Halothane Hepatitis: A Review

D. SPITERI

Introduction

The association of liver damage and Halothane, a divisive issue hotly debated in the '60's and 70's, is now an accepted finding following the accumulation of clinical and experimental evidence. However Halothane is too often blamed when a clinician is confronted with a patient with unexplained jaundice after anaesthesia. This prejudiced attitude has been inherited from the days of Chloroform anaesthesia. It is an understandable human weakness to try and find a scape goat for whatever goes wrong – in this case an idiosyncratic reaction to an otherwise safe drug.

Historical Background

Unexplained jaundice after Chloroform anaesthesia was first recorded in 1848, only one year after its clinical introduction by James Simpson – a Professor of Obstetrics from Edinburgh. This "Delayed Chloroform Toxicity" 1 - 2 days after the anaesthetic, also involved the heart, kidneys, pancreas and spleen causing "fatty degeneration". The cause and effect relationship between Chloroform and jaundice is not as clear as was once believed. Repeated short administrations were associated with an increased incidence and severity of the syndrome. Protective factors were:

a. a good nutritional state
b. good oxygenation
c. avoidance of carbon dioxide accumulation.

Another halogenated hydrocarbon anaesthetic Trichloroethylene causes hepatotoxicity in animals only. Ether and Nitrous Oxide have never been implicated in liver damage.

Since its introduction to anaesthesia in 1956, Halothane soon became the standard volatile anaesthetic – a postion which it still holds today – due to its potency, smoothness of use and its non-inflammability. Preliminary animal studies prepared during development of the drug had not shown any propensity for hepatitis but reports of unexplained jaundice started appearing in 1958[1].

Incidence

By 1963 at least 350 possible cases of Halothane hepatitis had been reported world wide.

A large scale retrospective epidiomological study – the American National Halothane study of 1969 – was inconclusive except in confirming that Halothane hepatitis was quite a rare event. In this study 850,000 patients were reviewed. Out of this cohort of patients

30% had been anaesthetised with Halothane and in 9% the exposure was repeated.

82 patients had hepatic failure at post-mortem of these 9 patients had jaundice that could not be explained either surgically or medically but 7 of these had received Halothane some time before dying. The mortality from anaesthesia with Halothane and without Halothane was not significantly different.

Mushin in 1971[2] estimated that 1.5 million patients were anaesthetised each year with Halothane in England and Wales (i.e. 80% of general Anaesthetics) 7% were re-exposed to it within a month. A yearly average of 7 - 9 cases of jaundice after Halothane was reported.

The frequency of Halothane hepatitis was estimated as 1 : 35,000 Halothane anaesthesia, a very low figure indeed.

From analysis of 313 well documented cases of jaundice following Halothane anaesthesia reported to the Committee on Safety of Medicine in the years between 1964 and 1985 the following facts can be studied:

1. 246 of the cases (78.5%) were multi-exposed
2. 169 of these cases (54%) were re-exposed within 28 days.

Out of the 313 cases described:

1. 146 patients (47%) died
2. Mortality was 32% for patients exposed only once
3. 41% for those exposed twice
4. 54% for those multi exposed

From results of experimental studies, two, probably distinct, forms of Halothane liver damage have been identified:

Dr David Spiteri, M.D. Accreditation in Anaesthesia, Leuven. Registrar in Anaesthesia St Luke's Hospital, Malta.

TYPE 1

Minor : Ser. Aminotransferase (AST) levels become raised during the first 1 - 3 days post-operatively in 20% of patients exposed to Halothane. These changes sometimes became manifest only in the 2nd post-operative week but the patients remain well clinically.

TYPE 2

Massive fulminant hepatic necrosis – a rare event. The onset of such a reaction takes 1 - 2 weeks to develop.

