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Progress report

Halothane hepatitis

Since its introduction in 1956, this anaesthetic has achieved wide popularity. It was therefore disappointing that in 1958 the first cases of hepatitis associated with it were observed, and by 1964 over 100 such instances had been published[1]. At first it was very difficult to decide whether the halothane was responsible or whether the patient was suffering from a coincidental virus hepatitis. Early retrospective trials gave conflicting results concerning the relationship between the hepatitis and the anaesthetic. Keeri-Szanto and Lafleur[1] from Montreal analysed 50,000 patient-anaesthetics, 35,000 of which were with halothane. They noted that from 1959 to 1962 there was an increase in postanaesthetic hepatic complications. They estimated that there was one death from liver necrosis for about every 8,000 'uneventful' anaesthetics. Two comparatively large retrospective surveys, one conducted in Boston[3] and the other in Cardiff[4] failed to show any increased incidence of hepatic necrosis after the administration of halothane when compared with that following other anaesthetic agents. Prospective controlled trials have proved almost impossible and, in view of the difference of opinion among large groups of anaesthetists, a large retrospective controlled trial was conducted by the Committee on Anesthesia of the National Academy of Sciences National Research Council of the United States[5]. This nation-wide study involved 34 centres. Clinical experience of the anaesthetic during the four-year period 1959-1962 was noted. Deaths believed tc be associated with massive hepatic necrosis and occurring within six weeks of operation were studied. Liver tissue sections were reviewed by a panel of pathologists with extensive experience in liver disease. The study covered about 850,000 anaesthetics, in about 30% of which halothane was used. The overall mortality was 1·87% for halothane and 1·93% for all other anaesthetics. The overall safety of halothane was therefore greater. There were 11,000 necropsies, but in only 82 was the panel unanimous concerning the diagnosis of fatal massive liver necrosis. In 73 of these the clinical and microscopical findings were consistent with shock or hypoxia, and in only the remaining nine could the hepatic necrosis not be explained by such factors. In these nine patients the clinico-pathological factors were similar to those associated with viral hepatitis or with hepatitic-drug reactions. Seven of the nine had received halothane, four of them more than once. In spite of these results the trial was interpreted by anaesthetists as a verdict of 'not guilty' for halothane, and this was particularly gratifying to them as halothane is otherwise such a safe anaesthetic. Nevertheless, notable hepatologists, despite being members of the National Halothane Panel, remained unconvinced that halothane was guiltless and wrote: 'The following conclusions and recommendations relative to medical practice result from our interpretation of this study: the first is that if halothane does induce fatal liver necrosis, it is uncommon or rare. Although halothane hepatotoxicity has not been established, nor an increased risk proved to follow multiple halothane administrations, we believe, par-

ticularly on the basis of independent sporadic investigations of our own, that some caution is warranted. A patient in whom unexplained fever or jaundice develops after halothane, having had this anaesthetic previously, should not be given it again[6].

The association between the anaesthetic and hepatitis was further emphasized by Trey and the Acute Hepatic Necrosis Fulminant Hepatitis Surveillance Group from Boston, Massachussetts[7]. In a survey of 150 patients with fulminant hepatic necrosis reported to this group from all over the world, 36 had received halothane, 27 on more than one occasion; 32 died.

Perhaps the strongest evidence that hepatitis and halothane are associated comes from observations after re-challenge with the halothane. The high mortality for hepatitis associated with halothane makes deliberate challenge in most cases unethical, but it has been noted under special circumstances. Tygstrup[8] observed a patient with a brain tumour who developed acute hepatitis, confirmed by hepatic biopsy, on three occasions following the administration of halothane for therapeutic or diagnostic procedures. Anaesthetists are particularly at risk of developing hepatitis for they are receiving multiple exposure to halothane. Belfrage and co-workers report such a case in an anaesthetist, and Combes[10] in a leading article in the *New England Journal of Medicine* notes two others. The most convincing example is probably that reported by Klatskin and Kimberg[11]. Their patient, a 44-year-old clinician, in 1961 commenced training as an anaesthetist and was exposed almost daily to halothane. During this training he suffered recurrent episodes of hepatitis. Each relapse coincided with his return to work and re-exposure to the anaesthetic. Deliberate re-challenge with halothane led rapidly to chills and fever. A liver biopsy was done and this showed the histological features of hepatitis and hepatocellular necrosis and collapse of the reticulum framework of the liver. Healing was followed by increased scarring and this ultimately led to cirrhosis. The patient gave a history of asthma and hay fever and this allergic diathesis may have been important. Since a liver biopsy was not performed at the onset of the illness, the possibility of a pre-existing cirrhosis cannot be excluded. However, the results with halothane re-challenge strongly suggest that the development of cirrhosis in this case was attributable to intermittent halothane-induced acute hepatic necrosis which led to progressive fibrosis. The condition has also been reported in a worker in a factory where halothane is produced[12].

