Severe hepatic dysfunction after sevoflurane exposure

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ABSTRACT

تعد الإصابة بتسمم الكبد بعد التعرض لغاز السيفوفلورين أثناء التخدير من الحالات القليلة منذ بداية استخدامه لأول مره عام 1990م في اليابان. كما تعد الأسباب الفسيولوجية المرضية للتسمم الكبدي غير محددة. في هذا البحث وصف لحالة اعتلال في وظائف الكبد بعد التعرض لغاز السيفوفلورين أثناء التخدير لعملية ناجحة لإستئصال ورم مخي لطفلة. ويعتبر تأثير غاز السيفوفلورين غير محدد بسبب وجود عوامل اخرى عديدة تستحق المناقشة.

Sevoflurane is thought to have a potential for hepatotoxicity. A few cases of hepatotoxicity have been reported since it was introduced in 1990 into clinical practice in Japan. The underlying pathophysiology of hepatotoxicity is nonspecific. We report a case of severe hepatic dysfunction after uneventful sevoflurane anesthesia in a child with posterior fossa resection of medulloblastoma. The case of sevoflurane being incriminated is unclear due to various confounding factors that is worthy of discussion.

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Sevoflurane anesthesia is commonly used in children during induction and maintenance phase of anesthesia. It is considered being safer than other halogenated gas, and it is not metabolized to hepatotoxic trifluoroacetyl proteins. However, nephrotoxic end product (compound A) may react with proteins, and may be transformed into antigenic materials.[1,2] Halothane gas is well known to cause hepatitis (**Figure 1**). Several cases of hepatic injury following sevoflurane exposure has been reported. We suggest that all halogenated anesthetics may be implicated with acute livers injury.

Case Report. A 6-year-old girl, weighting 20.5 kg, had one-month history of headache, associated with nausea, vomiting, blurred vision, and unsteady gait. Magnetic resonance imaging (MRI) of the brain revealed a posterior fossa tumor. She was scheduled for craniotomy, and excision of tumor. There was no other relevant medical disease with negative allergic history. She had previous general anesthesia for MRI of the brain and spine. She was on dexamethasone and ranitidine. The preoperative blood works were normal. No preoperative liver function tests were carried out. Preoperative vital signs were normal. Standard anesthesia monitors were connected. Anesthesia was induced with propofol, fentanyl, and rocuronium. Trachea was intubated, and the lungs were mechanically ventilated with Draeger Primus™ anesthesia delivery unit using the volume mode. Anesthesia was maintained with 1.5-2% sevoflurane in 40% oxygen and air, remifentanyl infusion of 0.2-0.3 mic/kg/min was administered.

Craniotomy was performed with the patient in the prone position. The blood pressure (BP) were monitored invasively using right ulnar artery and central venous pressure using right internal jugular vein. A Bair Hugger™ was used to maintain body temperature. She received cephazoline, dexamethasone, and ranitidine after induction. End tidal carbon dioxide, heart rate, BP, central venous pressure (CVP), oxygen saturation, and temperature remained normal throughout anesthesia. Arterial blood gases, hemoglobin, and blood sugar were measured every 2 hours and all parameters remained within normal limits. The surgical operating took 8 hours. Blood loss was estimated at 300cc, and no blood transfusion was required. She was transferred to the pediatric intensive care unit (PICU) in a good condition, and electively ventilated overnight. The initial blood analysis revealed severe elevated hepatic aminotranferase levels [aspartate aminotransferase (AST) 4144, alanine aminotransferase (ALT) 2891 U/I]. Serum bilirubin was normal. White blood cell count was 11,000, hemoglobin 106 g/dl, platelets was 344,000. Coagulation profile and electrolytes were normal. She had low grade fever up to 37.8°C. She had

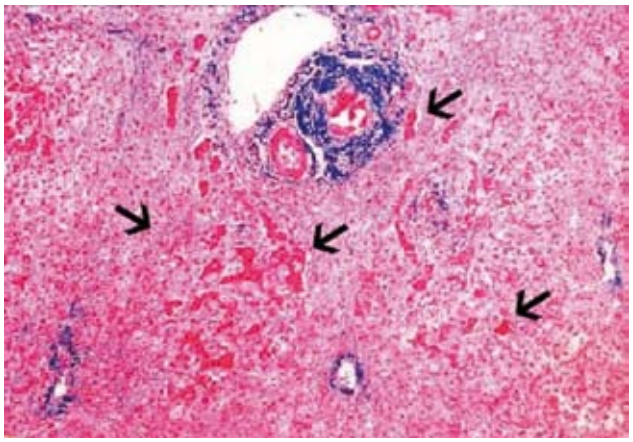

Figure 1 - Massive hepatic necrosis caused by halothane.

