Internal Medicine: Open Access

Shah, et al., InternMed 2015, 5:6
DOI: 10.4172/2165-8048.1000209

Case Report Open Access

Hepatotoxicity after Sevoflurane Exposure in a Patient with Chronic Hepatitis C

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Rec date: November 16, 2015 · **Acc date:** November 25, 2015 · **Pub date:** December 2, 2015

Abstract

Sevoflurane is considered a safe inhaled anesthetic of choice in patients with liver disease. Compared to other halogenated inhaled anesthetics, Sevoflurane is reported to lessen the severity of decreased hepatic blood flow and undergoes a different mechanism of hepatic metabolism. In patients with preexisting liver disease, there is potential for low-flow Sevoflurane to induce acute liver damage through other mechanisms. Limited data exists to guide clinical decision-making when quantifying the severity of cirrhosis in patients with hepatitis C and its relationship to anesthesia choice. Previous studies have found that exposure to general anesthesia during abdominal surgery may increase the risk of hepatorenal failure. This study has raised a concern that anesthetics may interfere with various hepatic functions secondary to viral infection. The generation of abnormal liver enzymes and hypercoagulation has provided further exploration for such toxicity.

Introduction

Previous studies have found that exposure to general anesthesia during abdominal surgery may increase the risk of hepatorenal failure. This study has raised a concern that anesthetics may interfere with various hepatic functions secondary to viral infection.

The generation of abnormal liver enzymes and hypercoagulation has provided further exploration for such toxicity. Sevoflurane is considered a safe inhaled anesthetic of choice in patients with liver disease. Compared to other halogenated inhaled anesthetics, Sevoflurane is reported to lessen the severity of decreased hepatic blood flow and undergoes a different mechanism of hepatic metabolism.

In patients with preexisting liver disease, there is potential for low-flow Sevoflurane to induce acute liver damage through other mechanisms. Limited data exists to guide clinical decision-making when quantifying the severity of cirrhosis in patients with hepatitis C and its relationship to anesthesia choice.

Case Description

A 53-year-old male with a history of hypertension and Hepatitis C underwent elective hernia repair. He was referred to the surgical clinic for intermittent abdominal discomfort secondary to a 10 × 8 cm ventral hernia. During the clinic visit, patient reported that he had history of Hepatitis C, but was otherwise asymptomatic and no physical stigmata of cirrhosis were evident. Patient stated that the ventral hernia was the result of abdominal trauma in 1983 requiring laparotomy, and has been progressively enlarging.

Aside from occasional discomfort while lying flat, the remainder of review of systems was negative. He had no other surgery besides the posttraumatic laparotomy, any allergies or organ dysfunction. Hypertension was controlled with Furosemide and Spironolactone. He was never symptomatic or treated for Hepatitis C. After discussing the risks, benefits and alternatives of a hernia repair, he was scheduled for operative repair.

Preoperative testing and laboratory were ordered according to best practice guidelines. Given this patient history of Hepatitis C, Complete metabolic panel and coagulation panel were ordered (as shown in Table 1). On admission, the patient had decreased platelet count (98 × 109/L) and hematocrit (35.7%). Liver aminotransferases and alkaline phosphatase were elevated as well as slightly elevated PT/INR (Table 1).

Serum electrolytes and kidney function tests were within normal ranges. Preoperative sedation with Midazolam 2 mg was administered. The operation happened as planned. Initially it took about 30 minutes of lysis of adhesions due to his prior hernia. Attention was focused on the hernia repair, therefore no effort was made to lyse adhesions which did not interfere with the procedure, or to explore the rest of the abdomen.

However, a portion of the liver, which was readily visible, revealed a hard and nodular appearance, consistent with cirrhosis. During the separation of components, the cutaneous flaps were not excessive, and the external oblique release provided enough length to achieve a tension free fascia approximation. A light weight polypropylene mesh was placed in the retrorectus space and fixated with transfascial absorbable sutures. The patient tolerated the procedure without any immediate complications.

