HALOTHANE IN BRITAIN TODAY

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In Britain today—and probably in the rest of the world, halothane is the most commonly administered volatile anaesthetic agent. This popularity is justified in the light of the many advantages of halothane over other agents. Its few deficiencies have been extensively studied and complications associated with the use of halothane are, in the main, readily explained and usually avoidable. Nevertheless, controversy as to whether a cause and effect relationship exists between halothane and postoperative liver damage is international. In this paper we review the present position of this vexed subject, with particular reference to views expressed in Britain, under two headings. Firstly, does halothane itself cause postoperative liver dysfunction, or is liver damage related non-specifically to anaesthesia and surgery? Secondly, if halothane does damage the liver, what is the mechanism?

DOES HALOTHANE ITSELF CAUSE POSTOPERATIVE LIVER DYSFUNCTION, OR IS LIVER DAMAGE RELATED NON-SPECIFICALLY TO ANAESTHESIA AND SURGERY?

In the literature over the past decade there has been an increasing acceptance of 'halothane hepatitis' as an entity. Study of this material, however, has made us increasingly uncomfortable about the validity of much of the evidence put forward (Simpson, Strunin and Walton, 1971).

If postoperative jaundice is taken as an index of liver damage it is perhaps pertinent that the incidence increased by a factor of four—regardless of the anaesthetic agent used—during the decade in which halothane was introduced (Henderson and Gordon, 1964). Today when halothane is used and jaundice occurs there is an unfortunate tendency to accept a cause and effect relationship and to investigate no further. This is regrettable as the need now is for more accurate and detailed information about cases of liver dysfunction occurring after surgical procedures, so that the extent of the problem as a whole may be determined and attempts made to elucidate its mechanism.

Much of the present information is derived either from individual case reports or retrospective surveys. It should be remembered that many authors are faced with the difficulty that their data may be at best secondhand and often incomplete. In addition they may not be fully familiar with the clinical conditions pertaining during anaesthesia and surgery.

During the past year a study has been undertaken of postoperative patients in both Oxford and Southampton (Smith, 1972, personal communication) in an attempt to assess any hepatotoxic effects of repeated halothane anaesthesia. This study has been designed as a prospective controlled trial. Patients have been included if they were adults who required a second anaesthetic within a year of a previous halothane anaesthetic, but were excluded from the study if they were thought to have had any previous adverse reaction to halothane.

The trial is designed with the patients divided randomly into two groups: those who on the second occasion receive halothane and a control group who on the second occasion are anaesthetized with any agent other than halothane or methoxyflurane. Patients in the control group are anaesthetized using special halothane-free anaesthetic machines. A system of restricted randomization has been adopted to allocate patients to the halothane or control group in each operating theatre in groups of ten.

Each patient has blood taken immediately pre- and postoperatively and with their co-operation on three or four further occasions spread over the next 10–14 days. On each visit they are asked to volunteer any symptoms and are then asked specifically if they have taken any drugs. On the blood taken at each visit, routine eosinophil counts and serum transaminase levels are measured. If these are abnormal, further liver function tests and immunological studies are undertaken. It is hoped that useful data will be forthcoming from this well designed study.

In an attempt to bridge the gap between retrospective and prospective studies we are presently

part of a group (Strunin and Simpson, 1972) engaged in a nationwide survey (London Hospital Study) of postoperative jaundice as it occurs. Late in 1970 we circulated all consultant anaesthetists in the British Isles and the major centres dealing with acute hepatic failure, asking them to notify us of any cases of jaundice occurring in their practice within three weeks of anaesthesia and surgery. All cases are seen personally, and an exhaustive history is obtained from hospital staff, the patient, his relatives, general practitioner and dentist. In addition, samples of blood are collected and subjected to a variety of immunological, metabolic and viral tests. Analysis of the first 90 cases in our study reveals that in some instances the cause is clear, e.g., stones in the common bile duct or massive haemolysis. It is of particular concern, however, that in a number of patients, some following minor surgical procedures, the aetiology of their postoperative jaundice is unexplained. Our study confirms that the incidence of jaundice and death is increased after multiple anaesthetics within one month. However these increases are seen after all anaesthetic agents and regardless of whether the cause of the jaundice is clear or unexplained (Walton, Strunin and Simpson, 1972).

