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EDITORIAL VIEWS

Is Enflurane Hepatotoxic?

TWENTY YEARS after the diagnosis of "halothane hepatitis" was first seriously entertained much has been learned and some issues have been settled, including that of its existence. Yet, ten years after the diagnosis of "enflurane hepatitis" first was suggested tentatively little has been learned, and the issue of its existence has not been settled,* despite a recent attempt to prove the point through review of a collection of isolated case reports.[1] The key issue is the extent to which the available evidence supports classifying enflurane as a hepatotoxin by use of specific predetermined criteria for defining an unpredictable hepatotoxin. The key problem is the exclusion of cases of concurrent viral hepatitis; as Lasagna noted recently "The bad things a drug does almost always can be seen in the absence of the drug."[2]

The criteria for ascribing hepatotoxicity used in the above review of cases were ". . . that other potential causes be excluded and that the clinical characteristics and pattern of injury be reasonably consistent and uniform among multiple instances of apparent toxicity."[1] These seem to be both nonspecific and vague enough to lack reliability and at variance with more specific criteria used by others in the field. It is difficult to establish a diagnosis by exclusion, particularly when the disease to be excluded is viral hepatitis. Although viral hepatitis can be ruled in under certain circumstances—positive immunologic tests, finding the virus in the liver, and a clear history of exposure—the absence of these factors clearly does not rule the disease out. Indeed, in one of the Boston Inter-Hospital Liver Group studies on viral hepatitis, two thirds of the patients carrying that diagnosis had no history of exposure.[3] Clearly, viral hepatitis often is also a diagnosis by exclusion. Shortly after the Boston group published its findings, I participated in an attempt to undertake a prospective study of "halothane hepatitis" in that city. The study was not undertaken in part because the critical diagnosis was deemed by the funding agency to be a diagnosis by exclusion. Epidemiologists are rightly wary of studying an entity that cannot be diagnosed reliably.[4] Great scepticism is in order when conclusions are based on retrospective studies with the same deficiency, let alone on uncontrolled collections of isolated case reports.

Babior and Trey[5] suggested three criteria that can be used to implicate drugs as hepatic sensitizing agents (unpredictable hepatotoxins): rechallenge of the patient with the suspected drug; definition of a specific clinical syndrome; and results of epidemiologic studies of the entity. Zimmerman[6] supports use of the first and third of these. When the minute amount of evidence relating to enflurane hepatotoxicity is evaluated according to these criteria, one finds that no specific clinical syndrome has been delineated and that no retrospective or prospective epidemiologic studies have been performed. Proof of the existence of the entity depends entirely on one patient who developed hepatic damage after both of two anesthetic exposures.[7] Unlike the situation with regard to halothane, no formal challenges have been performed.

A specific clinical syndrome of postanesthetic hepatotoxicity due to a specific drug cannot be elucidated by classifying the clinical features of a group of cases in which a temporal relationship happens to have been observed. As there is no doubt that some or even most of the cases are likely to be viral rather than drug hepatitis, this is circular reasoning. Proof that this is not an acceptable epidemiologic technique stems from the fact that it was used unsuccessfully to depict specific clinical syndromes for both chloroform and halothane hepatotoxicities. Some

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* Deutsch S: Chairman, Anesthetic and Life Support Drug Advisory Committee, Food and Drug Administration, 1982, Personal communication.

seem determined to repeat the errors of the past. Evidence supporting the fact that postanesthetic viral hepatitis is a real, not a theoretic, confounding diagnosis comes from several sources. First, it was estimated that approximately 4,000 patients in the United States per annum would receive halothane during the incubation period of what was then called IH hepatitis.[8] Although the figure is far from firm, it speaks to the magnitude of the problem. Second, further support for this point is provided by two studies that found the incidence of unsuspected preoperative hepatic dysfunction that worsens during the succeeding few days to be approximately 1 per 2,500 preoperative patients.[9,10] Third, the diagnosis of "halothane hepatitis" has been made in patients who never received halothane![8] Fourth, the diagnosis of "enflurane hepatitis" was made in a patient who was later found to have herpes hepatitis when electron microscopic examination of the liver was performed.[11] Hepatitis *associated with* administration of a drug is not the same entity as hepatitis *due to* the drug. The former may be a chance association; the latter clearly carries all the implications of a causal relationship. Evidence supporting a widespread serious misunderstanding of this crucial difference stems from several papers in which the authors used terms such as "halothane hepatitis" and "hepatitis associated with halothane" synonymously and interchangeably.[12]

