

Liver failure associated with the use of black cohosh for menopausal symptoms

Belal Naser and Eckehard Liske

TO THE EDITOR: The recent case report by Chow and colleagues raises questions about the causal link between black cohosh use and hepatotoxicity.¹ The authors state that the patient had no history of “significant alcohol consumption”, but a presumably related adverse drug reaction report available from the Therapeutic Goods Administration reveals her alcohol use was “3–4 units [of] alcohol per day, [with] 1–2 alcohol-free days per week”.² Alcohol misuse is a known risk factor for severe liver disease, as is gastric bypass surgery for obesity,³ also in the patient’s history. Unfortunately, because histological examination of the liver 6 weeks after first presentation found no recognisable residual hepatocytes, the diagnoses of alcoholic steatohepatitis, non-alcoholic fatty liver disease and non-alcoholic steatohepatitis cannot be excluded. Without this, the specific conclusion of the liver biopsy that the “Massive hepatocellular necrosis [was] associated with herbal medication”² cannot be substantiated.

The patient “was not taking any other medications, including other herbal preparations”, but the use of multivitamins was disclosed,² without further information on ingredients, indication, dosage and duration of use. Notably, an overdose of vitamin A can cause severe liver disease.

Finally, discontinuation of black cohosh failed to reduce the patient’s bilirubin levels, suggesting ongoing liver cell destruction by the as-yet unknown agent. Chow et al state “Extensive investigations to exclude other causes of acute liver failure gave negative results”.¹ It is unclear whether rare liver diseases were excluded, notably herpes infection, which has been reported to cause severe herpetic hepatitis. Nor was polymerase chain reaction testing performed for hepatitis viruses.

The authors mentioned other published case reports of hepatotoxicity potentially linked with black cohosh.¹ A recent assessment of 42 cases by the European Medicines Agency (EMA) concluded that most were insufficiently documented, or were otherwise inappropriate for analysis.⁴ A case in the United States initially described as “probable” (>1000% of the recommended dosage of black cohosh), based on the report that the patient “did not drink alcohol or use illicit

drugs and was not taking any medications”, was later corrected.⁵ The patient testified under oath that she drank wine regularly and used other drugs, and a US court judged there was no evidence to establish that black cohosh had caused her liver disease.⁶

There is no apparent credible evidence that black cohosh caused liver failure in the patient described by Chow et al.¹ A daily alcohol consumption of 30–40 g should be considered principally in any causality assessment. In addition, idiopathic reasons, rare or unclear liver diseases, and other medications should be considered as possible causes.

Even in patients with liver disease who consume little or no alcohol and have no exposure to other toxic agents, the cause of the disease remains unclear in up to 30%. In view of this, reliable and sufficient reporting of adverse drug reactions is a necessary precondition to any reliable assessment of causality.⁷

Competing interests: We are both employed by Schaper and Brümmer, manufacturer of black cohosh preparations.

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TO THE EDITOR: The case reported by Chow and colleagues of liver failure associated with the use of black cohosh¹ requires comment regarding causality. The case has also been the subject of an adverse drug reaction report by the Therapeutic Goods Administration (TGA), and a possible causality has been proposed.²

At presentation on 23 May 2006, the patient was aged 50 years (TGA),² not 51 as stated by Chow et al.¹ Her bodyweight was 88 kg (TGA)² after gastric bypass for obesity.¹ She had been taking black cohosh (20 mg daily) intermittently for 3 years. The subsequent temporal course is essential for assessing causality. According to the TGA report,² the patient increased the dose of black cohosh to 40 mg daily on 31 March 2006 and stopped taking it on 31 May 2006. The case report describes a 2-month history of lethargy, nausea and arthralgia,¹ obviously reported at first presentation. Back calculation shows symptom onset around 23 March 2006. Thus, symptoms emerged 1 week before the dose increase, suggesting a lack of temporal, and hence causal, association.

The patient had several risk factors for severe liver disease.¹ Risky use of alcohol for women is defined as more than seven standard drinks per week or more than three drinks on a single occasion.³ The patient had a daily intake of 3–4 units of alcohol, with 1–2 alcohol free days per week (reported by the TGA),² rendering her at some risk of alcoholic liver disease. Moreover, gastric bypass with partial resection reduces gastric mucosal alcohol dehydrogenase and consequent gastric ethanol metabolism. In combination with rapid gastric passage of alcohol into the jejunum, this leads to high blood ethanol concentrations, another risk factor for liver disease. Risk factors for possible non-alcoholic steatohepatitis and cirrhosis are obesity and gastric bypass.

Other causes were not excluded, including Wilson’s disease (by 24 h urinary copper measurement), hepatitis E, herpetic liver disease and infection by varicella zoster virus, parvovirus B19, parainfluenza virus, adenovirus and cytomegalovirus (by assessing for a change in IgG titre after disappearance of IgM). The marked hepatic mononuclear infiltrate is compatible with some viral infections.

Certainly, various herbal products may cause liver disease. A good example is kava,⁴ but not black cohosh.^{5,6} The European Medicines Agency examined 42 cases of liver dis-

ease with a suspected association with black cohosh, and found that only four patients had some grades of causality.⁵ Reassessment showed that two of these patients had herpetic hepatitis, one had autoimmune hepatitis, and the fourth was not assessable.⁶ Further studies are necessary to show clearly whether black cohosh is potentially hepatotoxic.

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IN REPLY: Teschke questions the temporal sequence in our reported case¹ by raising an ambiguity in dates. We wish to clarify: when the patient first presented on 23 May 2006, lethargy, arthralgia and nausea had been present for only about 3 weeks. This was well after the dose increase in black cohosh in March 2006. As such, the dose escalation definitely preceded the patient's symptoms and liver failure.

To further explore causality would require rechallenge with black cohosh, which we consider dangerous and unethical. Other unlikely causes of liver failure raised by Teschke, although theoretically possible, were not evident. The clinical course and histological findings in the pretransplant biopsy and explanted liver categorically excluded alcoholic cirrhosis and non-alcoholic steatohepatitis as causes of the liver failure. We also reiterate that there was no

previous history of liver disease or other medication use.

Increasing numbers of case reports are being published showing evidence of hepatotoxicity in patients taking black cohosh. Two well documented cases of seriously deranged liver function in patients taking black cohosh, which resolved on ceasing its use, have just been reported.² Teschke concedes that four other cases have been reported where some causality between black cohosh and hepatotoxicity was evident.³

Neither Teschke nor Naser and Liske offer any reassurance on the long-term safety or lack of toxicity of black cohosh by referencing any properly conducted safety study. Certainly, there is recent in-vitro and in-vivo evidence in a rat model that black cohosh is toxic to hepatocyte mitochondria and impairs oxidative phosphorylation, resulting in apoptotic hepatocyte death.⁴

It is notable that, based on available evidence, the Australian Therapeutic Goods Administration requires preparations containing black cohosh to carry a warning of potential liver toxicity, stating that "there appears to be an association between the use of black cohosh and liver damage, but that it is very rare".⁵ Furthermore, in the United Kingdom, the Medicines and Healthcare Products Regulatory Agency stated, "Warnings regarding rare adverse reactions in the liver should be added to the product information for black cohosh for both licensed and unlicensed products".⁶ Government authorities in Europe³ and Canada⁷ have raised similar concerns. Long-term studies as well as further animal studies would be welcome in this area.

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