Hepatic Venocclusive Disease Associated With the Consumption of Pyrrolizidine-Containing Dietary Supplements

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Veinocclusive disease, a form of Budd-Chiari syndrome, was diagnosed in a 49-year-old woman. The patient had portal hypertension associated with obliteration of the smaller hepatic venules. A liver biopsy specimen showed centrilobular necrosis and congestion. Analysis of food supplements the woman regularly consumed showed the presence of pyrrolizidine alkaloids. The major source was a powder purporting to contain ground comfrey root (Symphytum sp). We calculated that during the 6 months before the woman was hospitalized, she had consumed a minimum of 85 mg of pyrrolizidine alkaloids (15 μg/kg body wt · day). The clinical and analytic findings were consistent with chronic pyrrolizidine intoxication, indicating that low-level, chronic exposure to such alkaloids can cause veinocclusive disease.

The pyrrolizidine alkaloids comprise a group of some 200 substances, many of which are hepatotoxic. These alkaloids are widely distributed, both botanically and geographically. Pyrrolizidine poisoning is endemic in many areas, including Jamaica and many parts of Africa. Epidemics of pyrrolizidine poisoning have occurred in Afghanistan (1) and India (2). The plants responsible have been mainly Folistrium, Senecio, and Crotalaria species.

Pyrrolizidine poisoning of humans is not well documented in the United States. Intoxications have recently been reported for the Southwestern states in children given herbal teas prepared from the pyrrolizidine-containing plant Senecio longifolius (3). Other plants in this genus, particularly Senecio jacobaea, are major causes of livestock losses in the Northwest Pacific states (4).

It is known that pyrrolizidine alkaloids can enter the food chain in low concentrations in milk (5) and honey (6, 7). The extent of exposure, and the public health implications of such exposure, are unknown. Due to their widespread distribution, pyrrolizidine alkaloids probably occur in many herbal preparations. Symphytum sp (comfrey), in particular, is widely used as a herb and vegetable in North America, Japan, and other parts of the world. Although the presence of pyrrolizidine alkaloids in Symphytum sp is well established (10, 11), the risk associated with using preparations containing Symphytum sp have not been clearly delineated. A risk has been recommended, however, that people not consume such products (12). We report herein a case of pyrrolizidine poisoning in an adult consuming a powder purportedly containing ground comfrey (Symphytum) roots.

Case Report

A 49-year-old mother of two was admitted to the hospital because of progressive swelling of the abdomen and extremities over the preceding 4 mo. On admission, heart failure, peripheral edema, and ascites were noted. The liver was enlarged, with hepatomegaly. Bilirubin was 1.8 mg/dl, with a prothrombin time of 14.6 sec. Venography showed a wedge pressure of 23 mm Hg and a wedge pressure of 17 mm Hg were recorded, consistent with hepatic or hepatic venocclusive disease.
Dietary Venous Disease

There was, however, no stable obstruction of outflow either in the retrohepatic or suprarehepatic vena cava or in any of the major veins (Figure 2). Films taken during balloon dilatation of one of the intrahepatic venous tributaries demonstrated obliteration of the smaller hepatic veins with pressure, extrarrenalization of the dye into the liver parenchyma (Figure 2). Because of the intractability of symptoms, a side-to-side portocaval shunt was done. The pre- and post-shunt pressures were 23 and 14 mmHg, respectively. The patient made an uneventful recovery and is now well.
patient weighed 106 lb. Long-term follow-up has revealed no serious problems except for a transient bout of post-shunt encephalopathy that was related to ingestion of an amount of protein estimated to be >200 g in a 12-h period.

Analyses of Food Supplements

The patient was a heavy consumer of herbs, vitamins, and "natural" food supplements. These included daily supplementations of vitamins C, K, E, A, and B complex; calcium, magnesium, potassium, zinc, iron, selenium, and steroidal adrenal bovine extract. She drank 3 cups of chamomile tea per week, and for the 6 mo before admission had consumed 1 g/day of a herbal tea known as MU-16. In addition, for the 4 mo before admission, she had taken two capsules of "comfrey-pepsin pills" with each meal.

The "MU-16 herbal beverage with ginseng" (Erewhon Inc., Boston, Mass.) and "comfrey-pepsin" capsules (Nature's Way, Provo, Utah) were analyzed for pyrrolizidine alkaloid content. According to the label, the former is prepared in Japan.

The tea was extracted in a Soxhlet continuous extractor with ethanol for 20 h. The comfrey-pepsin capsules were opened, and the powder was extracted with boiling methanol in a round-bottomed flask for 2 h. The extracts were analyzed for pyrrolizidine alkaloids and pyrrolizidine N-oxides, as described by Hustable et al. (13). Monocrotaline was used as a standard, and pyrrolizidine concentrations were calculated assuming the same extinction coefficient (E = 48000) and the same molecular weight for the unknown alkaloids as for monocrotaline. The Ehrlich reaction used in the assay is a radiometric procedure specific for hepatotoxic pyrrolizidine alkaloids (14).

