Occasional Review

Halothane anaesthesia and liver damage

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A recent experience of the senior author when addressing a meeting of anaesthetists prompted this review, since it was apparent that there was still considerable disagreement between hepatologists and anaesthetists over the association between liver cell damage and halothane anaesthesia and the measures by which the risk could be minimised. Although during the 1960s and 1970s the evidence was hotly debated, there has since been increasing acceptance, both clinical and experimental, of a strong *prima facie* case for an association.¹⁻¹¹ Two, probably distinct, forms of liver damage have been defined.¹² Serum aminotransferase activities are raised in up to a fifth of patients anaesthetised with halothane during the first and second postoperative weeks (type I). Such minor forms of liver injury are to be distinguished from the rare occurrence of massive liver cell necrosis (type II).

Three well controlled studies of minor reactions have been reported from Britain.^{5,6,8} Significant rises in serum aspartate aminotransferase (AST) activity during the postoperative period were found only in those patients receiving halothane,⁵ and these activities were significantly higher than in those receiving trichloroethylene.⁶ Abnormalities in liver function were not always apparent until the second postoperative week. Rises of serum aminotransferase activity were also greater in those receiving halothane than with enflurane,⁸ and obese women were more likely to develop abnormalities.

Most patients who have developed massive necrosis have had a previous and milder reaction to halothane. Nevertheless, the frequency of minor abnormalities (up to 20%) and the very low incidence of massive necrosis make it clear that minor reactions are not necessarily followed by more severe effects. There is no way of predicting which patients will follow this course.

We have seen now 48 patients with otherwise unexplained massive liver cell necrosis after halothane anaesthesia referred to the liver unit over the period January 1965 to December 1983. In each of the 48 patients other possible causes of liver damage were excluded, including exposure to hepatotoxic agents, sepsis, hypotension during surgery, and infection with hepatitis A and B, cytomegalovirus, and Epstein-Barr virus. In no case was there evidence of pre-existing liver disease.

Thirty one of the 48 patients were women, giving a female to male ratio of 1.8:1. Ages ranged from 21 to 76 years (median 57 years), contrasting appreciably with the much younger age distribution of patients with fulminant viral hepatitis (fig 1). In comparison with the age distribution of patients undergoing anaesthesia in England and Wales, as given in the Hospital In-patient Enquiry,¹³ the patients with halothane hepatotoxicity are in

a slightly older age group. Sixty eight per cent of the patients were obese and there was a history of allergy to other drugs in one third of them.

The interval between the last exposure to halothane and the onset of jaundice ranged from two to 26 days, with a median of five days, and in only three cases was the interval greater than 10 days.

FIG 1—Age distributions of patients admitted to liver failure unit with unexplained hepatic failure after halothane anaesthesia or hepatic failure from viral hepatitis, and general population undergoing anaesthesia.¹³

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In all cases hepatic encephalopathy had developed within 28 days of the exposure to halothane (median nine days).

Of the 48 patients, 45 (94%) were known to have been exposed to halothane on at least one previous occasion, 24 (50%) had had two or more previous exposures, and four (8.5%) had been exposed three or more times. Of those who had received halothane on more than one occasion, the penultimate exposure was within a period of four weeks in 27 patients and one to two months in six patients. In only three was the penultimate exposure more than one year previously (two, six, and seven years). The shorter the interval between the most recent two exposures the more rapid was the

transferase activities returned to normal. Liver biopsy specimens taken on two occasions when serum aminotransferase activities were raised showed features of acute hepatitis. For the past eight years this surgeon has avoided halothane exposure and has remained healthy, with normal liver function tests. In both patients specific "halothane antibody" was present.¹³ Occupational exposure to halothane is likely to result in the induction of hepatic enzymes,²⁰ and the effect of this on halothane biotransformation in susceptible individuals may be important. A positive challenge has been carried out in three patients but is not recommended because of the risk of inducing a more severe reaction.

FIG 2—Proposed metabolic pathways of halothane (from De Groot and Noll²⁴ and Sipes *et al*²⁵).

onset of the jaundice ($r=0.48$, $p=0.05$).

