HALOTHANE AGGRAVATION OF CHRONIC LIVER DISEASE

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SUMMARY

A 33 year old woman developed a florid form of chronic active hepatitis after exposure to halothane. Histological and immunological data suggested that autoimmune type chronic active hepatitis antedated the acute hepatotoxic sequelae of the hatothane anaesthesia. Studies on the immuno regulatory functions of peripheral blood lymphocytes revealed a marked defect in suppressor cell function. It is suggested that this immunoregulatory defect in a patient with chronic liver disease may have rendered her more susceptible to the hepatotoxic effect of halothane or the maintenance of damaging immune reactions triggered off by this anaesthetic agent.

RESUMO

Agravamento de doença hepática crónica após exposição ao halotano

Uma doente de 33 anos desenvolveu uma forma grave de hepatite crónica activa após exposição ao halotano. Evidência histológica e imunológica sugere que uma hepatite crónica activa de tipo autoimune antecedeu as lesões hepatotóxicas agudas resultantes da anestesia pelo halotano. O estudo das funções imunoregulatórias dos linfocitos do sangue periférico revelou um defeito marcado da função supressora. Sugere-se que este defeito imunoregulatório numa doente com doença hepática crónica possa estar na origem de uma maior susceptibilidade ao efeito hepatotóxico do halotano ou da manutenção de reacções imunológicas lesivas desencadeadas por este agente anestésico.

INTRODUCTION

Massive hepatic necrosis induced by halothane is rare. It has been estimated to occur in about 7 cases per 10,000 multiple exposures to this anaesthetic agent.[1] However, in two prospective trials of repeated use of halothane anaesthesia, the incidence of elevated serum transaminase (aspartate or alanine aminotransferase) after multiple exposures was approximately eight [2] and twenty-two [3] per cent. There is no previous evidence that halothane aggravates chronic liver disease. We report a patient with pre-existing unrecognised chronic hepatitis in whom halothane anaesthesia resulted in severe hepatic necrosis, and during the subsequent year she developed florid evidence of chronic liver disease necessitating immunosuppressive therapy.

CASE REPORT

A 33 year old obese woman had a branchial cyst removed under general anaesthesia (nature undetermined) in 1971. Four years later, following a holiday abroad, she developed jaundice during a short influenza-like illness and was treated at home with a presumed diagnosis of viral hepatitis. Between 1973 and 1977, she developed severe low back pain due to spondylolisthesis and was treated with non-steroidal anti-inflammatory drugs and analgesics. She gave no history of atopy, allergies or asthma, and there were no known drug allergies.

In September 1977, she was admitted to hospital for lumbosacral fusion. A pre-operative haematological screen was normal but on biochemical testing, aspartate aminotransferase level was elevated (62 iu/L, N: 20-40).

Hepatitis B surface antigen was not detected but on subsequent testing of stored serum, anti-nuclear antibodies were found (1/40 titre, homogeneous pattern).

Lumbosacral fusion was performed under general anaesthesia (Thiopentone, halothane, nitrous oxide and oxygen) with minimal blood loss and maintained blood pressure. During the first 10 post-operative days, she developed a low grade fever, for which no cause was found.

Twenty-seven days post-operatively, she complained of upper abdominal pain, anorexia, nausea and vomiting, and two days later was found to be jaundiced and febrile (T: 37.6 °C). On abdominal examination, 2 cm hepatic enlargement and tenderness in the epigastrum and right hypochondrium were noted. Serum bilirubin was elevated at 170 μmol/L (N: 2-14) as were the aspartate aminotransferase (AST > 1000 iu/L) and alkaline phosphatase (470 iu/L, N: 30-130). The prothrombin time was prolonged by two seconds. HBsAg test was negative. Antinuclear antibody was again present (titre 1/160) with a homogeneous pattern. A percutaneous liver biopsy performed 7 days after the onset of jaundice revealed features suggestive of an acute toxic hepatitis superimposed on a picture of chronic hepatitis. These features included centrizonal hepatocyte loss, without Kupffer cell hyperplasia but with otherwise generalised he-

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patocyte hyperplasia and an inflammatory infiltrate in the portal tracts extending into the hepatic lobule.

During the subsequent 15 days, her condition deteriorated significantly with the development of ascites and oedema, but no encephalopathy. However by two months after the appearance of jaundice all her liver function tests had returned to normal apart from an AST of 80 iu/L.

Eight months later, physical examination showed no new findings. However, there was persistent elevation of the AST at 118 iu/L. Furthermore, the serum IgG level was elevated at 24.1 gr/L (N: 6-16) and circulating anti-smooth muscle antibodies were detected (titre 1/320). Tests for HBsAg, anti-core and anti-e antibodies were persistently negative. Percutaneous liver biopsy again showed marked hepatocyte hyperplasia with inflammatory cells now confined to the portal and periportal areas, associated with piecemeal necrosis. This confirmed the clinical diagnosis of chronic active hepatitis. Treatment with prednisolone (10 mg) and azathioprine (50 mg daily) resulted in rapid return of the AST to normal.

