Isoniazid-induced Enflurane Defluorination in Humans

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Serum inorganic fluoride (F⁻) levels were measured in 20 surgical patients treated with 300 mg isoniazid per day for periods of up to one year, prior to anesthesia with enflurane. Thirty-six control patients anesthetized with propofol, but taking no drugs, were also studied. Regression lines for peak serum fluoride were plotted against enflurane exposure in MAC-hours. Nine isoniazid-treated patients had fluoride levels significantly (P < 0.001) higher (y = 22.2x + 12.0) than either the 11 other isoniazid-treated patients (y = 5.6x + 8.2) or the 36 control patients (y = 5.4x + 6.3). Peak serum fluoride values in three patients exceeded 100 µM but in no patient did values exceed 10 µM by 48 h after anesthesia. It was concluded that isoniazid treatment resulted in enzyme induction in the nine patients with high peak fluoride levels. This pattern, i.e., induction occurring in approximately one-half of the patients, probably is related to the genetically determined bimodal distribution of rapid and slow acetylation of isoniazid. (Key words: Anesthetics, volatile: enflurane. Biotransformation: enzyme induction; fluorometabolites. Ions: fluoride. Kidney: function; nephrotoxicity. Metabolism: enzyme induction; metabolites. Pharmacology: isoniazid. Toxicity: metabolites.)

In 1976 we reported the case of a patient whose serum inorganic fluoride (F⁻) level peaked at 106 µM following six hours of anesthesia with enflurane.¹ Twenty-four hours after anesthesia his serum F⁻ level was 40 µM and he was able to concentrate urine to only 543 mOsm/kg in response to vasopressin administration. Forty-eight hours after anesthesia his serum F⁻ level had decreased to 8 µM and his maximum urinary osmolality after vasopressin administration was 911 mOsm/kg, approximately the same as his preoperative value. The patient smoked two packs of cigarettes per day, had a history of heavy alcohol intake, and was taking several medications, including chlorpromazine, diazepam, and isoniazid (INH;isonicotinic acid hydrazide). We thought that chronic exposure to one, or several, of these substances might have caused enzyme induction which then led to the high serum F⁻ levels we observed. This finding served as the impetus for a number of studies in which we have examined the effects of various drug treatments on enflurane defluorination.²⁻¹¹ In this report we detail the effects of isoniazid administration on enflurane defluorination in surgical patients.

Materials and Methods

The study group was made up of 20 surgical patients who had been treated with 300 mg per day of isoniazid for periods ranging from one week to one year. The control group consisted of 36 patients administered enflurane anesthesia who were not taking any drugs or who were not exposed to any chemicals known to cause enzyme induction. Data from 26 of the control subjects have been reported.⁷ The composition of the groups is presented in table 1. Informed consent was obtained from all patients and the study had the approval of the appropriate institutional human research committees. All patients were having elective surgical procedures; patients with abnormalities of renal function or diseases with possible renal complications were excluded from the study. Five-milliliter blood samples were obtained preoperatively and approximately 1 h, 3–6 h, 24 h, and 48 h after anesthesia for measurement of serum F⁻ levels using an Orion Model 801 I onalyzer and a F⁻ ion-specific electrode.¹² Serum creatinine and BUN levels also were measured before and, in most subjects, 24 or 48 h after operation.

Anesthetic management was not altered specifically for purposes of the study. Premedication was given according to the preference of the anesthesiologist. Induction of anesthesia was with sodium thiopental (3.0–6.5 mg/kg), succinylcholine (1.0–1.5 mg/kg) was used to facilitate endotracheal intubation, and d-tubocurarine (0.1–0.5 mg/kg) was used to provide surgical relaxation. Enflurane alone or enflurane and N₂O were administered using a semiclosed circle system; sodaline was used for CO₂ removal. MAC-hours of enflurane exposure were estimated from the percentages and times of enflurane administration as recorded on the anesthesia record.

Statistical Methods

The regression line for the control group was calculated by the least-squares method. The nine isoniazid-treated patients whose peak F⁻ values deviated from this line by 100 per cent or more were assigned to the isoniazid high peak F⁻ subgroup; the remaining eleven patients were assigned to the isoniazid low peak F⁻ subgroup. The slopes of the peak F⁻ regression lines for the two isoniazid treatment subgroups were compared with each other and with the slope of the regression line.
for the control group using t tests. Mean, preoperative and postoperative serum creatinine and urea nitrogen levels were calculated for each isoniazid treatment subgroup and were compared with similar data from the control group using t tests. \( P < 0.05 \) was considered significant.