In 1971 Mushin, Rosen and Jones reported that multiple anaesthesia with halothane within one month appeared to increase the risk of postoperative jaundice and death. However, the assumption was made that all of the cases studied—54 patients reported to the Committee on Safety of Drugs and 74 reported in the world literature—were due to an allergic reaction to halothane and no other aetiology was considered. Even so, this survey was of importance in drawing attention to the risk, in a small percentage of patients, of operations repeated within a short interval of time.

One aspect of the National Halothane Study (1966) which has perhaps not received its due publicity is the relationship between mortality and multiple operations. The crude overall death rates even for minor operations rose by a factor of four if there had been a recent previous minor operation. Similar relationships were demonstrated for operations of moderate and severe nature. In the low death rate group, i.e., the minor operations, the crude overall postoperative death rate was 18 in 10,000 where no previous anaesthetic had been given. This rose to 71 in 10,000 in patients who received two halothane anaesthetics and to slightly more—84 in 10,000 when halothane was not used for the second anaesthetic. It should be stressed that in these cases death was in no way attributed to the anaesthetic agent used.

In the report these findings did not receive much emphasis. For example the time interval between anaesthetics is not clear. Nevertheless a fourfold increase in mortality in patients undergoing minor surgical procedures—regardless of the anaesthetic agent used—associated apparently with multiple anaesthesia was disturbing and deserves further investigation.

The arguments presented by Sherlock (1971) for a cause and effect relationship between halothane and hepatitis are not convincing (Simpson, Strunin and Walton, 1971). This author however includes the statement that “unexplained postoperative fever is one of the most constant features indicative of liver damage related to halothane”. Furthermore Sharpstone, Medley and Williams (1971) in their paper “Halothane hepatitis—a preventable disease?” felt that the condition could have been avoided in ten patients out of eleven with acute hepatitis following multiple anaesthetics with halothane. “Unexplained fever occurred in nine patients; two of these and one other had had previous episodes of jaundice after halothane anaesthesia.” The report of the United States National Halothane Study also concluded that “unexplained fever and jaundice in a specific patient might reasonably be considered a contraindication to its subsequent use”. Nevertheless it must be pointed out that at least 60 per cent of postoperative patients develop fever (Klion, Schaffner and Popper, 1969; Carney and Van Dyke, 1972). Furthermore Trey and his colleagues (1968) showed that postoperative fever is as common after the use of other anaesthetic agents as it is after halothane. Dykes (1971) confirmed this finding and also described a variety of patterns of postoperative pyrexia—more than half of which were unexplained—regardless of the anaesthetic agent used. From our own study it can be seen that temperature changes following initial exposure to halothane in patients who became jaundiced following a subsequent halothane anaesthetic is without pattern (table I). Similarly it can be seen from our interim data that the opportunity to study the pattern of postoperative jaundice on a national basis reveals that the effects on the liver of re-exposure to halothane are not as predictable as has been supposed (table II).

We conclude therefore that at the present time there is no clear evidence to implicate halothane...
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TABLE I. London Hospital postoperative jaundice study; pattern of pyrexia following penultimate anaesthesia.

<table>
<thead>
<tr>
<th>Patients with multiple halothane exposures</th>
<th>Cause of jaundice</th>
<th>&quot;Normal&quot; post-op pyrexia</th>
<th>Pyrexia cause apparent</th>
<th>Pyrexia cause unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clear</td>
<td>16</td>
<td>5</td>
<td>8</td>
<td>10</td>
</tr>
<tr>
<td>Unexplained (39)</td>
<td></td>
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</tbody>
</table>

TABLE II. London Hospital Study: patterns of response to multiple anaesthesia.

