Rare disease

Ban Tu Wan hepatotoxicity

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Summary

Medications are thought to contribute to approximately 50% of the cases of acute liver failure in the USA. This number includes some herbal medications and supplements. However, little regulatory oversight of these later substances occurs. This report describes a case of fulminant hepatic failure secondary to Ban Tu Wan (a Chinese herb). We discuss the use of this herbal supplement and the relationship to drug-induced hepatitis.

BACKGROUND

The use of herbal supplements has been increasing over the last several decades.¹ Approximately one in eight older Americans uses at least five dietary supplements.² Annual sales of herbal products in the USA grew from approximately \$2 billion in 1994 to \$4.4 billion in 2007.

Herbal supplementation is a relatively unregulated entity in the USA, because of which, herbal preparations typically vary in concentration and content. Often substances are combined for synergy, and the efficacy and safety of each component is largely unknown. In contrast, traditional pharmacotherapy defines specific ingredients, discourages polypharmacy and has established efficacies and safety margins.^{1 3}

A common misconception is that herbal supplements are natural and safe. There are in fact minimal scientific data and research available to validate the safety of these products.⁴ Further, as use of herbal supplements continues to rise, so do the reports of adverse events from these substances. Such adverse events have involved the cardiac, pulmonary, renal, haematological, hepatic and endocrine systems. Besides having direct toxicity, herbal supplements can have interactions with other medications altering absorption, metabolism and renal clearance.¹ One such herb that is gaining popularity for its use in treating alopecia is Ban Tu Wan. We report a case of hepatotoxicity secondary to Ban Tu Wan, as described below.

CASE PRESENTATION

Mrs. X was a middle-aged, Asian woman who presented to a community hospital for confusion. The family described 1 week of general malaise, diarrhoea, myalgias and arthralgias. The patient visited her primary care physician 3 days prior to her hospitalisation for these symptoms. She was given a tentative diagnosis of systemic lupus erythematosus and was treated with an intramuscular dose of dexamethasone and a prescription for prednisone, which was never filled. The original symptoms persisted and the patient also developed confusion and disorientation. This prompted her hospital visit.

The patient presented to the emergency department with diffuse abdominal pain and mental status changes.

She was lethargic, confused and at times agitated. The patient's neurological exam was non-focal, pupils were equal, round and reactive and she had an initial Glasgow Coma Scale of 11. No scleral icterus was appreciated. The patient had clear lung sounds and was afebrile. Her abdomen was diffusely tender and distended without peritoneal findings. The skin was warm and dry with no notable rashes or jaundice. Her medical and surgical histories were unremarkable. She did not use tobacco, alcohol or recreational drugs. She began taking Ban Tu Wan for alopecia 2–3 months prior to presentation. According to family members, this was an oral preparation that the patient took sporadically. It was unknown as to how many times per day Ban Tu Wan was ingested and who the supplier was.

Initially, the patient was haemodynamically stable in the emergency department. However, secondary to her mental status changes she was electively intubated. The patient was subsequently admitted to the intensive care unit.

Upon admission the patient was found to be anaemic (haemoglobin 7.6 g/dl (76 mmol/l)) and thrombocytopenic (platelets 17 000/microlitre ($17 \times 10^9/l$)). The white blood cell count was within normal limits. A non-anion gap metabolic acidosis was identified. Initial arterial blood gas analysis revealed a normal pH, a slightly low pCO₂ and a decreased bicarbonate level. Acute renal failure was also identified, with a blood urea nitrogen to creatinine ratio consistent with a pre-renal aetiology, along with acute hepatic failure. Liver function tests revealed transaminitis (total bilirubin 4.1 mg/dl (70 micromol/l), direct bilirubin 3.8 mg/dl (65 micromol/l), albumin 2.3 g/dl (23 g/l), alkaline phosphatase 199 U/l, aminotransferase 1214 U/l and alanine aminotransferase 5386 U/l)). The coagulation studies revealed a coagulopathy. Fibrinogen and D-dimer levels were within the normal limits. Urine toxicology and infectious hepatitis panels were negative. Lactate and troponin levels were within the normal ranges.

Chest radiograph demonstrated a right lower lobe opacity (most consistent with atelectasis) and CT abdomen/pelvis demonstrated para-hepatic oedema with ascites. Ceftriaxone, azithromycin and a bicarbonate drip were initiated.