Jaundice[3,4]

Jaundice appearing in the days and weeks following general anaesthesia can be classified as:

a. Transfusion reaction; incompatibility and haemolysis of old, infected or heat haemolysed blood.
b. Effects of drugs on patients with some enzyme defects eg. G6PD deficiency.
c. Crises in certain abnormal Hb disease (eg. sickle cell).
d. Operative stress on pre-existing liver disease: Hypoxia, Hypoperfusion.
e. Drug toxicity
    1. Hepatitis: non-narcotic analgesics, antibiotics, cystotoxics, anti-epileptic drugs.
    2. Cholestasis: Antibiotics, cytotoxics, steroids, oral, hypoglycaemic agents, neuroleptic agents.
f. Hepatic infective process/abscess of the liver.
g. Viral infective A, B, non A, non B, CMV, Epstein-Barr virus. It remains true that viral hepatitis cannot yet be excluded in any patient with absolute certainty, Viral hepatitis and Halothane hepatitis are virtually indistinguishable clinically and histologically. IgM antibodies for Hepatitis A prove the presence of active infection. The presence of IgG antibodies only indicate a previous infection (Up to 80% of population have a positive test). The stress of an operation may also influence the severity of a viral hepatitis.
h. Biliary tract obstruction or leakage with biliary peritonitis.
i. Septicaemia.

Animal Studies

Different rat models have been studied[5]: one necessitates the pre-treatment of male rats with Phenobarbitone and then exposure to Halothane under hypoxic conditions (i.e. the REDUCTIVE PATHWAY). Other models require pre-treatment of guinea pigs with Thriiodothyronine or Polychlorinated biphenyl without the necessity of hypoxia during Halothane exposure, (i.e. the OXIDATIVE PATHWAY).

Although these models helped considerably in the understanding of Halothane hepatitis; they may not be totally relevant in man;

1. Halothane hepatitis in animal models is a temporary and relatively mild disorder.
2. Patients taking inducing drugs e.g. epileptics have not been shown to have a greater risk of Halothane hepatitis.
3. Mice, dogs, female rates, non-adult rats and a certain strains of rats are resistant to liver injury by Halothane but not to hypoxic liver damage. This highlights the considerable species, sex, age and even strain differences that exist in susceplibility to Halothane hepatitis.

Human Studies

Several features of Halothane hepatitis gave rise to the concept that allergy or hypersensitivity were implicated.

1. Multiple administrations increased both the incidence and the severity of the hepatitis; massive necrosis has happened. Rarely after a single exposure. There have been instances where patients had jaundice attributed to a 2nd Halothane anaesthetic who received a third exposure without mishap.
2. Serological abnormalities indicative of hypersensitivity reaction are often found in patients having Halothane jaundice. These are peripheral eosinophilia, circulating immune complexes, serum antibodies (notably liver-kidney microsomal antibody and antibody to thyroglobulin) could be demonstrated in 44% of cases during the liver failure.
3. Liver damage following occupational exposure to Halothane has been reported in operating theatre personnel. These exhibit raised AST's, evidence of hepatitis on liver biopsy, demonstration of specific antibodies to halothane, altered hepotocytes and in some cases positive 'challenge tests'. With avoidance of exposure the AST levels returned to normal values in four weeks.
4. Induction of liver enzymes, often occurs with chronic exposure, to trace concentrations.

Anaesthetics are known to alter cell membranes – this fact is the basis of one theory for their mode of action – but they do this reversibly. It is unlikely that the appearance of the antigen is due to a haptene

effect of Halothane on the membrane. The antigen is not present on the membrane immediately following exposure[6].

Enhanced metabolism of the drug cause the development of reactive metabolites which bind covalently to the endoplasmic reticulum. These potential antigenic complexes will later be incorporated in the cell surface membrane and thus become exposed to immune attack, an antigen – antibody reaction.

The biotransformation of Halothane was not known to exist before it had been in use for at least 6 years! But by 1967 it was established that about 18% of inhaled Halothane is in fact metabolised. Halothane may undergo metabolism through 2 pathways. Both can give rise to reactive intermediates.

a. OXIDATIVE METABOLISM is the major metabolic pathway for Halothane, and is stimulated by high oxygen tensions. Several compounds produced in this way but mainly it is Trifluoroacetic acid that dominates the picture.
b. REDUCTIVE METABOLISM of Halothane was first described in 1973 and noted to be stimulated by hypoxic conditions and pretreatment with enzyme inducers (eg. Phenobarbitone), Fluoride and bromide ions are released freely during this type of degradation.