<table>
<thead>
<tr>
<th>Patients</th>
<th>Halothane: liver dysfunction</th>
<th>Halothane: no liver dysfunction</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 Patients</td>
<td>Halothane: liver dysfunction</td>
<td>Halothane: no liver dysfunction</td>
</tr>
<tr>
<td>2 Patients</td>
<td>Non-halothane: liver dysfunction</td>
<td>Non-halothane: liver dysfunction</td>
</tr>
<tr>
<td>2 Patients</td>
<td>Non-halothane: liver dysfunction</td>
<td>Non-halothane: liver dysfunction</td>
</tr>
<tr>
<td>1 Patient</td>
<td>Halothane × 2: liver dysfunction</td>
<td>Halothane: no liver dysfunction</td>
</tr>
<tr>
<td></td>
<td>Halothane: liver dysfunction</td>
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</tbody>
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specifically in the aetiology of postoperative liver dysfunction. In addition, the occurrence of unexplained fever or jaundice after halothane anaesthesia seems of little prognostic value in the outcome of a subsequent exposure. Nevertheless the evidence does suggest that, regardless of anaesthetic agent involved, repeated — particularly short interval — anaesthesia may carry an increased risk of postoperative liver dysfunction and death.

IF HALOTHANE DOES DAMAGE THE LIVER, WHAT IS THE MECHANISM?

If halothane is directly concerned in causing liver damage at least four possible mechanisms must be considered: a direct toxic effect; some relationship to the metabolism of halothane; hypersensitivity; or a relation to viral hepatitis. Many aspects of these four possibilities have already been reviewed in detail (Simpson, Strunin and Walton, 1971; Carney and Van Dyke, 1972). What follows here is intended to bring these reviews up to date.

Metabolism of halothane.

It has been suggested that, as halothane itself is chemically inert, metabolites produced as a result of anaesthesia may be responsible for organ specific damage (Brown and Vandam, 1971; Cohen, 1971). Under normal circumstances about 10–20 per cent of inhaled halothane is metabolized to bromide, chloride and trifluoroacetic acid (TFA) and trifluoroacetyl ethanolamide (TFAET) as non-volatile salts. Of these TFA is the major metabolite and is detectable in the urine for many days after anaesthesia (Cascorbi et al., 1971; Blake, Barry and Cascorbi, 1972). The toxicity of TFA and TFAET in man has not been studied. In rats and mice the intraperitoneal LD₉₀ dose is in excess of 2,000 mg/Kg and when death occurs the liver is not primarily involved. The pattern of metabolism of halothane is constant in six animal species; rat, mouse, guinea pig, cat, dog and marmoset as well as in man. Cohen and Trudell (1972) recently described unidentified "macrometabolites" in the liver of the squirrel monkey, and argued that these could not be TFA or trifluoroethanol (TFE—a possible alternative metabolite of halothane) as they were still present after heating to 80°C; the boiling points of TFA and TFE are around 74°C. It now seems clear however that at a pH of around 7, i.e., that in the liver, TFA would be present as a non-volatile acid salt (Winrow, 1972); appropriate extraction and recovery procedures have shown that the "macrometabolites" are in fact salts of TFA and TFAET. Present evidence suggests, therefore, that in man and many other species normal metabolism of halothane does not give rise to any potentially toxic substances.

It has been suggested on theoretical grounds that trifluoroethanol (TFE) and trifluoroacetaldehyde (TFALH) could be metabolites of halothane. However, these substances have not been detected in man (Blake, Barry and Cascorbi, 1972) nor any animal species yet studied. Toxicological studies of these substances in rodents have shown fat accumulation in the liver, but no liver cell necrosis (Airaksinen, Rosenberg and Tammisto, 1970; Rosenberg and Wahlström, 1971).