In over two thirds (33 patients (69%)) the surgery was relatively minor (defined as lasting less than 30 minutes), the majority of these being gynaecological intervention—usually dilatation and curettage—eye surgery, or wound dressing. Of the 15 patients undergoing major surgery, five had had a laparotomy, three a hysterectomy, and two biliary tract surgery. Postoperative fever for which no other specific cause could be identified was recorded in 36 (75%) patients. Serum autoantibodies (antiliver kidney microsomal, antismooth muscle, and antinuclear) were found during the course of the liver failure in 21 (44%) of the patients.

Thirty eight of the 48 patients died, in each instance after conscious levels had deteriorated to grade III or IV hepatic encephalopathy, and with a clinical course similar to that seen with other causes of fulminant hepatic failure.¹⁴ Five of the 10 patients who survived had less severe encephalopathy (grades I and II) and all ultimately made a complete recovery. The duration of illness in those who died was 11 to 73 days (median 23 days).

Liver damage after occupational exposure to halothane has been reported in surgeons, anaesthetists, and operating theatre personnel.¹⁵⁻¹⁹ We have described two surgeons who developed abnormalities of liver function, in one of whom rises in serum aminotransferase activities were noted on four occasions, each time related to halothane.¹³ With avoidance of exposure serum amino-

A severe, idiosyncratic reaction is characteristically found after multiple anaesthetics (up to 10 times more frequently than that after a single exposure), often for relatively minor surgery, and the shorter the interval between successive halothane exposures the more rapid the onset of liver damage. Serological abnormalities indicative of hypersensitivity include peripheral eosinophilia and serum autoantibodies (notably the liver-kidney microsomal antibody), as well as circulating immune complexes.^{7 11 14 21} Obese women appear to be particularly susceptible, and some series have shown a significant frequency of eczema and drug allergy.^{7 10 11} The availability of specific serological tests for detection of hepatitis A and B has allowed these other causes of fulminant hepatic failure to be excluded with greater certainty. In addition, we have recently described a specific serum antibody which reacts with halothane altered liver cell determinants,²² thus providing a positive means of identification.^{22a}

Mechanisms of hepatotoxicity

The idiosyncratic reaction to halothane may be due to (a) enhanced metabolism of the drug through a minor pathway with the development of reactive metabolites, or (b) an immune response to "new" antigens.

METABOLIC ACTIVATION

Halothane undergoes metabolism through several pathways (fig 2).²³⁻²⁵ Oxidative metabolism is preferentially stimulated by high oxygen tensions and by pretreatment with the enzyme inducer β -naphthoflavone; reductive metabolism, in contrast, is preferentially stimulated by hypoxic conditions and by pretreatment with phenobarbitone. Both lead to the release of bromide, but only reductive metabolism causes that of fluoride. The metabolism of halothane through either pathway generates reactive intermediates which bind to cellular macromolecules such as proteins and lipids and cause lipid peroxidation, or inactivation of cytochrome P450 and other enzymes.

The importance of metabolic activation in producing altered liver cell membranes that are antigenic was shown by studies in rabbits, in which it was found that oxidative metabolism of halothane was necessary for the appearance of the antigen.²⁶ The latter may arise from metabolites reacting with cellular macromolecules, for such covalent binding might alter the quaternary structure of proteins or lipids, and thus render them immunogenic. Since proteins of cell surface membranes are synthesised on the endoplasmic reticulum, any interaction at this site might result in the immunogen being translocated to the cell surface through normal biosynthetic routes.²⁷

ANIMAL MODELS

Three animal models of halothane hepatotoxicity have been developed, in each of which massive necrosis was produced. Although in man similar mechanisms may underlie the development of minor hepatic damage, an exact model of the severe idiosyncratic reaction has not been developed.

Phenobarbitone-hypoxic model

Pretreatment of certain strains of male rats with phenobarbitone and exposure to halothane under hypoxic conditions results in necrosis of the liver cells within 24 hours.^{28,29} Since both hypoxia and phenobarbitone pretreatment are required, and since the degree of damage correlates with the amount of inorganic fluoride released, this type of liver damage is thought to be mediated through reductive metabolism. It has been suggested, however, that it is the hypoxia, possibly enhanced by fasting,^{30,31} rather than the halothane which is responsible.

