60 (Technicon Limited). In addition, haemoglobin concentration (Hb), packed cell volume (PCV) and white blood cell count (WBC) analyses were performed.

Student's *t* test for unpaired data was used for statistical analysis.

**RESULTS**

**Group 1**

*Serum inorganic fluoride.* Serum inorganic fluoride increased during anaesthesia from a control value of 5.3 μmol.litre⁻¹ (± SEM 3.0 μmol.litre⁻¹) to a peak concentration of 16 μmol.litre⁻¹ after a 2-h period of enflurane anaesthesia. Serum inorganic fluoride values peaked 3.5 h after anaesthesia at a mean of 15.8 μmol.litre⁻¹ (SEM ± 1.06 μmol.litre⁻¹) (fig. 1). During the 4 days after operation, serum inorganic fluoride decreased rapidly and on the 4th day after operation the values were less than the control values. The mean results (± SEM) are shown in figure 2.

**Blood enflurane.** Blood enflurane concentration increased to a mean peak of 95 μg.ml⁻¹ (SEM ± 8.6) after 30 min of enflurane anaesthesia. One patient who received 2% enflurane had a peak blood enflurane concentration of 97 μg.ml⁻¹ after 120 min of anaesthesia.

After discontinuing enflurane, the blood concentrations decreased quickly and were less than 0.5 μg.ml⁻¹ 90 min after operation.

**Daily urine inorganic fluoride excretion (U_F).** Normal U_F in man drinking fluoridated water is in the range 30–80 μmol.day⁻¹. After enflurane anaesthesia the urinary inorganic fluoride concentrations peaked at a mean value of 200 μmol.day⁻¹ on the 1st day after operation. By the 4th day after operation U_F was approaching the normal range (fig. 3).

**Group 2**

The only statistically significant changes (P < 0.05) in the biochemical and haematological variables were an increase in AST and blood-glucose and a decrease in serum phosphate at 24 h. All of these variables had returned to normal 5 days after operation. The mean
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values for the variables with statistically significant changes are shown in table I.

<table>
<thead>
<tr>
<th>Test</th>
<th>Before operation</th>
<th>24 h</th>
<th>5 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose</td>
<td>5.4</td>
<td>6.7*</td>
<td>5.8</td>
</tr>
<tr>
<td>(mmol. litre⁻¹)</td>
<td>(±1.7)</td>
<td>(±2.9)</td>
<td>(±1.2)</td>
</tr>
<tr>
<td>Phosphate</td>
<td>1.01</td>
<td>0.86*</td>
<td>0.89</td>
</tr>
<tr>
<td>(mmol. litre⁻¹)</td>
<td>(±0.22)</td>
<td>(±0.14)</td>
<td>(±0.27)</td>
</tr>
<tr>
<td>AST</td>
<td>39</td>
<td>56*</td>
<td>50</td>
</tr>
<tr>
<td>(i.u./litre)</td>
<td>(±13.9)</td>
<td>(±32.6)</td>
<td>(±22.7)</td>
</tr>
<tr>
<td>WBC₅₅</td>
<td>7.9</td>
<td>11.4*</td>
<td>9.1*</td>
</tr>
<tr>
<td>(x10⁶, litre⁻¹)</td>
<td>(±2.3)</td>
<td>(±3.1)</td>
<td>(±2.1)</td>
</tr>
</tbody>
</table>

* P<0.01 as compared with value before operation.

Renal function, as assessed clinically and by measurement of serum concentrations of urea, uric acid and creatinine, was normal in patients following enflurane anaesthesia.

DISCUSSION

The minor changes in the biochemical and haematological variables in the present study are similar to those of other studies of enflurane anaesthesia (Botty et al., 1968; Dobkin et al., 1968; Dobkin et al., 1969) and are probably related to the operation (Clark,

Doggart and Lavery, 1976). No evidence of an adverse effect on liver function was seen in this small group of patients. However, there have been isolated case reports (Denlinger, Lecky and Nahrwold, 1974; Sadove and Kim, 1974; Van der Reis et al., 1974) of liver damage, allegedly associated with enflurane. No data are available concerning liver function following repeated enflurane anaesthesia. About 10 million patients have received the drug, but no pattern of suspicion such as that concerning liver damage in respect of halothane (Walton et al., 1976) has emerged.

