Halothane hepatitis in a South African population — frequency and the influence of gender and ethnicity

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Aim. To review post-anaesthetic hepatitis in a South African population, given that halothane use is restricted in other countries because of the high mortality and morbidity of its associated type II (idiosyncratic) hepatitis, even though it is still widely used in South Africa.

Study design. Descriptive, retrospective analysis.

Patients and methods. Hepatitis cases that occurred after inhalational anaesthetic use were identified by means of a computer search of Groote Schuur Hospital records, 1980 - 1994. Cases of hepatitis caused by circulatory failure and viral hepatitis were excluded.

Results. Twenty-six episodes occurred in 22 patients (mean age 49.05 years, range 32 - 65 years), of whom 15 were women. This gave an estimated incidence of 3.53/100 000 anaesthetics (95% confidence interval 2.06 - 5.0/100 000). All had pyrexia (mean 38.7 ± 0.72°C), malaise, anorexia or nausea and vomiting, with onset a mean of 4.27 ± 3.5 days after exposure. Jaundice occurred in 86%, rash in 13.6%; 17 patients (77%) were obese. Alanine and aspartate aminotransferase levels were raised 47.49 ± 61.8 and 55.9 ± 54.5 times the upper limit of normal. Seven patients died and 1 underwent liver transplantation. Hepatitis occurred after the first exposure in only 2 patients (9%). Men and women had a similar risk, but the estimated relative risk for whites v. black or coloured patients was 3.33 (95% confidence interval 1.45 - 7.23; $P = 0.003$) controlling for gender. Awareness of the condition was suboptimal, and in 3 patients re-exposure to halothane occurred after an initial episode of typical halothane hepatitis.

Conclusion. Halothane hepatitis remains a major cause of morbidity and mortality in South Africa. It is more common in whites, but there was no gender-related excess risk.

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Halothane (2-chloro-2-bromo-1,1,1-trifluroethane) is a commonly used general anaesthetic which is thought to be significantly more hepatotoxic than other halo-alkane general anaesthetics.[1,2] While halothane may cause minor increases in serum transaminases in 25 - 30% of patients (type I hepatitis), the important problem associated with its use is the idiosyncratic, massive liver cell necrosis that frequently leads to fulminant hepatic failure (type II hepatitis).[3] Concern about this complication has led to the restriction of its use in many countries, including the UK[4] and the USA.[5]

The prevalence of and risk factors associated with halothane use have not been established in South Africa, where the agent remains widely used and where ethnic and genetic factors may influence the risk of type II hepatitis.

This study was therefore performed to establish the frequency, clinical features and outcome of hepatitis associated with inhalational halo-alkane anaesthetic use, and to identify the potential risk associated with race and sex in a South African population.

Patients and methods

All cases of hepatitis or jaundice that were documented within 1 month after exposure to an inhalational anaesthetic between the years 1980 and 1994 were identified using a computer-based search of Groote Schuur Hospital records. Cases were excluded when there was evidence of concomitant hepatotropic viral infection, circulatory failure, sepsis or another cause of postoperative jaundice. As Groote Schuur is a referral centre, prevalence was determined using only those cases where the anaesthetic was given at Groote Schuur Hospital or its associated hospitals. All referred patients were included in the clinical analysis, however.

The Cochran-Mantel-Haenszel statistic was used to establish the significance of differences between men and women and between different ethnic groups.

Results

Five hundred and fifty-three cases of postoperative jaundice were identified from the hospital records, of which 26 episodes of halo-alkane anaesthetic hepatitis were diagnosed in 22 patients (mean age 49.05 years, range 32 - 65 years), of whom 15 were women. All cases were due to halothane, and 4 had been referred to Groote Schuur.

Twenty-two of the 26 episodes of hepatitis occurred in Groote Schuur and related hospitals. During the same period 623 638 inhalational anaesthetics were given, yielding an estimated frequency of 3.53 hepatitis cases per 100 000 anaesthetics (1 case in 28 329 anaesthetics, 95% confidence interval (CI) 1 in 48 543 to 1 in 20 000).

Clinical features are shown in Fig. 1. Fulminant hepatic failure occurred in 9 cases, and halothane was the fourth most common cause of acute liver failure during this period (17%). Seven patients died and 1 underwent liver transplantation (36% mortality rate). Hepatitis occurred after the first exposure in 2 patients (9%).

