CASE REPORT

HALOTHANE INDUCED FULMINANT HEPATIC FAILURE

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ABSTRACT

A rare case of halothane-induced fulminant hepatic failure is reported in a 22 years old male, who developed fever, jaundice, coma and deranged coagulation profile, 2 days after undergoing laparotomy under halothane anaesthesia. Despite all supportive care, he died of fulminant hepatic failure, 6 days after surgery. Postmortem liver biopsy revealed massive predominantly centrilobular hepatic necrosis.

KEY WORDS: *Halothane hepatitis. Inhalational anaesthetics. Halothane hypersensitivity.*

INTRODUCTION

Halothane (fluothane) is a halogenic volatile anaesthetic agent, which was first synthesized in 1951 and used for the first time in England in 1956.[1] The halothane-induced hepatitis is usually mild and may be asymptomatic with slight elevation of serum transaminase levels, but in some predisposed individuals and more commonly after multiple exposures, hepatitis is severe and may proceed to fulminant hepatic failure with a mortality of 50%. It can complicate surgery, carried out for an apparently unrelated ailment.[2]

Its use has been decreased in USA and other developed countries but due to low cost, it is still widely used in Pakistan.

CASE REPORT

A 22 years old male, an air force employee, was admitted in PAF Hospital, Mianwali on 19th January 2005 with sub-acute intestinal obstruction. Two years ago, he had undergone appendicectomy under halothane anaesthesia without any complications. There was no history of jaundice, transfusion or any drug reaction. After routine investigations exploratory laparotomy was performed during which a distal ileal stricture was resected, and end-to-end ileal anastomosis was performed. Anaesthesia was induced with thiopentone and maintained with halothane. There were no per-operative complications and recovery from anaesthesia was uneventful. Patient developed jaundice on 1st postoperative day. His serum bilirubin was 139.4 umol/L, ALT was 645 IU/L and alkaline phosphatase (ALP) was 371 IU/L. HBsAg and Anti-HCV were both negative. USG abdomen showed normal hepatobiliary channels with no evidence of biliary obstruction. He became comatose the next day and serum bilirubin, ALT and alkaline phosphatase were raised to 363 umol/L, 3208 IU/L and 474 IU/L respectively. He was immediately transferred to Gastroenterology Unit of Military Hospital, Rawalpindi. His condition further deteriorated and became deeply comatose with Hb level of 10.5 gm/dl, prothrombin time of 50/13 (INR 4.17) and PTTK of 68/34 seconds. Serum D-dimers were 500-1000 and serum fibrinogen was 210 mg/dl. He was intubated and ventilated on CMV mode. High dose steroids along with broad-spectrum antibiotics, osmotic diuretics, and anticonvulsants were started. His condition deteriorated further and he went into cardiopulmonary arrest, 6 days after surgery, and could not be revived. Postmortem liver biopsy showed distortion of normal architecture by large areas of necrosis, mostly around central veins. The surrounding hepatocytes revealed degenerative and regenerative changes without any fibrosis. The findings were consistent with massive hepatic necrosis (Figure 1).

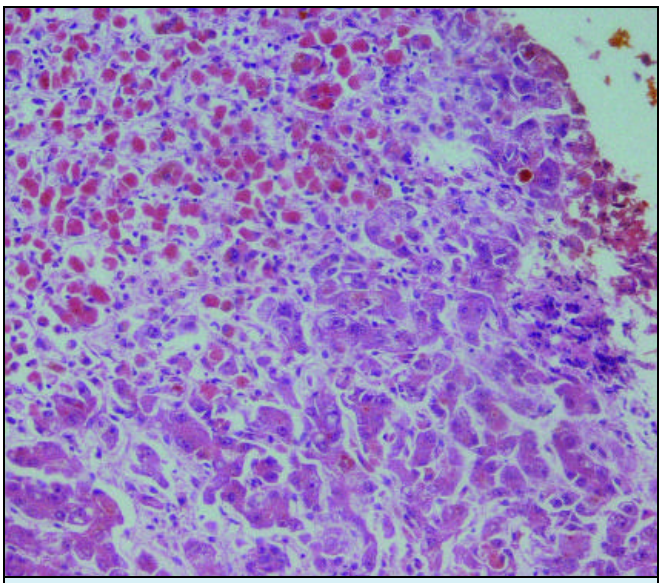

Figure 1: Photomicrograph of liver biopsy showing massive centrilobular necrosis.

