Review Article

Halothane and liver damage

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Introduction

Halothane was first synthesized by Suckling in 1952 and introduced into clinical practice a few years later.^{1,2} Its many advantages, such as quick action, easy administration, non-explosiveness, high potency and low cost, led to its widespread use within a short time.

Although initial animal work did not indicate any hepatotoxic effect,^{3–5} the first cases of unexplained hepatitis after exposure to halothane were reported only two years after its introduction into clinical use.^{6,7} During the following years an increasing number of reports dealt with the association between halothane exposure and liver damage.^{8–16} Despite the accumulation of clinical evidence, there was still considerable disagreement regarding this association. The controversy was based on whether post-anaesthetic hepatic dysfunction could be attributed only to halothane or also to other anaesthetic agents. Early clinical research also failed to show a significant rise in the frequency of liver damage following exposure to halothane, compared with other anaesthetic agents in use.^{11,17–24} The difficulty in proving an association results from the rarity of the phenomenon on the one hand, the widespread use of the agent on the other and the many other reasons for fever and jaundice following surgery.²⁵ Only during the 1960s and since have sufficient data accumulated to prove the existence of 'halothane hepatitis'.^{22,26–29}

Frequency

Two forms of hepatic damage following halothane anaesthesia have been described.³⁰ The more frequent one is asymptomatic and expressed by abnormal laboratory values only, such as a rise in hepatic transaminase levels and other liver enzymes. The incidence of this asymptomatic liver dysfunction is not known.³¹ Some reports indicate an incidence of up to 20% of all patients undergoing halothane anaesthesia,^{25,28,32–35} much higher than enzyme changes

observed in control groups. Minor reversible changes in liver function are common after surgery regardless of the anaesthetic agent used,³⁶ though in the case of other agents, the changes noted are of a much lower magnitude than with halothane. The other form of liver damage after halothane is severe acute hepatitis, with histological findings of massive hepatic necrosis. This form is sporadic and its frequency varies from 1:6000 to 1:3500^{12,31,36–40} with a mean frequency around 1:10000. Strunin³⁶ suggested a pyramidal morbidity model, in which many patients with mild hepatic dysfunction constitute the base, and those presenting severe liver disease are located at the apex of the pyramid.

Risk factors

Repeated exposure

Many reports indicate an association between repeated exposures to halothane within short intervals, and a rise in the rate of hepatic morbidity, mild or severe.^{6,22,28,34,40–43} Seventy seven to 95% of the cases occur after repeated exposures;^{22,27,30,34,38} most often (55–80%) repeat exposure took place within a month or less after the previous one.^{22,24,27,30,33,38,40,44} Since the rate of repeated exposure in uncomplicated halothane anaesthesia is only 7–9%,⁴⁰ the element of repeated exposure within a brief period is significant. Moreover, liver disease after a single exposure is rare. There is a direct relationship between the number of repeated exposures and the severity of hepatic dysfunction and it has also been found that an inverse relationship exists between the number of previous exposures and the duration of the latent period.^{16,22,30,37,38} It is also well known that most of the patients who developed massive hepatic necrosis had had a milder reaction when previously exposed to halothane.^{16,30} However, patients who have suffered liver dysfunction following the drug do not necessarily develop a further episode when re-exposed,^{22,45} and there is still no way to predict which patient will develop a recurrent reaction.³⁰

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Sex

Halothane hepatitis is more frequent among females, the male/female ratio being 1:2^{22,30,34} although it seems that males have a worse prognosis.^{22,34} Apparently, sex hormones play a role in the ability to reduce or increase the metabolism rate of halothane, and thereby influence the accumulation rate of toxic metabolites, as was shown in laboratory animals.⁴⁶

Age

The condition is extremely rare in children and is most frequent in middle age.^{22,30} According to one series, 68% of the patients were in the age group of 41–70 years.²² The mean age for morbidity is 56.5–57.^{27,30,34} The rarity of this condition in childhood results most probably from the absence of the immunological and/or metabolic mechanisms necessary for halothane to induce liver damage⁴⁷ and from the fact that less surgery (and probably less repeated surgery) is done in children. Only two cases of liver damage following halothane anaesthesia have been described among patients under 20 years, and even in those, the diagnosis was doubtful.²²

