Suspected Isoflurane Induced Hepatitis from Cross Sensitivity in a Post Transplant for Fulminant Hepatitis from Halothane.

V Sampathi, H Fisher, V Manmohansingh, E Pretto, R CM

Citation

V Sampathi, H Fisher, V Manmohansingh, E Pretto, R CM. *Suspected Isoflurane Induced Hepatitis from Cross Sensitivity in a Post Transplant for Fulminant Hepatitis from Halothane.*. The Internet Journal of Anesthesiology. 2009 Volume 25 Number 1.

Abstract

Halogenated anesthetic induced hepatitis has been well documented in the literature. Since the advent of halothane as the first member of the family in 1956, numerous reports of halothane induced hepatitis have been reported. Spectrum of liver toxicity by halothane can vary with an incidence of one in five patients mild self limiting hepatic injury to one in 30,000 patients with fulminant hepatic failure[1]. Next generation halogenated anesthetics such as Isoflurane, enflurane and desflurane though have different molecular structure, have also been known to cause hepatitis[2-4]. Cross sensitization among these agents has been well studied in experimental setting and supported by a few cases reports[5,6]. In liver transplantation isoflurane is the anesthetic of choice as it is considered to be less hepatotoxic nature, due to its minimal biotransformation. However it is known to cause hepatitis and rarely hepatic failure even on the first exposure [7]. To the best of our knowledge this is the first report of suspected isoflurane hepatitis in the liver graft of a patient who underwent liver transplant for halothane induced acute liver failure. It is important to be aware about this rare possibility of cross reactivity induced liver damage in a liver transplantation.

CASE PRESENTATION

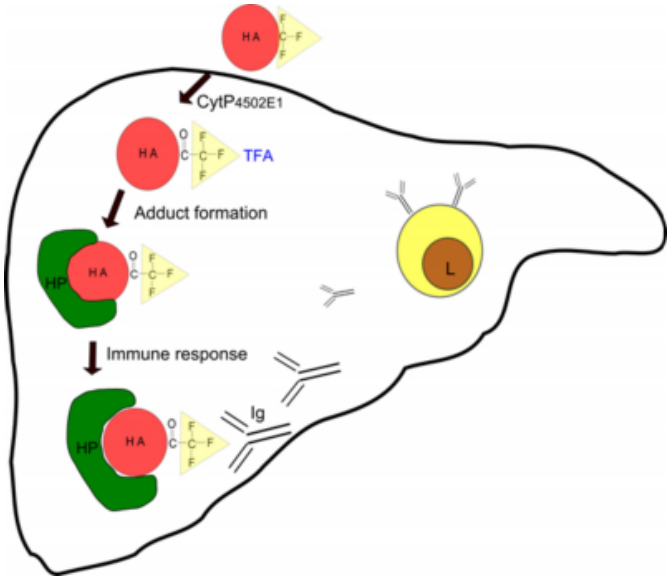
36 year old female was transferred from a Caribbean Island with jaundice, elevated liver chemistries and an abnormal coagulation profile. During the presentation, the patient denied any exposure or known history of viral hepatitis, acetaminophen over dose, over the counter herbal or natural supplement ingestion and substance abuse. Further patient was unaware of personal and family history of liver disease. Detailed history revealed that the patient underwent three cosmetic surgeries within a year and notably the last two procedures were done within a span of one month under halothane anesthesia. A week after the third surgery, she developed acute icteric hepatitis. The patient was transferred to United States for further care. Admission lab values were as follows: aspartate aminotransferase (AST): 734 u/L, alaninine aminotransferase (ALT): 348 u/L, Alkaline phosphatase (AP) 194 u/L, total bilirubin (TB): 19.6mg/dl with direct bilirubin (DB) being 14.6mg/dl, total protein: 7.1 g/dl, albumin: 3.2 g/dl, prothrombin time (PT): 32.2, International standardized ratio (INR): 3.47. Additional work up such as screening for pregnancy, Anti-nuclear antibody (ANA), Anti-smooth muscle antibody and anti-mitochondrial anti-body were negative. Hepatitis A, B, C viral serology was negative. Ceruloplasmin level was 16.7mg/dl (normal 20-40mg/dl). Over the next 72 hours patient underwent elective endo-tracheal intubation for grade-IV hepatic coma with significant cerebral edema. Laboratory parameters continued to increase with total bilirubin 21.8 mg/dl and PT 62.2 / INR 7.95. Successful orthotopic liver transplantation was performed with improvement in clinical condition and good graft function. Native liver biopsy showed: sub-massive confluent centri-lobular necrosis of liver with chronic inflammatory infiltration, but no signs any fibrosis. There was no evidence of any viral cytopathic changes.