DISCUSSION

Halothane (fluothane) [2-bromo 2-chloro 1, 1, 1-trifluoroethane], is mainly used for maintenance of anaesthesia and due to its non-pungent smell, is a popular agent for induction of anaesthesia in children. About 60% to 80% of halothane, taken by the body, is eliminated unchanged via the lungs in the first 24 hours after its administration. A substantial amount of halothane, not eliminated in exhaled gas, is biotransformed in the liver by a particular isozyme of cytochrome P450 (2 E1)

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enzyme system to its principal metabolite, trifluoroacetic acid.[3]

Halothane is a trigger agent for malignant hyperthermia. It may also cause the appearance of myocardial dysrhythmias, particularly in conjunction with hypoxia, hypercapnia or excessive catecholamine concentrations. The other rare but potentially fatal side effect is halothane hepatitis. Halothane is associated with two patterns of clinical hepatotoxicity which appear to be unrelated. Type I (mild) hepatotoxicity is benign, self-limiting, and relatively common (upto 25-30% incidence). It results from reductive (anaerobic) biotransformation of halothane rather than the normal oxidative pathway. It can lead to inactivation of CYP450, toxic hepatocyte necrosis and serum aminotranferase elevation.[4] This reaction is unlikely to take place under usual physiologic conditions because the main metabolic pathway under physiologic conditions is oxidative. Approximately 20 to 25 percent of these patients develop symptoms of mild clinical hepatitis characterized by nausea, lethargy and fever. Eosinophilia may also be present. An acute hepatitis-like injury is seen on histology. Type II (fulminant) hepatotoxicity is associated with massive centrilobular liver cell necrosis leading to fulminant hepatic failure. The incidence is 1 in 6000 to 1 in 35000 following a single exposure to the anaesthetic and increases to about 1 in 3000 following multiple exposures.[5] Other risk factors for severe hepatotoxicity may include female gender, age greater than 50, and obesity. The main metabolic pathway under physiologic conditions is oxidative which in susceptible individuals can lead to acute fulminant hepatitis. Oxidation leads to formation of a highly reactive metabolite, trifluoroacetylchloride (TFA).[6] Hydrolysis of TFA yields trifluoroacetic acid, which is non-toxic and excreted in the urine. However, TFA may also bind covalently to hepatocyte macromolecules and phospholipids, producing trifluoro-acetylated-protein adducts (TFA-protein adducts). Covalent binding to liver proteins may be the preliminary step in acute halothane hepatitis.[7] The TFA-protein adducts are viewed as foreign to the body and may act as sensitising neoantigens, evoking an immune response, which ultimately leads to fulminant hepatic necrosis.TFA-products have also been identified in the kidney, heart, testes, and lungs[8] although in smaller amounts than seen in liver and they are of unknown clinical significance. Type II hepatotoxicity after enflurane or isoflurane administration is extremely rare because these drugs are metabolized to a lesser degree and by different pathways than halothane. Approximately 20% of halothane is oxidatively metabolized, compared with only 2% of enflurane and 0.2% of isoflurane.

Symptoms generally occur about two days to three weeks after exposure. Patients present with fever (75%), anorexia, nausea, myalgias, arthralgias, and rash. Eosinophilia occurs in approximately 40% of cases, suggesting immunoallergic disease.[9] Tender hepatomegaly and jaundice are common. Some patients present with fulminant liver failure, markedly elevated serum aminotransferases, and prothrombin time. The combination of high aminotransferases (hepatocellular injury) and jaundice are reported to be related to mortality varying from 10 to 50% for different drugs. This phenomenon, known as “Hy’s rule”, has never been validated due to limited available data.[10]

Halothane hepatitis must be considered whenever postoperative jaundice occurs following its use. However, the differential diagnosis of postoperative jaundice remains broad. Among the conditions that must also be considered are surgical complications (particularly in bile-duct surgery), perioperative hypotension, sepsis, infections, other drug toxicity, and viral hepatitis. Liver biopsy is usually not necessary for diagnosis. When obtained, the histological appearance is often indistinguishable from viral hepatitis. Occasionally, an increase in eosinophils may be seen, and rarely, granulomata may be present.

The treatment of halothane hepatitis is supportive. Corticosteroids are of no proven value and there are little to no data in the literature to support their use. Severe, progressive cases may require emergent orthotopic liver transplantation.

The most effective preventive tool is to avoid the use of halothane in adults. Single-dose disulfiram may provide effective prophylaxis against halothane hepatitis.

The patient presented here developed jaundice with raised serum transaminase levels and prothrombin time, two days after second exposure to halothane. He went into fulminant liver failure and died on 6th postoperative day. His liver biopsy showed sub-massive hepatic necrosis predominantly centrilobular.

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