Obesity

The liver complication is most frequent in the obese.^{22,34,44} In one series, two thirds of patients with liver dysfunction following halothane exposure were fat.³⁰ This phenomenon can be explained by the ability of the adipose tissue to act as a reservoir for halothane, which delays its release into the circulation and prolongs its presence in the body.³¹ It may also be conjectured that obesity exposes to intra-operative hypoxia which was demonstrated to be a risk factor in laboratory animals.^{44,48–51}

A history of atopic diseases or allergy to other drugs

There is a link between known history of hypersensitivity and morbidity, as was indicated in some reports.^{22,27,34} In one series, a third of the patients had history of drug allergy.³⁰

HLA and genetic predisposition

Some studies show a tendency for certain races⁵² or families³¹ to develop liver dysfunction following halothane exposure. Perhaps genetic factors predispose to this sensitivity by an immunological and/or metabolic mechanism.^{35,52} There is evidence that specific HLA types are more prone to develop liver dysfunction with halothane.⁵³

No correlation has been shown between the morbidity rate and the type, duration or location of the

operation.^{25,30} Moreover, the condition may arise even after minor and non-abdominal surgery. It was found that 69% of the patients underwent a relatively minor operation of less than 30 minutes duration (most of them gynaecological procedures, eye surgery or wound debridement), and only 32% underwent a major procedure (4% of the patients underwent biliary operations).³⁰ The presence of previous biliary or compensated liver disease has not increased the risk,²⁵ but one must keep in mind the fact that any type of anaesthesia may affect liver function adversely in a patient suffering from active liver disease.⁵⁴

Other factors such as hypoxia, hypotension, impairment of hepatic blood flow during the operation, hypothyroidism, starvation, alcoholism, and enzyme inducers, do not increase morbidity rate, although exposure to one of these factors or a combination of them has been shown to be significant in laboratory animals.^{36,44,48,49,55–57}

Pathogenesis

Two different mechanisms have been proposed to explain the liver damage following halothane exposure in man.

The metabolic mechanism; (bio-transformation)

About 20% of halothane undergoes metabolism either in an oxidative or non-oxidative ('reductive') pathway, producing a number of intermediate products, especially chlorides, bromides, and trifluoro-acetic acid (TFAA).^{58–62} As in the case of other hepatotoxins, halothane is metabolized by cytochrome P450 and other liver enzymes.^{63,64} It has been postulated that the intermediate products generated in the non-oxidative pathway, especially under hypoxic conditions, play a major role in the hepatotoxicity^{44,48,49,55} probably due to their tendency to bind to the fatty and protein macromolecules in the microsomal fractions of the hepatocytes. Other intermediate products, such as free radicals, may also be implicated by a direct mechanism.⁶⁵ However, it should be emphasized that all the theories related to this metabolic mechanism arise from experiments in laboratory animals and are of doubtful applicability to human beings.^{59,66}

The immunological mechanism

Evidence that liver damage following halothane exposure is activated by a hypersensitivity mechanism to halothane or its metabolites, is supported by the following findings:

(a) The disease is extremely rare after a single exposure and the latent period, the severity and frequency of appearance are directly related to the

number of previous exposures, the explanation being idiosyncrasy which is not dose related.^{16,22,30,37,38} The fact that the event can occur, though very rarely, after a single exposure, can be explained on the basis of non-specific hyper-sensitivity.

