

## Successful Hemoperfusion and Plasma Exchange in Acute Hepatic Failure due to Snake Bile Intoxication

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Snake gallbladder is a traditional Chinese medicine that has been used for treating arthritis and detoxification for more than two thousand years. Sporadic cases of toxic hepatic and renal injury from snake gallbladder have been reported. The toxic effects are dose related and there is a high mortality rate after delayed renal failure. We present a 35 year-old man who was a hepatitis B surface antigen carrier who developed acute hepatic failure after ingestion of snake gallbladder capsules for 6 weeks. The serologic study for hepatitis C antibody, hepatitis B e antigen and hepatitis B virus-deoxyribonucleic acid (HBV-DNA) were negative. Progressively elevated liver enzymes were noted during lamivudine treatment, so blood purification therapy was done to remove possible toxins. The patient recovered after hemoperfusion preceding a series of plasma exchanges. We feel that blood purification can remove toxins and block disease progression to renal failure. In summary, we suggest that blood purification procedures should be done as soon as possible for snake gallbladder-related fulminant hepatitis due to its high mortality rate. (*Chang Gung Med J* 2008;31:207-11)

**Key words:** snake gallbladder, snake bile, acute hepatic failure, blood purification, hemoperfusion, plasma exchange

Management of patients who have ingested toxins is difficult due to the variable presentation and quick disease progression. More than half of toxins have no antidotes, and the nature and mechanism of the intoxication are usually unknown. Blood purification procedures are used to remove toxins, and the choice of procedure (hemodialysis, hemoperfusion with activated charcoal or resin,<sup>(1,2)</sup> plasma exchange, plasmaphoresis or continuous renal replacement therapy) depends on the nature and characteristics of the toxin. Snake gallbladder is a traditional Chinese medicine that has been used for two thousand years. Sporadic cases of hepatitis have occurred after ingestion of snake gallbladder in Taiwan,<sup>(3)</sup> China and Vietnam, and there is a high risk of mortality when late onset renal failure occurs. We

present our successful experience in the treatment of acute hepatic failure post ingestion of snake gallbladder before renal function impairment with activated charcoal hemoperfusion and plasma exchange.

### CASE REPORT

Our patient was a 35 year-old man who was a hepatitis B surface antigen carrier. His mother and two siblings were also hepatitis B surface antigen carriers. There was no history of hepatitis episodes before this event. He denied sexual exposure to prostitutes or abuse of intravenous drugs. His family had no history of liver disease. He had two hospitalizations for right endophthalmitis in 2001 and 2002. He had multiple verrucous papules on his face for 2

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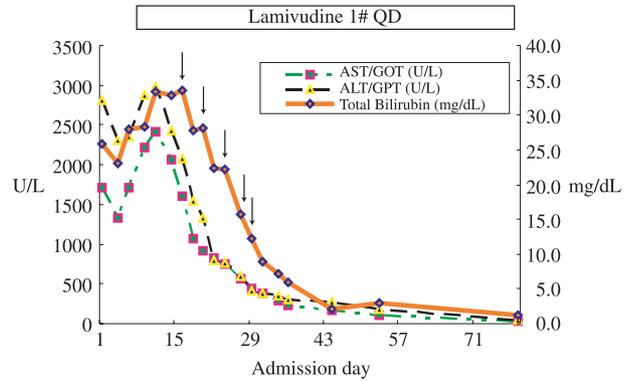
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years. The facial lesions did not improve after treatment by a dermatologist. Because of poor vision in his right eye and the facial lesions, a friend recommended snake gallbladder capsules. The capsule contained a crude powder made from snake gallbladder. He took six capsules per day for about 6 weeks. Two weeks before hospitalization, he developed general malaise and poor appetite, followed by deep-colored urine and yellowish discoloration of the skin two to three days later. He visited a local medical doctor and was immediately referred to our emergency department. On arrival, his body temperature was 35.9°C, pulse rate 80/min, respiratory rate 17/min, and blood pressure 148/96 mmHg. The physical examination showed he was alert, with icteric sclera, hepatomegaly and generalized yellowish discoloration of the skin. There was no palmar erythema, spider angioma, ascites or pitting edema in the legs. He had no fever, chills, abdominal pain, abdominal tenderness, diarrhea, or clay-colored stools. Biochemistry results were as follows: creatinine 1.2 mg/dL, alanine aminotransferase (ALT) 2,807 U/L, aspartate aminotransferase (AST) 1,705 U/L, total bilirubin 25.9 mg/dL, alkaline phosphatase (Alk-P) 97 U/L g/dL, and blood glucose 115 mg/dL. The blood cell count showed white blood cells 6,000 / $\mu$ L, hemoglobin 17 g/dL, hematocrit 49.4%, platelets 154,000 / $\mu$ L, segments 65.5%, lymphocytes 20%, and monocytes 13.8%. The prothrombin time (PT) was 14.7 sec/ control 11.1 seconds with an international normalized ratio (INR) of 1.32.

