Case reports

Herbal tea induced hepatic veno-occlusive disease: quantification of toxic alkaloid exposure in adults

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SUMMARY Four young Chinese women took daily doses of an unidentified 'Indian' herbal tea as treatment for psoriasis. Three (one of whom died), developed ascites, hepatomegaly and biochemical abnormalities within 19–45 days. The fourth patient discontinued herbal tea after 21 days when she developed a skin rash. Two patients had portal hypertension, while all had liver histology showing features of veno-occlusive disease. Pyrrolizidine alkaloids were identified spectrophotometrically in the brewed tea, and in the chopped leaves of the herbal mixture; the mean dose in the tea prepared for consumption being 12 mg/day of alkaloid base and 18 mg/day of N-oxide. The mean cumulative dose of alkaloids (base + N-oxide) before onset of symptoms (three patients), was estimated to be 18 mg/kg. In the asymptomatic patient with histological liver disease only, the corresponding dose was 15 mg/kg. These cases thus provide some measure of pyrrolizidine alkaloid toxicity in adults.

Hepatic veno-occlusive disease caused by pyrrolizidine alkaloid exposure occurs sporadically throughout the world, often involving locally practiced traditional folk medicine such as imbibing bush tea. Alternatively, accidental contamination of cereals may have been the most likely cause of large epidemics in areas such as Afghanistan and Central India. In this report we describe a small epidemic of hepatic veno-occlusive disease, due to a herbal tea folk 'remedy', which was not indigenous but imported from another subcontinent. All the patients were adults, prepared their own tea, and were also receiving conventional (western) medical care. Consequently, it was possible to quantify the extent of toxic alkaloid exposure in each patient.

Case reports

The patients were four young Chinese women with psoriasis each of whom brewed and imbibed the herbal tea. The tea was brought into Hong Kong by an Indian, who had experienced remission of his psoriasis, ascribed to drinking the very same tea while on a recent visit to India. All five individuals were consulting the same dermatologist. Everyday, each patient put a pre-packed mixture of herbs into about 800 ml water, which was brought to the boil and reduced to half its original volume by simmering. After adding one teaspoonful each of a dark paste and a dark syrup to the brew, the liquid was consumed; half in the morning and half in the evening. The full recommended course of treatment was six months.

Pertinent personal and laboratory data from the four patients are summarised in the Table. Patients 1, 2, and 3 developed abdominal distension (hepatomegaly with ascites), 45, 30, and 19 days respectively, after starting to imbibe the tea, and after a further period of 16, 36, and 49 days, respectively, they were admitted to Queen Mary Hospital. With the onset of symptoms, patients 1 and 3 stopped consuming the tea and experienced clinical and biochemical remission. Patient 2 persisted in taking the tea for 16 days after the onset of symptoms, against medical advice, and continued
Table  Personal and laboratory data. Accepted normal ranges and units are shown in brackets.

<table>
<thead>
<tr>
<th>Patient</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Adm QMH</td>
<td>After 36 d</td>
<td>Adm QMH</td>
<td>After 12 d</td>
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<tr>
<td>Age (yr)</td>
<td>28</td>
<td>26</td>
<td>23</td>
<td>27</td>
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<tr>
<td>Weight (kg)</td>
<td>51</td>
<td>61</td>
<td>49</td>
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<td>Liver function</td>
<td></td>
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<tr>
<td>Albumin (31–51 g/l)</td>
<td>36</td>
<td>46</td>
<td>34</td>
<td>31</td>
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<tr>
<td>Globulin (23–40 g/l)</td>
<td>21</td>
<td>33</td>
<td>22</td>
<td>29</td>
</tr>
<tr>
<td>Bilirubin (&lt;26 μM/l)</td>
<td>4</td>
<td>9</td>
<td>55</td>
<td>402</td>
</tr>
<tr>
<td>AST (&lt;30 IU)</td>
<td>52</td>
<td>36</td>
<td>232</td>
<td>237</td>
</tr>
<tr>
<td>ALT (&lt;29 IU)</td>
<td>63</td>
<td>27</td>
<td>122</td>
<td>128</td>
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<td>1.2</td>
<td>1.7</td>
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<tr>
<td>Ascites fluid</td>
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<tr>
<td>Protein (&lt;25 g/l)</td>
<td>34</td>
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<td>22</td>
<td>25</td>
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<td>Cells (&lt;500/mm³)</td>
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<td>28</td>
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<td>Mean pressures</td>
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<td>Hepatic vein (≤6 mmHg)</td>
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<td></td>
<td>9</td>
<td>6</td>
</tr>
<tr>
<td>Hepatic wedge (6-10 mmHg)</td>
<td>23</td>
<td></td>
<td>20</td>
<td>10</td>
</tr>
</tbody>
</table>