(b) Many patients with massive hepatic necrosis following repeated exposures to halothane have developed a milder reaction in the past.^{16,30}

(c) There is a high frequency of unexplained fever and eosinophilia.^{16,22,32,67-69}

(d) There have been descriptions of dysfunctions similar to those of serum sickness caused by an immunological mechanism: urticaria, arthralgia, proteinuria with impaired renal function, decrease in complement factors (C_3 , C_4 , C_{1q}) and the appearance of immune complexes in serum and synovial fluid.^{32,68,70,71} There was no correlation between the levels of the complexes in the serum and the severity of the disease. Reticuloendothelial function is suppressed, as was demonstrated by the clearance of ^{125}I microaggregated albumin, a fact which supports the immunological theory.⁷²

(e) There is a high frequency of drug allergy or atopic diseases among the patients.^{22,27,30,34}

(f) There is a greater frequency of liver and kidney microsomal antibodies (which appear in up to 25% of these patients, compared with 0.1% in a general hospital population). It should be noted that the appearance of these antibodies is transient, in contrast to the findings in chronic liver diseases.²² These antibodies are extremely rare in acute viral hepatic diseases.^{22,73} Other antibodies against thyroid,^{22,73} nuclear elements,³⁴ smooth muscle,³⁴ and mitochondria^{13,16,34,74} following halothane anaesthesia have been reported and it was suggested that patients prone to develop organ-specific autoimmunity seem to be more at risk.²² A specific antibody related to halothane exposure, which reacts with the hepatocyte membrane, was recently described.⁷⁵ It was found in the serum of patients who developed massive liver-cell necrosis following halothane anaesthesia. The antibody was of the IgG subclass and was detected by using a microcytotoxicity assay and indirect immunofluorescence. Its specificity suggests that it may be considered a marker of this condition.

(g) A provocation test after administration of a small non-anaesthetic dose of halothane was found to be positive in anaesthetists who had episodes of fever and jaundice after exposure to halothane.^{32,76}

(h) In many cases, lymphocyte transformation test (LTT), and leukocyte migration inhibition test (LMIT) are found to be positive in comparison to control groups,^{59,68,77,78} though false positive and negative results are often reported.^{79,80} Moreover, a stimulation capacity of patients' lymphocytes by their incubation with halothane metabolites was demonstrated up to 14 months following halothane

exposure.^{32,70} In some cases, atypical lymphocytes were also found.¹⁶

In summary, the pathogenesis of the liver damage caused by halothane is still not fully understood. It is possible that both mechanisms play a role in the pathogenesis. Halothane metabolites may bind to the hepatocyte membrane, and act as haptens, which provoke an immune response.^{35,52} It is also possible that mild liver dysfunction is caused by a direct toxic mechanism, while massive hepatic necrosis is caused by an immunological idiosyncratic mechanism.³⁵

Clinical findings

The fulminant form results from massive hepatic necrosis, and is characterized by high fever, chills, nausea, vomiting, malaise and anorexia.^{34,39,81} The fever is characterized by onset usually 5–8.5 days after exposure to halothane,^{27,34,38} but it can appear at any time within 1–26 days.^{30,39} Jaundice develops usually a few days later.^{8,24} The onset of the fever and jaundice appears earlier in a direct correlation to the number of repeated exposures, a fact which seems to support an immunological explanation.^{22,27,38} It was found that the clinical expression after a single exposure develops after 11.4–11.7 days on the average, while after the fourth exposure, the latent period shortens to about 4.1–5.3 days on average.^{27,39} Other symptoms are upper abdominal pain in a quarter of the cases,³⁴ and, less frequently, arthralgia and rash, resembling urticaria or a drug rash.^{32,68,70,71} Pruritus may also occur.³⁴

Fifty percent of the patients presented with a palpable liver and the mean liver weight at autopsy was 1170 g.³⁴ Hepatic encephalopathy often develops as a consequence of progressive liver failure.^{30,34} The mortality rate varies from 17% to 96%^{22,24,27,30,34,38,82} the average being about 50%.^{27,34,38,40} Among the non-survivors, the duration of the disease ranges from 11 to 73 days (23 days on the average); all die from hepatic encephalopathy.³⁰ The duration of the disease in the survivors averages 6 weeks (1–12 weeks)³⁴ and they usually recover without any clinical or pathological residue.^{30,83}