Biochemistry			
PT (seconds)	13.9	18.9	19
INR	1.4	2	1.9
Partial Thromboplastin Time (seconds)	29	32.7	34.25
Alk-Phos (units/L)	120	91.7	188
ALT (units/L)	148	1504.7	3810
AST (units/L)	169	3544.25	14598.5
Total Bilirubin (mg/dL)	1.1	3.27	5.85
Albumin (gm/dL)	2.7	2.36	3.25
BUN (mg/dL)	12	26.8	12.75
Cr (mg/dL)	0.9	3	2.375

ALT: Alanine Aminotransferase; AST: Aspartate Aminotransferase; Alk-Phos: Alkaline Phosphatase; BUN: Blood Urea Nitrogen; Cr: Creatinine; PT: Prothrombin Time; INR: International Normalized Ratio; IV: Intravenous ; P value<0.01.

Table 1: Coagulation and Liver Function Characteristics.

IV Fentanyl 150 mcg, Propofol 200 mg, Rocuronium 50 mg, and Ketamine 20 mg anesthesia was maintained with sevoflurane in end-tidal concentrations of 1.6% volume with oxygen and air (fresh gas flow 2 L/min) induced general anesthesia. Anesthesia lasted 4 hrs. Throughout the procedure, heart rate, blood pressure, and temperature remained within normal limits. Oxygen saturation stayed above 98%. Estimated blood loss was 700 ml. Postoperatively, the patient was extubated and he regained consciousness. After recovery in the PACU, the patient was transferred to the general floor. Pain was controlled with Dilaudid. Two days after surgery, the patient became tachycardic, tachypneic, and hypotensive. His abdominal wound was intact but his abdomen was distended and dressings were saturated with blood. After stat labs (Table 1) and imaging, the patient was transferred to the ICU due to impending shock. Labs showed metabolic acidosis with increased anion gap due to lactic acidosis. Despite hemodynamic support, he had a cardiac arrest required CPR. Once return of spontaneous circulation was achieved after 20 minutes, emergent hemodialysis was required for metabolic derangements.

Post-op day three, the patient continued to be hemodynamically unstable was in hypovolemic shock. Acute blood loss despite blood products suggestive of disseminated intravascular coagulation (DIC) and low urine output suggestive of acute renal failure. Increased abdominal distention and high bladder pressure were concerning for abdominal compartment syndrome which lead to emergent decompressive laparotomy. Intraoperatively, there was no major source of bleeding, the liver was cirrhotic but without injury, and there was no evidence of ischemic bowel. Patient was taken to the ICU for further care where he required continued multiple pressor support, hemodialysis, and blood products. Despite all efforts and aggressive measures, the patient became hemodynamically unstable due to multi-organ failure and suffered from cardiac arrest twice. After failure to resuscitate the patient, the decision was made to withdraw all lifesaving measures and the patient expired. With pending autopsy findings, the patient's cause of death is multi-system organ failure in the setting of hepatic dysfunction and DIC.

Autopsy was performed at the patient's family request. Findings revealed no direct anatomical cause of death; however, the patient was noted to have severe macronodular cirrhosis, diffuse pulmonary edema, and cardiomyopathy.

Discussion

Hepatitis C virus, a member of the Flaviviridae family with six known genotypes [1], causes a major public health problem and leading cause of decompensated chronic liver disease at a rate of 5% per year [2]. Hepatic decompensation is characterized by ascites secondary to hepatorenal syndrome, hepatic hydrothorax, spontaneous bacterial peritonitis, encephalopathy, bleeding varices, and coagulopathy [2].

The major risk factors for acquisition of hepatitis C is associated with intravenous drugs, transfusion of blood products, tattoos, sexual transmission or occupation risk [3,4]. This knowledge has allowed researchers to identify variables and various treatment options.

HCV elicits a weak T cell response in chronic infection. There is a progressive loss in the strength of reaction towards HCV antigens during chronic infection. Impaired CD8 responses are the consequence of dysfunctional T cell rather than persistent infection [6-7]. CD-8 induced liver damage or autoimmune phenomena occur. Viral persistence includes the suppressive effect of HCV antigens on the innate and adaptive immune systems [1]. Progression to persistent infection and immunologic mechanisms of liver injury are a consequence of complex interactions among the virus and host [1].

