awareness of a fire hazard. Our approach of procedural changes, equipment modifications, and staff education is directed toward providing greater safety for patients and personnel in the operating room.

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Halothane-associated Hepatitis in a 6-year-old Boy: Evidence for Native Liver Regeneration following Failed Treatment with Auxiliary Liver Transplantation

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ALTHOUGH halothane-associated hepatitis is a recognized entity in adults, few cases have been reported in prepubertal children. We describe a case of repeated halothane exposure in a 6-yr-old child resulting in halothane-associated hepatitis and fulminant hepatic failure that was treated using auxiliary liver transplantation.

Case Report

A 6-yr-old, 25-kg boy was involved in a motor vehicle accident and sustained bilateral pelvic fractures, a right femoral fracture, and urethral disruption. He was taken to the operating room the day of the accident for reduction of the hip and femoral fractures. Anesthesia was induced with thiopental, succinylcholine, isoflurane, and nitrous oxide. He received 2 L packed erythrocytes. The anesthetic and postoperative courses were uneventful. During the ensuing months, the patient underwent general anesthesia four times for dilatation of a urethral stricture and placement and subsequent replacement of a suprapubic catheter. On each of these four occasions, halothane was used for induction and maintenance of anesthesia. At no time during any of these anesthetic episodes was the patient hypoxic or hypotensive, and he was discharged home each time after an uneventful postoperative course. He did not receive any further blood transfusions, nor did he take any potentially hepatotoxic medications. The patient therefore had been exposed to four halothane anesthetic episodes (a total of 120 min) in a 6-week period.

Three and one half months after the initial injury and 2 days after the last anesthetic episode, the patient’s mother noticed that he was jaundiced. He had no prodromal symptoms suggestive of a viral illness. His primary pediatrician recommended symptomatic treatment with acetaminophen (a total of 4 G was administered by his mother in the 4 days preceding admission). Three days later he became febrile, nauseated, and anorexic. He was reevaluated the subsequent day and was found to be jaundiced with scleral icterus and hepatomegaly. On admission to the hospital (7 days after the last exposure to halothane), the patient was lethargic, nauseated, and oliguric. Vital signs were normal, and medications he was taking at that time in-
cluded ditropan, trimethoprim/sulfamethoxazole, and compazine. Laboratory results showed the following: hematocrit of 55%; leukocyte count of 39.7 × 10^3 cells/L; aspartate transaminase of 959 IU/L; alanine aminotransferase of 1,785 IU/L; lactate dehydrogenase of 412 IU/L; alkaline phosphatase of 307 IU/L; total bilirubin of 20.4 μM; direct bilirubin of 13.2 μM; indirect bilirubin of 5.7 μM; prothrombin time of 32.0 s; partial thromboplastin time of 53.9 s; and international normalized ratio of 7.6. The diagnosis of fulminant hepatic failure with grade 2 encephalopathy of unknown cause was made. The results of screening for hepatitis A, B, and C were negative, as were those of screening for cytomegalovirus and Epstein-Barr virus. The patient’s serum was sent to the University of Arizona for enzyme-linked immunosorbent assay (ELISA). All three samples (taken on days 13 and 14 after the last exposure to halothane) revealed a high immunoglobulin G (IgG) antifluoroacetate antibody titer. The presence of this immune response was reported by the University of Arizona as consistent with the diagnosis of halothane-associated hepatitis.

Liver enzymes, bilirubin, coagulation studies, ammonia, and factor V levels remained abnormal, and he was listed for transplantation. There was no improvement in liver function (based on clinical signs and liver function tests), and he underwent an auxiliary liver transplantation 24 days after the last exposure to halothane. His initial postoperative course was uneventful, his encephalopathy resolved, and there was a marked reduction in liver enzymes and improvement in coagulation profiles, which was consistent with good donor auxiliary liver function. A hepatobiliary scan using Tc-99m-labeled mebrofenin indicated active hepatocellular function in both livers. Eleven days after the transplantation, the patient became septicemic and at exploratory laparotomy was found to have a perforated jejunal. The native liver was noted to have extensive regenerative nodules. Unfortunately, he went on to develop septicemia and multiple organ failure with disseminated intravascular coagulation. He died 18 days after the auxiliary liver transplantation from overwhelming fungal infection.