Clinical Features

Halothane hepatitis is much more frequent after multiple anaesthetics and this occurrence makes the reaction almost certainly a hypersensitivity one. It is therefore likely to affect patients exposed to multiple surgical procedures. This is especially so in gynaecological practice, particularly with radium treatment of carcinoma of the cervix and uterus. Hughes and Powell[13] have described six patients who developed severe hepatocellular jaundice following multiple halothane anaesthetics for radium therapy of carcinoma of the cervix. Halothane hepatitis may complicate multiple orthopaedic or plastic operations and occurs in ophthalmological practice as a complication of operations to correct strabismus.

The clinical features of 32 patients with halothane-related hepatitis have been summarized by Klion, Schaffner, and Popper[12]. The first abnormal event

is usually fever developing seven days after the first operation and usually accompanied by malaise and non-specific gastrointestinal symptoms, including right-sided upper abdominal pain. Unexplained postoperative fever is one of the most constant features indicative of liver damage related to halothane[14]. Rise in temperature is found not less than seven days after the first operation (range eight-14 days). After several exposures the temperature is noted one to 11 days postoperatively. Jaundice appears rapidly after the pyrexia about ten to twenty-eight days after a single exposure, but with multiple anaesthetics some three to seventeen days later. This delay, usually of about a week before jaundice, is evidently helpful in excluding other causes of postoperative icterus such as transfusion reactions, septicaemia, shock, and benign postoperative cholestasis[15]. Hepatomegaly and splenomegaly are rare.

The total white cell count is usually normal but there may be an absolute eosinophilia in the peripheral blood. Serum bilirubin levels may be very high, particularly in fatal cases, but were under 10 mg in 40% of one large series[12]. The condition may be anicteric and if this is so, it is likely that it will not be diagnosed accurately. Clinicians must be alert to the possibility of halothane hepatitis in any patient with postoperative fever. Serum transaminases are usually in the range found in viral hepatitis. An occasionally high serum alkaline phosphatase level may be seen. If the condition is recognized and the patient becomes icteric, the mortality is very high, even up to 20%. If coma ensues and the one-stage prothrombin time falls markedly in spite of intramuscular vitamin K therapy, the outlook is virtually hopeless. The mortality is obviously less in the anicteric cases and many are probably unrecognized.

Hepatic Changes

Unfortunately, hepatic histological changes are virtually indistinguishable from those of acute viral hepatitis although leucocyte infiltration into the sinusoids, granulomas, and fatty change in the liver cells are somewhat suggestive of a 'toxic' origin for the hepatitis[12]. Peters and co-workers[14] from Los Angeles have studied hepatic material from 41 patients (33 fatal and eight non-fatal) with hepatic necrosis related to halothane anaesthesia. At necropsy the liver in 72% of those who died was shrunken to 1,000 g or less. Hepatic histology was classified into three stages, some with overlapping features. In the first or necrotic stage noted in patients who survived only up to eight days, necrotic cells of a zonal type were almost completely absorbed, leaving behind many lipochrome-filled macrophages and either dilated hyperaemic sinusoids or a collapsed ischaemic centrizonal zone in which there were areas of condensed stroma and collagen fibres. In the third or regenerative stage, usually two or more weeks after the onset of jaundice, the necrotic debris in the centrizonal areas had disappeared and the connective tissue framework was somewhat compressed. Lipochrome-filled macrophages were still present together with a few lymphocytes. The characteristic feature was the presence of regeneration in the periphery of the lobules. The main difference from acute fulminant hepatitis was the deposition of significant amounts of collagen within two weeks of acute hepatic necrosis. Acute viral hepatitis predominantly affects parenchymal cells. Hepatic necrosis associated with halothane

anaesthesia may destroy both parenchyma and stroma, thus causing the injured stroma to react by forming collagen.

Electron microscopy of the liver also reveals differences from acute viral hepatitis[12]. In halothane hepatitis the mitochondria show segmental loss of the outer membrane and infolding of the inner one. These changes are not seen in viral hepatitis, in which mitochondrial swelling occurs—and then only in severely damaged cells. The rough endoplasmic reticulum is intact and lysosomes are not prominent, unlike viral hepatitis, in which the rough endoplasmic reticulum is fragmented and lysosomes, consisting mainly of autophagic vacuoles, are numerous. Whether an increase in the smooth endoplasmic reticulum is related to prior drug administration (enzyme induction) or to exposure to halothane is uncertain.

