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CASE REPORT

Halothane Hepatitis in a Laboratory Technician

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Summary: A case report of hepatitis attributable to halothane in a laboratory technician is reported. The patient had been using the drug to anaesthetise rats for experimental procedures. Her initial illness was one of malaise, anorexia and vomiting. However on re-exposure she developed an accelerated reaction characterised by fever, rigors, rash, body aches and malaise, followed by jaundice. Liver biopsy showed a hepatitic picture with prominent eosinophilic infiltrate. Her Australian antigen was negative as well as tests for mitochondrial antibody. The patient made a rapid uneventful recovery.

Although the National Halothane Study reported a very low incidence of hepatic necrosis that could be ascribed to halothane anaesthesia[1], there have since been numerous reports of this association[2, 3, 4, 5, 6]. More recently it has been suggested that hepatitis associated with halothane anaesthesia may be a hypersensitivity reaction and not a direct toxic manifestation of the drug[7, 8, 9]. This has been based on a variety of evidence and has been strengthened by the report of reactivation of hepatic damage on rechallenge with halothane in an anaesthetist[7]. Most cases of hepatic damage caused by halothane have been in patients who have undergone surgery in which halothane has been used as an anaesthetic agent. There have been two reports of halothane hepatitis in anaesthetists[7, 10] and one in a factory worker employed by a company producing halothane[11]. We report here a case of hepatitis attributable to halothane in a laboratory technician, who was using the drug to anaesthetise animals for experimental procedures.

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Case Report

S.B. was a 26-year-old female laboratory technician, previously in good health and with no prior serious illnesses or liver disease. She took no medications and her alcoholic intake was small and confined to social occasions.

She was using rats as an experimental animal for studies on bile secretion. She had been using ether and pentobarbital (Nembutal) as anaesthetic agents but two months prior to her present illness she decided to change to halothane (Fluothane ICI) as an anaesthetic agent for a variety of technical reasons and after consultation with an anaesthetist and a veterinary surgeon. Halothane was administered to the rats with a "Trilene" Vaporizer via an open funnel system. This meant that there was halothane vapour in the immediate vicinity of the animal but of such low concentration that this was not considered dangerous. Her first use of halothane anaesthesia was not followed by any symptoms. A few hours following the second use of the agent, a month later, she developed a headache and slight malaise. These passed off overnight and she did not seek medical attention. On 16/3/1970 and on 17/3/1970 she again used halothane anaesthesia in the mornings. On both afternoons she developed a headache and some malaise. During the remainder of the week she continued to work but felt slightly unwell and she noticed a slightly itchy macular rash on both arms. On the morning of 22/3/1970 she woke feeling sick. She had malaise, a dry mouth and headache. At midday she felt nauseated and vomited. In the afternoon she developed a fever and had severe rigors, aches and pains in her legs and back. On the next day she visited her local medical officer who diagnosed influenza and tracheitis and gave her penicillin. However on 26/3/1970 she still felt unwell with malaise, anorexia and nausea so returned to her local practitioner. He again could find no specific abnormality. She recovered sufficiently to return to work on 1/4/1970, and remained well at work during the week and over the weekend. On 6/4/1970 she again performed experiments in the morning on some rats using halothane as an anaesthetic. After finishing the experiments she

TABLE 1

Serial Liver Function Tests

	6/4	8/4	9/4	10/4	13/4	15/4	20/4	24/4
S. Bilirubin mg/100ml.	0.8	2.4	1.1	1.1	0.7	0.9	0.8	0.5
S. Protein mg/100ml		7.1		6.0	6.1		6.7	
Serum Alkaline Phosphatase* ..	8	5	7	7	18	4	4	5
Serum Glutamic Oxalacetic Transaminase†	140	3750	2100	1260	255	110	30	35