The question now arises as to whether other factors may influence "normal" metabolism of halothane with detrimental effects. It has been postulated that induction of the microsomal drug metabolizing enzymes in the liver increases the amount of halothane metabolized, and that "over
production” of metabolites may lead therefore to hepatic damage. The evidence available from animal studies is conflicting. Clauberg (1970) and Davis and his colleagues (1971) could demonstrate no difference in rats exposed to halothane before or after enzyme induction. In contrast, Stenger and Johnson (1972) claimed that halothane produced multifocal hepatic parenchymal necrosis and evidence of impairment of hepatic microsomal drug metabolizing enzyme systems in rats pretreated with phenobarbitone. As these authors administered the halothane by intraperitoneal injection, perhaps an inappropriate experimental model, it is difficult to compare their results with other work.

Cascorbi, Blake and Helrich (1970) found that anaesthetists tended to excrete more halothane metabolites in their urine than pharmacists, suggesting that halothane may stimulate its own metabolism. Their more recent work however (Cascorbi, Blake and Helrich, 1972) shows that there is considerable variation between individuals, and the evidence that halothane induces its own metabolism is not convincing. Carney and Van Dyke (1972) have suggested that anaesthetists, if they require an anaesthetic, should be given halothane as they are “least likely to develop hepatitis since they have been enzymatically induced and therefore are best able to metabolize the halothane administered to them”. Furthermore, Carney and Van Dyke postulate that when multiple halothane anaesthetics are given close together, intermediate metabolites may be formed which the liver is unable to cope with, and these accumulate and may reach toxic levels or be available to form protein or other complexes. The patient who has undergone enzyme induction, however, will have an increase in the amount of drug metabolizing enzymes available and will be better able to deal with an increase in intermediary metabolism. It is difficult at the present time to fit this theoretical concept to the known facts on halothane metabolism, since as yet none of the postulated intermediate metabolites have been detected in man or experimental animals.

**Hypersensitivity.**

There are two general ways by which immunological sensitization to an anaesthetic agent might be expected to develop. First, the agent itself may be immunogenic in its own right; and, second, the agent or a metabolite may act as a hapten and acquire immunogenic status by association with host macromolecules. The small size of the halothane molecule (CF₃—CHBrCl) renders it unlikely that free halothane acts as a true immunogen. In addition halothane is inert and there is no evidence to suggest that halothane or an intermediate metabolite combine covalently with protein or other large molecules. The possibility does exist however that non-covalent (e.g., hydrophobic) association with “Schlepper” host protein (e.g., albumin, liver cell protein) or lipoprotein (e.g., β-lipoproteins or structural constituents of intra-cellular membranes) could form the molecular mechanism by which halothane or a metabolite might achieve immunogenic status in some individuals.

The lymphocyte transformation test is an accepted method of demonstrating cell mediated hypersensitivity responses. Paronetto and Popper (1970) used this test to study fifteen patients with alleged “halothane hepatitis” and concluded that the test was positive in 10 patients. However their methodology has been questioned (Bruce and Raymon, 1972) and in cases arising out of The London Hospital Survey of postoperative jaundice we have been unable to confirm their findings (Walton et al., 1972). Our subjects comprised 10 patients and 5 physicians whose jaundice following exposure to halothane was unexplained and whose overall case records indicated a high index of suspicion that halothane might be incriminated. All, except one subject, had been exposed to halothane on more than one occasion. The study consisted of two parts. First, a series of control tests undertaken on lymphocytes from 11 normal subjects, and second, tests on lymphocytes from our subjects. The cells were exposed to known concentrations of halothane, methoxyflurane, trichloroethylene, diethyl ether and a non-specific stimulant of lymphocyte transformation—the plant mitogen phytohaemoglutinin. The results showed that there was no significant difference between the control group and the subjects, and none showed a positive transformation test as defined by Paronetto and Popper (1970). No other work has as yet been published on this type of testing for an immune response to halothane. The small amount of data that is available does not clearly support the concept that halothane or a metabolite can cause a hypersensitivity reaction. Nevertheless there is increasing evidence that anaesthesia and surgery are associated with profound changes in the body immune responses (Bruce and Wingard, 1971; Park et al., 1971). It may be that halothane is more active in this respect than other anaesthetic agents?
Viral hepatitis.