Subsequently, the patient developed progressively worsening hypotension requiring multiple pressors for cardiovascular support. A Gram-negative bacteraemia (eventually identified as *Enterobacter cloacae*) was noted on preliminary culture results. This was thought to be secondary to her immune compromise and systemic inflammatory response syndrome from her liver failure, rather than shock liver from sepsis as she was previously healthy with no risk factors for bacteraemia (recent procedures, trauma, wounds and indwelling catheters). In addition, on presentation no definitive foci of infection was discovered nor did she have abnormal vital signs, elevated lactate, fever or other stigmata of sepsis. The coagulopathy and thrombocytopenia were corrected with fresh frozen plasma and platelet transfusion.

OUTCOME AND FOLLOW-UP

The patient was evaluated by the hepatobiliary and transplant consultants but did not meet transplantation requirements secondary to septicaemia. The final diagnosis, as determined through consensus opinion of critical care medicine, hepatology, infectious disease and poison control/toxicology, was drug-induced hepatotoxicity likely secondary to Ban Tu Wan. Transaminase levels continued to rise and the patient developed worsening cerebral oedema. The patient's code status was changed to Do Not Resuscitate-Comfort Care (DNR-CC) and care was withdrawn. The patient expired shortly thereafter.

DISCUSSION

The pathogenesis of drug-induced hepatotoxicity occurs via direct cellular toxicity, metabolite cytotoxicity or hypersensitivity reactions leading to liver dysfunction. The category of hepatic injury caused by the drug can be classified as either hepatocellular necrosis or cholestasis. Hepatocellular necrosis is commonly seen in drugs such as acetaminophen and ketoconazole, whereas chlorpromazine and haloperidol cause liver damage via cholestasis.⁵

The degree of hepatotoxicity from an offending agent is very subjective. Some patients may present with asymptomatic transaminitis while other patients may present with fulminant hepatic failure and encephalopathy. These differences are attributed to numerous factors including variation in metabolic pathways and enzyme activation, the use of concomitant substances, the amount and duration of the exposure and individual idiosyncracies.⁵

The key to identifying drug-induced hepatotoxicity is the history. Physical exam findings and laboratory tests are non-specific. Hepatomegaly, abdominal tenderness, jaundice, altered mental status and elevated liver function studies are not consistent findings. Once stabilised, immediate emergency department management includes supportive care, discontinuing the agent and admission to the hospital for continued management. Initial work-up should include complete blood counts, routine chemistries, viral hepatitis serology, toxicology screen, alcohol and acetaminophen levels, pregnancy test, autoimmune antibodies, blood cultures, liver function tests, HIV testing, lipase, amylase and coagulation studies.⁶ If acute hepatic failure is present, the patient is admitted to an intensive care unit at a centre with transplant capabilities.⁵

Most information known about drug-induced hepatotoxicity focuses on traditional pharmacotherapy.⁷ However, with the rise in complementary medicine use and the lack of regulation of the substances, the true incidence of herbal hepatotoxicity from these is difficult to determine. In many clinical encounters, patients fail to report or physicians fail to inquire about alternative medication use. The astute physician must keep herbal toxicity included in the differential diagnosis, which is often considered the aetiology of the hepatic failure once other causes have been excluded. Additionally, as many supplements contain multiple ingredients, it is often impossible to determine which ingredient in the herbal preparation was responsible for the hepatotoxicity.⁸

Several of the key points discussed above are demonstrated in this case presentation. A detailed history was difficult to obtain secondary to language barriers and cultures differences despite interpretive services and culturally competent healthcare workers. Physical exam and laboratory findings were non-specific, and there were multiple confounding factors such as the history of antibiotic use and the questionable history of systemic lupus erythematosus. Lastly, Ban Tu Wan is a Chinese herbal preparation consisting of multiple ingredients creating a difficult clinical scenario for identifying potential drug toxicities. Ingredients are listed in table 1.⁹

Ban Tu Wan consists of nine different ingredients used for the treatment of hair loss in Eastern medicine. Its bodily actions include nourishing the liver, kidney, blood and growing hair. The dose is 4–6 pills and the frequency is three times a day. The duration of treatment is for 3–4 months.⁹ Each ingredient has a Chinese name, a common name and a scientific name.

