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File: ■ Black Cohosh (*Actaea racemosa* syn. *Cimicifuga racemosa*)
■ Hepatotoxicity
■ Liver Damage

HC 071151-429

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RE: Black Cohosh Causality in Cases of Hepatotoxicity Unproven Due to Inadequate Evidence and Failure to Confirm Product Content

Teschke R, Schwarzenboeck A, Schmidt-Taenzer W, Wolff A, Hennermann K-H. Herb induced liver injury presumably caused by black cohosh: a survey of initially purported cases and herbal quality specifications. *Ann Hepatol*. 2011;10(3):249-259.

Black cohosh (*Actaea racemosa* syn. *Cimicifuga racemosa*) is used to treat menopause symptoms. There are reports of alleged herb-induced liver injury associated with black cohosh use. The purpose of this report was to analyze and review the evidence provided in all published reports of alleged black cohosh-induced hepatotoxicity.

No clinical trials or meta-analyses of black cohosh have reported any adverse reactions related to liver toxicity. Nonetheless, it is possible that rare hepatotoxicity events can occur. The authors reviewed 16 published case reports and 24 spontaneous case reports. The spontaneous cases were reported to regulatory agencies in Canada (n = 2), Australia (n = 13), the United States (n = 7), and Europe (n = 2). The authors state that before it can be said that hepatotoxicity is related to black cohosh, the definition of herb-induced liver injury must be established. The Council for International Organizations of Medical Sciences states that the liver enzymes alanine aminotransferase (ALT) or alkaline phosphatase (ALP) must be abnormally elevated by at least two times the normal range upper limit to diagnose liver injury. Despite this clear definition, ALT and ALP levels "have rarely been considered in spontaneous cases of primarily purported cases of black cohosh hepatotoxicity." Therefore, the authors state that liver injury may have been erroneously assumed in many of the reports.

The authors explain that for certain diagnosis of herb- or drug-induced liver injury the evaluation must include challenge, dechallenge, and re-exposure: (1) Any assessment of causation is open to challenge. There was comedication with other drugs or herbs in 11 of 16 case reports and 19 of 24 spontaneous reports, an important consideration for a challenge. (2) In the case of black cohosh, dechallenge is assessed when ALT levels are normalized after discontinuation of black cohosh. ALT dechallenge has been reported in only 4 of 16 published case reports and in only 1 spontaneous case report. The authors state that reports "without ALT dechallenge data are difficult to be used for causality

assessments." (3) Re-exposure tests are considered the gold standard for diagnosis of herb- and drug-induced liver injury when there are no convincing surrogate markers. None of the case reports contain a valid positive re-exposure test.

The authors explain that the poor data reporting in the spontaneous case reports was not unexpected. Spontaneous cases are reported by patients, not healthcare providers who could provide additional details. Also, when the clinical data were transferred from the regulatory agencies to the United States Pharmacopeia (USP), important data were misinterpreted or ignored. The USP utilized the Naranjo scale that is not specific for liver injury so that a possible causality can be claimed "under practically any circumstances." Further, when patients' data have been presented in both a case report and a spontaneous report, in some instances the data differed.

Viral liver infections can simulate herb- and drug-induced liver injury, so viral infections must be ruled out. Not all case reports and spontaneous case reports ruled out all types of viral infections. For example, varicella zoster virus and herpes simplex virus were only ruled out by 1 and 4 of 16 case reports, respectively, and no spontaneous reports. The authors state that, "Diagnoses of other viral infections may have easily been overlooked." Imaging of the liver and biliary system is mandatory for proper evaluation of causality. Only 2 of 24 spontaneous reports included biliary tract imaging. Alternative diagnosis of hepatotoxicity such as alcohol abuse must be excluded with certainty, and this was rarely done.

It is necessary to clearly identify the black cohosh product in any causality assessment. The authors state there are 3 published case reports of black cohosh-induced hepatotoxicity where the patients were not sure that they had even used a black cohosh product. In 10 of 16 case reports and 7 of 24 spontaneous reports, the black cohosh product was undetermined. In addition, herbal mixtures were reported in 4 of 16 case reports and 12 of 24 spontaneous reports. Black cohosh composition and source were generally not reported in the case reports. Therefore, the products consumed could have contained impurities or adulterants. Adulteration with other related species has been documented in 4 recent spontaneous cases in Canada.

The authors conclude that there is no evidence for a causal relationship between black cohosh and hepatotoxicity. Nonetheless, they believe that the cautionary statement issued by regulatory agencies should be maintained, to err on the side of caution.

—Heather S. Oliff, PhD

Referenced article can be accessed at http://www.annalsofhepatology.com/PDF/vol10n3/HP113-02.pdf.