The association with hypoxia led some investigators to implicate hypoxia as a necessary factor in all cases of hepatotoxicity in man. However it is rare that liver necrosis is the primary and sole untoward event seen with hypoxic episodes in man. Hypoxia and splanchnic hypoperfusion are much more common during anaesthesia than we would like to remember and yet massive liver necrosis is rare. Furthermore the timing and type of lesion occuring with hypoxia is quite different from that with Halothane hepatitis.

Features Associated with Halothane Hepatitis

Brown et al.[7] and Travel et al. [8] when describing the adverse effect to volatile anaesthetics could classify the following:

1. Female to male ratio 1:8:1
2. More than 2/3 of the patients were obese.
3. The age range of 21 to 76 years (mean 57) is somewhat older than the general age distribution of patients undergoing anaesthesia. It also contrasts appreciably with the much younger age distribution for viral hepatitis – (10 - 60 years (mean 25).
4. There is no association with type or length of surgery.
5. Repeated exposure to Halothane within a 'relatively' short time. However cases are known where the interval was 6 and 7 years.
6. 60% may show retrospective evidence of an adverse reaction to Halothane.
7. In one third a history of allergy to some other drug was obtained.
8. In 75% of cases, unaccountable post-operative high pyrexia is seen.
9. Deep jaundice appearing in about 5 days (2 - 26 days) post-op. The shorter the period of re-exposure the quicker the onset of jaundice. The presence of other signs of severe liver damage: Prothrombin time, 18 raised to 150 secs, Serum Aspartate 386 raised to 10,272 units and hepatic encephalopathy.
10. Exclusion of viral hepatitis with the generally available serological tests.
11. Demonstration of antibody which reacts with Halothane-altered liver-cell preparation – a positive means of diagnosis – but not generally available except in certain research centres.

Halothane Hepatitis in Malta

In St Luke's Hospital, Malta over 18,000 General Anaesthetics are administered yearly and Halothane is the agent used in 80% of these cases. The incidence of Halothane hepatitis is rare but I could find confirmation of two cases of this happening.

In the first case Mrs G.P. 54 years, 80Kg body weight, married with three children had been operated in 1950 for uterine fibroids. She was allergic to Penicillin and Tetanus Toxoid. She suffered from hypertension and was on Methyldopa 50mg and Frusemide 40mg daily. As she was also suffering from an anxiety neurosis she was having Lorazepam 3mg and Maprotilene 50mg daily. She smoked 40 cigarettes a day.

In September 1986 she was admitted with a lump in the breast and after frozen section biopsy, mastectomy and axillary lymph node clearance was performed. She was given Midazolam 0.005mg per kg b.w. and Atropine 0.01mg per kg b.w. as premedication and then Fentanyl 0.001mg per kg b.w., Pentothal 5mg per kg b.w. and Suxamethonium 1mg per kg b.w.

After recovery from the intubating dose of Suxamethonium, breathing was spontaneous and the patient had Halothane 2% in N_2O and Oxygen, 4 litres each. Pentazocine 0.5mg per kg b.w. was given for pain post-operatively on a pro re neta basis (3 doses in all).

Three days post-operatively she had a temperature (39°C) and was started on Erythromycin Stearate 5mg per kg b.w. peros. Her BP was controlled by Pindolol 10mg and Clopamide 5mg, daily, and for sedation Diazepam 10mg and Lorazepam 4mg given.

The histology result was reported as infiltrating ductal carinoma with metastasis in the axillary lymph nodes present. She still had a swinging temperature and the antibiotic was changed to Gentamicin 3mg per kg b.w. Both a skeletal survey and an ultra-sound done some days later showed absence of liver metastasis.