The incidence of viral hepatitis remains unknown, but there is a general impression that it is increasing and perhaps affecting an older age group.

The gel-diffusion test for hepatitis associated antigen (HAA-Australia antigen), which is found in serum hepatitis (virus B), has a low sensitivity (Blumberg et al., 1970). The recently developed radioimmunoassay test for HAA has proved much more sensitive and has enabled antibodies to HAA to be detected. On the basis of this test Lander, Alter, and Purcell (1971) concluded that hepatitis with a positive HAA is endemic in the U.S.A. and is transmitted by parenteral and non-parenteral routes. In Britain it is likely that the same situation applies (Zuckerman, 1972). In addition, it should be remembered that no satisfactory test exists at present for infective hepatitis (virus A) or other viruses causing hepatitis.

In The London Hospital Study only one patient was HAA positive by the gel-diffusion technique. Repetition of tests for HAA using the radioimmunoassay technique revealed that 12 patients were positive. Nine of these had been categorized as having no adequate explanation for their postoperative jaundice, for which therefore halothane was considered as a possible cause.

The present situation would seem to be that patients, who are undetected carriers of either HAA or antibodies to it and almost certainly other viruses as well, are undergoing anaesthesia and surgery; as there is evidence that immune responses are altered in these circumstances it is unwise to rule out the possibility of viral hepatitis in any patient who develops postoperative liver dysfunction.

DISCUSSION

There is no clear evidence at the present time to support the concept of a cause and effect relationship between halothane and postoperative liver dysfunction following either single or multiple exposures. Equally, it is not possible to make a firm and categorical statement to the effect that halothane, as with other anaesthetic agents, is never primarily involved when postoperative liver dysfunction occurs. There are those (Williams, 1971) who say that absolute proof will never be forthcoming and that the entity of halothane hepatitis must be accepted on "clinical" merit alone. It is of interest that these opinions are in general expressed by physicians rather than surgeons or anaesthetists; perhaps their impressions are derived from a close association with the limited admissions to highly specialized "Liver Units". The situation has arisen therefore that the anaesthetist is being subjected to increasing social and medicolegal pressures on his use of halothane. Indeed this topic has been the subject of a commercial film and medicolegal action has already been taken against anaesthetists in North America (Vasquez v. Gatehouse, 1972; Ganczewski v. Smith, 1972).

The practising anaesthetist is faced, therefore, with the difficult question of which anaesthetic agent should be used in a patient who has had pyrexia of unknown origin, or liver damage, following a previous operation with halothane anaesthesia? Unfortunately eliciting such a history of pyrexia, or liver damage, or eosinophilia, or changes in serum enzymes, or the presence of antimitochondrial antibodies after a previous anaesthetic, does not appear to be of significant value in predicting the outcome of a second anaesthetic—either with or without halothane (Simpson, Strunin and Walton, 1971). In those patients thought to be at hazard however, it would seem logical that if the proposed second operation is one of election, consideration should be given to the possibility of delaying the procedure in order to increase the interval between periods of exposure to non-specific stress. What this time interval should be is unknown, but three months would seem reasonable on the present evidence. If the operation cannot be postponed, or if it is one of emergency, then no logical reason can be presented against the use of halothane. On the other hand, one cannot say that if further halothane, or any other agent, is used in these circumstances that postoperative liver damage will not occur. Furthermore, if such damage does occur, it will be impossible to say that the anaesthetic agent was or was not the cause. The dilemma therefore remains and no clear answer can be given to the question on choice of anaesthesia. It would seem at present that the decision should rest with the individual anaesthetist concerned and be made in the best overall interest of each particular patient as this problem arises.

REFERENCES

col. toxicol., 28, 299.


