SPECIFIC SEROLOGICAL MARKERS IN THE DIAGNOSIS OF FULMINANT HEPATIC FAILURE ASSOCIATED WITH HALOTHANE ANAESTHESIA

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SUMMARY

The aetiology of massive liver-cell necrosis which developed in 16 patients following halothane anaesthesia was investigated by means of new serological techniques. In eight patients a specific halothane-related antibody was found, indicating that these patients were sensitized to halothane-altered liver-cell membrane components. In four patients, hepatitis A viral infection was responsible and among the remainder one was receiving anti-tuberculous drugs and one had received a blood transfusion, thus raising the possibility of a non-A non-B viral infection. There were no biochemical or histological differences between patients in the three groups.

In recent studies of the pathogenesis of the liver-cell necrosis which develops in some patients after halothane anaesthesia, we have identified an antibody which reacts specifically with a membrane determinant on halothane-altered hepatocytes. This antibody is not found in patients with minor, or no abnormality, of liver function nor in patients with other forms of liver injury (Vergani et al., 1980; Davis et al., 1980). As a result of developments in the techniques for the specific diagnosis of hepatitis A viral infection, and hepatitis B viral infection, where the surface antigen is cleared from the serum unusually quickly, it is now recognized that surface and anticore antibodies provide much better markers of recent infection (Mathiesen et al., 1980; Woolf et al., 1976). We have looked for each of these serum markers in 16 patients in whom severe hepatic necrosis developed within 1 month of exposure to halothane, in an attempt to determine the cause of the liver-cell necrosis.

PATIENTS AND METHODS

The records of all patients admitted to the Liver Failure Unit at King’s College Hospital in the years 1978–79 were examined. Of the 111 patients admitted, 16 (14%) had developed fulminant hepatic failure within 1 month of exposure to halothane anaesthesia. In these 16 patients severe hepatic necrosis was demonstrated by an increased serum aspartate aminotransferase concentration (maximum 386–10,272 i.u. litre\(^{-1}\)) and a prolonged prothrombin time (by 18–150 s). No patient had a history of pre-existing liver disease.

Signs of grade IV hepatic encephalopathy appeared in all, and all but two of the patients died. Serum samples taken on admission (within 2 weeks of the last anaesthetic and within 4 days of the onset of jaundice) were tested for serum autoantibodies including the liver–kidney microsomal autoantibody which has been reported frequently in fulminant hepatic failure attributed to halothane anesthesia. Hepatitis B surface antigen and antibody, and anticore antibody were identified by sensitive tests (Austria II, Ausab Corab and Radioimmunoassay, respectively) and the specific immunoglobulin M (IgM) to hepatitis A virus by the enzyme-linked immunosorbent assay (Organon). The halothane-related antibody was detected by a microcytotoxicity assay and indirect immunofluorescence as described previously (Vergani et al., 1980). Sera from all patients were tested for the presence of these antibodies at intervals of 4 days; there were no changes in the presence, or otherwise, of the antibodies with time. In those patients who died, a percutaneous liver biopsy was taken immediately after death for histological examination.

RESULTS

Halothane-related antibody was found in the serum of eight of the 16 patients using both immunofluorescence and microcytotoxicity techniques (patients 1–8: table I). The time between the last exposure to
# TABLE I. Characteristics of 16 patients in whom fulminant hepatic failure developed after halothane anaesthesia.

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<tr>
<th>Patient No.</th>
<th>Age (yr)</th>
<th>Sex</th>
<th>Operation</th>
<th>Anaesthetic</th>
<th>Interval between anaesthetics (days)</th>
<th>Time to onset of symptoms (days)</th>
<th>Pyrexia after op.</th>
<th>Auto-antibodies</th>
<th>Outcome</th>
<th>Antibodies**</th>
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1. Previous exposure to halothane more than 1 yr previously. **All patients were HBsAg negative. †Receiving rifampicin, isoniazid, pyrvinamid and streptomycin. ‡Received 7 pints of blood at first operation. §Receiving rifampicin, isoniazid and ethambutal. LKM = Liver-kidney microsomal antibody; SMA = Smooth muscle antibody; Hal = halothane.
halothane and the onset of symptoms varied from 2 to 10 days. Six patients had been exposed to halothane twice and two had been exposed on three occasions. Serum markers for hepatitis A and B viral infections were negative in all these patients. The use of specific fluorescein-conjugated antibodies to IgG and IgM in the indirect immunofluorescence assay showed that the halothane-related antibody was of the IgG subclass in all patients.