no jaundice, dark urine, or clinical hepatomegaly. On the first postoperative day, tracheal tube was removed when she was fully awake. The hemoglobin level was 78 g/dl, and platelet count dropped to 28.000/μL. To exclude bleeding at the surgical site a brain CT scan with and without contrast was carried out and showed no bleeding. Abdominal ultra sound reported there was evidence of periportal increase echogenicity with slightly fine granular liver parenchyma without definite evidence of focal lesion. The liver was not enlarged, and there was no evidence of intra- and extra hepatic biliary duct dilatation. The serologic tests for Epstein-Barr virus, cytomegalovirus, and hepatitis A and C viruses were negative. Hepatitis B antigen and antibodies were negative. Hepatic biopsy was refused by the family. Hepatic aminotransferase levels improved steadily to the normal level, 7 days following exposure to sevoflurane. As the hemoglobin level and platelet count were not improved, CT scan of the brain and abdomen were repeated with and without contrast, with result of mild intraventricular hemorrhage, intrabdominal bleeding, and left hepatic lobe infarction.

She was on supportive treatment with frequent blood, platelets, and fresh frozen plasma transfusions. She was on prophylactic cefazolin and vancomycin inspite of negative blood cultures. On the fourth day post operative she developed sudden deterioration in the level of consciousness with dilated pupils 5-6 mm in diameter. Urgent CT brain revealed severe intra ventricular hemorrhage, and obstructive hydrocephalus. She was taken to the operative room for urgent evacuation of hematoma and external ventricular drainage insertion. Intraoperatively she was hemodynamically stable. On this occasion sevoflurane was not used, and instead a total intravenous anesthesia (TIVA) technique was used. She continued in deep coma, and dilated pupils on supportive treatment until she expired on the 9th day postoperatively.

Discussion. This is a perplexing case of hepatotoxicity following an uneventful 8 hour anesthetic with sevoflurane in a 6 year-old child in the prone position for posterior fossa neurosurgery. In the immediate postoperative period elevated liver enzymes were measured, and then decreased to near-normal levels within 7 days. She also developed hepatic artery thrombosis, and liver infarction. Her postoperative course was further complicated by a thrombocytopenia of unknown origin resulting in intra ventricular hemorrhage and brain death, despite further surgery. This case report discusses the conundrum of confounding and multiple factors that may possibly implicate sevoflurane.

Our patient with posterior fossa tumor has been exposed twice to sevoflurane anesthesia. There was no routine checkup for hepatic function preoperatively if it is clinically not indicated. Anesthesia and surgery may be followed by hepatic function changes.[1] Many factors may result in the development of hepatic injury, such as hypoxia, hypotension, direct liver compression, blood transfusion, viral hepatitis, and the use of hepatotoxic drug. In the present case, there was no blood transfusion, or surgical handling of the liver. She had no history of viral hepatitis. There was no episode of hypoxia or hypotension during surgery. Different classes of drugs can cause hepatitis including antibiotic, antihypertensives, anticonvulsants, analgesic, and tranquilizers. Some drugs, such as acetaminophen may cause hepatic failure following sevoflurane anesthesia.[3] Our patient did not receive drugs, which may alter hepatic function, although, dexamethasone has been reported to be associated with hepatomegaly elevated liver enzymes in pediatric.[4] Several cases of hepatic injury after sevoflurane anesthesia have been reported.[1,2,5-7] Approximately 2-5% of sevoflurane metabolizes in the liver primarily by cytochrome P450 2E1 to inorganic fluoride ions. and organic metabolites.[7] Compound A is detectable when sevoflurane is used in a closed circuit with a soda lime. If glutathione is reduced by fasting or a large dose of acetaminophen, compound A may become nephrotoxic and hepatotoxic.[8] In our case, we minimized the accumulation of compound A by using a semiclosed anesthesia circle system, and renal function remained normal.[9] Sevoflurane unlike other halogenated agents is considered to be free of hepatotoxic effect due to 85% of its organic metabolites are rapidly glucuronated, and excreted in the urine.[8,10,11]

Postoperative liver injury following sevoflurane, isoflurane, and enflurane anesthesia has been

described.[5,12] Repeated exposure of halogenated agent may also cause cross sensitization that can affect hepatic function.[1] However, this may be considered in our case as this was her second exposure to sevoflurane. At the third time, patients has general anesthesia without sevoflurane exposure, hepatic aminotransferase enzymes remained stable.

The condition of our patient had deteriorated as a result of thrombocytopenia (20,000-30,000) which was not responding to conservative treatment that lead to intracranial bleeding, obstructive hydrocephalus, and death. Several factors can cause thrombocytopenia either by bone marrow suppression (tumor, infection or drugs) or peripheral destruction such as idiopathic thrombocytopenic purpura.[13,14] In our case the diagnosis was unclear, she was treated as acute idiopathic thrombocytopenic purpura secondary to viral infection, or marrow infiltration by tumor. Bone marrow biopsy was not performed as the patient was unstable.

In conclusion, we report a 6 year-old-child who developed elevated liver enzymes following posterior fossa resection of medulloblastoma. Sevoflurane was the most likely cause in our patient. We recommend that pediatric patients going for prolonged surgery should have preoperative liver function test. However, further investigation regarding sevoflurane hepatotoxicity in children is indicated.

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