**Results**

Individual peak serum F\(^{-}\) levels for all patients are presented in figure 1; mean values are presented in table 2. Three patients had peak values in excess of 100 \( \mu M \) with two others above 75 \( \mu M \). Peak values for all patients occurred 1–6 h after the end of anesthesia. Group data were expressed as the linear regression of peak serum F\(^{-}\) on MAC-hours of enflurane administration. The difference in regression lines between the two isoniazid subgroups was highly significant (\( P < 0.001 \)) as was the difference between the isoniazid subgroup with high F\(^{-}\) levels and the control group (\( P < 0.001 \)). The difference between the isoniazid subgroup with low F\(^{-}\) levels and the control group was not significant (\( P > 0.4 \)).

Serum creatinine and urea nitrogen levels did not change significantly after anesthesia in the treatment or control groups; values for all patients remained within normal limits. Serum creatinine data are presented in table 3.

**Discussion**

Our laboratory has studied the effects of enzyme-inducing agents on anesthetic defluorination for many years.\(^{2,11,13,14}\) Animal studies with methoxyflurane, isoflurane, and sevoflurane have consistently shown enhanced defluorination, in *vivo* and in *vitro*, following exposure to classical enzyme-inducing agents, such as phenobarbital and phenytoin.\(^{2,6,8-11,13,14}\) Induction of methoxyflurane metabolism has been of the greatest magnitude, the degree of enhanced defluorination reaching more than tenfold above control in *vitro*, and 2- to 3-fold in *vivo* in Fischer 344 rats. Changes with sevoflurane and isoflurane have been about one-third as great as those seen with methoxyflurane. Similar results have been reported by others.\(^{13}\) Studies in surgical patients have not been as clear-cut as those in animals, but there is some evidence that barbiturate therapy has led to toxic nephropathy after low-dose methoxyflurane anesthesia.\(^{16,17}\)

Results of studies of the effects of enzyme-inducing agents on enflurane defluorination have been inconsistent compared with those of other anesthetic agents. In an in *vitro* study, Greenstein *et al.*\(^{3}\) reported a statistically significant increase in enflurane defluorination, i.e., to 1.6 times the control value, using micromoles prepared from rats treated with phenobarbital. In that study, methoxyflurane defluorination was increased ninefold above control. On the other hand, Caughhey *et al.*\(^{14}\) were unable to demonstrate a significant increase in enflurane defluorination by hepatic microsomes prepared from rats treated with phenobarbital or phenytoin. Methoxyflurane defluorination was enhanced 11-fold in enzyme-induced animals in that study. Hitt *et al.*\(^{4}\) also failed to see enhanced enflurane defluorination using microsomes from phenobarbital-treated rats. Barr *et al.*\(^{2}\) reported no increase in enflurane defluorination in Fischer 344 rats in *vivo* treated with phenobarbital prior to anesthetic exposure. Hitt *et al.*\(^{18}\) however, demonstrated that chronic subanesthetic exposure of rats to enflurane, increased its own metabolism and also resulted in increased hepatic cytochrome P-450 levels.

Similar disparities have been noted in studies of hu-

**Table 1. Comparison of Groups**

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean Age (Years)</th>
<th>Sex</th>
<th>Race</th>
<th>Mean Duration INH (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (n = 36)</td>
<td>51</td>
<td>34 Male, 2 Female</td>
<td>28 White, 8 Black</td>
<td>—</td>
</tr>
<tr>
<td>Isoniazid, high peak F(^{-}) (n = 9)</td>
<td>47</td>
<td>6 Male, 3 Female</td>
<td>5 White, 4 Black</td>
<td>6.4</td>
</tr>
<tr>
<td>Isoniazid, low peak F(^{-}) (n = 11)</td>
<td>52</td>
<td>6 Male, 5 Female</td>
<td>7 White, 4 Black</td>
<td>7.6</td>
</tr>
</tbody>
</table>