Of the remaining eight patients, without the halothane related antibody, four (patients 9–12; table I) had evidence of recent infection with hepatitis A virus (high titres of IgM antibody). Two of these patients had been exposed to halothane once and two had been exposed twice within 4 weeks. The time from anaesthesia to the onset of symptoms varied from 2 to 23 days. One of these patients (patient 10) had tuberculous meningitis and had been receiving rifampicin, isoniazid, pyrazinamide, and streptomycin. In the other four (patients 13–16: table I) all serological tests were negative. A 24-year-old woman (patient 13), had received seven units of blood during her first operation, thus raising the possibility of an infection with non-A non-B hepatitis virus. Another patient (patient 16) was receiving antituberculous drugs (ethambutal, isoniazid, and rifampicin) while in the other two patients there were no factors, other than halothane anaesthesia, which could be implicated in the liver-cell necrosis.

No patient demonstrated evidence of peripheral eosinophilia. Autoantibodies were present in three of the eight patients in whom the halothane-related antibody was found (liver–kidney microsomal in two and smooth muscle in one). One patient with hepatitis A viral infection had smooth muscle antibody and the patient with possible non-A and non-B hepatitis had liver–kidney microsomal antibody. Postoperative pyrexia was a feature in five of the eight patients with halothane-related antibody and in three of the other patients.

Liver histology showed massive hepatocellular necrosis, mainly centriflobular, with some cholestasis. In two of the patients with the halothane antibody there was a cellular infiltrate in the portal tracts with mononuclear and plasma cells; otherwise there was no difference in histology between the various groups.

**DISCUSSION**

The presence of the halothane-related antibody in eight of these 16 patients suggests sensitization to liver membrane components altered by a metabolite of halothane (Neuberger et al., 1981). No patient in whom antibody was detected had serological evidence of any other causes of liver cell necrosis. The ability of the antibody to induce normal lymphocytes to become cytotoxic to hepatocytes coated with the antibody (Vergani et al., 1980) suggests that it has a role in the pathogenesis of hepatocellular damage, and its specificity suggests that it may be considered a marker of this condition. The finding that the antibodies were always of the IgG subclass and not of the IgM subclass suggests that sensitization to halothane-altered liver cell components had occurred following an earlier exposure. If the antibodies were purely secondary to halothane-related liver cell damage, IgM subclass antibodies would be expected. The interval between the exposure of the patient to halothane and the detection of the halothane antibody was short in two patients (nos 1 and 3) and it is surprising that an antibody was generated so rapidly. However, the possibility of an earlier unrecorded exposure to halothane cannot be excluded.

It has also been shown experimentally that halothane may have a direct hepatotoxic effect (Sipes and Brown, 1976; Cousins et al., 1979) although the clinical relevance of this has been questioned (Strunin, 1977). In two large controlled trials, small increases in serum aminotransferase concentrations were observed in a considerable proportion of patients, and it was shown that subsequent exposure to halothane was not followed by severe liver-cell damage (Wright et al., 1975; Trowell, Peto, and Crampton-Smith, 1975). The halothane antibody is not present in such patients (Davis et al., 1980) and this is consistent with direct hepatotoxicity and the restriction of the immunological mechanisms to the much rarer severe liver damage leading to fulminant hepatic failure. It is possible that the direct toxic effects of halothane may be important in those patients in whom no other cause of liver damage was found or may contribute to the hepatotoxic effect of other drugs.