During the first five post-operative days the liver chemistries showed a downward trend. From the sixth post-operative day onwards the bilirubin, SGOT, SGPT and PT /INR were markedly elevated, minimal elevation of alkaline phosphatase was also noted. There were no documented episodes of hypotension or hypoxemia. The work up for septicemia, biliary duct obstruction or hepatic artery thrombosis with imaging was negative. Graft liver biopsy was performed with histology showing centri-lobular necrosis with cholestatic balloon degeneration. All the

administered drugs patient care during pre and post transplant care were reviewed carefully. During the intra-operative period for liver transplantation, patient had an exposure to isoflurane intermittently for a total of 15 minutes along with propofol as intravenous anesthesia. Since all other potential causes were excluded a diagnosis of isoflurane hepatitis was suspected. Fortunately the hepatitis was self limited and the graft function recovered after a period of 3 weeks. After a follow-up of two months the patient continues to have good graft function.

Figure 1

Figure 1: Diagram illustrating the mechanism of immunological damage.



The halogenated anesthetic (HA) is metabolized in the liver by cytP4502E1 into a tri-fluoro acetyl (TFA) metabolite. TFA forms adduct with hepatic protein (HP) which acts as a hapten. The immunological response that follows, results in liver damage. (L-Lymphocyte, Ig-Immunoglobulin).

Figure 2

Figure 2 & 3: Graphs illustrating the trend of the liver chemistries. Aspartate Aminotransferase (AST), Alanine Aminotransferase (ALT), Alkaline Phosphatase (Alk. Phos), Total Bilirubin (Tbilirubin) and International normalized ratio (INR).

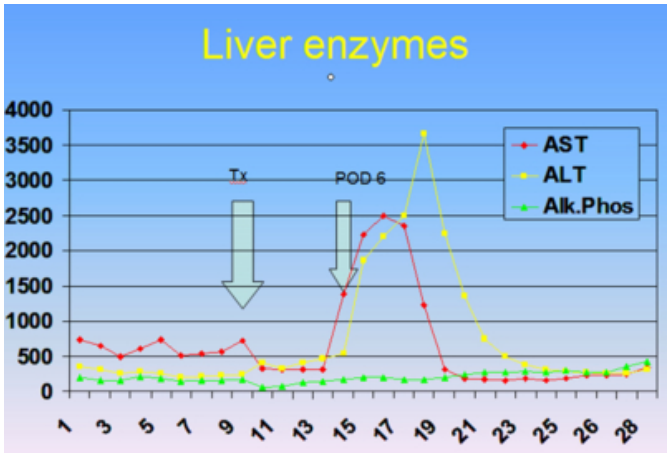


Figure 3

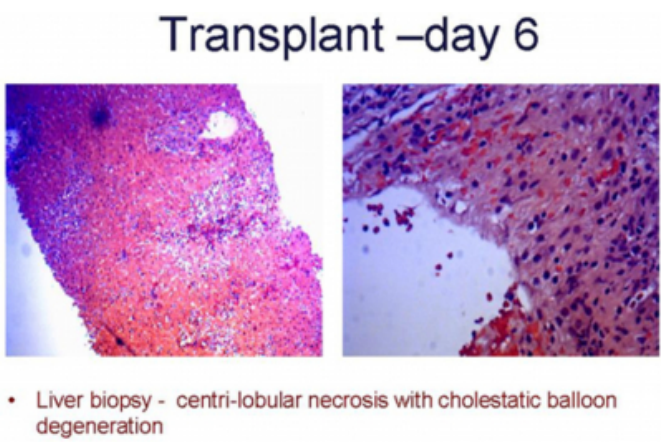
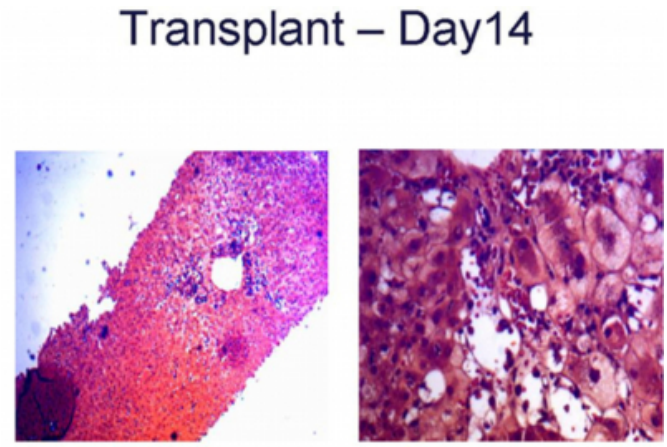


Figure 4



DISCUSSION

Hepatitis from methyl-ethyl esters such as enflurane, isoflurane, and desflurane is less common due to much lower metabolism compared to halothane8. Molecular architecture of the above agents has to be explained.