Based on large numbers of cases, interesting differences have therefore been shown both by light and electron microscopy between halothane and viral hepatitis. The detection of such differences, however, largely depends on the experience of the pathologist. In the individual case there is no absolute diagnostic difference between the two conditions and usually only a tentative conclusion can be drawn concerning the aetiology of the hepatitis.

Halothane anaesthesia should not be repeated if there is the slightest suspicion of even a very mild reaction after the first anaesthetic. In view of its otherwise desirable properties it may be used on a single occasion for operations such as portacaval shunts. There is no increased likelihood of a patient with underlying liver disease having an adverse reaction[9]. There is no indication how long the hypersensitivity to halothane persists.

Mechanisms

The mechanism of halothane hepatitis is still unclear. Adverse reactions seem unrelated to the methods of administration, the length of operation, or the surgery being performed. Halothane is at least partially enzymatically degraded as a glucuronide and it is possible that this enzymatic breakdown could bring about the formation of toxic by-products. Cohen[17] suggests that variation in enzymatic activity from one person to another could be an important factor in possible toxicity. There seems to be no animal model capable of detecting halothane hepatitis. The recent observations of Biebryck and co-workers[18] are therefore of considerable interest. Rats were exposed to repeated halothane anaesthetics and their livers were subsequently isolated and perfused. Bromsulphthalein retention in the perfusate of these isolated livers was greatly increased one to three weeks after the last exposure to halothane and the BSP glutathione conjugating enzyme activity in homogenates of the livers was found to be depressed. These findings did not occur after many exposures to di-ethyl ether or following a single exposure to halothane.

The increased susceptibility after many exposures, the granuloma formation in the liver, and the eosinophils all suggest a hypersensitivity mechanism. There are other evidences of disturbed immunity in halothane hepatitis. Antimitochondrial antibodies were found in seven of nine sera from patients with jaundice after halothane anaesthesia[19]. In another study, two patients with halothane-related hepatitis gave positive mitochondrial tests by immunofluorescence, and in one the complement-fixation test was positive[20]. The titre of mitochondrial antibodies was usually low and transient. It has been

postulated that halothane might combine with mitochondria to produce mitochondrial damage and form stable drug-mitochondrial complexes to elicit an immunological reaction[19]. A positive result for antinuclear factor and thyroid and gastric parietal cell antibodies is more common than in matched controls[20]. If lymphocytes of patients suffering from halothane hepatitis are incubated with a halothane-containing solution, there is an increased uptake of ^{3}H thymidine into them[21]. The effect disappears with recovery. This indicates increased DNA synthesis and supports the suggestion that the patient's lymphocytes have been sensitized to halothane. Six of the eight patients studied showed positive antimitochondrial tests in the serum and these in general correlated with the results for lymphocyte culture. Popper and Paronetto[21] suggest that this lymphocyte test might be a useful method of diagnosing halothane-related from viral hepatitis.

Tests for hepatitis-associated (Australia) antigen are negative in drug-related jaundice[21,22], making it unlikely that the drug activates the virus and that the halothane reaction is merely a coincidental virus hepatitis.

Methoxyfluorane

Hepatic reactions have also been reported after another halogenated ether anaesthetic, methoxyfluorane (Penthrane), usually with repeated administration[23]. It has been reported in an operating-room nurse[24]. The picture is a hypersensitivity one and very similar to that of halothane hepatitis[25].

Conclusion

It has now been accepted, at least in most quarters, that halothane hepatitis exists. The last three years have seen important developments in its differentiation from viral hepatitis—clinically, by morbid anatomy, and by immunological means. Increased alertness to the significance of delayed postoperative fever may allow diagnosis of the milder cases. The complication is probably rare although it is difficult to quote accurate figures. Mushin and co-workers[4] gave a figure of 1 in 10,000 administrations. On the other hand, Peters and co-workers[14] scrutinized the findings of the National Halothane Study and report that if hepatic necrosis per cases of multiple exposures to halothane is used for assessment, the incidence is 7 per 10,000 or 0·7 per 1,000. The figure may be even higher if the number of patients who had received halothane more than once in a one-month period was used for calculation. It is exceedingly important that all cases of suspected halothane hepatitis be reported to the Committee on the Safety of Drugs so that more accurate figures may be obtained. There is no question that halothane is a valuable anaesthetic for major operations. Its place in minor surgery, such as in dentistry, particularly if repeated, might be questioned.

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