Adverse prognostic signs include early appearance of jaundice, male sex, obesity and impairment in coagulation profile.^{22,34} No correlation has been found between prognosis and age, type of operation and bilirubin levels.³⁴

Laboratory findings usually reveal leukocytosis (though leukopenia also occurs⁷⁹), eosinophilia, and rise in bilirubin (two thirds – indirect), transaminases and other liver enzymes.^{16,32,34,67,70,76} The levels of serum antibodies of the kind noted before are frequently high,^{13,16,22,34,73,74} and in one of the series, 44% of the patients had elevated titres of one kind or more of these antibodies.³⁰

Diagnosis

Fever and impairment of liver function after anaesthesia and surgery occur frequently.^{24,28} The differential diagnosis has to take into account other conditions such as acute viral hepatitis (A, B and non-A non-B), exacerbation of previous chronic liver disease, haemolysis after blood transfusion, liver damage due to hypoxia, hypotension, shock or sepsis, or liver damage due to other hepatotoxic drugs.²⁵ As mentioned before, an operation *per se* may cause changes in liver function regardless of the type of anaesthesia used.^{34–36} Although halothane hepatitis is a very rare condition, it constitutes the second most frequent cause of fulminant hepatic failure after viral hepatitis, and is responsible for 25–37% of the cases.^{22,24}

The differential diagnosis should be made by elimination of causes, which can be easily identified by anamnestic or serological tests. In addition, the use of clinical and epidemiological criteria (high fever, leukocytosis and eosinophilia in middle aged females after repeated exposures to halothane) and serological tests will altogether be helpful in distinguishing halothane hepatitis from other causes of hepatitis. Although it is not always easy to identify the cause of acute hepatitis, a history of halothane exposure is very helpful. From a histopathological point of view, it is impossible to distinguish hepatic necrosis due to halothane from hepatic necrosis caused by viruses.³⁴ In both cases, there is a centrilobular necrosis with mild cholestasis and fatty infiltration.^{14,41,68} In a small percentage of the cases, eosinophilic infiltration also occurs.³⁴ Some authors report ultrastructural changes in hepatocyte mitochondria which are specific to liver damage following halothane exposure,^{13,84} while others disagree with this finding.⁸⁵

Treatment

There is no specific treatment for halothane hepatitis; conservative management is the rule, including intravenous glucose, oral neomycin, intramuscular vitamin K and symptomatic treatment.^{83,86} Some authors support the use of steroids although their

value is unproven.⁸⁷ Liver transplantation is a treatment option for fulminant hepatic failure.⁸⁸ With regard to prevention the pre-operative transaminase level has been proposed as of value in identifying patients who are prone to develop liver damage following halothane.³³ Other authors claim that there is no way to predict which patient will develop a reaction,²⁸ and that furthermore, there is no way to predict which ones will develop another episode of liver damage among those who developed reactions in the past.³⁰

Conclusions

1. Severe liver damage is extremely rare following a single exposure to halothane in a previously healthy individual.
2. There is no contraindication to the use of halothane in the presence of pre-existing compensated liver disease.
3. The major risk factor for liver damage is repeated exposure to halothane over a short period of time, particularly in obese, middle aged women. The 'safe time interval' between one exposure and the next one is unknown. When repeated surgery is necessary within a short period, other anaesthetic agents should be used.
4. In patients with unexplained fever and jaundice or abnormal liver function tests following anaesthesia with halothane, the drug should not be subsequently administered, regardless of the time interval.
5. In typical cases the history allows a confident diagnosis of halothane hepatotoxicity to be made. Nevertheless, the diagnosis is sometimes difficult, as no specific test exists, when the diagnosis is by exclusion.
6. As the disease is apparently not dose-dependent, the use of a minimally effective dose to decrease morbidity rate does not seem logical.
7. It has been shown that cross-reaction and cross-sensitivity between halothane and methoxyflurane may occur.⁶⁷ Therefore, exposure to this agent following halothane exposure (or *vice versa*) should be avoided.

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