Food and Chemical Toxicology 107 (2017) 472–501

Contents lists available at ScienceDirect

Food and Chemical Toxicology

journal homepage: www.elsevier.com/locate/foodchemtox

Invited review

Liver toxicity related to herbs and dietary supplements: Online table of case reports. Part 2 of 5 series

Amy Christine Brown

Department of Complementary and Alternative Medicine, John A. Burns School of Medicine, 651 Ilalo Street, MEB 223, University of Hawaii at Manoa, Honolulu, HI, 96813, USA

ARTICLE INFO

Article history:
Received 8 February 2016
Received in revised form
30 June 2016
Accepted 1 July 2016
Available online 8 July 2016

Keywords:
Hepatotoxicity
Toxicity
Liver
Herb
Dietary supplement
Hepatitis

ABSTRACT

Background: No online current list of potentially life-threatening, hepatotoxic herbs and dietary supplements based on PubMed case reports exists in a summarized tabular form.
Methods: Documented case reports of herbs or dietary supplements (DS; includes herbs) appearing to contribute to liver injury were used to create an online "DS Toxic Table" of potentially hepatotoxic herbs and dietary supplements (PubMed, 1966 to June, 2016, and cross-referencing). The spectrum of DS induced liver injuries (DSILI) included elevated liver enzymes, hepatitis, steatosis, cholestasis, hepatic necrosis, hepatic fibrosis, hepatic cirrhosis, veno-occlusive disease, acute liver failure requiring a liver transplant, and death.
Results: Over the past 50 years, approximately 21 herbs (minus germander and usnic acid that are no longer sold) and 12 dietary supplements (minus the nine no longer sold and vitamin A & niacin due to excess intake) posed a possible risk for liver injures in certain individuals. The herbs with the most number of reported publications (but not cases studies) in descending order, were germander, black cohosh, kava extract, and green tea extract.
Conclusion: These online DS Toxic Tables will contribute to continued Phase IV post marketing surveillance to detect possible liver toxicity cases and serve to forewarn consumers, clinicians, and corporations.

Contents

E-mail address: amybrown@hawaii.edu.

http://dx.doi.org/10.1016/j.fct.2016.07.001
0278-6915/

1. Introduction

This is the second of five review articles investigating dietary supplements (DS; includes herbs): Article one covers DS definitions, usage, efficacy and safety, and an overview of DS regulation in the United States (Brown, 2017a); and articles two through five cover case reports in tabular form related to liver toxicity, kidney toxicity, cardiotoxicity, and cancer published in the medical literature (Brown, 2017b,c, 2017a,b). Interest in complementary and alternative medicine (CAM), also known as functional, integrative, traditional, or holistic medicine, continues to grow, but "natural" is not always safe. Although the majority of botanical products appear inherently safe (Marcus and Grollman, 2002), and some have demonstrated efficacy, this review focuses on the potentially life-threatening dietary supplements that increase liner injury risk as detected through PubMed case reports. Case reports do not always demonstrate causation or association, but reoccurrences raise concerns (Haaz et al., 2006).

In this review, the characteristics and prevalence of liver injuries are defined, the literature search methods employed are described, and a summary table of the results along with a brief discussion of selected DS are presented.

2. Defining hepatotoxicity

2.1. DILI versus DSLI

The equivalent of drug-induced liver injury (DILI), which is caused by drugs, is herb- and DS-induced liver injury (DSILI; previously described as HILI, which only covers herbs and thus excludes many products in the broader DS category). The vast majority of pharmaceuticals have beneficial effects, but adverse events (AE) or serious adverse events (SAE) related to either drugs or DS do occur, though they are rare events. Because the liver is responsible for eliminating toxins from the body, it is at risk for drug- or DS-related liver injuries caused directly by these substances or indirectly through their metabolites (Au et al., 2011). Subsequent injury can occur through cell stress, mitochondrial inhibition, and/or immune reactions. Table 1 lists the selected possible liver injuries associated with either drugs or DS in ascending order of severity (Stedman, 2002).

2.2. Hepatoxicity symptoms

Consumers need to recognize liver injury symptoms so that the harmful substance can be immediately removed/discontinued to improve chances of recovery. Unfortunately, the typical symptoms—including fatigue, nausea, vomiting, loss of appetite, itching, abdominal pain or swelling, and dark urine color—are vague and mimic many other conditions. A physician should be immediately consulted if these symptoms appear, and especially if jaundice (yellowing of eye whites and inner palms) appears (note, however, that jaundice does not always develop) (Zheng and Navarro, 2015).

2.3. Unpredictable versus predictable hepatotoxicity

Hepatotoxicity, like all toxicities, is either unpredictable (idiosyncratic, meaning peculiar to the individual) or predictable (classical or intrinsic) (Brent, 1999; Gunawan and Kaplowitz, 2004). Most reactions to drugs or DS are idiosyncratic because they cause toxicity in only a small percentage of the population, may not be dose dependent, may not be reproducible in animal models, and may result from an immune-mediated reaction (indicated by fever, rash, and eosinophilia) (Brent, 1999; Gunawan and Kaplowitz, 2004).