Adm QMH = on admission to Queen Mary Hospital (before this, patients 2 and 3 had been inpatients elsewhere); d = days; AST = aspartate aminotransferase; ALT = alanine aminotransferase; PT = prothrombin.

to deteriorate. Despite treatment with diuretics and aspiration of ascites, she developed increasing symptoms and ultimately died from hepatic failure, portal hypertension, and terminal gastrointestinal haemorrhage eight weeks after stopping tea consumption. Patient 4, stopped taking tea after 21 days on account of a new skin rash, unlike her previous psoriasis. When traced and clinically assessed 77 days later, she was found to have mild hepatomegaly only. None of the patients had been treated with cytotoxic drugs, and none were taking oral contraceptive pills at the time of presentation or during the preceding three years; both agents being known to cause hepatic veno-occlusive disease. Ultrasonography revealed that all the patients had homogenously enlarged livers, patent hepatic and portal veins of normal calibre, and splenic measurements at the upper limit of normal. The absence of portal vein dilatation or splenomegaly despite patients 1 and 2 having documented portal hypertension (see Table), presumably reflects the short duration of the latter. All four cases developed symptoms within 21 days of each other, thus constituting a small epidemic. The psoriatic man who was the source of the herbal tea has not been seen or assessed by us, as he is now living abroad. Evidently he remains well, even though he claimed to have consumed a full course of the same tea. There was conflicting information as to whether the tea originated in India or Pakistan.

In all four patients the liver biopsies, revealed histological features (Fig. 1) of hepatic veno-occlusive disease. The biopsy specimen from patient 2 (who eventually died), showed centrilobular areas of intense sinusoidal dilatation with haemorrhage accompanied by liver cell atrophy and necrosis, also many of the central and sublobular hepatic veins were significantly narrowed by intimal oedema and loose fibrosis. Necropsy, revealed a slightly enlarged liver with a marked 'nutt' appearance and reverse lobulation, and there was extensive centrilobular haemorrhagic necrosis with scarring which centred around the severely narrowed, sclerotic sublobular and central veins (Fig. 2). Other findings included three litres of ascites, a single oozing oesophageal varix and bloody mucus in the stomach. The spleen was not enlarged. The liver biopsy findings from patients 1 and 3 were similar to those of patient 2, but congestion and liver cell changes in the centrilobular zone were much milder. The biopsy from patient 4 exhibited only slight residual sclerosis of some of the sublobular hepatic veins with dilatation of the feeding venules.