Autopsy showed that the donor liver had a firm consistency and all vascular and bile duct anastomoses were patent. There was no microscopic evidence of rejection. The native liver had areas of subcapsular hemorrhage and parenchymal hemorrhage with a dense consistency. Histologic examination of the liver revealed massive necrosis and collapse of lobules and small collections of cells representing areas of regeneration. There was evidence of disseminated aspergillosis.

Discussion

The exact incidence of halothane-associated hepatitis in children is unknown, but is estimated to be in the region of 1 in 82,000 to 1 in 200,000. Although extremely rare in children, there have been isolated case reports of halothane-associated hepatitis in the literature. Kenna et al. reported seven cases of halothane-associated hepatitis in children (age range, 11 months to 15 yr), all of whom had undergone multiple episodes of halothane anesthesia (median, 3). The interval between final exposure to halothane and the onset of jaundice ranged from 2–4 days. Halothane antibodies were identified in six of the seven children. Lewis and Blair reported a 4-yr-old girl who developed hepatitis after the fourth administration of halothane with positive antibodies (this case was included in the series by Kenna et al.). Our patient developed jaundice 2 days after his fourth exposure to halothane. The presence of a high antibody titer with good specificity toward the trifluoroacetate–protein residue found in this patient’s serum, together with negative viral studies and drug-related causes of hepatotoxicity, make the diagnosis of halothane-associated hepatitis highly likely. Although the possibility remains that liver failure in this child may have been attributable to other drugs or causative factors, we believe that the most likely cause was exposure to halothane.

Halothane can produce two types of hepatotoxicity. One is a mild self-limiting increase in liver enzymes in plasma that appears in up to 20% of adult patients exposed to halothane. The other is a more severe insult that may result in massive hepatic necrosis and death. Fulminant hepatic failure after repeated exposure to halothane in children appears to be an immune-mediated hypersensitivity reaction. Wark et al. were unable to demonstrate qualitative or quantitative differences between adults and children in their ability to metabolize halothane, and therefore there is no explanation for the lower incidence of halothane-associated hepatitis observed in children. Halothane is metabolized mainly by an oxidative pathway yielding trifluoroacetate–halide, which is believed to be responsible for the immune reaction that can result in fulminant hepatic failure.

The immunologic mechanism of halothane-associated hepatitis has been well described in the review article by Elliott and Strunin and is summarized briefly. Trifluoroacetate–halide binds to free amino groups within liver proteins forming microsomal hapten–protein complexes. These complexes induce an immune response, which results in antibody or T cell formation. The endogenous liver proteins are then changed from “self” to “nonsself” secondary to the formation of hapteng–protein complexes, thus becoming immunogenic. On secondary exposure to halothane, the immune system responds to the production of these hapten–protein complexes by mounting an immune response against the liver, resulting in an autoimmune form of hepatitis.

Several features of halothane-induced hepatotoxicity support hypersensitivity as a mechanism in the development of halothane-associated hepatitis in children. Common features in most reported cases include multiple
exposures; history of allergy, atopy, or previous adverse reaction to halothane; association of postoperative fever and cosinophilia; provocation with deliberate challenge; and the demonstration of circulating antibodies. These antibodies are of the IgG subclass, which suggests previous sensitization after an earlier exposure. These circulating antibodies bind to the surface membrane of halothane-altered rabbit hepatocytes. This reaction is demonstrated in 70% of patients with fulminating hepatic failure associated with halothane.

Testing of patients suspected of having halothane-associated hepatitis is based on the detection of antibodies directed against the trifluoroacetyl neoantigens. To detect the IgG antitrifluoroacetyl antibodies, the serum is first screened by ELISA with antitrifluoroacetyl albumin activity. If the result is positive, the specificity of the antibody reactivity is determined by testing the ability of trifluoroacetyl-lysine to block the antibody binding to the trifluoroacetyl-albumin in a competitive direct ELISA analysis. The combination of these two techniques results in 92% of sera from presumptive halothane hepatitis patients testing positive for antibodies associated with halothane-related hepatitis. These IgG antitrifluoroacetyl antibodies have not been found in patients with liver disease secondary to other causes, in patients exposed to halothane that did not result in fulminant hepatic failure, or in healthy control study participants. The antitrifluoroacetyl testing procedure is therefore highly specific for true halothane-associated hepatitis, and although there is some crossreactivity with other anesthetic agents, there is no crossreactivity with other medications. The ELISA analysis used at the University of Arizona is comparable to that used by the laboratory of Martin et al.