The relevance of these findings to human disease must be questioned. In man liver cell damage rarely occurs after one exposure to halothane and multiple exposures greatly increase the risk. It is unlikely that this increased risk is related to an enzyme inducing effect of halothane³²; the interval between exposures may be more than a month, and patients taking enzyme inducing drugs—for example, epileptics—do not have a greater risk of halothane induced liver damage.³³ Moreover, if hypoxia occurs during halothane anaesthesia liver failure is only rarely observed.³⁴

Triiodothyronine model

Male rats pretreated with triiodothyronine and then exposed to halothane develop hepatic necrosis.³⁵ This differs from the phenobarbitone model in that hypoxia is not a prerequisite for liver damage and the reductive pathway is not implicated.³⁶ It has been suggested, however, that liver cell necrosis is mainly due to hypoxic damage as a result of induced hypermetabolism of centrilobular cells and anaesthetic depression of splanchnic blood flow.³⁷

Polychlorinated biphenyl model

Rats pretreated with the broad spectrum inducing agent polychlorinated biphenyl and then exposed to halothane also

develop hepatic necrosis.³⁸ This may be analogous to the triiodothyronine model but the liver cell necrosis can be prevented.³⁹ The possible role of polychlorinated biphenyl induction in man is highlighted by the report of a woman occupationally exposed to polychlorinated biphenyl who developed liver cell damage after halothane anaesthesia.⁴⁰

IMMUNOLOGICAL SENSITISATION

Initial attempts to demonstrate sensitisation to halothane or a metabolite, with either lymphocyte transformation or leucocyte migration inhibition, produced conflicting results.⁴¹⁻⁴⁵ Halothane is a small molecule and therefore unlikely to be antigenic, but it might act as a hapten. Liver homogenate from a rabbit killed 18 hours after exposure to halothane, thus allowing generation of the antigen *in vivo*, was used as a source of antigen for leucocyte migration inhibition to avoid previous problems with selection of the appropriate antigen.⁴⁶ Sensitisation was shown in eight of 12 patients, and isolated lymphocytes from three of four patients were directly sensitised to a halothane related antigen present on the membrane of isolated hepatocytes.⁴⁷

We showed sensitisation to halothane altered liver cell membranes in eight of 16 consecutive patients admitted during 1979 and 1980 with fulminant hepatic failure after halothane anaesthesia.⁴⁸ IgM class antibodies to the hepatitis A virus were present in four of the patients with negative test results, only one of whom had been exposed to halothane on more than one occasion. (All those with the halothane antibody had been exposed two or more times.) Halothane anaesthesia may exacerbate a pre-existing, but mild, hepatitis A infection. One of the other four patients had received seven units of blood at the first operation, raising the possibility of a non-A, non-B viral hepatitis; another was receiving rifampicin and isoniazid, whose toxicity may have been potentiated by halothane.⁴⁹ The clinical and biochemical features of patients with and without sensitisation to halothane altered cell determinants are no different, so that our failure to show sensitisation may be due to absorption of antibody by hepatocytes, or to its presence as immune complexes.⁵¹ The time at which samples are obtained is also important: antibodies cease to be detectable in the serum as the clinical condition deteriorates.

Specific antibodies reacting with halothane altered liver cell membranes have been shown by indirect immunofluorescence and induced cytotoxicity techniques²² and confirmed by an enzyme linked immunosorbent assay. A subpopulation of normal lymphocytes (K cells) is used to bind to and lyse antibody coated target cells. Antibody specificity is such that it cannot be shown in patients with liver damage from other causes, patients exposed to multiple halothane anaesthetics without liver damage, or anaesthetists with normal liver function. The antibody persists for at least six months in those patients who survive fulminant hepatic failure (Neuberger, unpublished data). Its development is unlikely to be a secondary response to liver cell damage, as selective second antibodies in the indirect immunofluorescence assay showed the presence of IgM antibodies (which would be expected with a primary immune response) in only two patients. Furthermore, the antibody has not been shown in those patients who, after being given halothane, developed necrosis from other causes, such as sepsis, hypotension, or carcinomatous infiltration of the liver.

