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File: ■ *Pelargonium sidoides*
■ Hepatotoxicity

HC 041253-455

Date: August 31, 2012

RE: Critical Evaluation of Hepatotoxicity Data for *Pelargonium sidoides*

Teschke R, Frenzel C, Schulze J, Eickhoff A. Spontaneous reports of primarily suspected herbal hepatotoxicity by *Pelargonium sidoides*: Was causality adequately ascertained? *Regul Toxicol Pharmacol*. 2012 Jun;63(1):1-9.

Pelargonium sidoides (PS) is a flowering plant originating from Southern Africa. It is used to treat acute bronchitis and respiratory tract infections, including the common cold. It has been on the market since 1976. There have been reports that *P. sidoides* consumption is associated with liver injury. The authors question the validity of the association. Therefore, the purpose of this report was to examine the reports of spontaneous cases of PS-associated hepatotoxicity and evaluate the data quality and causality.

PS is considered an herbal medicine product and is dispensed in film-coated tablet and oral liquid (European Medicines Agency [EMA], 2011) forms. For adult patients, the recommended dose is 30 drops 3 times daily, which corresponds to 3 times daily of 1 tablet of 20 mg each. According to the patient leaflet, duration should not exceed 3 weeks.

The authors evaluated 8 suspected cases of PS-associated hepatotoxicity reported to the Drug Commission of the German Medical Association (DCGMA) and 7 suspected cases reported to the German regulatory agency (Bundesinstitut für Arzneimittel und Medizinprodukte [BfArM]; Germany's equivalent to the Food and Drug Administration). Information on the 15 cases was obtained from the DCGMA, the BfArM, and Dr. Willmar Schwabe Pharmaceuticals (Karlsruhe, Germany; the manufacturer of the PS herbal medicine, Umckaloabo®).

A causality algorithm was used that contained 4 steps:

- Step 1: Assessment of key items related to a temporal association, such as start and end dates of PS use and appearance of symptoms/abnormal liver values.
- Step 2: Criteria of PS hepatotoxicity and definition of the pattern of liver injury; specifically, values of alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase (ALP) were required as clear

criteria for liver injury and for the differentiation between the hepatocellular, cholestatic, or mixed hepatocellular-cholestatic pattern.
- Step 3: Application of a liver-specific, quantitative, and structured causality assessment method. The Council for International Organizations of Medical Sciences (CIOMS) scale was used.
- Step 4: Exclusion of alternative diagnoses.

The case reports included 10 men and 5 women (aged 1.7 to 82 years; average age: 39.1 years). Patients used PS to treat upper respiratory tract infections. All patients used drops, except 1 patient who used tablets. The daily dose and start and end dates were only known for 8 of the cases. The duration of treatment was not known or reported for many of the cases; however, treatment duration was usually restricted to a few days, except for 1 case where the patient took PS prophylactically for 13.5 months. For 10 patients, there was a clear temporal association between PS use and emerging liver disease. Comedication with other drugs or herbal products was reported for 5 patients. A table reports the clinical details of each case.

Data were lacking to make a sound causality assessment. The authors state that the cases were poorly documented and difficult to assess. Differential diagnosis to exclude other causes for liver toxicity was not adequately assessed. Specifically, there were only 3 cases that imaged the liver and biliary tract; 4 cases that excluded hepatitis A, B, and C; and only 1 case that excluded cytomegalovirus (CMV) and Epstein-Barr virus (EBV). The authors think that it is possible that any of the poorly assessed patients could have had hepatotoxicity from hepatitis A, hepatitis B, hepatitis C, or hepatitis caused by CMV, EBV, herpes simplex virus (HSV), varicella zoster virus (VZV), or even chronic liver disease. In addition, ALT and ALP changes that are required for identifying hepatotoxicity were only available for 6 cases. Four cases had ALT and/or ALP levels that might not have met the criteria for hepatotoxicity (2 times the upper limit of normal).

Using the CIOMS scale to assess causality, causality for PS was found to be possible for 3 cases, unlikely for 8 cases, and excluded for 4 cases. These causality levels differed substantially from that provided by the DCGMA (they used the World Health Organization [WHO] scale) (Table 1, below). The DCGMA reported possible/probable causality for 2 cases and possible causality for 6 of the cases; they did not assess 7 cases from the BfArM. The causality conclusions of the BfArM were not provided to the authors.

The authors point out that the WHO scale used by the DCGMA is not liver-specific, is not validated for liver toxicity, and in no way fulfills the criteria required for a thorough causality assessment of herb-induced liver injury. Interestingly, the authors cite that even in the best liver units with sophisticated diagnostic procedures, the cause of acute liver failure remains undetermined in 30% of patients. The authors conclude that in these 15 cases, there is little, if any, evidence for hepatotoxicity by PS.

When looking at the data in Table 1, it is hard to understand how the two different assessments could generate such different conclusions. Recall that a similar disparity occurred with suspected cases of hepatotoxicity by black cohosh (*Actaea racemosa* syn. *Cimicifuga racemosa*) and kava (*Piper methysticum*), where government agencies concluded an association, but independent analysis did not find causality for all cases. This appears to be a pattern of inadequate data assessment by the governing bodies. The governing bodies need to take notice and change their practices.

—Heather S. Oliff, PhD

Table 1

Case Number	Causality for PS by		
	CIOMS (authors)	**DCGMA**	**BfArM**
1	Excluded	Possible	Not available
2	Unlikely	Possible	Not available
3	Excluded	Possible	Not available
4	Possible	Possible	Not available
5	Unlikely	Possible	Not available
6	Unlikely	Possible/Probable	Not available
7	Unlikely	Possible/Probable	Not available
8	Unlikely	Possible	Not available
9	Possible	Not evaluated	Not available
10	Excluded	Not evaluated	Not available
11	Unlikely	Not evaluated	Not available
12	Possible	Not evaluated	Not available
13	Excluded	Not evaluated	Not available
14	Unlikely	Not evaluated	Not available
15	Unlikely	Not evaluated	Not available

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