**Fig. 1. Peak serum F\(^{-}\) levels for individual patients and the linear regression lines for the two isoniazid-treated subgroups and the control group. Isoniazid treatment enhanced defluorination in nine of 20 subjects.** The equation for the regression line for the isoniazid high peak F\(^{-}\) (n = 9) group is \( y = 22.2x + 12.0 \) (\( r = 0.87 \)); for the isoniazid low peak F\(^{-}\) (n = 11) group, \( y = 5.0x + 8.2 \) (\( r = 0.88 \)); and for the control group, \( y = 5.4x + 6.3 \) (\( r = 0.83 \)). The isoniazid (n = 9) group is different than the other two groups (\( P < 0.001 \)).
IONSIAZID-INDUCED ENFLURANE DEFLUORINATION

Table 2. Postanesthesia Serum F⁻ and Enflurane Exposure (Means ± SE)

<table>
<thead>
<tr>
<th>Group</th>
<th>Postanesthesia Serum F⁻ (μM)</th>
<th>Enflurane Exposure (MAC hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Peak F⁻, 1-6 hours</td>
<td>24 hours</td>
</tr>
<tr>
<td>Control (n = 36)</td>
<td>17.5 ± 1.4</td>
<td>9.9 ± 0.9</td>
</tr>
<tr>
<td>Isoniazid, high peak F⁻</td>
<td>74.8 ± 11.3</td>
<td>16.0 ± 2.8</td>
</tr>
<tr>
<td>(n = 9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isoniazid, low peak F⁻</td>
<td>20.1 ± 3.2</td>
<td>8.2 ± 1.2</td>
</tr>
<tr>
<td>(n = 11)</td>
<td></td>
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</table>

In volunteers, Berman et al. demonstrated that a single anesthetizing exposure of enflurane enhanced steroid metabolism suggesting that enzyme induction had occurred. The opposite conclusion was reached by Dooley et al. in a study of 102 surgical patients, 76 of whom had been treated with various enzyme-inducing substances prior to anesthesia, including ethanol, phenobarbital, and phentoin. No patient had a F⁻ level higher than 44.7 μM regardless of anesthetic exposure, which ranged from 0.5 to 6.0 MAC-hours.

Thus, it initially seemed that enzyme induction was not the explanation for the high F⁻ levels in the surgical patient originally reported by Cousins et al. However, we recently demonstrated that isoniazid treatment significantly increased the in vitro hepatic microsomal defluorination of enflurane and three other volatile ether anesthetics. Compared with saline treatment of control rats, isoniazid increased microsomal defluorination of enflurane 370 per cent, methoxyflurane 259 per cent, sevoflurane 283 per cent, and isoflurane 168 per cent. Of particular interest, enhanced enflurane defluorination was not associated with an increase of total cytochrome P-450 levels. Rather, a subspecies of cytochrome P-450 was induced, i.e., a reduced cytochrome plus CO with a spectrum absorption maximum at 451 nm as opposed to the usual peak seen at 450 nm in microsomes from saline-treated and phenobarbital-treated rats. Rice and Talcott characterized the pattern of catalytic activities associated with isoniazid induction. They found that isoniazid treatment significantly increased the rate of metabolism of p-nitroanisole, ethoxyresorufin, and aniline; significantly decreased the rate of metabolism of aminopyrine; and did not alter the activity of NADPH-cytochrome c reductase and the microsomal contents of cytochromes b₅ and P-450, per mg of microsomal protein. Thus, the catalytic activities associated with isoniazid treatment do not resemble that of either phenobarbital or β-naphthoflavone induction. Findings in vitro have been supported by the results of in vivo studies in Fischer 344 rats. Compared to control rats simultaneously exposed to enflurane, isoniazid-treated rats had significantly higher peak serum F⁻ levels (149 vs. 33 μM).

Isoniazid-treated rats also showed evidence of renal dysfunction compared to control rats.

