HEPATIC DAMAGE AFTER EXPOSURE TO HALOTHANE IN MEDICAL PERSONNEL

J. NEUBERGER, D. VERGANI, G. MIELI-VERGANI, M. DAVIS AND R. WILLIAMS

SUMMARY

Two surgeons, in whom liver damage developed after occupational exposure to sub-anaesthetic doses of halothane, were found to have a circulating antibody which reacted specifically with halothane-altered hepatocyte membrane components. This antibody has been found previously only in those patients in whom severe hepatic necrosis developed after exposure to halothane and in no other form of liver injury. It may provide a specific diagnostic marker in patients in whom there are other possible causes of liver damage and could, therefore, remove the need for a challenge exposure and its attendant risks.

Although massive hepatocellular necrosis after exposure to halothane is rare (Strunin, 1977), up to 20% of patients have evidence of mild hepatic damage (Trowell, Peto and Crampton-Smith, 1975; Wright et al., 1975). There have been a few reports of liver damage developing in medical and paramedical personnel after exposure to sub-anaesthetic doses of the drug (Belfrage, Ahlgren and Axelsson, 1966; Klatzkin and Kimberg, 1969; Johnston and Mendelsohn, 1971; Lund, Skulberg and Helle, 1974). The evidence for the association is circumstantial, based on detection of abnormal liver function tests after exposure and exclusion of other causes.

In recent studies of the mechanisms of hypersensitivity-induced liver damage, we have shown that patients in whom fulminant hepatic failure develops after multiple exposures to halothane may have a circulating antibody which reacts with a specific halothane-related hepatocyte membrane determinant (Vergani et al., 1980). We describe two medical practitioners in whom hepatic damage developed after occupational exposure to halothane and in whom the antibody was detected.

CASE REPORTS

Patient 1

An Italian surgeon aged 41 yr had been working for 15 yr in operating theatres where he was exposed to both halothane and methoxyflurane.

Seven years before presentation he suffered an episode of acute hepatitis; no cause was found and he recovered completely. Six years later (May 1974), he had a further illness with features similar to hepatitis which resolved after bed-rest. Two months later, after returning to work, an increase in serum glutamic-oxaloacetic transaminase (SGOT) was noted (fig. 1). He was absent from work for 2 months during which the transaminase concentration returned to normal. He returned to work, but again felt unwell and plasma SGOT was found to be increased. He stayed away from work again. Liver biopsy showed a conspicuous mononuclear-cell infiltrate in the portal tracts but without extension to the parenchyma; there was some necrosis of single hepatocytes. This combination resembled unresolved acute hepatitis. Subsequently, after he returned to hospital duties, an increase in SGOT was noted on two occasions, both associated with halothane exposure. The patient was referred to the Liver Unit, King's College Hospital. There was no history of eczema, allergy or exposure to other known hepatotoxins or excess alcohol. On examination, there were no skin signs of chronic liver disease and no enlargement of liver or spleen. Hepatitis B surface antigen, antibody, and antitope antibody and specific immunoglobulin M (IgM) to hepatitis A virus could not be detected by radioimmunoassay and enzyme-linked immunosorbent assay. Antiagastic parietal cell antibodies were present in small titres (1 in 20). Liver biopsy showed a dense but well-defined infiltration of the portal tracts by mononuclear cells which were associated with some mononuclear cells within the parenchyma.

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This resembled unresolved hepatitis. The patient was advised to work only in a halothane-free environment and since then he has remained well with a normal serum transaminase concentration.

**Patient 2**

A Canadian doctor aged 26 yr developed a pyrexial illness with increased plasma SGOT after 3 months exposure to halothane. He returned to work but, 1 month later, was admitted to a local hospital with a 5-day history of fever, sore throat and conjunctivitis for which he was given penicillin with no effect. There was no history of exposure to hepatitis or known hepatotoxins. On examination, there was periorbital swelling and conjunctivitis, but there were no skin signs of chronic liver disease and no hepatomegaly. Plasma SGOT on admission was greater than normal (51 iu litre\(^{-1}\)) and increased the next day (90 iu litre\(^{-1}\)). There was no eosinophilia and serum autoantibodies were not detected. Tests for markers of hepatitis A and B viral infection were negative and antibody titres to Epstein Barr virus and cytomegalovirus were normal. Serum transaminases decreased gradually and were within normal limits 2 months later. Liver biopsy was not performed, at the patient's request. He changed his specialty to avoid further exposure to halothane and has remained well since.

