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FILE: ▪ Kava (*Piper methysticum*)
▪ Hepatotoxicity

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RE: Critical Analysis of Suspected Cases of Kava Hepatotoxicity: Kava Taken as Directed is Rarely Hepatotoxic

Teschke R, Schwarzenboeck A, Hennermann K-H. Kava hepatotoxicity: a clinical survey and critical analysis of 26 suspected cases. *Eur J Gastroenterol Hepatol*. 2008;20:1182-1193.

Hepatotoxicity has been associated with the use of chemically defined drugs and herbal remedies taken as dietary supplements. A thorough causality assessment of herbal hepatotoxicity has rarely been performed, say the authors. Some published and spontaneous reports of a possible link between observed liver disease and the use of kava (*Piper methysticum*) extracts are available, but causality in these cases was assessed on an ad hoc basis by the German regulatory agency BfArM (Bundesinstitut für Arzneimittle und Medizinprodukte, Bonn) for 20 patients in Germany and by the Swiss regulatory agency Swissmedic (formerly IKS, Interkantonale Kontrollstelle Schweiz) for six patients in Switzerland, to be very probable, probable, or possible.[1] These authors examine the details of those 26 cases to assess the causal relationship using the validated and commonly accepted quantitative criteria of CIOMS (Council for International Organizations of Medical Sciences).[2] Because the basic information provided by the national regulatory agencies for the patients was scanty, the authors obtained additional patient data from various sources.

According to the authors, the 26 patients ranged in age from 23 to 81 years, and the ratio of males to females was 1:8. Kavapyrones (syn. kavalactones) were consumed in ethanolic (n=14) or acetonic (n=10) kava extracts; the extraction medium was unknown in the remaining two patients. The German patients had taken either an acetonic or ethanolic kava extract, and those from Switzerland all used an acetonic one. The ingredients of the kava extracts were derived from the dried rhizome of kava which has been used in the South Pacific for centuries as a water extract of the fresh or dried rhizome with no evidence of hepatotoxicity.

Of the 24 patients for which the daily kava dose and duration of treatment was known, only five adhered to the German Commission E recommendations regarding both the daily kava dose and the duration of treatment (60-120 mg kavapyrones daily for no longer than three months for a cumulative dose of 10.8 g). For the 24 evaluable patients, the cumulative kavapyrone dose ranged from 1.3 to 432.0 g. Information regarding comedications was presented for 22 out of 25 patients; polytherapy included up to five chemical drugs and dietary supplements in addition to kava. Liver histology was available in 21 of the 26 patients, showing a wide range of findings: necrosis alone and combined with hepatitis; hepatitis and intrahepatic cholestasis; hepatitis and bile duct proliferation; hepatitis, intrahepatic cholestasis, and bile duct proliferation; intrahepatic cholestasis; and hepatitis, intrahepatic cholestatis, and cholangitis.

The clinical course was severe in nine out of 26 patients and included death (n=1), death after liver transplantation (LTX) (n=2), and LTX with good outcome (n=6).

According to the authors, causality was unassessable because of the lack of temporal association (n=3), and excluded, based on kava or drug-independent causes alone (n=12) or combined with lack of temporal association (n=1). Low CIOMS scores resulted in causality being either excluded (n=1) or unlikely (n=1), leaving a total of eight evaluable patients with various degrees of causality for kava, with or without comedications.

The authors report the following characteristics of hepatotoxicity revealed by the evaluation of those eight patients:

- Kava hepatotoxicity may occur after daily doses of 45-1,200 mg kavapyrones and a therapy ranging between one week and 24 months.
- Comedication was a risk factor for the development of kava hepatotoxicity.
- Kava treatment, widely beyond regulatory recommendations, may be associated with the risk for life-threatening acute liver failure requiring LTX.
- Kava hepatotoxicity may exhibit high serum levels of alanine aminotransferase compared with alkaline phosphatase and is characterized by liver cell necrosis, hepatitis, or both.
- The ratio of males to females was 1:3 [Note: The text says 1:4, but 2 males to 6 females is 1:3.].
- Half of the patients used an acetonic kava extract and the other half an ethanolic kava extract.
- Under kava-only use, within the recommendations, hepatotoxicity occurred in a single patient with both a probable causality of hepatotoxicity for kava in the absence of comedication and a good outcome after kava cessation.
- In five patients, causality of hepatotoxicity for kava was graded as only possible and thus weak.
- Two patients required LTX and survived. One had a daily kava overdose, increased length of kava therapy, and comedication, with probable causality regarding both kava and comedicated drugs. The other patient had a daily kava overdose and an increased cumulative kava dose, with a possible causality for kava.
- Kava hepatotoxicity is the result of an idiosyncratic reaction of the metabolic rather than the immunologic type.

The authors conclude that "kava taken as recommended is associated with rare hepatotoxicity, whereas overdose, prolonged treatment, and comedication may carry an increased risk." These findings apply specifically to therapeutic use of acetonic and ethanolic extracts associated with the hepatotoxicity cases. Use of kava water extract as a traditional social beverage has not been similarly implicated.

—*Shari Henson*

References

[1]BfArM (Bundesinstitut für Arzneimittel und Medizinprodukte, Bonn. Federal Institute for Drugs and Medicinal Products in Germany), 2002. http://www.bfarm.de/de/arzneimittel/am_sicher/stufenpl/Besch-kava-Final.pdf.
[2]Danan G, Bénichou C. Causality assessment of adverse reactions to drugs. I. A novel method based on the conclusions of international consensus meetings: application to drug-induced liver injuries. *J Clin Epidemiol*. 1993;46:1323-1330.

The American Botanical Council has chosen not to include the original article.