Significantly higher rate of liver complications include age (>50 years), blood transfusion, HCV genotypes 1 and 4, fibrosis and cirrhosis [8]. In addition, abnormalities in bilirubin (>40 μmol/L), albumin, prothrombin time, thrombocytopenia (<50,000 cells/dL) and detection of AFP(>20 μg/L) [8]. Patients are at a higher risk of developing liver complications from chronic hepatitis C with advanced hepatic fibrosis or cirrhosis. Infected individuals are predominantly asymptomatic, but can progress to end stage liver disease, liver cirrhosis, portal hypertension, hepatocellular carcinoma and premature death. The rate of fibrotic progression in chronic hepatitis C is highly variable and natural history extends over decades [9]. Factors that influence the rate of progression include age at diagnosis, male gender, HCV genotype, and a weak association towards alcohol consumption [10-11]. Personal, viral and disease related factors that influence the development remains poorly documented [9].

Approximately 80% of those who become infected fail to clear the virus and progress to chronic infection, with poorly defined outcomes [1]. Some people recover, remain viremic without overt liver damage, remain static with elevated AST without symptoms, progressive with fibrosis and cirrhosis, or develop liver failure or hepatocellular carcinoma [12]. The course of the disease spans 20 to 40 years before the outcome is reached. Reduced life expectancy with transfusions, drug use, and other exposures exacerbates HCV mortality [13].

Fibrotic scar tissue within the liver causes blood to back up within the splanchnic circulation resulting in adverse complications. Clinical symptoms were identified in approximately 10% of patients [10]. These include [14] ascites (abdominal distention, shifting dullness, and confirmed fluid by paracentesis or abdominal imaging), variceal bleeding (endoscopic evaluation with upper gastrointestinal

hemorrhage, 35-85% with cirrhosis; bleeding 25-40%; 30-50% 3 month survival), spontaneous bacterial peritonitis (>500 white blood cells/mL, >250 polymorphonuclear cells/mL, positive culture), hepatic hydrothorax (right sided pleural effusion), and hepatic encephalopathy (asterixis flapping tremor). Management requires aggressive diuresis, pleural taps, and immediate consideration for liver transplantation based on the MELD (Model for End Stage Liver Disease) [15].

Therapy for hepatitis C is indicated for patients 18 to 60 years with persistently abnormal alanine aminotransferase levels, HCV RNA in serum, liver biopsy showing chronic hepatitis with fibrosis or inflammation [16]. The goal is to prevent complications and death from HCV infection. Short-term outcomes are measured by normalization of serum ALT, undetected HCVR RNA by sensitive PCR analysis, and non-detectable fibrosis on histology [13]. The most important labeled treatment is considered by sustained virological response, defined as the absence of HCV RNA from serum by sensitive PCR assay 24 weeks after cessation of therapy [1]. Rapid virological response [13,17] is defined as undetectable HCV RNA at 4 weeks of treatment with a lower limit of detection of 50 IU/mL, with a higher likelihood for achievement. Early virological response [12,17], defined as absence of serum HCV RNA at 12 weeks, is the most accurate predictor of not achieving sustained viral response.

Despite management, HCV RNA levels do not change, and relapses occur soon after cessation of treatment. The therapeutic regimen includes interferon-α given subcutaneously in a dose of 3 million units three times weekly for 12 months [2]. Modifications include a combination therapy with interferon-α and ribavirin [18-20]. Patients receiving interferon-α alone or in combination, had low to non-detectable HCV RNA 6 months after therapy (indicating sustained virology response) [12,18-20]. Residual viral indices maintain persistent humoral and cellular immunologic responses once the therapy reduces viral load [5,21]. An additional option is a long-term continuous interferon or ribavirin therapy in patients with extrahepatic manifestations, those with marked fibrosis on liver biopsy or those at high risk for hepatocellular carcinoma [1].

Chronic HCV infection is the leading indication for liver transplantation in the U.S. population [22]. Criteria for liver transplant includes [1-2,13] signs of hepatic decompensation, encephalopathy, variceal bleed, MELD score[15] >10 (indicated by bilirubin, creatinine, and INR). Immunocompromised patients have a higher recurrence and lower survival rate, which advocates the use of interferon-based antiviral therapy. Other studies have suggested that patients with mild histological disease respond better compared to those with more advanced liver diseases [2,13]. This allows for closer monitoring of post-transplant patients using liver biopsy to monitor progressive fibrosis and initiate treatment [12,23-24]. Graft re-infection is universal with 25% to 30% graft loss from recurrent HCV with progressive fibrosis [23-24]. Profound graft dysfunction may occur after viral clearance, which necessitates immediate management [25]. Efforts to define criteria for diagnosis, therapy, optimal timing, duration to treat recurrence, are important. Once cirrhosis develops, hepatic decompensation is common with poor results of re-transplantation [13].