**DETECTION OF HALOTHANE- AND METHOXYFLURANE-RELATED ANTIBODIES**

Target hepatocytes were isolated from female New Zealand white rabbits, exposed 18 h previously to either 1% halothane or 1% methoxyflurane and 99% oxygen (Vergani et al., 1980). Antibodies in the serum were detected both by an indirect immunofluorescence technique and a microcytotoxicity assay. Serum was heat-inactivated and absorbed with normal hepatocytes to remove any antibodies reacting with normal liver cell determinants. For immunofluorescence studies, hepatocytes were isolated by mechanical means and incubated with the patient or control serum (diluted 1 in 10) for 30 min. After three washes, the hepatocytes were incubated for a further 30 min with FITC-conjugated anti-human immunoglobulin (diluted 1 in 4). After three more washes, the cells were examined under ultraviolet microscopy.

To assay microcytotoxicity the hepatocytes were isolated by collagenase digestion and seeded
into microculture test wells. Test and control serum diluted 1 in 100 were added to the wells for 2 hours to allow any antibody present in the serum to react with specific determinants on the hepatocytes. After the hepatocytes were washed, lymphocytes isolated from normal individuals were added so that antibody-coated hepatocytes could be killed by a subpopulation of the lymphocytes, K cells. After 48 hours, the number of viable hepatocytes was counted and the percentage cytotoxicity determined.

RESULTS
Halothane-related antibody was found in the serum of both patients by both methods. Characteristic granular fluorescence was produced by both sera with halothane-treated hepatocytes (fig. 2) and no fluorescence was seen with normal hepatocytes. In the cytotoxicity assay, both sera induced significant cytotoxicity to halothane-treated hepatocytes whereas neither did to normal hepatocytes (table I). Methoxyflurane-related antibodies were not found in the serum of patient 1 against methoxyflurane-treated hepatocytes.

DISCUSSION
The role of halothane-related antibody in the mechanism of the liver damage following halothane anaesthesia is not known. A direct involvement in the process of hepatic necrosis is suggested by its ability to render halothane-treated hepatocytes susceptible to lysis in the K-cell mediated antibody-dependent cytotoxicity assay in vitro—although in vitro findings cannot be equated directly with in vivo effects. Studies have shown the specific antibody response only in those patients in whom severe liver damage has developed after several halothane exposures and not those in whom there has been only a minimal increase in serum transaminase concentrations. Furthermore, this halothane-related antibody has not been detected in the serum of anaesthetists, exposed to halothane, who have normal liver function tests (Davis et al., 1980; Vergani et al., 1980). This is the first report of an association with a relatively minor degree of liver damage. This may be because anaesthetists are exposed to relatively small doses of the drug over a long period of time. Such occupational exposure to halothane has been shown to result in enhanced enzyme induction, as measured by antipyrine clearance (Duvaldestin et al., 1981); in susceptible individuals, this might be enough to enhance halothane biotransformation and generate the halothane-related antigen.

In both these patients, there was other evidence implicating halothane in the aetiology of recurrent hepatitis. On each occasion the increase in serum transaminase concentrations was closely related to exposure to halothane and the transaminases

<table>
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<tr>
<th>Patient</th>
<th>Hepatocytes</th>
<th>1</th>
<th>2</th>
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<tr>
<td>Control</td>
<td>12</td>
<td>22</td>
<td></td>
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<tr>
<td>Halothane</td>
<td>48</td>
<td>38</td>
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<td>Methoxyflurane</td>
<td>13</td>
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return to normal when the patient was no longer in contact with halothane. Liver histology, available in only one patient, was compatible with drug-induced liver injury (Zimmerman, 1978).

