The Biotranformation of Éthrane in Man

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The biotranformation of Éthrane was studied in seven healthy female patients by measuring urinary fluorine excretion. The total amount of Éthrane recovered was 85.1 per cent of the amount absorbed; 82.7 ± 18.8 per cent was recovered as unchanged Éthrane in exhaled air and 2.4 per cent as nonvolatile fluorinated metabolites in urine. Of the urinary fluorine, 0.5 per cent was excreted in inorganic form and 1.9 per cent in organic form. Following anesthesia, urinary excretion rates of fluoride ion reached a maximum in seven hours. Maximum excretion of organic fluorine metabolites was reached on the second day. Urinary excretion then assumed a simple exponential decay, with half-times of 1.55 days for inorganic fluoride and 3.09 days for organic fluorine. The excretion of unaltered Éthrane in exhaled air assumed a three-term exponential decay, with half-times of 17.8 minutes, 3.2 hours, and 30.2 hours. (Key words: Biotransformation; Éthrane; Enflurane; Fluoride; Organic fluorine metabolites.)

The halogenated anesthetics, trichloroethylene, halothane,2,3 fluoro- xene,4 and methoxy- flurane,5 undergo significant biotransformation in man. Éthrane6 (CHF₂OCF₂CHFCI) has been introduced recently as a potentially useful clinical anesthetic; however, no studies regarding its metabolic disposition in man have been reported. Measurements of bromide3 and fluorine excretion4 in the urine have been used to detect the biotransformation of halothane and methoxyflurane, respectively. Similarly, we have studied Éthrane biotransformation in man by measuring urinary fluorine excretion. In addition, we have evaluated the dynamics of Éthrane excretion via the lungs.

Methods and Materials

ANESTHESIA PROTOCOL

Anesthesia was induced with thiopental (250–350 mg iv) in seven healthy female patients scheduled for routine gynecologic operations (table 1). Tracheal intubation was facilitated by succinylcholine (60–100 mg iv), following which the patients were attached to a closed-circle carbon dioxide absorption system with oxygen flows of 150–250 ml/min. Ventilation was controlled with an Ohio ventilator throughout anesthesia. Arterial blood gases were periodically determined to insure adequacy of oxygenation and ventilation. The rubber components of the anesthesia system were replaced by polyvinyl plastic and nylon to minimize anesthetic loss due to rubber solubility. The rate of loss of Éthrane from the system was measured prior to each study to predict anesthetic loss from the circle during the period of study.

In each patient, an alveolar Éthrane concentration of 1.5 per cent was maintained by injecting liquid Éthrane into the anesthetic system at predetermined rates by means of a Harvard infusion pump.6 The pump was driven at variable speed by a potentiometer curve follower (Data-trak, Research Inc., Model 511) so as to deliver Éthrane at a rate...
calculated to be taken up by the body with time at a constant alveolar concentration of 1.5 per cent.⁷

**Analysis of Expired Gas**

End-expiratory gas samples were analyzed for Éthrane using a gas chromatograph (Aerograph HIFI Model A-600C) equipped with a hydrogen flame ionization detector. A 4-inch copper column, 12 inches long, was packed with Chromosorb P 60/80 mesh coated with 10 per cent diisodicylphthalate and operated at 35 C with a carrier gas flow of 30–40 ml of nitrogen/min. The samples were introduced with a 1-ml gas syringe (Precision Scientific Instruments, Inc.). The chromatograms were quantitated by peak area as measured by a disc integrator.

Ten minutes prior to the termination of the operation, the administration of Éthrane was stopped (table 1). At the onset of spontaneous ventilation and as signs of awakening appeared, a nonrebreathing system was substituted, with 100-liter capacity laminated mylar and aluminum bags (Biomedical Research Instruments) attached to the expiratory port. Exhaled gases were collected continuously in 10-minute samples for the first hour and then periodically for 5–10 minutes during the course of the next four to five days. The gas volumes were measured with a dry-gas meter (American Meter Co., Albany, New York), and samples were analyzed for Éthrane.

