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Biotransformation of Halothane in Humans

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Halothane biotransformation in man: A quantitative study. By Kai Rehder, Joseph Forbes, Helmuth Alter, Otto Hessler, and Anton Stier. ANESTHESIOLOGY 1967; 28:711–5.

The metabolic breakdown of halothane was quantitatively determined in two patients. Trifluoroacetic acid and bromide were found as metabolites in the urine. Both metabolites have a protracted excretion rate. Since the biological half-life of trifluoroacetic acid is unknown, one can calculate only the least amount of halothane that had been metabolized on the basis of the excreted trifluoroacetic acid: 12% in both patients. On the basis of the excreted urinary bromide, 20% and 17%, respectively, of the halothane taken up by the body was calculated to be metabolized, if one assumes a biological half-life of 12 days for bromide.

THE impetus to study and quantify halothane biotransformation in humans[1] resulted from a discussion about hepatic necrosis associated with halothane anesthesia[2] at a weekly seminar organized by the Department of Pharmacology and Toxicology at the University of Würzburg, Würzburg, Germany, in spring 1963. At this meeting, the Chairman of the Department of Pharmacology and Toxicology, Wilhelm Neumann, Professor Dr. med. and Dr. phil. (1898–1965), asked how halothane was biotransformed. This question surprised the anesthesiologists present, because the accepted dogma was that, with the exception of trichloroethylene, volatile anesthetics did not undergo biotransformation. In examining the chemical formula of halothane, Professor Neumann speculated that it would be dechlorinated, debrominated, and oxidized to trifluoroacetic acid in the body. He subsequently asked Anton Stier, Dr. med. habil., Dr. rer. nat., Dr. h. c., Research Assistant, Department of Pharmacology and Toxicology, University of Würzburg (1928–2001), who was working at that time on the metabolism of trichloroethylene, to test this hypothesis by injecting halothane intraperitoneally into rats, collecting their urine, and determining the urinary bromide levels.

None of us in Würzburg were aware that, in 1962, Russell A. Van Dyke, Ph.D. (Biochemistry), Research Scientist in the Biochemical Research Laboratory (1930), together with Maynard B. Chenoweth, M.D., Senior Research Scientist in the Biochemical Research Laboratory (1917–1988), and Eric R. Larsen, Ph.D. (Chemistry), Research Scientist in the Halogens Research Laboratory (1928), all at The Dow Chemical Company in Midland, Michigan, had begun to study the metabolism of volatile anesthetics, including halothane. In 1963, Van Dyke reported that halothane was biotransformed in a paper presented to the New York Society of Anesthesiologists, and in spring 1964, Van Dyke and Chenoweth presented data on the metabolism of halothane and methoxyfluorane in rat liver slices at the Federation of American Societies of Experimental Biologists meeting.[3] In 1964, Van Dyke *et al.* published evidence for the *in vivo* dechlorination of halothane and suggested that this process is enzymatic.[4] In another article, the same authors observed that the carbon-fluorine bond in the halothane-1-^{14}C molecule is biologically nearly stable, because little $^{14}CO_2$ is produced.[5]

Working independently in Würzburg in 1964, Anton Stier reported that intraperitoneal injections of halothane resulted in the urinary excretion of inorganic bromide in rats[6] and of trifluoroacetic acid in rabbits.[7] Because trifluoroacetic acid is a man-made molecule and both it and bromine were excluded from the animals' diet, Stier suggested that the presence of these substances in the animals' urine confirmed halothane biotransformation.

Later in 1964, Stier, together with Hellmuth W. O. Alter, Dr. med., Research Assistant (1929), Otto Hessler, Dr. med., Research Assistant (1921–2002), and Kai Rehder, Dr. med. habil., Head of Section (1928), all in the Section of Anesthesiology at the University of Würzburg, demonstrated a significant and consistent rise in

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the bromide:halide ratio and a prolonged, increased urinary bromide excretion in 12 of 13 patients anesthetized with halothane (see Web Enhancement for photographs of the researchers mentioned in this article).[8] By contrast, five patients anesthetized without halothane showed no increased urinary excretion of bromide. These results suggested that humans metabolize a portion of absorbed halothane.

