Hepatotoxicity of herbal remedies

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Herbal medicines may be potentially toxic, and inquiry about their intake should not be overlooked

The hepatotoxic effects of conventional drugs are well recognised, but herbal medicines are often assumed to be harmless and are advertised as such. The error of this assumption has recently received attention in the press,[1] but we think that doctors are not sufficiently aware of the potential toxicity of herbal medicines. We report on four women, three from Edinburgh and one from Tyneside, who sustained liver damage after taking herbal medicines for relieving stress. All had been in good health previously; none could recollect having been in contact with jaundice or hepatitis; none had travelled abroad, or had abused drugs parenterally or otherwise, or had been given blood or blood products; and none took alcohol in excess.

Case reports

CASE 1

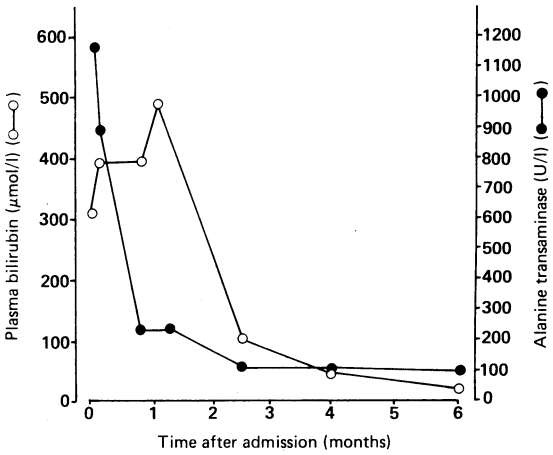
The table shows the results of biochemical and serological tests for all the cases.

A 57 year old woman presented with jaundice having felt vaguely unwell for the previous two weeks. She had had dark urine and pale stools but no abdominal pain. She had taken indapamide, one tablet daily for many years, and Neurelax, a herbal medicine sold for relieving stress, for the previous three weeks (about 30 tablets). Her alcohol intake was about 12 units (120 g absolute alcohol) per week. On examination she was icteric, did not have a fever, and had no stigmata of chronic liver disease or hepatosplenomegaly. Ultrasonography did not show focal hepatic abnormality; a transjugular liver biopsy obtained insufficient tissue for diagnosis.

Her clinical state deteriorated and she developed ascites and encephalopathy. With intensive medical support her clinical condition and liver function tests improved slowly (figure). A second liver biopsy three months later disclosed chronic aggressive hepatitis with advanced fibrosis. Ten months later she returned to work and the results of liver function tests had almost returned to normal.

CASE 2

A 48 year old woman presented with jaundice, dark urine, and pale stools in the previous week. She had taken Kalms tablets, two daily for the previous two months; alcohol abuse was not suspected. On examination she was jaundiced and did not have a fever or stigmata of chronic liver disease; she had mild hepatomegaly. Ultrasonography disclosed a small gall stone in the gall bladder with no dilatation of the bile ducts. Liver biopsy disclosed severe acute hepatitis with centrilobular and bridging necrosis. After stopping the herbal tablets her liver function test results subsequently returned to normal over the following three months.



Plasma bilirubin concentration and alanine transaminase activity on admission and during six months' follow up after taking herbal medicine (Neurelax) (case 1)

CASE 3

A 41 year old woman presented with jaundice, dark urine, and pale stools; she had been unwell for two months. She had taken a low dose contraceptive pill for five years without ill effects and four Kalms tablets daily for the previous three weeks. She had taken a course of Kalms tablets nine months previously but had had to stop because of nausea. She did not have a history of alcohol abuse. On examination she was jaundiced with no stigmata of chronic liver disease; an abdominal examination showed no abnormality. An isotopic liver scan was normal. Liver biopsy disclosed moderately active acute hepatitis. She stopped taking the tablets and, two months later, felt completely well; her liver function test results had returned to normal.

CASE 4

A 42 year old woman presented with jaundice, nausea, and right hypochondrial pain. She had taken one Kalms tablet daily for three days a fortnight before. Alcohol abuse was not suspected. On examination she was icteric and did not have a fever or stigmata of chronic liver disease. Ultrasonography showed no abnormality, and liver biopsy was unsuccessful. She stopped taking the tablets and her jaundice resolved within weeks. The results of the other liver function tests, however, took nineteen months to return to normal values.

Results of biochemical and serological investigation on admission in cases of suspected hepatotoxicity from herbal preparations

	Case 1	Case 2	Case 3	Case 4
Plasma bilirubin (μmol/l) (normal range 2-17 μmol/l)	315	232	484	273
Serum alanine transaminase (IU/l) (normal range 10-40 IU/l)	1165	293	ND	935
Serum aspartate transaminase (IU/l) (normal range 10-35 IU/l)	ND	581	617	ND
Alkaline phosphatase (IU/l) (normal range 40-100 IU/l)	232	190	97	730
Prothrombin ratio	1·9	1·5	1·3	ND
Antinuclear antibody				Positive
Rheumatoid factor	ND	ND	ND	Positive

*Results for viral serology (including serological tests for hepatitis A virus, hepatitis B virus, Epstein-Barr virus, and cytomegalovirus (not case 3)) and tests for antibodies to smooth muscle and mitochondria were all negative.
ND=not done.