Four years after the halothane anaesthesia, her liver function tests remain entirely normal, and a further biopsy performed two years after exposure to halothane revealed a diminution in hepatocyte plate hyperplasia, a sharply defined inflammatory infiltrate, as well as a mild portal tract fibrosis, consistent with a picture of treated chronic active hepatitis.

IMMUNOLOGICAL STUDIES

Two years after halothane exposure, in vitro ^{3}H-thymidine incorporation into DNA of this patient's lymphocytes was measured in the presence of halothane at three different concentrations with RPMI medium as control, as had previously been reported by Paronetto and Popper.[4] No lymphocyte stimulation was observed with any of the doses of halothane used (data not shown).

Studies on suppressor T cell function were also performed, using two separate systems, namely the concanavalin-A induced suppressor cell model[5] and the short lived suppressor cell model.[6] Experimental conditions have been described elsewhere.[7, 8] As shown in Table 1 both systems have revealed a decrease in supressor cell activity in this patient when studied approximately two years after receiving halothane anaesthesia. The suppressor index indicates the ratio of ^{3}H-thymidine incorporation into lymphocytes receiving the mitogen, concanavalin A, after a 24 hours incubation to that of lymphocytes stimulated immediately.[6] The result obtained using the con-A induced suppressor cell model was − 6 %; this indicates enchancement rather than suppression, and is a phenomenon that is not observed in normal subjects.

TABLE 1 **Studies on Suppressor Cell Function**

	Con-A induced suppression % suppression	Short-lived suppressor cells Suppressor index
Controls	18 ± 4.1 (SEM) % range 0-45 %; n = 13	2.9 ± 1.8 (SEM) range 1.5-4.9; n = 20
Patient	− 6 %	1.3

DISCUSSION

The component of acute hepatitis seen on liver biopsy was attributable to halothane toxicity. It occurred within a month of halothane exposure (suggesting this was her first exposure), and was accompanied by fever, a recognised feature of Halothane-induced liver damage. The early percutaneous liver biopsy showed acute centrizonal necrosis, characteristic of halothane hepatitis, without Kupffer cell hyperplasia, suggesting the hepatitis was unlikely to be viral in origin.

However, her subsequent course, after an initial severe hepatitis, was not that of uncomplicated toxic hepatitis. Over the ensuing 2 years, she manifested signs of typical chronic active hepatitis. Review of the previous episode of jaundice, the serological findings of anti-nuclear antibodies, and elevated AST prior to halothane anaesthesia suggested pre-existing liver disease. Of critical importance in this regard is the presence of hyperplasia of the liver plates in a biopsy taken merely seven days after the onset os jaundice. For these reasons, it is unlikely that acute halothane hepatitis progressed to chronic liver disease in this patient. Patients surviving the acute hepatitis have an excellent prognosis with restoration of hepatic function and structure to normal.[9] There is only one well documented case of chronic liver disease developing after exposure to halothane, and this occurred in an anaesthetist who developed recurrent acute hepatitis during occupational exposure, and eventually developed cirrhosis.[10] Another case reported by Thomas [11] with chronic aggressive hepatitis induced by halothane was followed up for only 3½ months, and doubt remains on the chronicity of this patient's lesion.[9]

It is generally accepted that halothane may induce massive hepatic necrosis particularly in patients receiving multiple exposures to the anaesthetic agent. Inman and Mushin [12] have analysed the effects of halothane exposure and found an overall mortality of 49 % following massive hepatic necrosis due to halothane. Among patients with massive necrosis following a single exposure, death occurred in 35 % of patients, while after 2 or more exposures, a 51-52 % mortality was recorded.

The precise mechanism of halothane hepatic toxicity remains controversial.[13] The delay of 27 days between exposure and clinical manifestation of hepatic injury in our patient makes a toxic mediation unlikely. On the other hand, the presence of predominantly centrizonal necrosis in the initial biopsy may suggest a direct toxic effect on the liver by halothane or one of its metabolites. An immunological pathogenesis for the hepatotoxicity may also be considered, as several parameters of immunological function have been reported to be abnormal in acute halothane hepatitis.[4, 14] Furthermore, halothane or one of its metabolites might covalently bind to carrier protein to become immunogenic.[13] Thus, altered immune function may have allowed the development of antibodies to halothane-altered hepatocyte membrane.[15]

It is intriguing that our patient had the abnormalities in suppressor cell function characteristic of chronic active hepatitis;[7, 10, 16] this deranged immunoregulatory function may have predisposed to the development of antibodies to altered hepatocyte membrane (resulting in the expression of acute hepatitis) and the maintenance of damaging immune reactions resulting in aggravation of chronic liver disease, as assessed on biochemical and histological grounds.

The failure to demonstrate lymphocyte sensitisation to halothane using lymphocyte transformation tests was not unexpected. Most authors have, in fact, failed to detect lymphocyte sensitisation in patients suffering acute halothane hepatitis;[17-19] even when such a phenomenon was observed,[4] it was only temporary, being limited to the weeks following exposure.

Our experience with this patient would suggest that halothane anaesthesia should be avoided in patients with pre-existing chronic active hepatitis because of difficulties in interpretation of clinical disease and because it may lead to aggravation of the liver damage. This report illustrates the value of early liver biopsy in cases of post-operative jaundice in order to facilitate diagnosis and treatment.

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