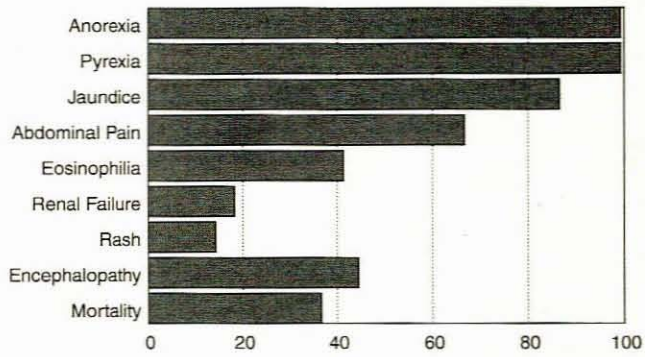

Fig. 1. Clinical features in 22 patients with halothane hepatitis (%).

The estimated relative risk for men compared with women, adjusted for ethnicity, was 0.63 (95% CI 0.26 - 1.54; $P = 0.3$, Cochran-Mantel-Haenszel statistic). The risk ratio was similar, with and without adjustment for ethnicity (0.63 v. 0.64, respectively).

A significant difference in the risk of halothane hepatitis was found according to ethnicity, controlling for gender ($P = 0.024$, Cochran-Mantel-Haenszel statistic). The unadjusted frequency, expressed as cases per 100 000 anaesthetics, in whites v. coloureds v. blacks was 8.2 v. 2.5 v. 2.5. As the coloureds and blacks had an identical frequency of cases, these groups were combined for analysis of risk according to race. The estimated relative risk for white v. black or coloured patients was 3.33 (95% CI 1.45 - 7.23, $P = 0.003$).

Awareness of the entity among both anaesthetists and physicians was suboptimal, and in 3 patients re-exposure to halothane occurred after an initial episode of typical halothane hepatitis. One patient had multiple re-exposure after an initial presentation with typical halothane hepatitis. Each subsequent re-exposure led to worse hepatitis, and culminated in death from acute liver failure after a third exposure. Of 17 cases, where information was available about possible previous anaesthetic reactions, 8 patients had a prior minor adverse reaction to halothane.

Case reports

Case 1

A 35-year-old genetically female patient with gender dysphoria underwent 7 operations between 1988 and 1993 for gender reassignment. Halothane was given on three occasions without causing any fever or any documented rise in transaminase levels. In 1993, 1 day after halothane anaesthesia, she became pyrexial and was noted to be jaundiced on day 5. Prior to surgery, aspartate aminotransferase (AST) (20 IU/l) and alanine aminotransferase (ALT) (20 IU/l) levels were normal (normal < 25 for AST and ALT). Total and conjugated bilirubin concentrations rose to 138 and 77 µmol/l respectively, AST to 713 IU/l and ALT to 530 IU/l; international normalised ratio (INR) was 2.2. Hepatitis serology was negative and liver biopsy showed submassive necrosis with collapse fibrosis, in keeping with toxic hepatitis. Testosterone hepatitis was diagnosed and she made a full recovery over the following

6 weeks. Isoflurane was used for a subsequent operation in October 1993, and the postoperative course was uneventful. In February 1994 halothane was again administered. On day 1 postoperatively, the patient's temperature rose to 38.5°C, and AST and ALT levels to 1 218 and 990 IU/l respectively. Levels peaked on the 3rd postoperative day, the INR rose to 1.4 and the patient made an uneventful recovery over the following 5 weeks.

The case illustrates the association between multiple, recent exposures to halothane and the onset of hepatitis. In addition, this case was not unique in that the diagnosis was not even entertained, despite its classic presentation; a subsequent halothane anaesthetic was given, with a consequent recurrence of typical hepatitis.

Case 2

An obese 41-year-old lecturer underwent arthroscopy in March 1994 and 3 weeks later had an anterior cruciate ligament repair. On both occasions, halothane was used. The course was uncomplicated after the first operation, but he became pyrexial, confused and developed acute liver failure on the first day after the second operation. Transaminase levels rose to over 2 500 IU/l, the INR to 8, and creatinine to 111 mmol/l. He had a successful orthotopic liver transplant on the 5th postoperative day and made a full recovery following this.