These anesthetics are metabolized via cytochrome P4502E1 and an intermediary trifloroacetyl (TFA) metabolite is formed. The TFA-hepatic protein adducts acts as a hapten inducing humoral and cellular immune response. Since the trifluoroacetyl metabolite is common for all the above agents, re-exposure to any agent among this group elicits an immunological response directed against the hepatocytes. There are isolated reports of hepatotoxicity with single exposure to isoflurane7,9 or desflurane2. Njoku et al suggested that the acylated proteins are the mediators for anesthetic induced hepatitis (AIH)5,6. The literature supports the fact that there is a cross reactivity between halothane, enflurane, desflurane and isoflurane5.

It still unknown why only some patients develop hepatic injury, even when all the patients exposed to fluorinated anesthetics develop TFA-hepatic protein adducts10. All these adducts may not be immunogenic. It is still to be determined if there is dose related immunogenicity. The risk factors predisposing to AIH are obesity, female sex, middle age, CYP4502E1 induction with ethanol or isoniazid and genetic predisposition11.

It is suggested that patients sensitized to halothane, isoflurane, enflurane or desflurane could be safely anesthetized with sevoflurane. Metabolism of sevoflurane is through to hexafluoroisopropanol intermediary, which is an aldehyde from of inorganic fluoride, thus does not lead to the formation of hapten. Theoretically therefore sevoflurane should not cause anesthetic induced hepatitis11. However this agent has been shown in animal models to cause liver dysfunction which manifests as elevated liver chemistries (clinical/subclinical) and the package label warns to avoid sevoflurane in any patient with unexplained liver injury following exposure to any fluorinated inhaled anesthetic 12.

In our patient, initially the liver allograft recovered from cold ischemia with improvement in liver chemistries, reversal of coagulopathy and hepatic encephalopathy. On day six liver chemistries worsened, which was attributed to cross sensitivity related injury after other causes of immediate graft dysfunction were excluded. This patient may have developed anti-TFA antibodies due to the previous exposure to halothane and on exposure to isoflurane during the liver transplantation elicited an immunological response culminating in isoflurane hepatitis of the graft liver.

The etiological differential for post transplant liver dysfunction /necrosis is wide. Differential diagnosis includes reperfusion injury, primary non-functioning of graft, hypotension, hypoxemia, acute rejection, viral hepatitis, biliary duct obstruction and hepatic artery thrombosis. Isoflurane hepatitis is a diagnosis of exclusion. In non transplant patients, it has been shown , AIH manifests in 6-28 days on the first exposure and can manifest earlier on the second exposure. Immunoassay for antibodies to hepatic TFA microsomal proteins can help in diagnosing AIH. However, it is not available in our institute5,10.

CONCLUSION

We recommend Total intravenous anesthesia (TIVA) for patients with fulminant hepatic failure undergoing liver transplantation, as this avoids inhalational anesthetics which can aggravate the cerebral edema. In a setting of liver transplantation, in order to limit confounding variables it is not safe to use halogenated anesthetic for suspected inhalational induced liver damage. We also recommend the usage of an anesthesia machine which has never been exposed to halogenated anesthetic agent or flushing the anesthetic machine with 100% oxygen at 10litres/min for 10 min. It has been stated trace amount of anesthetic gas which is attached to the circuit is enough to trigger immunological injury10.

We believe that this case is due to isoflurane hepatitis in view of the history of exposure, cross reactivity, the lack of

any other obvious etiologic agent, the marked similarity of the clinical and histological picture to halothane hepatitis, and previous reports of isoflurane hepatitis.

References

Author Information

V Sampathi, MD
Department of Anesthesiology, Division of Solid Organ Transplant Program, Jackson Memorial Hospital, University of Miami, Miller School of Medicine

H Fisher, MD
Department of Anesthesiology, Division of Solid Organ Transplant Program, Jackson Memorial Hospital, University of Miami, Miller School of Medicine

V Manmohansingh, MD
Department of Anesthesiology, Division of Solid Organ Transplant Program, Jackson Memorial Hospital, University of Miami, Miller School of Medicine

E Pretto, MD
Department of Anesthesiology, Division of Solid Organ Transplant Program, Jackson Memorial Hospital, University of Miami, Miller School of Medicine

Reddy CM, MD
Department of Medicine, Division of Hepatology, Jackson Memorial Hospital, University of Miami, Miller School of Medicine