**Analysis of Urinary Fluorine**

Starting 24 hours prior to operation, urine was collected for as long as ten days postoperatively in polyethylene bottles and stored at 4 C until the fluorine content was analyzed. For fluoride ion determination, 5 ml of urine were adjusted to approximately pH 6.5. Five ml of 5 per cent sodium–EDTA were added to the urine to release fluoride from complexes which it may form with polyvalent cations present in the urine. Fluoride ion concentration was measured with a fluoride ion activity electrode (Orion, Model 96–09) connected to a Radiometer pH potentiometer while the urine samples were stirred on a magnetic stir plate.

For the determination of total nonvolatile urinary fluorine, urine samples were adjusted to pH 9, using phenolphthalein as an indicator. Depending on the fluorine concentration, 5 ml or less of each sample was transferred to a black ignitor paper using a syringe infusion pump and dried in hot air. The paper with the dried sample was combusted in a Thomas Ogg Combustion Flask containing 10 ml of 5 per cent Na–EDTA and oxygen. After 20 minutes the solution was transferred to a plastic 50-ml beaker and fluoride ion was determined. The difference between the fluoride ion concentrations in the combusted sample and the noncombusted sample represented fluorine excreted in urine as nonvolatile organic compounds (organic fluorine). All statistical evaluations were computed using the geometric mean.

**Results**

**Expired Gas**

End-expired Éthrane concentrations averaged 1.51 per cent (range 1.10–2.0 per cent) during the anesthetic period. Upon switching to room air, the end-expired Éthrane concentrations initially fell rapidly, followed by a slower decline. Minute ventilation during the collection of expired gases averaged 6.08
Fig. 1. The excretion of Êthane in exhaled air following Êthane anesthesia. The solid line represents the equation

\[ Y = 91.6e^{-0.23t} + 20.6e^{-0.04t} + 1.88e^{-0.0032t} \]

The experimental points are plotted for each patient. The straight lines are logarithmic functions representing the vessel-rich group (VRG), muscle group (MG), and fat group (FG).

± 0.69 l/min. The excretion of Êthane by the lungs followed an exponential function which is given by the equation:

\[ Y = 1.1e^{-k_1t} + 1.2e^{-k_2t} + 1.3e^{-k_3t} \]  \hspace{1cm} (1)

where \( Y \) is the excretion rate of Êthane expired in minutes \( t \), \( k \)'s are rate constants, and \( A \)'s are the excretion rates for the presumed three compartments extrapolated to zero time.

NOXLIN, a computer program for parameter estimation in nonlinear situations, was used in the IBM-360/65 computer to calculate the constants \( k \) and \( A \) in equation 1. The correlation coefficients varied from 0.90 to 0.98 for individual patients \( (P < 0.01) \). The excretion of Êthane via the lungs for the population studied is characterized by:

\[ Y = 91.6e^{-0.029t} + 20.6e^{-0.045t} + 1.88e^{-0.0032t} \]

where \( Y \) is expressed in mg/min and \( t \) in minutes. This curve is presented in figure 1 with the experimental values for six patients. The excretion curves for each patient varied narrowly when corrected for body surface area

(m²) and the amount of Êthane administered (fig. 2).

The total amount \( (A) \) (mg) of expired Êthane was calculated for each patient according to the equation:

\[ A = \frac{A_1}{k_1} + \frac{A_2}{k_2} + \frac{A_3}{k_3} \]  \hspace{1cm} (2)

This amount represented 82.7 ± 18.8 per cent of the absorbed Êthane (range 50-107.5 per cent; table 2). Fifty per cent of the absorbed Êthane was exhaled within 18 hours following anesthesia, and 50 per cent of the amount recovered was exhaled within five hours following anesthesia.

Urinary fluoride excretion rates before anesthesia were 0.84 mg/day (range 0.24-1.68 mg/day). Urinary excretion of unaltered Êthane was negligible.