*King Armstrong Units

†Karmen Units

developed a headache, and following lunch she felt nauseated and vomited. During the afternoon she developed a fever with aches in her limbs and back. Because of these symptoms she reported to the hospital sick bay. On examination she looked pale and ill. Her temperature was 37°C. However on physical examination there was little to find. Her throat was normal. She was nonicteric and there were no rashes. Her chest and cardiovascular systems were clear on auscultation. She had no lymphadenopathy or hepatosplenomegaly. She was thought either to have infectious mononucleosis or to be in the anicteric phase of hepatitis and was therefore admitted for observation. Investigations on admission confirmed the diagnosis of hepatitis. She had urobilinogen present in her urine and her liver function tests revealed hepatocellular damage (Table 1). In view of her history, the clinical features of rash, aches in her limbs, fever and explosive onset following re-exposure to halothane it was thought possible that the hepatitis had been induced by halothane. Other investigations revealed a haemoglobin 15.0 g/100 ml, erythrocyte sedimentation rate (Westergren) 6 mm/hr., leucocyte count 5,000 cmm with 22% eosinophils, 200,000 platelets. Blood urea, serum electrolytes and serum amylase were normal. A slide test for heterophil antibodies was negative and Australian antigen (Au) was also negative.

The following day she was clinically icteric and her liver had become palpable. Her bilirubin and transaminase rose sharply and fell rapidly. She had a persistent eosinophilia of about 10%. Her clinical condition improved rapidly and she was discharged from hospital after nine days. Her serial liver function tests are shown in Table 1.

On the fourth hospital day a liver biopsy was performed. This showed a marked hepatitic reaction with focal hepatocellular necrosis. In these zones the reticulum had collapsed and the liver cells were small with pyknotic nuclei. There were prominant mononuclear aggregates in the portal tracts and infiltrating the liver parenchyma. A striking feature was the numerous eosinophils in the inflammatory cells in the portal tracts (Fig. 1).

Serology for auto-immune disorders was negative for cell mitochondrial antibody but weakly positive for smooth muscle antibody.

Following discharge her liver function tests remained normal and she felt well and was able to return to work after two weeks' convalescence.

Discussion

Most cases of hepatitis following exposure to halothane have occurred in postoperative patients in whom the drug was employed as an anaesthetic agent. In these cases other complicating features such as trauma, septicaemia, blood transfusions and drugs often obscure the association. In this case there were no complicating factors and the contact was only superficial. Two cases have been reported in anaesthetists[7, 10] and one in a factory worker who also did not receive an anaesthetic dose[11].

The case conforms to those previously reported: fever was a prominent symptom, and there was a rash and eosinophilia. Furthermore,

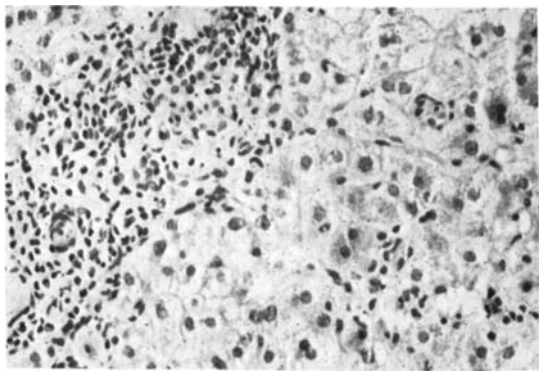

FIGURE 1. Photo micrograph of liver biopsy showing hepatic picture, with liver parenchyma necrosis and a marked cellular infiltrate in portal tracts. A striking feature of the mononuclear infiltrate is the number of oesinophils.

her initial illness after the third exposure to halothane took four days to appear and undoubtedly was accompanied by hepatocellular damage though no liver function tests were performed during this episode. However following re-exposure to halothane she had an accelerated reaction, with fever and rigors appearing within hours and an elevation of her serum transaminase within four hours.

It is generally agreed that halothane hepatitis and viral hepatitis cannot be distinguished histologically[5, 11]. However, the presence of a peripheral eosinophilia, marked eosinophilia in the liver biopsy and a negative test for Australian antigen[12, 13, 14, 15] make it probable that the aetiological agent in this case was a sensitivity reaction to halothane.

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