The role of halothane in the development of fulminant hepatic failure in those patients in whom halothane-related antibody was not found is uncertain. The four patients with specific IgM antibodies to hepatitis A virus had, almost certainly, been infected recently by that virus. IgM antibodies to the hepatitis A virus appear in the serum during the acute phase of the illness and persist during early convalescence. The presence of IgG class antibodies
to the virus merely indicates previous infection with the virus and may be found in up to 80% of the general population. Although its appearance may be coincidental following operation, it is conceivable that halothane anaesthesia exacerbates a pre-existing, but mild, infection although both viruses themselves are well recognized causes of fulminant hepatic failure (Mathiesen et al., 1980). In vitro tests of immune function carried out after surgery have shown suppression of immune function although this is possibly a result of the stress of surgery rather than the direct immunosuppressive effects of anaesthetic agents themselves (Cullen and Van Belle, 1975). On present evidence, the hepatitis A virus seems to be directly cytopathic and any decrease in host immunocompetence could result in enhanced virulence.

One of the patients in whom the halothane antibody was not detected was taking the antituberculous drugs isoniazid and rifampicin—a combination known to produce fulminant hepatic failure in some individuals (Cullen and Van Belle, 1975; Zimmerman, 1978). It has been suggested that the hepatotoxic effect of isoniazid is increased by the enzyme-inducing effects of rifampicin and potentiated by the agents used for anaesthesia—factors which could explain the same close temporal relationship with halothane anaesthesia noted in the other patients (Pessayre et al., 1977).

Peripheral blood eosinophilia and circulating autoantibodies, previously demonstrated as markers of halothane hepatitis (Moult and Sherlock, 1975; Walton et al., 1976) are found in patients with hepatitis A viral infection as often as they are found in those with presumed halothane hepatitis. Unexplained pyrexia after operation is more common in the latter group, but its lack of specificity makes it of poor diagnostic value (Dykes, 1971).

The results demonstrate the potential of the halothane-related antibody as a specific diagnostic marker and also that, in some patients, other factors may be implicated in the development of massive liver-cell necrosis following halothane anaesthesia.

REFERENCES


MARQUEURS SEROLOGIQUES SPECIFIQUES DANS LE DIAGNOSTIC D'INSUFFISANCE HEPATIQUE FULMINANTE EN RAPPORT AVEC UNE ANESTHESIE A L'HALOTHANE

RESUME

L'étiologie de la nécrose hépatocellulaire massive survenue chez 16 patients après une anesthésie à l'halothane a été étudiée grâce à...
de nouvelles techniques sérologiques. Chez huit patients, nous avons retrouvé un anticorps spécifique lié à l’halothane, indiquant que ces patients étaient sensibilisés à des composants de la membrane hépatocytaire altérés par l’halothane. Chez quatre patients, une infection au virus de l’hépatite A était responsable et parmi les restants, un patient recevait des antituberculeux et un avait reçu une transfusion sanguine, ce qui rendait possible une infection à virus non A non B. Il n’y avait pas de différences biochimiques ou histologiques entre les patients des trois groupes.

MARCADORES SEROLÓGICOS ESPECÍFICOS EN EL DIAGNÓSTICO DE UNA FALLA HEPÁTICA FULMINANTE ASOCIADA A LA ANESTESIA POR HALOTANO

SUMARIO
Mediante técnicas serológicas nuevas, se investigó la etiología de una necrosis masiva de células hepáticas que se desarrolló en 16 pacientes a raíz de la anestesia halotano. En ocho pacientes, se encontró un anticuerpo específico relacionado con el halotano, lo que indica que los pacientes se hallaban sensibilizados a los componentes de la membrana de las células hepáticas alteradas por el halotano. En cuatro pacientes, fue una hepatitis viral A infecciosa que fue el agente responsable y entre los demás pacientes, uno recibía drogas antituberculosas y otro había recibido una transfusión de sangre, lo que aumentaba la posibilidad de una infección viral no-A no-B. No hubo diferencias bioquímicas o histológicas algunas entre los pacientes de los tres grupos.