Initially, hepatitis B virus (HBV) -related acute exacerbation was considered. Lamivudine, 100 mg, per day orally was given shortly after hospitalization began (from day 6). However, anorexia and fatigue persisted. The subsequent liver biochemistry results (Fig. 1) showed persistently high transaminase and bilirubin levels. The hepatitis marker study showed the patient was seropositive for hepatitis B surface antigen (HBsAg) and antibodies to hepatitis B e antigen (HBeAg), but seronegative for hepatitis C antibody (anti-HCV) and HBeAg. HBV-DNA was undetectable on a Digene test ( $< 0.14$  mcps/mL;  $< 0.5$  (0.5/D) pg/mL) on the 4<sup>th</sup> hospital day.

Therefore, snake bile -related toxic hepatic failure was considered. On the 13<sup>th</sup> hospital day, the prothrombin time was 17.2 sec/control 11.1 seconds with an international normalized ratio of 1.54, AST was 2,067 U/L, ALT was 2,427 U/L and total bilirubin



**Fig. 1** Lamivudine was prescribed from day 6. Arrows show hemoperfusion on day 16 and plasma exchange on days 20, 24, 27 and 29. ALT/GPT alanine aminotransferase AST/GOT aspartate aminotransferase.

bin was 32.9 mg/dL. Both a toxicologist and the liver transplantation team were consulted. Hemoperfusion was started on the 16<sup>th</sup> day.

After the first eight-hour hemoperfusion with activated charcoal, the patient felt better and had an increased appetite. The biochemistry results showed improvement in liver function (AST 1,063 U/L, ALT 1,539 U/L, total bilirubin 27.7 mg/dL, and prothrombin time 15.9/11.1 seconds and INR 1.43). But a mildly rebounding elevated bilirubin level was found on the 20<sup>th</sup> day, so a plasma exchange was done. The liver function test results improved after plasma exchange but the PT increased on day 24. (PT 14.5/11.1 seconds with INR 1.30 on day 22 to 15.1/11.1 seconds with INR 1.36 on day 24) Further plasma exchanges were done on days 24, 27 and 29. There was a dramatic change in the clinical course, and the total bilirubin decreased to 5.9 mg/dL before discharge on hospital day 36. The liver function test results were in the nearly normal range in our outpatient clinic 79 days after presentation in the emergency room (total bilirubin 1.3 mg/dL, AST 31 U/L and ALT 51 U/L.). The patient returned to the outpatient clinic 3 months later without any symptoms. The liver biochemistry results were within normal limits and a hepatitis C virus antibody test was negative. Lamivudine was discontinued at that time. The patient was well 9 months after this episode and is followed periodically in the liver clinic.

## DISCUSSION

We had no direct evidence of snake bile toxin in this patient, so we had to exclude other etiologies for acute liver injury. The HBeAg and HBV-DNA were both negative, thus the possibility of chronic hepatitis B with acute exacerbation was low. HCV coinfection was excluded, because of two negative anti-HCV study results in 3 months. We were unable to exclude hepatitis delta virus superinfection, because there was no commercially available test in our hospital. However, the patient denied sexual exposure to prostitutes and abuse of intravenous drugs. The chance of hepatitis delta virus infection was also low.

A diagnosis of Wilson's disease should be considered in patients presenting with acute hepatic failure. The initial presentation of acute hepatic failure in Wilson's disease often occurs in children or young adults. Our patient was 35 years old, which is not a typical age for initial presentation, and there was no history of Wilson's disease in his family. In addition, no neurological signs or hemolytic anemia were observed throughout the course of his disease. Therefore, Wilson's disease was unlikely.

There were unusually high levels of hepatic enzymes (AST and ALT > 50 x UNL) on the 13<sup>th</sup> hospital day, so toxic and drug-related hepatitis had to be ruled out. Besides the snake gallbladder capsules, the patient denied taking any other medicine in the past half year, including acetaminophen. In addition, he had no occupational exposure to hepatotoxic agents (e.g. carbon tetrachloride, trichloroethylene, dimethylformamide), and no history of eating any toxic foods, such as mushrooms (e.g. *Amanita phalloides*). He had no arthralgia, fever, rash or eosinophilia, so systemic toxic effects were ruled out. He had only taken snake gallbladder capsules for verrucous papules for 6 weeks, so snake bile-related acute hepatic failure was diagnosed.

The gallbladders of snakes have traditionally been used for detoxification in China. The use of this folk medicine is now widespread in Taiwan, China (especially Guangzhou), and Vietnam. Sporadic cases of side effects, such as acute hepatic failure, have occurred. If the disease progresses to renal failure, the mortality under supportive care is high. Taipei Veterans General Hospital reported 4 cases of

fulminant hepatitis with late onset renal failure due to snake gallbladder intoxication. Oliguric renal failure usually occurred about 30 days post-ingestion and the mortality rate was high (3 patients died).