As there was partial wound breakdown secondary suturing was necessary in 4 weeks time. It was a short procedure done under Pethidine 1mg per 1 kg b.w. Scoline 1mg per kg b.w. for intubation, Nitrous Oxide, Oxygen and Halothane 2% were used for maintenance of the 15 minutes procedure. Breathing was spontaneous. Post-operatively she was put on Gentamicin, 3mg per kg b.w. and for pain relief had Pethidine 1mg per kg b.w. for two doses at 6 hour intervals.

On the day following she had a temperature 39°C and on the 3rd post-operative day jaundice was first noticed. Murphy's sign was negative. Stools were normal in colour. Urinalysis showed urobilin and absence of urobilinogen. All current drugs were stopped. Coombs' test was negative. Serum testing for Hepatitis A, Australia antigen and Paul Bunnel were negative. She was started on IV 5% Dextrose and KCL, 1gm given in the bottle to correct a low pressure and a multi vitamin preparation and oral luctose were started. By 10 days she was afebrile, but lethargic showed a slight flap of the outstreched hands, the liver was palpable for 1 - 2 fingers. The spleen was not felt and no ascites could be demonstrated. The abdomen was not tender anywhere. Urine output was good. (See Table 1).

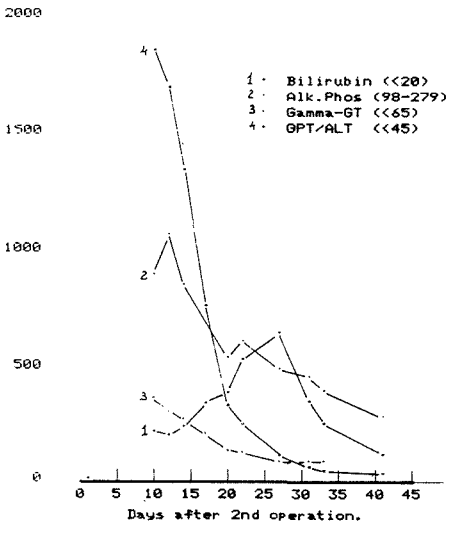
On the 12th day she fainted while straining at stools, her condition deteriorated and the jaundice became deeper, she started vomiting and became drowsy, and the next day the BP was 95/60 and she had a decreased urine output. Plasma and Mannitol 10% were given in adequate amounts.

A liver biopsy performed on the third day of jaundice showed an inflammatory infiltrate arranged in septal patterns, composed of mononuclears and some eosinophils with necrotic foci and areas of bile stasis. This was said to be compatible with Halothane induced hepatitis.

The wound was infected but the temperature was now normal. A swab from the wound gave Staph, aureus on culture. An ultra-sound showed no intra/extrahepatic biliary-duct dilation. CT-Scan confirmed generalised liver enlargement but no biliary tree dilatation. She was much better by the 15th day although the wound showed delayed healing, and a swab now yielded Pseudonomas aureginosa on culture. Some days after she was discharged from hospital without further problems.

TABLE 1

Liver function tests



In the second case of Halothane hepatitis Miss JGS. 15 years, with no past medical complaints, or allergies was admitted on the 20th of February 1986 with a fracture of shaft left tibia and fibula following a sports injury. Closed reduction under Thiopentone 5mg per 1kg b.w. I.V. and Nitrous oxide in Oxygen 4 litres in each and Halothane 2% carried out the same day. After 15 days she was readmitted as the fracture was displaced and re-manipulation was again carried out under the same kind of anaesthesia. She was discharged home later in the day. Next day she came back with a pyrexia of 40 degrees C and vomiting. Jaundice was noted on the third post op date. LFT's showed:

ALT 46, Alk.phos 650 u/l, Bilirubin 166 u/l and Gt 140 u/l. Her parents took her to a London Hospital and repeat LFT's showed:

AST 46, Alk.phos 112, Bilirubin 29 and Gt 95. Prothrombin time 0.9.

Serum testing for Hepatitis A, B, CMV and Epstein Barr virus were negative. Halothane antibody testing by ELIZA technique was not confirmed.

