How Safe is Halothane?*

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Halothane (2-bromo-2-chloro-1, 1, 1-trifluoroethane) is the most popular inhalation agent in today's anesthetic practice. Its desirable properties include high potency, nonflammability, patient acceptance, a low incidence of nausea and vomiting, ability to produce bronchodilatation, and ease of maintenance. Prior to its introduction in 1956, it was subjected to an intense examination for both general and hepatic toxicity. Although these investigations disclosed no evidence of adverse effects, reports of liver dysfunction after halothane administration have appeared constantly in the literature. Thus, although the general safety of this drug continues to be excellent, the clinician is confronted with a dilemma each time he elects to use this agent. I hope to give some perspective to this question.

The first thing to understand is that administration of any of the anesthetics currently in use may be followed by mild and reversible evidence of liver derangement. Studies conducted over twenty years ago showed that administration of diethyl ether or cyclopropane was followed by significant bromsulfalein retention, a phenomenon also observed when spinal anesthesia was used. Subsequent investigations have shown this to be true in the case of methoxyflurane and halothane. Other work has indicated that clearance of indocyanine green (ICG) is markedly diminished during anesthesia. It would thus appear that all anesthetics have the ability to produce mild and reversible evidence of hepatic abnormalities; findings which are probably of no physiologic significance. This property is shared by halothane.

Halothane also produces reversible abnormalities of hepatic mitochondrial function. Oxygen uptake of mitochondria stimulated by adenosine diphosphate is diminished in the presence of clinically effective concentrations of halothane. Halothane, however, is no different from methoxyflurane, diethyl ether, and ethrane which also produce these changes. Thus, although halothane has specific metabolic effects, it shares these in common with other inhalation agents.

Perhaps halothane exerts its effects through altered hepatic circulation. Studies performed in man during halothane anesthesia indicate that splanchnic blood flow decreases as mean arterial pressure is lowered; ICG clearance is diminished also. However, when arterial carbon dioxide tension is elevated, splanchnic vasodilatation occurs and splanchnic blood flow is increased. In spite of the return of blood flow to normal, ICG clearance remains depressed. Cyclopropane, on the other hand, increases arterial pressure while hepatic blood flow is decreased. Again, ICG clearance is lowered. When hexamethonium is infused, splanchnic vascular resistance decreases and splanchnic flow is elevated. As in the case of halothane, the return of hepatic perfusion to normal does not result in a normal ICG clearance. Again, we must consider the abnormality in ICG clearance to be a nonspecific anesthetic effect rather than the pathologic manifestation of a low perfusion state. We must also realize that halothane does not have a specific effect, and that this phenomenon is observed with all the inhalation agents.

It is clear that the major question which must be answered for any anesthetic agent concerns its overall safety. It is because of this problem that a retrospective study of anesthetic safety during the years 1959-1963 was undertaken. This study, known as the National Halothane Study, evaluated the records of 865,515 anesthetics. In this group, 16,840 deaths were reported of which 11,289 underwent autopsy. There were two significant questions which

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were posed: (1) Were there differences among anesthetic agents and techniques in overall death rates and in the incidence of massive hepatic necrosis? (2) Were there any differences among anesthetic agents and techniques in the death rate or incidence of massive hepatic necrosis when surgery in the biliary tract was performed? The overall results of the study suggested that halothane was at least as safe as the other agents examined. Furthermore, it was no less safe than the other drugs when biliary surgery was performed.

Although the data suggested that halothane's safety was at least equal to that of other drugs and techniques, a certain nagging doubt persisted. Most of the cases of hepatic necrosis were obviously caused by factors such as hemorrhagic shock, sepsis, or previous transfusion. However, in nine cases no etiology was obvious and of these, seven had received halothane. Furthermore, four of these seven had been exposed previously to halothane. It must be realized that the National Halothane Study had an element of volunteer bias in that several of the unexplained cases of massive hepatic necrosis had already been published, and most probably the institution volunteered to participate in the study because of this. Nonetheless, the possibility was considered that halothane might be responsible for certain cases of hepatic dysfunction.

In subsequent years, a number of events were reported which indicated that exposure of unoperated man to extremely low concentrations of the agent might rarely produce hepatic abnormalities. It was from a consideration of such events that the concept of halothane hypersensitivity arose. This theory stated that halothane is not a direct hepatotoxin. In the rare cases (the incidence of unexplained hepatic necrosis following halothane was 1:35,000), the individual might be hypersensitive or "allergic" to the agent. This would explain the increased likelihood of observing the phenomenon after more than one exposure, and might also explain the occurrence in unoperated man receiving sub-anesthetic concentrations of the drug. Additional support to this theory was evidence of lymphocyte transformation produced by incubating lymphocytes of affected man with halothane. It should be noted that many individuals with what appears to be halothane-induced hepatitis did not show positive lymphocyte transformation. Furthermore, occasional false positive results have been reported. Thus, although the hypersensitivity theory is not unreasonable, it should not be considered to be the sole explanation of this unfortunate phenomenon.

We have recently studied the concentrations of immunoglobulins in man following surgery performed during halothane anesthesia. Observations were made prior to and up to 30 days after surgery; data obtained was compared with similar studies when anesthesia was provided by nitrous oxide supplemented with narcotic. No significant changes were produced by either nitrous oxide-narcotic or nitrous oxide-halothane. In another group of individuals receiving halothane anesthesia, measurements of serum glutamic oxaloacetic transaminase concentration and bromsulfalein retention accompanied the assays of immunoglobulin concentrations. Although transient abnormalities of hepatic function were observed, no alterations in the immunoglobulin pattern were noted during observations lasting as long as 60 days.

