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Title: THE EFFECTS OF DEUTERATION ON HALOTHANE METABOLISM IN THE RAT

Authors: Anthony Gyamfi, M.D. and Duncan A. Holaday, M.D.

Affiliation: Department of Anesthesiology, University of Miami School of Medicine, Miami, Florida 33101

Introduction. McCarty, et al. (1) demonstrated that substitution of deuterium for hydrogen in halothane decreased the amount of bromide released into the serum of rats, whereas Sipes, et al. (2) have reported that deuteration has no effect on the release of fluoride (F) and other metabolites of reductive metabolism of halothane in hypoxic rats. Our purpose was to determine if the decrease in metabolism observed by McCarty takes place in the oxidative pathway, and to correlate the amount of trifluoroacetic acid and organic fluorine excreted by noninduced, air breathing rats.

Methods. 26 male Sprague-Dawley rats weighing 200-300g were placed individually into metabolic cages and urine was collected for 72 hours. After two days of rest in standard rat cages, they were divided into two groups by random selection. The first group of 12 were injected i.p. with 0.15-0.2g/kg commercial halothane (halo) and returned to individual metabolic cages for 72-100 hours of urine collection. The rats breathed air and had access to standard rat chow and deionized water. The second group of 14 were treated the same, but using deuterated halothane (D-halo) (90%D, 99.9% purity). Urine volumes and time of collection were noted. Samples of urine were analyzed for F^- with a fluoride ion specific electrode, for total, nonvolatile fluorine following combustion in a Thomas-Ogg flask, and for TFAA by gas chromatography following ethylation using diethylsulfate for esterifiction and an internal standard of formic acid. The animals were then sacrificed, and heart, lungs, liver, kidney, brain and a sample of muscle were removed and weighed. The tissues were frozen, pulverized, dried, combusted and analyzed for nonvolatile fluorine as described above.

Rates of urinary excretion of organic fluorine were plotted against time, and the halftimes of excretion were calculated from the average slope of each group. Excreted organic fluorine plus tissue fluorine was calculated as a fraction of the injected dose, and the percentages of anesthetic metabolized by the two groups were compared. The concentrations of organic fluorine and TFAA in urine were correlated.

Results. The fraction of the dose of halo metabolized was 15% greater than that of D-halo, a significant difference. The half times for excretion and the total metabolites retained in the tissues were not significantly different in the two groups. The rates of fluoride ion excretion by both groups decreased after injection, significantly in the case of halo treated rats. The amount of TFAA in urine samples of both groups correlated strongly with the organic fluorine contents of the samples. The measured mean contents of TFAA exceeded those of organic fluorine in urine samples of both groups by 14% ($p<0.02$) indicating existance of a bias in one or the other method of analysis and suggesting that TFAA constituted the major urinary metabolite.

Discussion. TFAA accounted for all or almost all of the organic fluorine metabolites. Fluoride ion excretion was not increased, but decreased slightly, possibly a reflection of intake of fluoride-free water for 100 hours. These results strongly suggest that oxidative metabolism was operative exclusively during this experiment. Hence, we confirm McCarty's observation that deuteration decreases the metabolism of halothane and establish that proton extraction is rate limiting to the oxidative pathway of halothane metabolism. These observations, do not support the conclusion that deuteration will decrease the potential toxicity of halothane.

References

1. McCarty LP, Malek RS, Larsen ER: The effect on the metabolism of halogenated anesthetics in the rat. Anesthesiol 51:106-110, 1979.

2. Sipes IG, Gandolfi RM, et al: Metabolism and toxicity of deuterated halothane. (Abstract) Fed Proc 38:2406, 1979.

	HALOTHANE MEAN (SEM)	D-HALOTHANE MEAN (SEM)
Fraction of dose metabolized (%)	N = 12 2.48(0.12)	N = 14 2.15(0.17)*
Fluoride excr'n(μg/hr) Control	N = 9 2.18(0.13)	N = 12 2.21(0.16)
Exper.	1.66(0.22)**	1.81(0.12)
Organic F μM/ml	N = 80 0.95(0.09)	N = 87 0.85(0.07)
TFAA μM/ml	1.14(0.12)	0.99(0.08)
	r = 0.87	r = 0.76

* unpaired "t" test, $p < 0.02$

** paired "t" test, $p < 0.01$