Title: DEUTERATION REDUCED SIGNIFICANTLY THE BIOTRANSFORMATION OF SEVOFLURANE

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Introduction. Sevoflurane, an experimental inhalational anesthetic, has several desireable properties including rapid induction and awakening, in man, 1-4% of the absorbed drug is metabolized, producing a peak serum fluoride ion ($F^-$) of 31uM after one hour of anesthesia which returns to preanesthetic levels in 24 hours (1). The objective of this study was to determine if substitution of deuterium for hydrogen atoms on the methoxy moiety would reduce significantly the extent of biotransformation.

Methods. Male Sprague Dawley rats, 200-250 g, were divided into two groups each having three subgroups of seven animals each. Subgroups 1 received saline, 0.25 ml, IP for 7 days; subgroups 2, phenobarbital 0.2 g/100 ml in drinking water for 6 days; and subgroups 3 isoniazid 0.50 mg/kg IP for 7 days. Twenty-four hours following pretreatment one set of subgroups received IP sevoflurane, 10 mmol/kg dissolved in an equal amount of Tween 80; the other set of subgroups was similarly injected with deuterated sevoflurane (99.9% on the methoxy group). Six nontreated and noninjected animals were maintained in each group.

All animals were placed in metabolic cages (Nalgene) on pretreatment days 1 and 2 for 24 hour urine collections. Immediately after the injection of the anesthetic, the animals were placed in metabolic cages for two 24-hour urine collections. At 48 hours plasma was analyzed for fluoride ion, $F^-$, and total fluorine and liver was analyzed for total fluorine. Urinary $F^-$ and total urinary and tissue fluorine were measured using methods previously described (2). Organic fluorine, RF, was calculated as total fluorine minus $F^-$.

Results. At 48 hours after exposure, plasma contained no significant increase of $F^-$ or RF over that of unexposed rats, and liver contained less than one percent of the total fluorine excreted as urinary metabolites by rats exposed to nondeuterated sevoflurane.

Animals in each subgroup given deuterated sevoflurane excreted significantly less urinary $F^-$ and RF than did animals in the corresponding subgroup that received non-deuterated drug (Table). Among the subgroups that received nondeuterated sevoflurane, the saline pretreated animals excreted 0.31% of the dose, the phenobarbital subgroup excreted 0.94%, and the isoniazid subgroup excreted 0.63%. In the subgroups exposed to deuterated sevoflurane these amounts were reduced to 0.10%, 0.20% and 0.19%, respectively, of the dose, representing highly significant reductions in the extent of metabolism of 66%, 79% and 70%, respectively.

Discussion and Conclusions. Deuteration of the methoxy moiety reduced metabolism of sevoflurane to between 21 and 34 percent of the extent exhibited by rats treated with nondeuterated sevoflurane. This suggests that the initial enzymatic attack is the insertion of an active oxygen in place of a proton on the one carbon fraction with subsequent hydroxylation followed by cleavage of the ether linkage and release of a single fluoride ion. The organic metabolite has been identified as the glucuronide of hexafluoroisopropanol. The absence of any significant quantity of metabolites in plasma or liver at 48 hours after exposure indicates that the excretion of parent drug and metabolites is essentially complete by that time. These experiments have also confirmed that biotransformation of sevoflurane is increased by both phenobarbital and isoniazid (3), with phenobarbital causing the greater degree of induction.

Sevoflurane releases fluoride ion somewhat more rapidly in man during exposure than enflurane. Although the quantity released may not represent a significant threat to the urine concentrating ability of most patients, exploitation of the greater bond strength of the C-D bond as compared with the C-H bond may remove this potential flaw from an inhalation anesthetic with many clinically desireable features (1).

References.

1. Holaday DA, Smith FR: Clinical characteristics and biotransformation of sevoflurane in healthy human volunteers. Anesthesiology 54:100-106, 1981.

2. Chase RE, Holaday DA, Fiserova-Bergerova V, et al: The biotransformation of Ethrane in man. Anesthesiology 35:451-455, 1971.

3. Rice SA, Talcott RE: Effects of isoniazid on selected hepatic mixed-function oxidase. Drug Metab Dispos 7:260-262, 1979.

URINARY METABOLITES FOLLOWING SEVOFLURANE EXPOSURE

| | Pretreatment | | |
|---|---|---|---|
| | Saline | Phenobarb | Isoniazid |
| **Fluoride Ion** | | | |
| Pre-exposure (14) | 116 ± 6.3 | 85.8 ± 3.9 | 106 ± 4.2 |
| Non-deuterated (7) | 200 ± 22.3 | 367 ± 55.2 | 297 ± 36.4 |
| Deuterated (7) | 123 ± 8.1* | 131 ± 12.3** | 165 ± 12.4** |
| **Organic Fluorine** | | | |
| Pre-exposure (14) | 75.4 ± 19.5 | 32.9 ± 12.9 | 27.1 ± 11.6 |
| Non-deuterated (7) | 1436 ± 162 | 4602 ± 470 | 2955 ± 317 |
| Deuterated (7) | 429 ± 37.7*** | 914 ± 96*** | 814 ± 136*** |

Values are mcg/48 hours following exposure, mean ± standard error. Parentheses indicate number in sample. Organic fluorine is total fluorine minus fluoride ion.

*p < 0.02, **p < 0.01, ***p < 0.001 compared to nondeuterated (by 2-tailed Student's t-test).