Before publication of the article, we gave copies of it to representatives of Hoechst AG (Frankfurt/Main, Germany) and Rhein Chemie Pharma Arzneimittel GmbH (Heidelberg, Germany). The latter company distributed halothane for Imperial Chemical Industries Ltd. (ICI) in Germany. Hoechst AG produced halothane, because they (like ICI) held a patent on halothane. Within a few hours after we had distributed the copies, ICI contacted us. I believe it was Dr. William A. M. Duncan (Research Department, ICI, Ltd., Pharmaceuticals Division, Alderley Park, Macclesfield, Cheshire, United Kingdom [1929]) who visited us to discuss our findings. He and Dr. James Raventós (Research Department, ICI, Ltd., Pharmaceuticals Division, Alderley Park, Macclesfield, Ceshire, United Kingdom [1905–?]) had suggested in a classic paper that halothane was inert.[9]

Although our investigation was not designed to be quantitative, we were able to make some calculations and interesting inferences. Assuming an average urinary output and halothane uptake, we estimated that, interestingly, up to 15% of the halothane taken up by these patients had been biotransformed. To test this unexpectedly high estimate, we designed a study to determine quantitatively the metabolism of halothane in humans.

Three years later, in 1967, we published the results of this study.[1] Its goals were to test our estimate that as much as 15% of absorbed halothane is biotransformed, to examine whether urinary trifluoroacetic acid excretion occurred in humans, and to confirm in humans that the carbon-fluorine bond of the number-one carbon of the halothane molecule is nearly stable; *i.e.,* that no fluorine is broken off to any significant degree. To quantify the biotransformation of halothane, we determined its pulmonary uptake and the urinary excretions of bromide and trifluoroacetic acid in two patients. Based on the urinary excretion of bromide and assuming that bromide has a biologic half-life of 12 days, we calculated that between 17% and 20% of the halothane taken up by the body was metabolized. Based on the urinary excretion of trifluoroacetic acid, we estimated that as much as 12% of the absorbed halothane was converted into this product. To test the stability of the carbon-fluorine bond of the number-one carbon, we determined urinary fluorine excretion and found that it is almost entirely organic in form, which suggested a nearly stable carbon–fluorine bond of the halothane molecule[5] in humans. These results confirmed and extended observations that, in humans, a large proportion of absorbed halothane is biotransformed by debromination, dechlorination, and oxidation, and that the carbon–fluorine bond at the number-one carbon of the halothane molecule is nearly stable.

A number of anesthesiologists and other scientists became interested in this new field of research in subsequent years and published several review articles on this subject in rapid sequence in the Journal.[10–12] The major question of whether biotransformation is a detoxifying or a toxifying process led to studies on the long-term effect of halothane exposure of operating room personal. Scientific inquiry centered on the microsomal enzymes responsible for biotransformation and on whether the toxic effects of volatile anesthetics resulted from an increased rate of biotransformation in some patients because of their genetic makeup. Researchers also sought to determine the effects of hypercarbia and hypoxemia on the rate and pathways of biotransformation for halothane and the intermediary products of biotransformation and their potential toxicity. Currently, many of these important questions must be answered before the U.S. Food and Drug Administration approves a new anesthetic for marketing by the pharmaceutical industry.

References

1. Rehder K, Forbes J, Alter H, Hessler O, Stier A: Halothane biotransformation in man: A quantitative study. ANESTHESIOLOGY 1967; 28:711–5
2. Lindenbaum J, Leifer E: Hepatic necrosis associated with halothane anesthesia. New Engl J Med 1963; 268:525–30
3. Van Dyke RA, Chenoweth MB: Biotransformation of methoxyfluorane and halothane in liver slices (abstract). Fed Proc 1964; 23:179
4. Van Dyke RA, Chenoweth MB, Van Poznak A: Metabolism of volatile anesthetics: I. Conversion *in vivo* of several anesthetics to $^{14}CO_2$ and chloride. Biochem Pharm 1964; 13:1239–47
5. Van Dyke RA, Chenoweth MB, Larsen ER: Synthesis and metabolism of halothane-1-^{14}C. Nature (Lond) 1964; 204:471–2
6. Stier A: Zur Frage der Stabilität von Halothan (2-brom-2-chlor-1, 1, 1-trifluoraethan) im Stoffwechsel. Naturwissenschaften 1964; 51:65
7. Stier A: Trifluoroacetic acid as metabolite of halothane (abstract). Biochem Pharm 1964; 13:1544
8. Stier A, Alter H, Hessler O, Rehder K: Urinary excretion of bromide in halothane anesthesia. Anesth Analg 1964; 43:723–8
9. Duncan WAM, Raventós J: The pharmacokinetics of halothane (Fluothane) anaesthesia. Br J Anaesth 1959; 31:302–15
10. Van Dyke RA, Chenoweth MB: Metabolism of volatile anesthetics. ANESTHESIOLOGY 1965; 26:348–57
11. Greene NM: The metabolism of drugs employed in anesthesia: Part II. ANESTHESIOLOGY 1968; 29:327–60
12. Cohen, EN: Metabolism of volatile anesthetics. ANESTHESIOLOGY 1971; 35: 193–202

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