**BIOCHEMICAL AND BOTANICAL ANALYSIS OF THE HERBAL TEA**

The daily portions of herbal medicine to which we had access weighed 48–70 g. The mixture consisted of chopped leaves (about 64% by weight), acorns (13%), dates (10%), seeds, sticks, cones, pods and other miscellaneous material (13%). Samples of the
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individual constituents of the herbal mixture, diluted paste, and diluted syrup were analysed spectrophotometrically for the presence of unsaturated pyrrolizidine alkaloids. No such alkaloids were detected in the acorns, dates, seeds, sticks, cones, paste or syrup. Spectra characteristic of unsaturated pyrrolizidine alkaloids after reaction with Enrich's reagent were obtained only in the leaves. Quantification was based on absorbance at 565 nm and the alkaloid content was calculated as senecionine base. The alkaloid base and N-oxide levels in the leaves were 0.42 and 1.4 mg/g, respectively; the corresponding doses of each in one day's herbal mixture being about 16 and 53 mg. Three specimens (each one day's supply) of brewed tea (250, 380 and 390 ml) prepared by the three surviving patients were also analysed in the same manner. The daily intake of alkaloid base and N-oxide were found to be 12±1 and 18±4 mg (mean±SD), respectively, and thus, could all have been derived from the leaves. By assuming that the above mean values were representative of each patient's daily intake, respective cumulative doses of alkaloid (base + N-oxide) consumed by patients 1, 2 and 3 up to the onset of symptoms were calculated to be 1350 mg over 45 days, 900 mg over 30 days and 570 mg over 19 days. While having irrefutable

Fig. 1 Liver biopsies: congestion, haemorrhage and necrosis around the partially occluded sublobular hepatic vein (HV) in patient 1 (PT1) and patient 2 (PT2); haematoxylin and eosin (×70 original magnification). Residual venous sclerosis and dilatation in patient 3 (PT3) and patient 4 (PT4); Masson's trichrome (×170 original magnification).

Fig. 2 Necropsy liver from patient 2 (PT2): centrilobular haemorrhagic necrosis around severely sclerotic and narrowed sublobular hepatic vein (HV); Masson's trichrome (×70 original magnification).
histological involvement, patient 4, who did not develop symptomatic hepatic veno-occlusive disease must have consumed about 630 mg over 21 days. Patient 2 who died, continued taking the tea for a further 16 days after the onset of symptoms and thus took a total dose of about 1380 mg over 46 days.

Although the condition of the chopped leaves (source of toxic alkaloids), made definite botanical identification very difficult, an attempt was made to classify them based on surface processes and general anatomy. The leaves were found to belong to the family of Compositae, but on balance it seemed unlikely that they were from any Senecio species.

Discussion

Hepatotoxic pyrrolizidine alkaloids occur in a large number of plants, notably in the Boraginaceae (genus Heliotropium), Leguminosae (genus Crotalaria) and Compositae (subdivision Senecioneae). The occurrence of two cases of veno-occlusive disease in Northern China was associated with the use of the plant t’u-san-ch’i’i (Gynura segetum, family Compositae) in quantities of 36-45 g daily, as a medicinal tea. The species of poisonous plant taken by our patients though not identified precisely, also appeared to belong to the Compositae family. Of further relevance to the source of the herbs obtained by our patients, is a report by Gupta and others from New Delhi describing hepatic veno-occlusive disease occurring after unidentified herbal medicines were used in the treatment of a patient with ichthyosis and a patient with psoriasis.

Total pyrrolizidine alkaloid consumption producing infantile intoxication in Arizona has been estimated to be about 70-147 mg given over 14 days in a 6 month old baby who lived, and 66 mg given over four days in a 2 month old baby who died. Assuming that these infants weighed about 8 and 5 kg respectively, the corresponding dosage would have been about 9-18 and 13 mg/kg. In our series by comparison, the estimated cumulative doses before development of symptoms in patients 1, 2 and 3 were 26, 15 and 12 mg/kg respectively. Patient 4, who had asymptomatic hepatic veno-occlusive disease, consumed about 15 mg/kg. In patient 2 who died, the estimated cumulative dose up till the onset of symptoms was the same as that in patient 4 who was asymptomatic. Moreover, the total calculated dosage consumed by the fatal case was 23 mg/kg and compares with 26 mg/kg for patient 1 who survived.

Thus, though from a small number of cases, our results provide some data on the extent of alkaloid exposure liable to produce toxicity. They also suggest considerable individual variation in susceptibility among patients who were of the same sex and race, and nearly the same age. To our knowledge, this report is the first such quantitation of pyrrolizidine alkaloid hepatotoxicity in adults.

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References

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