No definitive antidote or therapeutic procedure has been found to treat acute hepatic injury due to snake gall bladder. The components of snake bile juice are cholic acid, chenodeoxycholic acid, lithocholic acid, deoxycholic acid, taurochenodeoxycholic acid and glycolithocholic acid, as shown by high pressure liquid chromatography (HPLC).<sup>(4)</sup> An animal model of the toxic effects of snake bile acid in rats showed that the hepatic and renal toxicity due to bile acids was dose dependent.<sup>(4)</sup> But the definitive mechanism of the toxic hepatic and renal injury is still unknown. So, we considered detoxication therapy before oliguric renal failure occurred in our patient. Hemoperfusion with activated charcoal was done first to remove any unknown toxins, such as bile acids.<sup>(1,5)</sup> The clinical symptoms and signs improved post-hemoperfusion, so we thought the toxic material had been removed. After a mild rebound of the total bilirubin, a series of plasma exchanges was done which decreased the liver enzymes step by step.

The usual procedures for blood purification are hemodialysis, hemoperfusion and plasma exchange. Hemodialysis is based mainly on the principle of diffusion, so it is used to remove small (low molecular weight) and water-soluble toxins. Plasma exchange is designed to remove large molecular weight substances from the plasma, so it is used to remove high molecular weight and lipid-soluble toxins. Plasma exchange is not usually effective in the treatment of acute poisoning, because of limitations on the amount of plasma that can be exchanged, especially in the case of toxins with large distribution volumes. The role of plasma exchange in treating this case remains unclear. A new technique, the molecular absorbent re-circulating system, does not have the disadvantages of plasma exchange but it is too expensive for common use.<sup>(6)</sup> The technique of hemoperfusion is based mainly on the absorption of toxins by passing blood through an activated charcoal cartridge, so it is used to remove lipid soluble and protein binding toxins.<sup>(7)</sup> Hemoperfusion has been used for toxin and drug overdoses for severe decades.<sup>(7-11)</sup> Selection of an effective and useful extracorporeal elimination technique improved the

clinical outcome and clearance of poisons in some studies.<sup>(1)</sup> Due to suspicion of a high distribution volume and the lipid-soluble characteristics of the toxins (bile acid is water-insoluble), hemoperfusion was done first in our patient.

Even with blood purification, toxins cause high mortality and morbidity. The critical points are the time of initial treatment and the distribution of the toxins.<sup>(5)</sup> In our experience, the time of the initial blood purification is important to avoid delayed renal failure. In addition, snake gallbladder toxins may have more lipid soluble and protein binding properties than other toxins. But hemoperfusion is not always available, even in hospitals in large cities such as New York.<sup>(12)</sup>

Raw snake bile and gallbladder has induced cases of hepatitis and parasite infection. As in our case, acute hepatic failure occurred after ingestion for one and a half months. Some types of bile and gallbladder can induce toxic reactions in other species,<sup>(13,14)</sup> but the cause of this toxicologic reaction is unknown. Yeh found the components of snake bile acid using HPLC (5 alpha- cyprinol sulfate is absent in snake bile juice) and administered a synthetic bile acid which mimicked snake bile acid to rats. Histological findings of hepatic and renal tissue necrosis were similar in the groups which ingested synthetic and raw snake bile acid.<sup>(4)</sup> The toxic effects of snake bile juice in rats, especially acute renal failure, were dose related.<sup>(4)</sup> Hence, bile acids may be the cause of hepatic and renal failure from snake bile juice.

In the summary, sporadic cases of toxic hepatitis have been found after ingestion of snake gallbladder, especially with high doses of toxin such as in our case. Blood purification must be done as soon as possible before renal failure occurs. We suggest blood purification should be done if snake bile-related acute hepatic failure occurs.

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## 血液灌洗暨血漿置換成功治療蛇膽造成之急性肝衰竭

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蛇膽使用於中國傳統醫學上已有兩千年歷史，主要用來治療關節炎及有解毒功能。但因食用蛇膽所造成的毒性肝腎傷害偶爾會被報導。根據以前經驗，此毒性反應是與劑量大小有關且當遲發性腎衰竭發生後，其死亡率會明顯偏高。我們提出的病例是35歲B型肝炎表面抗原帶原的男性，在連續食用蛇膽膠囊6週後發生急性肝衰竭。其抗C型肝炎抗體，B型肝炎e抗原和B型肝炎DNA病毒量為陰性反應。在嘗試使用lamivudine情況下，肝指數仍持續上升，故我們安排血液淨化術來嘗試移除可能的毒物。其臨床症狀及表徵在經過血液淨化後（血液灌洗及血漿置換術）完全恢復。故我們認為血液淨化術可以移除此毒性物且中斷其疾病進展，尤其在遲發性腎衰竭發生前效果更佳。總結來說，我們建議當發生蛇膽造成的急性肝衰竭時，要盡快使用血液淨化術來改善高死亡率。（長庚醫誌 2008;31:207-11）

**關鍵字：**蛇膽，蛇膽囊，急性肝衰竭，血液淨化術，血液灌洗，血漿置換

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