There have been reports of liver damage in medical and paramedical personnel exposed to sub-anaesthetic doses of halothane (Belfrage, Ahlgren and Axelson, 1966; Klatskin and Kimberg, 1969; Johnston and Mendelsohn, 1971; Lund, Skulberg and Helle, 1974). Hepatitis has also been reported in those who have abused halothane (Schatzki, Kay and Dickinson, 1973; Kaplan et al., 1979) although they may have been exposed to much greater doses of halothane. Of the former group, three had a history of allergy or eczema, two had peripheral eosinophilia, and one had serum autoantibodies (table II). Liver histology showed a hepatitis which progressed in one patient to cirrhosis. Other causes of liver damage, especially A and B viral hepatitis, were not always excluded.

If a patient is thought to be sensitive to halothane, it is possible to ensure that he is not exposed to it again. It is much more difficult for an anaesthetist. In practice, it may mean a change in his work. Therefore every effort should be made to determine whether or not a person is sensitized to halothane. Controlled re-exposure would put a patient already sensitized at serious risk of developing potentially fatal hepatic necrosis. Furthermore, an increase in serum transaminase concentration may indicate only that halothane is exacerbating pre-existing liver disease. By providing a specific marker of sensitization, the halothane-related antibody obviates the need for a challenge test.

ACKNOWLEDGEMENTS

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REFERENCES


**LESION HEPATIQUE APRES EXPOSITION DU PERSONNEL MEDICAL A L’HALOTHANE**

**RESUME**

On a trouve que deux chirurgiens souffraient d’une lesion hepatique consecutive a leur exposition professionnelle a des doses non anesthesiantes d’halothane et qu’ils avaient dans leur circulation sanguine un anticycorps qui reagissait specifiquement aux composants de la membrane d’hepatocytes modifiees par l’halothane. On n’avait precedemment trouve cet anticycorps que chez les patients sur lesquels une necrose hepatique grave s’etait developpee apres exposition a l’halothane, mais dans aucune autre forme de lesion du foie. Il peut constituer un facteur d’identification specifique de diagnostic chez les patients ayant d’autres causes possibles de lesion du foie et pourrait, donc, eliminer la necessite d’une exposition d’epreuve avec tous les risques que cela comporte.

**LEBERSCHADEN BEI MEDIZINISCHEM PERSONAL NACH AUSGESETZTSEIN AN HALOTHAN**

**ZUSAMMENFASSUNG**

Bei zwei Chirurgen, bei denen Leberschäden nach berufsbetätigtem Ausgesetztsein an Subanästhesie-Dosen von Halothan auftraten, wurden kreisende Antikörper gefunden, die spezifisch mit halothanveränderten Hepatozytenmembranbestandteilen reagierten. Dieser Antikörper ist bis jetzt nur bei Patienten gefunden worden, bei denen eine schwere Lebernekrose nach Ausgesetztsein an Halothan auftrat, und bei keiner anderen Form von Leberschaden. Er könnte einen spezifischen Hinweis bei Patienten geben, bei denen andere Ursachen vorliegen könnten und somit die Notwendigkeit eines herausfordernden Aussetzen und die damit verbundenen Gefahren vermeiden.

**DANO HEPATICO EN EL PERSONAL MEDICO DESPUES DE SU EXPOSICION AL HALOTANO**

**SUMARIO**

Se averió que dos cirujanos que habían desarrollado complicaciones en el hígado después de su exposición a dosis subanestésicas de halotano, como consecuencia de sus actividades profesionales, presentaban un anticuerpo en circulación que reaccionaba de forma específica con los componentes de la membrana hepática que habían sufrido alteración a causa de dicho halotano. Este anticuerpo se había encontrado anteriormente sólo en aquellos pacientes en los que se desarrolló una necrosis hepática aguda después de su exposición al halotano, no habiéndose presentado en ningún otro tipo de complicación hepática. Puede que esto provea un indicador específico para efectuar diagnósticos en aquellos pacientes en los que, seguramente, las complicaciones hepáticas tengan otro tipo de causas y, por lo tanto, podía hacer innecesaria la exposición de prueba y sus riesgos congénitos.