Preoperatively, it is important to evaluate patients for liver disease since it has been associated with increased postoperative complications and mortality [26]. With the patient's history of hepatitis C, the next step was to assess the severity of liver dysfunction. Our patient had confirmatory HCV testing with a high viral load using quantitative HCV RNA by PCR (1,678,859 Intl Unit/mL). Additionally, he was never treated for HCV with pegylated interferon or ribavirin which aims to slow the progression of fibrosis and prevent the development of cirrhosis [27]. Preoperative lab evaluation (Table 1) showed platelets <140,000 and AST/ALT ratio ≥ 1 which are highly suggestive of cirrhosis in patients with chronic HCV [28]. Using noninvasive methods, the Child-Turcotte-Pugh (CTP) and the Model for End Stage Liver Disease (MELD) scoring systems can be used to quantify the severity of hepatic dysfunction. The CTP score predicts severity of liver dysfunction and postoperative morbidity and mortality risk. Preoperative, this patient fell into CTP class B, associated with a 10% surgical mortality rate. The MELD score can be used to predict 30 day mortality postoperatively in patients with cirrhosis by estimating the severity of liver disease. We have found that this patient had a MELD score of 11 that predicts a 10.3% 30- day mortality rate [29-30].

Although no specific guidelines have been widely established, there are several considerations that have been suggested by the American College of Gastroenterology, which include, contraindication to elective surgery in patients with CTP class C, high MELD score, ASA class V, acute hepatitis, severe coagulopathy, or severe extrahepatic manifestations of liver disease [31]. Management of ascites, coagulopathy and encephalopathy are required before proceeding with surgery. In general, for asymptomatic patients with mildly elevated aminotransferase levels, and a normal total bilirubin, cancellation of surgery is rarely needed [32].

We suggest that sevoflurane may have attributed to this patient's demise through several mechanisms of injury. Since its introduction in 1990, sevoflurane has been established into clinical practice, and considered safer than other halogenated anesthetics. Yet hepatic injuries have been reported over the years [33].While many factors contribute to our patient's hepatic injury, such as chronic hepatitis, he was hemodynamically stable preoperatively and intraoperatively. However over time, this patient suffered hypercoagulability unresponsive to supportive therapy, and eventually expired. Postoperatively, liver enzymes were dramatically elevated (Table 1) and it became clear to investigate further into sevoflurane toxicity with underlying viral illnesses such as hepatitis C.

Clinicians are warned to avoid sevoflurane with unexplained liver injury following any exposure to fluoridated inhaled anesthetic. Sevoflurane is metabolized to hexafluoroisopropanol inorganic fluoride, and formaldehyde [34], which are eliminated in urine. Sevoflurane defluorination is metabolized by human P450 2E1 and is responsible for anesthetic toxicity, predominantly in the liver. Heme oxygenase has also been postulated to react with sevoflurane, because it may be stimulated by Kupffer cells to prevent reperfusion injury, in the pericentral region. Free radical release can also be expected through tissue interaction with sevoflurane, with the induction of P450 E1 metabolism [35].

Total intravenous anesthesias with sevoflurane and propofol have proven to show variable results based on patients with renal and liver functions. In a study in 2009 and 2013, [36-37], hepatic and renal function tests were conducted during preoperative and postoperative days 1 and 3. AST and alkaline phosphatase were also shown to increase. Coagulopathy and hyperbilirubinemia are also known to increase with drug induced sevoflurane hepatic necrosis. Additionally with an underlying HCV infection and the exposure to sevoflurane there is a risk of hepatic necrosis with life threatening consequences [38]. It is important to note that at a low concentration of sevoflurane, compound A toxicity would not affect this patient either through beta lyase pathway or N-acetylation. Even though this patient was at a low

flow rate of 2L/min, anesthesia providers should be aware of the accumulation of compound A and its association with sevoflurane in the setting of renal and hepatic toxicity [39].

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