Discussion

We think it important that these four women had taken similar herbal medicines before their hepatic illnesses, for which no other cause could be found. The two preparations implicated (Kalms and Neurelax) are sold in health shops for relieving stress and are described as non-habit forming natural plant remedies

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free from the risks of side effects. Other instances of hepatic injury after taking herbal remedies have been recorded, although the details have been brief; a patient with acute hepatitis attributed to mistletoe in a herbal remedy was reported on in 1981,[2] prompting considerable debate,[3-7] and since then veno-occlusive disease of the liver secondary to ingestion of medicinal herbs has been reported.[8,9] The Welsh Drug Information Centre has received several communications concerning jaundice after ingestion of Kalms and Neurelax tablets and also Box's nerve tablets and of hepatic illness developing after taking skullcap tablets, alone and in combination with valerian (personal communication).

The liver damage in these four cases was probably caused by the two types of herbal tablets, which have similar formulations. Identifying any toxic component(s) in herbal medicines, however, is a major problem in that such medicines contain multiple ingredients, individual components may not be pure substances, and not all components may be listed or, indeed, known. Furthermore, formulations may change, as in the case of Kalms tablets, which contained skullcap only before October 1984. Currently they contain valerian, asafetida, hops, and gentian. We do not know which of the formulations our patients took as stocks of the tablets long after 1984 may well have contained skullcap.

Several ingredients are common to Neurelax and Kalms tablets, but we think that skullcap and valerian are the most likely hepatotoxic components. A combination of them has been associated with jaundice (Welsh Drug Information Centre, personal communication), and skullcap was present in the preparation containing mistletoe that caused acute hepatitis.[2] Box's nerve tablets have an identical formulation to Neurelax and have also been associated with jaundice (Welsh Drug Information Centre, personal communication).

Ninety three products containing skullcap and 85 containing valerian are available in the United Kingdom.[10] The British Herbal Pharmacopoeia states that scullcap has sedative and anticonvulsant activities and is recommended for nervous tension, epilepsy, and hysteria.[11] During an investigation of herbal medicines available in the United Kingdom it was found that skullcap available from some wholesalers was not a *Scutellaria* sp,[10] which highlights the problem of accurate formulation. There are no reports to date suggesting any toxic effects from oral ingestion of skullcap. Valerian (Valeriana) was listed in the British Pharmaceutical Codex until 1963,[12] and the British Herbal Pharmacopoeia notes its sedative, hypnotic, spasmolytic, and hypotensive effects.[13] A recent report has shown that some of its chemical constituents are powerful alkylating agents and are capable of inhibiting incorporation of thymidine radiolabelled with carbon-14 into the DNA of certain carcinoma cells.[14]

These case reports show that herbal remedies should not be assumed to be free of hepatotoxic potential. In three of the four cases the onset of liver damage occurred rapidly after the herbal medicine was started, suggesting a hypersensitivity reaction; one patient had felt unwell enough to stop the medicine previously (case 3). In each case the biochemical pattern was of a hepatic injury, which in case 1 caused hepatic fibrosis and probably permanent liver damage.

The incidence of hepatic damage caused by herbal medicines is unknown, but instances are probably often unrecognised as patients may not be asked about such drugs or may discontinue them because of adverse reactions without seeking medical attention. Pharmacists have expressed reservations about the availability of herbal remedies,[15] and their advertisement as being free from side effects should certainly be discontinued. Finally, and most importantly, doctors should always ask patients about all medicines they are taking, whether prescribed or otherwise, when liver damage induced by drugs is suspected.

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ANY QUESTIONS

What advice should be given to a family, one of whose sons is a hepatitis B carrier and stays in the house from time to time?

The question raises issues regarding the ease of transmission of hepatitis B virus within the family. The virus is not easily transmitted by casual, non-sexual contact or by sharing household items such as linen and towels. Prudence dictates that crockery and cutlery should be washed in boiling water with detergent. Transmission usually requires blood to blood contact. Sharing of abrasive items such as toothbrushes, razors, and other sharp objects must be avoided. Gloves must be worn while cleaning any spillages of blood or other infectious body fluids, which should be absorbed into disposable paper towels soaked in bleach (sodium hypochlorite) that are then incinerated in sealed plastic bags. In view of the slight risk of transmission within a family all regular contacts, especially children, should be screened for serological markers of hepatitis B virus infection (hepatitis B surface antigen and antibodies to hepatitis B core antigen and hepatitis B surface antigen) and susceptible seronegative individuals should be vaccinated against hepatitis B.[1] Vertical transmission from mother to child is common so other siblings as well as the mother should be screened. If the son is in one of the high risk groups for hepatitis B virus infection, such as homosexuals or intravenous drug abusers, this will raise social issues for the family.

The term "carrier" is most commonly applied to a symptomless person who is positive for hepatitis B surface antigen. This is misleading because long term persistence of the antigen in the serum, even in asymptomatic subjects, can be associated with the development of chronic liver disease, cirrhosis, and primary liver cancer. Antiviral treatment with interferons can now achieve clearance of hepatitis B surface antigen and e antigen in 30-40% of carriers. Serum hepatitis B virus DNA, a measure of active viral replication, should be sought because this reflects progression of the liver disease as well as the potential risk of infection. Liver histology is useful for prognosis.—ROGER WILLIAMS, *consultant physician, London*

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