Several new techniques of transplantation in children have resulted in greater availability of organs and better survival rates, including liver reduction techniques, transplants from related donors, and auxiliary transplantation. In the latter technique, the native liver is left in situ, and an additional segment of liver is transplanted subhepatically. The suprarehepatic vena cava is not clamped, and there is no dissection of the perihepatic structures as in traditional orthotopic liver transplantation. It was anticipated in this case that the transplanted liver would provide temporary support until the native liver recovered. This would then allow immunosuppressive therapy to be withdrawn and the auxiliary liver to be removed or allowed to atrophy. This technique has been used successfully in the treatment of halothane-associated hepatic failure in adults. There was clinical and scintigraphic evidence of improved liver function after the transplantation in this child and macroscopic and microscopic evidence of regeneration within the native liver. This suggests that had sepsis not complicated the postoperative course, auxiliary liver transplantation might have been successful in the palliation of the hepatic failure, allowing significant regeneration of the native liver. In one series, the overall survival rate after auxiliary liver transplantation in 30 patients was 63%. Of the survivors, 15 (68%) regained normal native liver function, and the auxiliary liver was removed in 9 and left to atrophy in 4, with no deleterious effect on native liver function. Bismuth et al. concluded that auxiliary liver transplantation was an attractive treatment for fulminant hepatitis in the presence of good prognostic factors for native liver regeneration (young age, rapid onset, and viral hepatitis) but should be considered cautiously in those patients with advanced encephalopathy. With these criteria in mind, it would appear that this patient was a suitable candidate for this procedure, although it is a matter of speculation as to whether an orthotopic liver transplant would have been successful.

We described a case of halothane-associated hepatitis in a patient who developed fulminant hepatic failure and died after liver transplantation. To our knowledge, this is the first report of this rare condition being treated by auxiliary liver transplantation in a child. Halothane remains the mainstay of pediatric inhalational anaesthesia, and although repeated exposure is not recommended in adults, it is not contraindicated in children. One must remember that halothane-associated hepatitis is extremely rare, and concerns about this disorder should not serve as an impediment to the use of this drug in pediatric anaesthesia, at least until an alternative agent with proven safety is available.

References


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Intravenous Regional Clonidine in the Management of Sympathetically Maintained Pain

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INTRAVENOUS regional anesthesia (IVRA) can contribute to the management of sympathetically maintained pain. A variety of medications have been used in IVRA, including local anesthetics with guanethidine, reserpine, bretylium, steroids, and ketorolac. Clonidine, an α2-adrenergic agonist, has been used successfully in the management of refractory reflex sympathetic dystrophy when administered via the epidural or the intrathecal route. The current series of treatments was designed to test the efficacy and safety of intravenous regional clonidine (IVRC). This report presents the results of such treatment in 10 patients who were selected on the basis of having symptoms of sympathetically maintained pain for <3 months.

After approval by our committee on human research, written informed consent was obtained from all patients before procedural intervention. A 22-gauge catheter was inserted into a distal vein of the affected extremity. After application of an electrocardiogram monitor, a pulse oximeter, a noninvasive blood pressure cuff, and an occlusive double tourniquet, the affected extremity was exsanguinated by elevating the extremity and wrapping it with an Esmarch bandage. After inflation of the tourniquet, the intravenous regional solution was injected over 3 min. It included 1 μg/kg clonidine in a total volume of 40 ml for upper extremities and 50 ml for lower extremities. Normal saline or 0.5% lidocaine was used as the diluent. After 30 min, the cuff was deflated and all patients were monitored for an additional 60 min before discharge. Concentrations of clonidine in plasma were determined using a radioimmunoassay method on blood sampled from the arm (contralateral to the IVRA site for patients with upper extremity pain) 30 min after deflation of the tourniquet. Pain was assessed using a verbal pain score (VPS) in which 0 = no pain and 10 = worst pain imaginable.

Case Reports

A typical case is that of a 57-yr-old woman who presented to the Pain Management Center 47 days after undergoing surgical repair for

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