In the present study, isoniazid treatment enhanced enflurane defluorination in some surgical patients but not in others. A possible explanation for this finding may be the large differences in drug metabolism ordinarily seen among individuals. However, isoniazid is a relatively unique compound so far as its metabolism is concerned. A bimodal distribution is frequently described with the isoniazid half-lives of rapid metabolizers ranging from about 45–110 min and that of slow metabolizers from 120–270 min. The primary metabolic route which determines the rate of isoniazid elimination from the body is acetylation to acetylisoniazid. Among slow acetylators, the rate constant for acetylation is similar to that for elimination of isoniazid by all other routes, i.e., via the kidneys, by hydrazine formation with pyruvic and α-keto-glutaric acids, and by hydrolysis to isonicotinic acid. Among rapid acetylators, however, acetylation was four times more important as a route of elimination than were these other routes. The trait for acetylation of isoniazid is inherited in a simple Mendelian fashion; slow acetylators are homozygous for the gene controlling slow acetylation while rapid acetylators are either heterozygous or homozygous for the gene controlling rapid acetylation. Approximately equal numbers of whites and blacks in the United States are rapid and slow acetylators of isoniazid. Thus, with a 9:11 ratio of high to low F⁻ levels after enflurane anesthesia in isoniazid treated pa-

Table 3. Serum Creatinine (Means ± SE) *

<table>
<thead>
<tr>
<th>Group</th>
<th>Preanesthesia</th>
<th>48 hr Postanesthesia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (n = 32)</td>
<td>1.03 ± 0.04</td>
<td>0.95 ± 0.03</td>
</tr>
<tr>
<td>Isoniazid, high peak F⁻</td>
<td>0.96 ± 0.08</td>
<td>0.84 ± 0.06</td>
</tr>
<tr>
<td>(n = 7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isoniazid, low peak F⁻</td>
<td>1.06 ± 0.11</td>
<td>1.03 ± 0.11</td>
</tr>
<tr>
<td>(n = 9)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Patients for whom both preanesthesia and postanesthesia data are available.
tients, increased defluorination is probably related to acetylator phenotype.

It is now known that treatment with several hydrazine-containing compounds results in increased anesthetic defluorination. Rice and Fish\textsuperscript{9} reported that Fischer 344 rats treated with the isoniazid metabolites, acetylisoniazid and hydrazine sulfate, but not with the non-hydrazine-containing metabolite, isonicotinic acid, had significant increases in methoxyfluorane, enfuran, isoflurane, and sevoflurane defluorination. Thus, increased anesthetic defluorination may be related to the rapidity of isoniazid metabolism. Rapid acetylators presumably would have higher metabolite levels than slow acetylators; these, in turn, would lead to higher serum F\textsuperscript{-} levels after enfuran anesthesia. Treatment with iproniazid, a hydrazine-containing monoamine oxidase inhibitor no longer in clinical use, also results in increased anesthetic defluorination.\textsuperscript{22} Although not tested in their study, Rice and Fish\textsuperscript{9} suggest that treatment with clinically useful hydrazine-containing compounds, such as hydralazine, may lead to enhanced enfuran defluorination.

The peak F\textsuperscript{-} levels we measured in the present study clearly were in the nephrotoxic range. We saw no evidence of renal dysfunction but it is possible that a more sensitive test of kidney function, such as the vasopressin test, would have detected an abnormality of urine concentrating ability. However, if such a defect did occur, it would likely have been only transient, as the rapid pulmonary excretion of enfuran after its administration is discontinued reduces anesthetic concentration in the body quickly, thus keeping postanesthetic F\textsuperscript{-} values at relatively low levels. This hypothesis is supported by the low serum F\textsuperscript{-} values 48 h after anaesthesia. In addition, the renal defect in the case reported by Cousins \textit{et al}.\textsuperscript{1} was short-lived.

One additional point should be made. Results of the present study are in disagreement with those of Miller \textit{et al}.\textsuperscript{24} regarding the rate of enfuran defluorination. They reported the equation for the linear regression line for defluorination for non-obese subjects was $y = 2.96x + 10.6$, and for morbidly obese subjects was $y = 5.5x + 10.6$, where $x$ is equal to MAC hours of enfuran exposure. Because of this approximate twofold difference, they concluded that morbidly obese subjects may have an increased risk of developing nephrotoxicity after enfuran anesthesia. In the present study, the equations for the linear regression lines for defluorination for the control and low peak F\textsuperscript{-} isoniazid groups, neither of which contained any obese patients, were very similar to that of the morbidly obese group in the study of Miller \textit{et al}.\textsuperscript{24} It is not apparent why this difference occurred.

References

23. Fish MP, Rice SA: Isoniazid metabolites and anesthetic metabolism. \textit{Anesthesiology} 51:5256, 1979