Following anesthesia, fluoride ion excretion rates increased significantly, reaching a maximum in seven hours (20-60 mg F⁻/day). Fluoride ion excretion then followed a single exponential decay curve toward normal values, with a half-time of 1.55 days (range 0.51-2.94 days; table 3). The excretion of organic
metabolites containing fluorine was slower, reaching a maximum the day following anesthesia (15-70 mg/day) and then declining, with a half-time of 3.69 days (range 2.01-8.15 days; table 3). Fluoride ion concentrations in urine returned to normal in less than a week; however, it is estimated that organic fluorine metabolites were excreted for about 17 days. The excretion curve for urinary fluorine of Patients 2 is shown in figure 3 to illustrate these findings. Of the fluorine administered as Ethrane, 0.51 per cent (range 0.31-0.94 per cent) was excreted as fluoride ion and 1.91 per cent (range 1.30-3.60 per cent) was excreted as nonvolatile organic metabolites (table 3).

Discussion

Ethrane biotransformation occurred to the extent of at least 2.42 per cent of the Ethrane administered to our patients. This degree of metabolism is much less than values reported for trichloroethylene, methoxyflurane, fluroxene and halothane. This is probably related to the chemical stability attributed to the high degree of fluorination of the Ethrane molecule and the relatively low blood/gas partition coefficient, 1.91. Based upon urinary fluorine analysis, most of the recoverable fluorine was in the form of nonvolatile organic metabolites. The organic-to-inorganic fluorine ratios averaged 3.8 (table 3), suggesting dehalogenation of the beta carbon of the ethyl moiety of Ethrane. However, it has been shown in experimental animals that following absorption of fluoride ion and fluorinated anesthetics, there is a significant increase in fluoride ion in the bone. 8-9

Assum-

![Fig. 2. The excretion of Ethrane in exhaled air following Ethrane anesthesia, normalized for body surface area and dose. The lines were visually fitted to the corrected experimental values.](http://anesthesiology.pubs.asahq.org/pdfaccess.ashx?url=/data/journals/jasa/931574/)

<p>| Table 2. Recovery of Ethrane in Exhaled Air of Patients Following Anesthesia |
|---------------------------------|--------------------|---------------------|-----------------|-------------------|---------------|-----------------|-------------------|</p>
<table>
<thead>
<tr>
<th>Patient</th>
<th>Ethrane Absorbed (mg)</th>
<th>Ethrane* Recovered in Exhaled Air (mg)</th>
<th>Per Cent Recovery</th>
<th>Vessel-rich group (Min)</th>
<th>Muscle Group (Hours)</th>
<th>Fat Group (Hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 1</td>
<td>11.98</td>
<td>11.1</td>
<td>92.7</td>
<td>18.2</td>
<td>3.0</td>
<td>35</td>
</tr>
<tr>
<td>Patient 2</td>
<td>16.12</td>
<td>14.0</td>
<td>86.8</td>
<td>18.2</td>
<td>3.2</td>
<td>36</td>
</tr>
<tr>
<td>Patient 3</td>
<td>15.27</td>
<td>11.1</td>
<td>72.7</td>
<td>16.1</td>
<td>1.5</td>
<td>45</td>
</tr>
<tr>
<td>Patient 4</td>
<td>32.12</td>
<td>16.7</td>
<td>52.0</td>
<td>34.6</td>
<td>2.1</td>
<td>32</td>
</tr>
<tr>
<td>Patient 5</td>
<td>19.06</td>
<td>20.5</td>
<td>107.5</td>
<td>20.4</td>
<td>3.7</td>
<td>38.5</td>
</tr>
<tr>
<td>Patient 6</td>
<td>15.77</td>
<td>13.3</td>
<td>84.3</td>
<td>9.6</td>
<td>1.6</td>
<td>65</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td></td>
<td></td>
<td>82.7 ± 18.8</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* $A = \frac{A_1}{k_1} + \frac{A_2}{k_2} + \frac{A_3}{k_3}$

† $T = \frac{0.693}{k}$, where $k$ is the NONLIN computed representative rate constant.
ing a similar skeletal fluoride ion deposition in man, approximately half of the inorganic fluoride ion formed during the biotransformation of Ethane would be taken up by bone, thereby reducing the organic-to-inorganic fluoride ratios of our patients to about 1:9. This would imply further degradation of the molecule, presumably by cleavage of the ether linkage accompanied by autolytic defluorination of one or both of the adjacent carbon atoms.