Although these data do not definitely rule out an immunologic basis for halothane-induced hepatic necrosis, they do suggest that a systematic immunologic abnormality does not occur usually following anesthesia with this agent. Furthermore, they indicate that short-lived abnormalities of hepatic function following halothane anesthesia are similar to those observed with other anesthetic drugs and are not the result of immunologic factors. Finally, these observations furnish a base line should the opportunity arise to obtain samples from a patient with severe hepatic failure following halothane anesthesia.

Are there any other mechanisms which might be responsible? In the past few years, increasing emphasis has been placed on the ability of the hepatic microsomal system to detoxify a wide variety of drugs. Many of the inhalation anesthetics, among them halothane, are so metabolized. Furthermore, prior exposure to halothane produces enzyme induction which results in a more rapid rate of halothane biodegradation. It is not inconceivable that abnormal pathways of biodegradation might produce toxic metabolites which could result in hepatic necrosis.

At the present time, the evidence is not clear as to what might be the mechanism for the extremely rare case of halothane-induced hepatic necrosis. Indeed, it is still a moot point as to whether this entity can be definitely proven to exist. However, the answer to the question of this lecture can be easily made. The National Halothane Study supplied excel-

lent data indicating that in the overwhelming majority of patients the drug is as safe as any currently used. I would suggest that the main factor determining patient safety is the individual administering the anesthetic rather than the specific agent itself. However, although the drug is exceedingly safe, a small number of patients may be at risk. It is the task of future investigation to delineate these individuals so as to prevent the occurrence of this syndrome.

REFERENCES

BECKMAN, V., BROHAULT, J., AND REICHARD, H. Elevations of liver-enzyme activities in serum after halothane, ether, and spinal anaesthesia. *Act. Anaesth. Scandinav.* 10:55–63, 1966.

BELFRAGE, S., AHLGREN, I., AND AXELSON, S. Halothane hepatitis in an anesthetist. *Lancet* 1466, Dec. 31, 1966.

CASCORBI, H. F., BLAKE, D. A. AND HELRICH, M. Differences in the biotransformation of halothane in man. *Anesth.* 32:119, 1970.

COHEN, P. J. AND MCINTYRE, R. The effects of general anesthesia on respiratory control and oxygen consumption of rat liver mitochondria. *Cellular Biology and Toxicity of Anesthetics,* B. R. Fink (ed.). Baltimore: Williams and Wilkins, 1972, pp. 109–116.

CORSSEN, G., SWEET, R. B., AND CHENOWETH, M. B. Effects of chloroform, halothane, and methoxyflurane on human liver cells in vitro. *Anesth.* 27:155, 1966.

ELKINGTON, S. G., GOFFINET, J. A., AND CONN, H. O. Renal and hepatic injury associated with methoxyflurane anesthesia. *Ann. Int. Med.* 69:1229, 1968.

EPSTEIN, R. M., *et al.* Splanchnic circulation during halothane anesthesia and hypercapnia in normal man. *Anesth.* 26:654, 1966.

FAIRLIE, C. W. *et al.* Metabolic effects of anesthesia in man. IV. A comparison of the effects of certain anesthetic agents on the normal liver. *New Eng. J. Med.* 17:615, 1951.

FRENCH, A. B., *et al.* Metabolic effects of anesthesia in man. V. A comparison of the effects of ether and cyclopropane anesthesia on the abnormal liver. *Ann. Surg.* 135:145, 1952.

GALL, E. A. Report of the pathology panel. National Halothane Study. *Anesth.* 29:233, 1968.

GRONERT, G. A., SCHANER, P. J., AND GUNTHER, R. C. Multiple halothane anesthesia in the burn patient. *JAMA* 205:878, 1968.

JOHNSTONE, M. Halothane: the first five years. *Anesth.* 22:591, 1961.

KLATSKIN, G. Mechanisms of toxic and drug induced hepatic injury. *Toxicity of Anesthetics,* B. R. Fink (ed.). Baltimore: Williams and Wilkins, 1968.

KLATSKIN, G. AND KIMBERG, D. V. Recurrent hepatitis attributable to halothane sensitization in an anesthetist. *New Eng. J. Med.* 280:515, 1969.

KLEIN, N. C. AND JEFFRIES, G. H. Hepatotoxicity after methoxyflurane administration. *JAMA* 197:1037, 1966.

KLION, F. M., SCHAFFNER, F., AND POPPER, H. Hepatitis after exposure to halothane. *Ann. Int. Med.* 71:467, 1969.

LECKY, J. H. AND COHEN, P. J. Hepatic dysfunction without jaundice following administration of halothane. *Anesth.* 33:371, 1970.

LITTLE, D. M. JR. AND WETSTONE, H. J. Anesthesia and the liver. *Anesth.* 25:815, 1964.

PARONETTO, F. AND POPPER, H. Lymphocyte stimulation induced by halothane in patients with hepatitis following exposure to halothane. *New Eng. J. Med.* 283:277, 1970.

PRICE, H. L., *et al.* Can general anesthetics produce splanchnic visceral hypoxia by reducing regional blood flow? *Anesth.* 27:24, 1966.

REHDER, K., FORBES, J., AND ALTER, *et al.* Halothane biotransformation in man: A quantitative study. *Anesth.* 28:711, 1967.

RODRIQUEZ, M., *et al.* Antimitochondrial antibodies in jaundice following drug administration. *JAMA* 208:148, 1969.

Summary of the National Halothane Study. *JAMA* 197:775–788, 1966.

TREY, C. *et al.* Fulminant hepatic failure. Presumable contribution to halothane, *New Eng. J. Med.* 279:798, 1968.