Editorial

Isoflurane and post-operative hepatic dysfunction

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Postoperative hepatic dysfunction predictably evokes questions as to the possible etiologic role of the halogenated volatile anaesthetic which had been administered. The role of halothane and enflurane as hepatotoxins has been frequently alleged and often denied.¹⁻⁶ Perhaps it was predictable that any halogenated anaesthetic subsequently introduced would eventually receive similar status. Indeed, 45 reports of postoperative hepatic dysfunction in patients given an anaesthetic which included isoflurane, from 1981 through 1984, have been filed with the United States Food and Drug Administration (F.D.A.).

A sub-committee of four members of the F.D.A. Anaesthetic and Life-Support Advisory Committee evaluated the 45 adverse drug reports to determine if a causal relationship existed in these patients between isoflurane administration and the subsequently diagnosed hepatic dysfunction. The committee failed to confirm a reasonable likelihood of a cause and effect relationship between administration of isoflurane and development of postoperative hepatic dysfunction.⁷ Instead, factors such as hepatocyte hypoxia, circulatory shock, cholestasis, viral infections, sepsis, cholangitis, administration of known hepatotoxic nonanaesthetic drugs and preoperative liver disease were considered more likely causes of liver dysfunction than isoflurane in the majority of the 45 patients. In the few patients that isoflurane could not be excluded as a cause, the symptoms and characteristics of postoperative hepatic dysfunction were not different from those patients with hepatic dysfunction clearly due to causes other than the anaesthetic. Furthermore, each of these 45 patients had also received nitrous oxide, an anaesthetic agent more likely than isoflurane to cause liver damage in an hypoxic rat model.⁸

Why do halogenated anaesthetics continue to be incriminated as causes of postoperative liver dysfunction? I believe there are two explanations. First, all halogenated

anaesthetics are assumed by many physicians to be hepatotoxins, based on the known effects of chloroform. In the context of modern anaesthetic practice such a sweeping generalization is clearly not valid. At the same time, it is undeniable that halothane, administered to uniquely susceptible individuals may be a hepatotoxin. Nevertheless, the incidence of halothane hepatitis remains infrequent (probably less than one in every 10,000 administrations) and the proposed mechanism remains unsubstantiated.

The presumption is that other halogenated anaesthetics, including isoflurane and enflurane have the potential to produce similar toxicity as halothane. It is this erroneous assumption (proof by analogy) that is often cited to make the diagnosis of anaesthetic-induced hepatitis, especially in the absence of other obvious causes of hepatic injury. Clearly, differences in chemical structure, magnitude and pathways of metabolism and in impact on hepatic blood flow between halothane and other halogenated anaesthetics, plus failure to demonstrate a syndrome for these drugs similar to that considered typical for halothane hepatitis, speak against the assumption that all halogenated anaesthetics produce "halothane-like hepatotoxicity."

The second theoretical answer to the above question deals with failure to consider causes other than the anaesthetic for the development of postoperative hepatic dysfunction. Even if other causes are not evident, it is not scientifically acceptable, by a process of elimination, to indict the halogenated anaesthetic. The literature confirms the validity of this statement with descriptions of hepatitis first attributed to the anaesthetic until more intense evaluation discovered viral particles in hepatocytes examined under the microscope or the presence of previously unrecognized hepatotoxic drugs.^{4,5,7}

The incidence of postoperative non-A, non-B hepatitis is reportedly 3.3 per cent in patients undergoing surgical procedures not requiring blood transfusion.⁹ Furthermore, there seems to be an inherent incidence of "postoperative hepatitis" of about one in every 2200 to 2500 previously asymptomatic adult patients, even in the absence of anaesthesia and surgery.^{10,11} Considering this inherent incidence, the reported frequency of isoflurane

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hepatitis (45 reports during a period when an estimated 14 million anaesthetics were conducted with isoflurane) is less than the "background noise." Furthermore, animal evidence suggests that hepatocyte hypoxia with or without concomitant administration of an anaesthetic is the most likely cause of hepatic damage.¹² Anaesthetics, by virtue of their potential effects on hepatic blood flow and its distribution, hepatocyte utilization of oxygen, blood pressure and alveolar ventilation, might accentuate hepatocyte hypoxia but these changes would not necessarily represent unique hepatotoxic effects of a single drug. Therefore, the implicated anaesthetic may be an "innocent bystander" rather than an explanation.