Repeated halothane anaesthetics in close succession may cause severe hepatitis. His acute severe liver failure had a short latent period, indicative of a poor prognosis; liver transplantation was probably life-saving.

Discussion

This is the first series of halothane hepatitis reported from South Africa. The overall incidence of 3.53/100 000 (1 in 28 329) with a 95% CI of 2.06 - 5.00/100 000 (1 in 48 543 to 1 in 20 000), is similar to that reported by the National Halothane Hepatitis Study[6] but lower than the frequency of 1/3 500 suggested by some authors.[3,7,8] It is possible that incomplete case-finding may account for this difference. However, care was taken to screen all patients in whom postoperative hepatitis or jaundice was documented, even when a diagnosis of halothane hepatitis had not been made at the time. It is unlikely that any severe cases were missed, but it is possible that mild cases discharged before the onset of symptoms, or not investigated for postoperative symptoms or fever, could have been missed. Our figures therefore represent the minimum frequency of the disease in a South African population. In addition, no exact figures were available for non-halothane anaesthetics given during the period of the study, but it is estimated that < 10% of all anaesthetics were non-halothane. The incidence may therefore have been up to 10% higher than given.

All ethnic groups are at risk of developing halothane hepatitis, but in this study ethnicity was found to be associated with a significant difference in this risk. White patients had a higher risk of developing halothane hepatitis than coloured and black patients (risk ratio 3.24; CI 1.47 - 7.23, $P = 0.003$). This factor has not previously been documented, but most previous studies have been performed in more homogeneous populations. A genetic predisposition to halothane hepatitis has been suggested[9-11] and the different frequencies that we have demonstrated in different ethnic groups may support this suggestion. However, the retrospective nature of the study does not allow for firm conclusions, as we could not control for other factors which could potentially have influenced the incidence of hepatitis cases, such as the number of repeated anaesthetics, and the prevalence of obesity in the black and coloured patients compared with white patients.

Our finding that women did not have a greater relative risk of halothane hepatitis is at variance with the findings of most previous studies. Although more than twice as many women as men developed hepatitis (15 women, 7 men) in our series, women also underwent significantly more anaesthetics (365 021 v. 258 617), and the estimated relative risk for men compared with women, adjusted for ethnicity, was 0.63 (95% CI 0.26 - 1.54, $P = 0.3$). Previous studies have not given a sex-related incidence of disease, but overall, 66% of reported cases have been in women.[10,12-16] The large number of patients screened in this study makes it unlikely that the result is due to a lack of statistical power.

We have confirmed that, with rare exceptions, hepatitis only develops after multiple exposures to halothane, often when these are given over a short period of time. All but 2 patients had had at least 1 previous halothane anaesthetic (mean number of previous exposures 2.54 ± 2.4). Previous studies have shown that the risk of hepatitis may be significantly reduced if repeated exposure, especially within the space of 1 month, is avoided.[14,17]

Clinical features were similar to those previously described. All our patients had fever, anorexia and nausea, and jaundice was present in 86%. Eosinophilia and rash occurred in fewer than 20%, and these features were not diagnostically useful. The mortality rate in our series was 36%, which is similar to that reported in previous series (14 - 79%, average 52%).[10,12-15]

Three patients with halothane hepatitis were misdiagnosed despite their having a classic presentation; they underwent subsequent halothane exposure, with fatal consequences in 1 case. This indicates that a high index of suspicion should be maintained at all times and, when doubt exists as to the diagnosis, subsequent halothane use should be avoided.

Conclusion

This is the first reported series of halothane hepatitis from South Africa. The frequency of hepatitis following anaesthesia is similar to or slightly lower than that reported in the UK and USA. There is a higher frequency in whites than in blacks and patients of mixed race, but women and men had a similar risk. Obesity and repeated halothane exposures were almost universally present in those who developed hepatitis. Awareness of the condition was suboptimal and in many cases hepatitis could have been avoided if standard international guidelines on halothane use had been followed,[3] in particular the avoidance of repeated exposures in a short space of time, and avoidance of halothane use in patients who report even mild prior postoperative adverse reactions to anaesthetic.

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