After 6 weeks she underwent internal fixation under spinal anaesthesia and Midazolam sedation. Recovery was uneventful and repeat LFT's were normal.

Discussion

Halothane hepatitis is widely held to be almost non-existent in children. Wark (9) reviewed 23 years of Grt. Ormond Street paediatric operation performed under general anaesthesia, from 1957 - 1979 (165,400 patients) and only found two unexplained cases of hepatitis, 267 patients underwent multiple exposure within 28 days with impunity. He concluded that the chances of a child developing Halothane hepatitis are 1:82,000. The reportage of major adverse drug reactions is similar in children and adults: 1:2,000 - 1:10,000 but no explanations can be given why the condition of Halothane hepatitis is rare in children.

Enflurane hepatotoxicity occurs – since its introduction in 1973 15 cases have been assessed by Eger and colleages from 88 reported cases as being probable Ethrane Hepatitis (1 in 800,000). This is far below the spontaneous viral hepatitis attack rate. Mortality following Enflurane hepatitis is 21% so far.

Only one unconvincing report of jaundice with Isoflurane (introduced in 1984) has been reported. One may note that whereas Halothane is 20% metabolised, Enflurane is only 2% and Isoflurane less than 0.2% metabolised. One cannot forget the expense of these more recent introduced agents:

Halothane which used to be called 'Liquid Gold' costs 7.50 pounds sterling, Enflurane 29 pounds and Isoflurane 72 pounds per 250ml.

The modern anaesthetist may be fortunate in having alternative techniques at his disposal but they have by no means been shown to be safer for the patients[10]. In children the position is even more vague. Should an incidence of 1:82,00 influence the usage of Halothane which has been proved to be of great value with regards to overall safety?

Conclusion

It seems prudent in the light of present knowledge to recommend that:

1. In the pre-operative evaluation previous exposure to halothane and any possible reaction to it are looked for.
2. Unless any overiding consideration exists re-exposure to Halothane within 3 months should be avoided in adults.
3. A patient with a history of unexplained jaundice or pyrexia following exposure to Halothane should not be re-exposed to Halothane. This fact should be clearly marked on the case-history.
4. In those patients who are likely to require multiple anaesthetics (eg. burns patients) and those associated with a higher risk (eg. females, obesity, familial history) (allergy ?); Halothane is best avoided.

Since Halothane hepatitis has been reported appearing after the first exposure while many patients undergo repeat re-exposure with impunity, and still others develop Halothane hepatitis after an exposure many years after a series of operations, it is quite clear that no firm 'safe period' between repeat Halothane exposure can be scientifically agreed upon, however avoiding re-exposure within a 3 month period has been recommended for medico-legal purpose.

References

1. **Editorial**. Anaesthesia 1986 41 page 515-578.
2. **Inman and Mushin**. Analysis of CSM reported Halothane hepatitis cases in U.K. BMJ 1974 1 page 5.
3. **Lewis L and Blair J.** Halothane hepatitis in children. BJA 1982 54 page 349-354.
4. **Wilbur and Sumner**. Halothane Hepatitis in an 11 month old Asian child. Anaesthesia 1986 10 page 611-613.
5. **Vergagni et alter**. Antibodies to the surface of Halothane-altered rabbit hepatocytes in patients with severe halothane associated hepatitis. NEJM 1980 303 page 66-59.
6. **Neuberger et alter**. Specific serological markers in the diagnosis of fulminant hepatic failure associated with halothane anaesthesia. BMJ 1985 289 page 113.
7. **Brown et alter**. Adverse effects of volatile anaesthetics BJA 1987 59 page 14-23.
8. **Trowel et alter**. A study of LFT's after Halothane anaesthesia. Lancet 1975 1 page 821.
9. **Wark J.** Halothane hepatitis in children. Anaesthesia 1982 38 page 237-242.
10. **Strunin and Simpson**. A study of LFT after Halothane anaesthesia Proc. R. Soc. Med. 1973 66 page 56.