Enflurane is metabolized to inorganic fluoride; in this respect it resembles methoxyflurane. Cousins and Mazze (1973) have concluded that dose-related nephrotoxicity is associated with methoxyflurane, following serum inorganic fluoride concentrations in excess of 50 μmol. litre⁻¹. Using the expression \( U_{F,V} \), Norgate, Sharp and Cousins (1976) have proposed a nephrotoxic threshold of 2500 μmol. day⁻¹. In the present study and that of Cousins and his colleagues (1976) both serum and urine inorganic fluoride concentrations were well below the potential nephrotoxic values, both during and after enflurane anaesthesia.

Isolated liver microsomes, from rats pretreated with phenobarbitone, caused increased enflurane defluorination which was not seen in vivo (Norgate, Sharp and Cousins, 1976). Enflurane's physical characteristics may explain this paradox. The low fat solubility permits rapid clearance of the drug from the body and thus the time available for enflurane metabolism by the liver in vivo is limited. Therefore, one might predict that previous induction of drug-metabolizing enzymes would not affect enflurane metabolism significantly. In the present study and that of Cousins and his colleagues (1976), enflurane defluorination appeared to be very variable between patients. However, it is of interest that the greatest serum inorganic fluoride concentration (28 μmol. litre⁻¹) in our study occurred in a patient who was receiving phenytoin (a well-recognized enzyme-inducing agent) at the time of anaesthesia. Cousins and his colleagues (1976) described a patient with a peak serum inorganic fluoride concentration of 106 μmol. litre⁻¹ which was thought to be a result of enzyme induction. Although these two patients may still be within the normal variation in enflurane metabolism, the possible effect of enzyme induction cannot be discounted. In addition, the degree of enflurane defluorination is apparently not dose-related. Whether the response of a damaged kidney to fluoride is different from that of a normal kidney is not clear.
Any interference with glomerular filtration rate will affect the clearance of inorganic fluoride adversely. For these reasons the administration of enflurane to patients with pre-existing renal disease is probably unwise.

It is concluded that enflurane anaesthesia does not disturb the commonly measured biochemical and haematological variables significantly. Although defluorination of enflurane to inorganic fluoride appears to be variable, it seems unlikely that nephrotoxic concentrations of inorganic fluoride will occur in patients with normal hepatic and renal function. However, it is reasonable to express caution concerning the administration of enflurane to patients with renal disease and those treated with enzyme-inducing drugs.

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REFERENCES


ANESTHESIE PAR L’ENFLURANE (ETHRANE)
CHEZ L’HOMME

Metabolisme et effets sur les variables biochimiques et hematologiques

RESUME

Après 2 h d’anesthésie par l’enflurane sur 10 malades, le fluorure inorganique qui se trouvait dans le sérum a atteint une valeur de crête moyenne de 16 µmol.litre⁻¹. Quatre jours après l’anesthésie, le fluorure inorganique du sérum est retombé aux valeurs qui existaient avant l’opération. L’excrétion journalière maximale de fluorure inorgaïnique dans les urines (UᵥV) n’a pas dépassé 200 µmol.litre⁻¹. Sur un groupe de 20 malades on a mesuré avant et après l’anesthésie par l’enflurane les variables biochimiques et hematologiques habituelles. On n’a constaté que des variations mineures dans ces variables et celles-ci ont été attribuées au processus chirurgical. Il en a été conclu que le dèrèglement renal ne suit vraisemblablement pas l’anesthésie par l’enflurane chez les malades qui avaient antérieurement des fonctions rénales et hépatiques normales.

ENFLURAN-(ETHRAN)NARKOSE BEIM MENSCHEN

Stoffwechsel und Auswirkungen auf variable biochemische und hämatologische Werte

ZUSAMMENFASSUNG

ANESTESIA CON ENFLURANO (ETRANO) EN EL HOMBRE

Metabolismo y efectos sobre las variables bioquímicas y hematológicas

SUMARIO

El fluoruro inorgánico sérico de 10 pacientes aumentó a un valor máximo medio de 16 μmol.litre⁻¹ transcurridas 2 h de anestesia con enfurano. Cuatro días después de la anestesia el fluoruro inorgánico sérico había disminuido a los valores anteriores a la operación. La máxima excreción diaria de fluoruro inorgánico en la orina (UFV) no excedió de 200 μmol.litre⁻¹. En un grupo de 20 pacientes se midieron las variables hematológicas y bioquímicas rutinarias, antes y después de la anestesia con enfurano. Se produjeron solamente menores cambios en estas variables, atribuibles a la técnica quirúrgica. Se concluye que no es probable una disfunción renal consecutiva a la anestesia con enfurano en los pacientes con función hepato-renal previamente normal.