Even though the antibody may induce K cell mediated cytotoxicity *in vitro*, the importance of this reaction in the pathogenesis of liver damage *in vivo* has to be determined⁵⁰; how halothane exposure results in the generation of a new antigen has not been established. Anaesthetic agents alter the character of liver cell membranes,⁵¹ but it is unlikely that the appearance of the antigen is due to a direct effect on the membrane. The antigen is not present on the membrane immediately after the animal has been exposed to halothane (Neuberger, unpublished data), and metabolic activation is more likely to be concerned in its generation.

Other halogenated hydrocarbon anaesthetics

Methoxyflurane was introduced into clinical practice in the 1960s in the United States and in the next decade in the United Kingdom; enflurane appeared on the British market in 1973 and isoflurane in 1984. According to a recent review from the United States,⁵² methoxyflurane has been implicated in 25 cases of hepatotoxicity during 14 years of clinical use and enflurane in 25 cases. Over 10 years enflurane has been given to more than 20 million people, and the validity of some of the reported cases of hepatotoxicity has been questioned.⁵³ Isoflurane has yet to be definitely implicated.

The clinical picture is similar to that seen with halothane hepatotoxicity. There is a higher incidence in those exposed previously, and the onset of jaundice occurs sooner after multiple exposures than after a single exposure. A similar proportion of patients have allergy (15-21%), unexplained fever (50-79%), and eosinophilia (20-50%). A rash occurs in 5-12%. Mortality from enflurane hepatotoxicity is 21% compared with 58% for methoxyflurane and about 50% for halothane.⁵⁴ It may be relevant that, like halothane, methoxyflurane undergoes considerable biotransformation in man in contrast to the minimal change of enflurane and the almost nil change of isoflurane. There are, however, cases of cross reactivity between halothane and enflurane and isoflurane.^{39 40 56}

It is difficult to obtain accurate figures on the overall use of halogenated hydrocarbons in Britain. Figures from Abbott Laboratories suggest that halothane is used in about 72% of procedures and enflurane in about 25%. Methoxyflurane is used less frequently and is likely to be withdrawn from the market shortly. The newer agents are considerably more expensive: enflurane costs £29 and isoflurane £72 per 250 ml compared with £7.50 for halothane.

Conclusions

There may have been a decline in the number of adverse hepatic reactions and deaths from halothane induced liver injury. Between 1967 and 1977 there were 289 reports to the Committee on Safety of Medicines (personal communication), with 134 deaths, whereas between 1978 and 1982 the numbers were 52 and 19 respectively. Such figures are affected by the interest of the medical community (and acceptance of the association between the two) at any one time, and we would question from our own experience whether there has been such a sharp drop. Halothane may cause both minor and occasionally massive hepatocellular injury. The major risk factor for the latter is repeated exposure to the agent. In 1978 Inman and Mushin,¹⁰ after an analysis of all reported cases in England, recommended that halothane anaesthesia should not be repeated within a short period, and the advice is incorporated in the data sheets. In spite of this just over half the patients seen by us since then have been exposed to halothane twice within four weeks. Some 60% of patients in whom adequate data were available had had a documented adverse reaction to halothane previously, and care should be taken in examining case records, as information from the patient may be misleading.

Two groups of patients need special consideration before halothane is used. Firstly, those who are likely to require multiple anaesthetics within a short period should not be given halothane more than once; other anaesthetic agents should be considered for subsequent operations. Secondly, those who may be at greater risk because of factors such as female sex, obesity, and a history of allergy should be carefully assessed, especially if more than one exposure is likely. If a patient develops unexplained abnormalities of liver function after halothane the information should be stamped on the front of the case records and the patient informed. Both actions may ensure that the anaesthetist can be properly alerted if further anaesthesia becomes necessary.

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