Pyrrolizidine Analyses

Each packet of MU-16 tea contained eight 6-g bags. Samples purchased 2 yr apart were analyzed. An earlier sample, obtained from the patient, contained 0.21 nmol pyrrolizidine/g dry wt of tea. A later sample purchased by us, contained 2.3 nmol pyrrolizidine/g tea, and 3.0 nmol pyrrolizidine N-oxide/g tea. Each comfrey-pepsin pill contained 400 mg of a white powder. The powder contained 0.027 nmol/g pyrrolizidine alkaloids and 0.042 nmol/g pyrrolizidine N-oxides (Figure 3).

The patient had consumed 400 g of MU-16 tea over the 6-mo period. Our analyses suggest that she had, therefore, consumed between 12.9 and 38.4 nmol of total pyrrolizidines. This is equivalent to between 0.43 to 1.45 µg/kg body wt/day.

The patient had consumed six capsules per day of the comfrey-pepsin pills. Her daily consumption of pyrrolizidine alkaloids from this source was, therefore, 2.07 µmol/day (86 µg/kg body wt/day). Over a 4-mo period, she had consumed 2.50 µmol, or 1700 µg/kg body wt/day, of total pyrrolizidines from the comfrey-pepsin capsules.

Discussion

In South Africa, it was noted many years ago that pyrrolizidine poisoning due to the ingestion of Senecio plants produced a condition similar to Budd-Chiari syndrome (15). Crotalaria plants cause numerous cases of pyrrolizidine poisoning in livestock.
The highly characteristic venocclusive disease induced has striking similarities to the Budd-Chiari syndrome (16,17).

The patient reported herein suffered a clinical condition suggestive of pyrrolizidine poisoning. At least two of the food supplements she was regularly consuming contain pyrrolizidine alkaloids. The variability in content found in the MIU-16 tea may be due to its composition of a complex mixture of plants, different proportions of which vary from batch to batch. Within a species, the content of pyrrolizidine alkaloids vary throughout the year, and differs between the roots and aerial parts, and between the young and old leaves (18). A higher concentration of pyrrolizidine alkaloids was found in the comfrey-pectin capsules the woman was consuming. "Comfrey" is Symphytum officinale, or other Symphytum species or hybrids. Symphytum species contain both pyrrolizidine alkaloids and pyrrolizidine N-oxides.

The alkaloidal content of comfrey is highly variable. Stolk (18) reporting a range for leaves of 0.003%–0.115%. The roots of S. asperum contain between 11% and 6.4% alkaloids (19). Our analyses show that levels to be approximately seven times higher than free alkaloid levels. This underscores the importance of N-oxide analysis where pyrrolizidine poisoning is suspected, as analyzing for alkaloids may give an erroneously low estimate of pyrrolizidine exposure.

The total pyrrolizidine consumption we can establish for this patient is relatively low. It is possible that she had other sources of exposure, and it is also possible that she had been consuming pyrrolizidine-containing supplements for longer than the period could establish. We calculate a minimum daily intake of 700–740 µg, or ~15 µg/kg, over a period of several months. Severe liver disease has been found in humans with an estimated daily intake of 30–40 µg (11); Heliotropium alkaloids (11). In pigs, liver and kidney disease have been produced after exposure to monocrotaline for 20 wk at a daily level of 80 µg/kg (20).

The toxicity of comfrey has been recently reviewed (21). In rats, high levels of comfrey (0.5%–8% of the diet) are carcinogenic. The dangers to humans of chronic consumption are unknown. However, subacute exposure to the pyrrolizidine alkaloid monocrotaline produces toxic changes in rats that are only seen on acute dosing at higher levels (22). Our patient was consuming substances containing pyrrolizidine alkaloids on a daily basis, she had the symptoms of pyrrolizidine poisoning, and she showed structural changes in the liver characteristic of such poisoning. We believe, therefore, that her condition was the result of prolonged consumption of low levels of pyrrolizidine alkaloid.

Pyrrolizidine poisoning due to the use of herbal teas is being increasingly reported in the United States. Several cases have been found of children poisoned after being administered teas prepared from Senecio longilobus (3,4,23), and a case has been reported involving a woman using a Crotalaria-containing tea (although identification of pyrrolizidine alkaloids was not made) (24). To our knowledge, this is the first report of venocclusive disease in any human after the use of a preparation claiming to be made from comfrey.

References
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