The Ethane recovered as unaltered drug and urinary metabolites was 85.1 per cent of that absorbed, with 82.7 ± 18.8 per cent being recovered in the exhaled air. The amount recovered was not related to the duration of anesthesia. Extraneous sites for the excretion of Ethane and its metabolites would be expected to represent a small portion of the 14.9 per cent not recovered. Small amounts of inhalational anesthetics have been demonstrated in the sweat and feces following anesthesia, and percutaneous losses during anesthesia have been reported. The major fraction of Ethane not recovered, however, was probably related to the techniques used to sample expired gas, which do not account for all variations in ventilation and physical activity which would be expected to affect the excretion of Ethane.

The excretion rates of exhaled Ethane were similar for all patients (fig. 2). Variations in excretion between individual patients were most evident after 48 hours, and may be related in part to the effects of variations in physical activity on excretion rates and the anatomic and functional characteristics of each patient.

The excretion of Ethane in exhaled air was presumed to follow a three-term exponential decay, as described by equation 1. The initial rapid excretion represented by the first decay constants $A_1$ and $k_1$ presumably describes desaturation of the vessel-rich group of tissues with a half-time of 17.8 minutes, (range 10-35 min). Seventeen per cent of the Ethane recovered was excreted from this compartment. The intermediate decline in exhaled Ethane is characterized by the second decay constants $A_2$ and $k_2$, presumably representing excretion from the muscle group, with a half-time of 3.2 hours (range 1.5-3.7 hours). The amount excreted from this tissue group was 41 per cent of the Ethane recovered. The prolonged excretion phase given by the third decay constants $A_3$ and $k_3$ presumably characterizes excretion from the fat group, with a half-time of 36.2 hours (range 32-68 hours). The remaining 42.2 per cent of Ethane recovered came from this tissue group.

The urinary excretion of inorganic and organic fluoride assumed single exponential decay curves following their respective maximum peak excretion rates (fig. 3). This excretion pattern is similar to that reported following methoxyflurane anesthesia. The slower excretion rates of organic fluoride compared to that of inorganic fluoride suggest

Table 3. The Recovery of Inorganic and Organic Fluorine in Urine of Patients Following Ethane Anesthesia

<table>
<thead>
<tr>
<th>Patient</th>
<th>Ethane Absorbed (g)</th>
<th>Fluorine Absorbed (g)</th>
<th>Inorganic Fluorine (mg)</th>
<th>Organic Fluorine (mg)</th>
<th>Total Fluorine Excreted (mg)</th>
<th>Recovery of Fluorine (per cent)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Inorganic (days)</td>
<td>Organic (days)</td>
<td>Inorganic (mg)</td>
<td>Organic (mg)</td>
<td>Inorganic (mg)</td>
<td>Organic (mg)</td>
</tr>
<tr>
<td>Patient 2</td>
<td>16.12</td>
<td>8.31</td>
<td>1.11</td>
<td>8.15</td>
<td>52.1</td>
<td>203.6</td>
</tr>
<tr>
<td>Patient 3</td>
<td>15.37</td>
<td>7.9</td>
<td>2.94</td>
<td>4.70</td>
<td>48.5</td>
<td>109.1</td>
</tr>
<tr>
<td>Patient 4</td>
<td>32.12</td>
<td>16.56</td>
<td>1.45</td>
<td>2.38</td>
<td>53.5</td>
<td>247.2</td>
</tr>
<tr>
<td>Patient 5</td>
<td>19.96</td>
<td>9.84</td>
<td>1.2</td>
<td>2.69</td>
<td>45.3</td>
<td>195</td>
</tr>
<tr>
<td>Patient 6</td>
<td>15.77</td>
<td>8.14</td>
<td>0.51</td>
<td>2.01</td>
<td>76.4</td>
<td>283.3</td>
</tr>
<tr>
<td>Patient 7</td>
<td>18.23</td>
<td>9.40</td>
<td>0.81</td>
<td>2.42</td>
<td>29.4</td>
<td>120</td>
</tr>
<tr>
<td>Geometric mean</td>
<td>1.55</td>
<td>3.69</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>
that the renal clearance of organic metabolites differed from that of fluoride ion. This could be related to tissue and plasma protein binding of organic metabolites of fluorine.1,12

References