Why is it so important to insist on convincing evidence before a causal relationship is accepted for drug-induced hepatic dysfunction? With respect to halogenated anaesthetics, especially isoflurane and enflurane, such an assertion may unnecessarily restrict the use of valuable and safe drugs. Secondly, acceptance of a causal relationship provides a reason to stop looking for other causes.²

The rarity of severe liver damage after anaesthesia with isoflurane makes a prospective randomized investigation of a possible relationship economically unfeasible. A more realistic approach is case collections of patients having unexplained postoperative hepatic dysfunction that is temporally related to administration of a drug. Existence of large numbers of such reports may suggest a relationship, particularly if the associated findings are consistent and unique (i.e., a syndrome exists). Nevertheless, no number of anecdotal case reports can prove a causal relationship between administration of an anaesthetic and hepatic injury in the absence of a control group. If the comparison drug was equally toxic there would not be an apparent difference between the drugs. Likewise, even if the anaesthetics were not hepatotoxins one cannot prove the absence of toxicity – you cannot disprove the existence of dragons.¹³

In conclusion, it seems highly unlikely that isoflurane is, even rarely, a selective and unique hepatotoxin. In the 45 cases reported to the Food and Drug Administration causes of hepatic dysfunction other than the anaesthetic were usually apparent and a typical syndrome as described for halothane was not present. The medical community and our patients will be best served by continued critical surveillance of isoflurane and other anaesthetic drugs for hepatotoxicity. Equally important will be avoidance of the diagnosis of anaesthetic-induced hepatic dysfunction that cannot be substantiated by extensive laboratory investigations and thorough analysis of the patient's medical history and perioperative course. Indeed, it is my conviction that more detailed investigation of many of the reported cases of alleged anaesthetic-induced hepatic

dysfunction would have discovered other causes and exonerated the anaesthetic.

Dysfonction hépatique post-opératoire et isoflurane

Lorsqu'administrés les anesthésiques volatiles halogénés soulèvent certainement des questions concernant leur rôle étiologique possible dans l'installation de la dysfonction hépatique postopératoire. Le rôle de l'halothane et de l'enflurane comme hépatotoxines a été fréquemment présumé et souvent réfuté.¹⁻⁶ Il serait peut-être prévisible que tous les agents anesthésiques halogénés introduits par la suite pourraient éventuellement considérer être aussi hépatotoxiques. Quarante-cinq cas de dysfonction hépatique postopératoire chez des patients ayant reçu de l'anesthésie incluant l'isoflurane entre 1981 à 1984 ont été rapportés aux Etats-Unis au "Food and Drug Administration" (F.D.A.).

Un sous-comité de quatre membres du F.D.A. "Anesthetic and Life Support Advisory Committee" a évalué les 45 cas rapportés afin de déterminer l'existence d'une relation causale chez ces patients entre l'administration de l'isoflurane et la dysfonction hépatique. Le comité ne pouvait prédire avec certitude une relation de cause à effet entre l'administration de l'isoflurane et l'installation de la dysfonction hépatique postopératoire.⁷ Par contre, dans la majorité des 45 patients des facteurs comme l'hypoxie hépatocytaire, l'état de choc, la cholestase, les infections virales, la septicémie, la cholangéite, l'administration de substances hépatotoxiques non anesthésiques et la présence de maladies hépatiques préopératoires étaient considérés comme étant des causes plus probables de dysfonction hépatique que l'isoflurane. Dans les quelques patients où l'isoflurane ne pouvait être exclus comme responsable des symptômes et caractéristiques de la dysfonction hépatique postopératoire, ceux-ci n'étaient pas différents de ceux des patients ayant une dysfonction hépatique nettement due à d'autres causes. De plus chacun de ces 45 patients a reçu aussi du protoxide d'azote, un agent anesthésique plus susceptible que l'isoflurane à provoquer des commages hépatiques chez le rat rendu hypoxique.⁸

Pour quoi les agents anesthésiques halogénés continuent-ils à être incriminés dans les causes de dysfonction hépatique postopératoire? Je pense qu'il y a deux explications