Occasional Review

Halothane hepatitis in children

J GERARD KENNA, JAMES NEUBERGER, GIORGINA MIELI-VERGANI, ALEX P MOWAT, ROGER WILLIAMS

Abstract
It is often stated that halothane hepatitis in children is non-existent or extremely rare. This syndrome occurred in seven children aged between 11 months and 15 years, one of whom, a 3½ year old boy, died with fulminant hepatic failure. All the children had received multiple halothane anaesthetics (range 2-6, median 3). In all cases other causes of liver diseases were excluded, and in all but one the diagnosis was confirmed serologically by antibodies to halothane altered liver cell membrane antigens.

These findings suggest that halothane hepatitis occurs in children, and the risk of halothane hepatitis should therefore be considered when choosing which agents to use in children who require multiple anaesthetics.

Introduction
After many years of controversy it is now established that in adults severe liver damage is an important but rare event after repeated exposures to halothane. The diagnosis can now be confirmed serologically by showing in vitro serum antibodies reacting with halothane altered liver cell membrane determinants. These antibodies are present in about three quarters of such patients. Despite the increased awareness of the possibility of halothane toxicity in childhood it is often stated that the risk of halothane hepatitis is particularly low or even non-existent in children. There have been anecdotal reports of children developing unexplained hepatitis after halothane exposure, although other possible aetiologies were not excluded in all cases. One of these children died with fulminant hepatic failure. We describe the findings in seven children with halothane hepatitis.

Methods
Since the advent of diagnostic assays for halothane hepatitis we have been asked to test serum for the presence of the "halothane antibodies" and have also been referred patients with fulminant hepatic failure after halothane anaesthesia. Between 1978 and 1985 we analysed the clinical and laboratory features of nine children with presumed halothane hepatitis, two of whom (cases 4 and 6, table) were treated at this hospital. Two children (cases 1 and 3) have been fully reported elsewhere and one (case 6) has been referred to in a letter. In all cases family histories were non-contributory. None of the children had received blood transfusions. Serum was tested for markers of hepatitis A and B virus, cytomegalovirus, Epstein-Barr virus, and toxoplasmosis. Since α1 antitrypsin deficiency has been considered a risk factor for hepatitis after halothane anaesthesia, serum was also tested for the α1 phenotype by isoelectric focusing. Halothane antibodies were detected in serum using either antibody dependent cell mediated cytotoxicity, enzyme linked immunosorbent assay (ELISA), or immunoblotting, as described in detail elsewhere. All three tests have a similar sensitivity and specificity. Because halothane antibodies are stable at −20°C serum samples were kept frozen until tested.

Results
Of the nine children referred with the presumed diagnosis of halothane hepatitis, two were excluded from further analysis because other factors may have contributed to the jaundice. One, a 13 year old boy, developed jaundice after halothane anaesthesia but had a Burkitt’s lymphoma, which may have affected his liver. The other was a 12 year old girl who developed transient jaundice after an enflurane anaesthetic, although 12 days earlier she had received halothane. Neither had serological evidence of halothane sensitisation.

Of the remaining seven children, four were girls. Ages ranged from 11 months to 15 years (table). None had serological evidence of infective causes of hepatitis or a history of exposure to other known hepatotoxic drugs. None had the PiZ phenotype for α1 antitrypsin. All had received more than one documented halothane exposure (range 2-6, median 3) including that immediately preceding their jaundice. The interval between the penultimate and ultimate halothane exposure ranged from 13 days to five months (median four months), with two patients having received halothane twice within three weeks. Unexplained postoperative fever had been noted after previous halothane anaesthesia in two patients, and one child developed a maculopapular rash. One (case 2) had a history of eczema, but none had a history of drug allergy or was obese. No child had had intraoperative problems.

The interval between the final halothane exposure and the onset of jaundice ranged from two to four days (median three days). Maximum concentrations of serum aminotransferases ranged from 960 to 5080 IU/l (upper limit of normal 40 IU/l), and maximum serum bilirubin concentrations ranged from 93 to 861 μmol/l (upper limit of normal 15 μmol/l). Of the six survivors, none developed hepatic encephalopathy, all made an uneventful recovery and the results of standard liver function tests returned to normal. The case history of the child who died is given below.

Halothane antibodies were detected in six of the seven children, the exception being the child in case 7.