To our knowledge, there is no literature to date that describes drug-induced hepatitis secondary to Ban Tu Wan. In June 2011, a literature search was conducted for each ingredient in Ban Tu Wan, using both scientific and Chinese names. Overall, there is minimal research addressing Ban Tu Wan toxicity.

Diagnosing drug-induced hepatotoxicity is difficult and determining causality is even more of a challenge. A thorough history should be taken in patients with hepatotoxicity, including the use of non-prescription medications and herbal supplements. Clinically, packaging information is useful for determining ingredients and dosages. The retailer should be contacted to provide additional information about the herbal supplement.⁸

Table 1 Ban Tu Wan ingredients

	Chinese name	Common name	Scientific name
1	He Shou Wu	Fo-Ti root, Fleece-flower root	<i>Radix Polygoni multiflori</i>
2	Shu Di Huang	Prepared Rehmannia root	<i>Radix Rehmanniae preparata</i>
3	Sheng Di Huang	Fresh Rehmannia root	<i>Radix rehmanniae</i>
4	Dang Gui	Angelica root	<i>Radix Angelicae sinensis</i>
5	Dan Shen	Red Sage root, Salvia	<i>Radix Salvia miltiorrhiza</i>
6	Wu Wei Zi	Schisandra fruit	<i>Fructus schisandrae</i>
7	Dang Shen	Pilose Asiabell root	<i>Radix Codonopsis pilosulae</i>
8	Mu Gua	Chaenomeles fruit	<i>Fructus chaenomeles</i>
9	Qiang Huo	Notopterygium root	<i>Rhizoma seu Radix notopterygii</i>

From an emergency department perspective, the management of acute hepatic failure includes supportive care, identifying the potential complications (acute renal failure, hepatic encephalopathy, cerebral oedema—exact mechanism unknown but found to occur more regularly in the presence of high-grade encephalopathy and infection/sepsis—common secondary to diffuse inflammatory response and multisystem failure) and admitting to the appropriate level of care, which is often an intensive care unit in a tertiary care centre with transplant services. Most cases of fulminant acute liver failure progress rapidly to death if not treated with a transplant. However, obtaining a thorough history from family members and/or prehospital providers is also key and such information may only be attainable in the emergency department.

Some problems that be addressed in the emergency department are cerebral oedema, hyperammonaemia and encephalopathy, infection, seizures, renal failure and electrolyte disturbances. Cerebral oedema should be aggressively managed with mannitol and hyperventilation, especially with impending herniation. Steroids are not currently recommended. Lactulose for encephalopathy is thought to be beneficial and may even decrease the likelihood of developing cerebral oedema. Infections are very common in liver failure, as demonstrated in our case. Currently, no guidelines exist for prophylactic antibiotic administration. However, if infection is suspected broad spectrum antibiotic coverage should be initiated.

Seizures should be controlled with phenytoin and low-dose benzodiazepines. If concomitant renal failure is present, haemodialysis is indicated. Closely monitor and manage electrolytes, especially glucose, potassium, magnesium and phosphorus. If the patient has active bleeding or requires a procedure administer vitamin K, fresh frozen plasma and platelets. As with all critically ill patients hemodynamic monitoring is essential. If vasopressors are needed one should avoid vasopressin.

With regard to *N*-acetylcysteine, its use is recommended in liver failure secondary to acetaminophen. Newer studies have shown a benefit in liver perfusion and haemodynamic stability for other causes of acute liver failure; however, no guidelines currently exist for empirical use.⁶

With regard to future endeavours, increasing awareness appears to play a vital role. Primary care physicians

should educate patients about complementary medicine and healthcare workers should maintain a high suspicion for potential adverse effects. On a larger scale, national online databases may improve product identification and toxicity recognition.

Learning points

- ▶ Herbal supplementation is a relatively unregulated entity in the USA that is becoming increasingly common.
- ▶ A common misconception is that herbal supplements are natural and safe; however, there are limited data regarding the safety of these products.
- ▶ Ban Tu Wan is a Chinese herb gaining popularity for its use in treating alopecia.
- ▶ Diagnosing drug-induced hepatotoxicity is difficult and determining causality is even more of a challenge.
- ▶ The management of acute hepatic failure includes supportive care, treating potential complications and admitting to the appropriate level of care.

Competing interests None.

Patient consent Obtained.

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