There are two additional reasons for concern about this recent review of a collection of isolated case reports of hepatic damage after enflurane.[1] First, although the authors planned to exclude cases in which enflurane could not be incriminated and include those in which they were convinced that enflurane was the likely cause of hepatic injury, they included two cases, the validity of which they admitted had been questioned. Second, they commented that none of the patients who had received enflurane previously had had hepatitis after the prior exposure, when in fact one of the patients, as noted above, had indeed exhibited such a history.[7]

Is there a role for light and electron microscopy in the diagnosis of postanesthetic hepatitis? Although some investigators believe that certain morphologic features favor the diagnosis of halothane over viral hepatitis, most pathologists have rendered their judgments, knowing which anesthetic a particular patient had received. This lack of the use of blinding techniques seems to have been a persistent problem, as Chalmers saw fit to comment on it in his Presidential Address To The American Gastroenterological Association in 1969.[13] As long as the pathologists evaluating the liver slides from the patients who constituted the National Halothane Study remained blinded to the anesthetic agents used, they could not pick out those who had received halothane from those who had not.[12] In addition, pathologists have been unable to agree on the implications of the microscopic findings in cases of hepatic damage after enflurane.† Clearly, the pathologists cannot answer the diagnostic dilemmas at this time.

The answer to the question posed in the title of this editorial is that the totality of the evidence incriminating enflurane consists of a single case report.[7] This is hardly sufficient evidence either to seriously incriminate a drug or to formulate firm clinical guidelines. Yet it is easy to imagine situations that will demand difficult clinical judgments. Whereas there seems to be a clear consensus that patients known to have developed unexplained hepatitis after halothane should not receive the drug again, should the same caution be applied to enflurane? I would answer "yes," not because enflurane hepatotoxicity has been documented but in the same spirit in which the authors of the National Halothane Study noted "the usual medical doctrine that any treatment followed by ill effects should ordinarily not be repeated."[14] A more difficult decision is whether a different halogenated inhalation agent should be used when a prior administration of another such agent had been followed by development of bonafide hepatic damage. The totality of the evidence suggesting that cross-sensitization between these agents might occur, also consists of only a single case report; a patient who developed evidence of hepatic damage after halothane and 2 years later developed a similar entity after methoxyflurane.[15] Once again, this is hardly the stuff of firm clinical decision making. Nevertheless, even in the absence of convincing evidence and largely for the protection of these invaluable agents themselves, I would counsel avoidance of any of them under these circumstances. I would consider their use only if it was strongly indicated—for example, the need for general anesthesia with an endotracheal tube in a severe asthmatic—when I might consider using a different agent, probably one less completely metabolized than the one under suspicion. Hopefully, if minds are kept open, any sound new evidence will be evaluated objectively and used to illuminate the issue of the hepatotoxicity of the halogenated inhalation agents and if necessary to modify clinical practice accordingly. Reports of collections of isolated cases are not going to provide the much desired convincing epidemiologic evidence that is required to document hepatotoxicity and to elucidate its clinical characteristics.

MICHAEL H. M. DYKES, M.D., M.ED.
Professor of Clinical Anesthesia and Associate Chairman
Department of Anesthesia
Northwestern University Medical School,
and Northwestern Memorial Hospital
Chicago, Illinois 60611

† Deutsch S: Chairman, Anesthetic and Life Support Drug Advisory Committee, Food and Drug Administration, 1982, Personal communication.

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