CASE REPORT
A 3½ year old boy weighing 1800 g underwent his first halothane anaesthetic in September 1985 for surgical correction of hypospadias; further halothane anaesthesia was given for further dilatation on 29 November, after which he became unwell and nauseated. The final

King's College Hospital, London SE5 8RX
J GERARD KENNA, PHD, research fellow, liver unit
JAMES NEUBERGER, DM, MRCP, consultant physician, liver unit
GIORGINA MIELI-VERGANI, MD, PHD, senior lecturer in paediatric hepatology, department of child health
ALEX P MOWAT, FRCP, consultant paediatric hepatologist, department of child health
ROGER WILLIAMS, MD, FRCP, director, liver unit
Correspondence to: Dr Mowat.
halothane anaesthetic was given, again for urethral dilatation, on 13 December 1985. Three days later he was noted to be jaundiced, with pale stools and dark urine. Seven days after the third halothane anaesthetic he was taken to the casualty department of a different hospital. The results of investigations showed haemoglobin concentration 12·6 g/dl, white blood cells 18·9 x 10^9/l, and platelets 557 x 10^9/l; prothrombin time was 35 seconds; and liver function tests showed bilirubin concentration 87 μmol/l, aspartate aminotransferase 960 IU/l, and albumin concentration 33 g/l. He was diagnosed as suffering from viral hepatitis and discharged home. Because of progressive deterioration in his condition 14 days after the last anaesthetic he was admitted to this hospital in grade III hepatic encephalopathy. There were bruises over the legs, and the liver edge was palpable 2 cm below the costal margin. The results of investigations showed haemoglobin concentration 11·5 g/dl, white blood cells 20·8 x 10^9/l, with no eosinophilia, and platelets 513 x 10^9/l. The prothrombin time on admission was 86 seconds, the serum bilirubin concentration 390 μmol/l, and the serum aminotransferase concentration 404 IU/l. Serological markers for viral infection were negative, and cultures of the blood and urine were negative.

Because the mortality of grade III/IV fulminant halothane hepatitis in adults approaches 100% he was put immediately on the emergency list for liver grafting and was started on methylprednisolone 30 mg/kg/day in an attempt to abrogate the immune response to hepatocytes. His condition, however, deteriorated, and he died on the 18th postoperative day before a suitable donor liver was found. At necropy the liver was shrunken and weighed 480 g, microscopic examination showing a confluent necrosis with extensive cell loss and reticulin collapse.

Discussion

In all seven cases described the most likely cause of the liver damage was halothane. Other causes of postoperative hepatitis, including viral and bacterial infection, hypoxia, hypotension, and other drug toxicities, were absent. Although liver biopsies were not performed, the return to normal liver function in all survivors suggests that none had pre-existing liver disease. In all cases there was a history of previous halothane anaesthesia, and three children had had features of possible halothane sensitisation, such as postoperative fever or a rash. None of the children had the presumed risk factor of obesity, and only one had a history of eczema. The incidence of the halothane related antibodies in six of the seven children is similar to that observed in adults. It is of interest that in some seronegative patients the in vitro culture of unstimulated lymphocytes isolated during the hepatic phase of the illness is associated with secretion of the halothane antibodies. Thus in some cases, such as in the child in case 7, it may be that the antibody is produced but is undetectable since it is bound onto the antigen on the liver cell or bound in immune complexes. In this study serum samples were tested only once so it could be argued that follow up testing might have detected the antibody in this child also.

We have, however, always failed to detect halothane antibodies in follow up samples from patients who were seronegative during the acute phase of the illness. One of the two children excluded from the analysis had a history of enflurane exposure. It has been suggested that there may be cross sensitisation between halothane and enflurane; in our experience, however, the halothane antibody does not react with the enflurane antibody.

Because of the nature of referral we are unable to establish whether the severity and incidence of halothane hepatitis in children is similar to that observed in adults. Between 1978 and 1985 we tested serum from 86 adults who developed severe hepatitis after halothane anaesthesia. The mortality was 56% and was similar in those 75% with the halothane related antibodies detectable in serum and those who were seronegative. Retrospective studies have identified only a few cases of possible halothane hepatitis in children—two out of 165 400 halothane anaesthetics in one study and one out of 200 311 in another. This low incidence may be due in part to the difficulty in retrospective studies of obtaining full records and to the fact that many children are discharged from hospital at an early stage after having had anaesthesia and may, like the boy described above, be admitted with jaundice to another hospital.

Furthermore, since some authors still think that halothane is not associated with liver damage in children the association may not be considered by the attending physician. One prospective study of

Clinical details of and results of biochemical tests in seven children with halothane hepatitis

<table>
<thead>
<tr>
<th>Case No</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Last operation</th>
<th>No of halothane exposures</th>
<th>Bilirubin (μmol/l) (normal &lt;15)</th>
<th>Serum aspartate transaminase (IU/l) (normal &lt;40)</th>
<th>Halothane antibody</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>13</td>
<td>F</td>
<td>Ureterocoele</td>
<td>3</td>
<td>372</td>
<td>3755</td>
<td>+</td>
<td>Alive</td>
</tr>
<tr>
<td>2</td>
<td>1½</td>
<td>F</td>
<td>Scar removal</td>
<td>3</td>
<td>Not assessed</td>
<td>&gt;1500</td>
<td>+</td>
<td>Alive</td>
</tr>
<tr>
<td>3</td>
<td>11 months</td>
<td>M</td>
<td>Fistula repair</td>
<td>6</td>
<td>214</td>
<td>5080</td>
<td>+</td>
<td>Alive</td>
</tr>
<tr>
<td>4</td>
<td>14</td>
<td>F</td>
<td>Orthopaedic repair</td>
<td>3</td>
<td>300</td>
<td>4000</td>
<td>+</td>
<td>Alive</td>
</tr>
<tr>
<td>5</td>
<td>15</td>
<td>F</td>
<td>Orthopaedic manipulation</td>
<td>2</td>
<td>215</td>
<td>1005</td>
<td>+</td>
<td>Alive</td>
</tr>
<tr>
<td>6</td>
<td>3½</td>
<td>M</td>
<td>Hypoplasia</td>
<td>3</td>
<td>861</td>
<td>900</td>
<td>+</td>
<td>Died</td>
</tr>
<tr>
<td>7</td>
<td>4</td>
<td>M</td>
<td>Orthopaedic repair</td>
<td>2</td>
<td>93</td>
<td>3120</td>
<td>+</td>
<td>Alive</td>
</tr>
</tbody>
</table>

References

Philosophers and other threats to health

GEORGE DUNEA

Can philosophers ever be a threat to health? The thought fleetingly and irreverently crossed my mind as I was reading the latest article by Professor Ivan Illich, a long time critic of the medical establishment. After all, Socrates was enough of a threat to be put to death by the ancient Athenians. Tolstoy thought that Nietzsche was completely mad by the time he wrote Zarathustra. Yet philosophers like Nietzsche have exerted enormous influence. Some have inflamed susceptible minds with their seductive theories even while staying put quietly at the British Museum in the reading room. Could they conceivably be even more pathogenic than doctors?

But now Professor Illich has told us that science is a form of medicine, and the practice of science is a medical form of magic. In 1975, Illich began picking apart the social, scientific, and medical structures of our society. He advised that we might as well take back our lives and live them as we choose, or perhaps even better, as we need to.

How could one possibly fault a message as noble as Illich’s? Perhaps he is not so much a prophet as a very wise and experienced teacher. He has given us a wonderful gift—a way to think about the world. But what is the world without a body? And what is a body without a mind?

I have a bet with myself on this: I’ll bet that it was Illich who said “Everything is medicine.” Or was it Illsby who said “Nothing is medicine”? Either way, it sounds much more sensible than the slogan “Nothing was ever so good for you.”

Modem day witch hunts

Among these reprints were some about witchcraft. I learnt that witch hunts are precipitated not by the sudden invasion of squadrons of bags riding on broomsticks but by some threatening event unleashing the dark forces of evil in an otherwise advanced society. Hence these persecutions took place not in the Dark Ages but during the enlightenment of the Renaissance and of modern Germany and the McCarthy era. Witch hunts tend to occur when societies lack the checks and balances that stop a single group (judges, military, the media) from becoming too powerful. They may be precipitated by political or social disasters or by epidemics—such as syphilis was in the 1500s and the acquired immune deficiency syndrome (AIDS) could become some day. In New England, in 1692, the culprit may well have been an outbreak of ergotism. Thus the reported tinglings and firinations, convulsions, twitchings, muscle spasms, deliriums, and hallucinations would have been caused not by the devil but by Claviceps purpurea growing on rye. This may have occurred at a time of increased dependency on rye, the wheat crops having failed during a series of cold winters—as suggested by study of tree rings. Yet direct information about the food supply at that period is largely lost or has been long forgotten. For this was before tetrahydroaminoacrine or THA, the new memory drug. Not available for general use, it cannot even be prescribed by doctors.