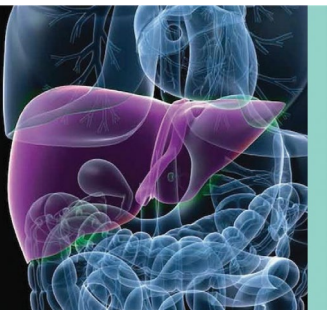

Severe Acute Hepatitis Attributed to the Herbal and Dietary Supplement OxyELITE Pro

Robert J. Fontana, M.D.

Herbal and dietary supplements (HDSs) incorporate a wide range of over-the-counter products including vitamins, minerals, dietary elements, herbal preparations, and synthetic compounds. There are increasing reports of untoward HDS-related hepatotoxicity, with HDS products accounting for 20% of adults enrolled in the ongoing US Drug-Induced Liver Injury Network (DILIN) registry study.[1,2] In this article, we review the presenting features and outcomes of severe acute hepatitis attributed to a commonly used multi-ingredient supplement, OxyELITE Pro (OEP), including a previously reported exemplary case.[3-7]

CASE

A 31-year-old Korean-American female presented with new-onset nausea, vomiting, and pruritus.[3] The patient reported taking one tablet of OEP per day for the past 4 months in an effort to lose weight associated with a recent full-term pregnancy. She was receiving no other medications, did not drink alcohol, and denied any recent sick contacts or travel. Her body mass index was 33.8 kg/m^2; scleral icterus was present, but the remainder of her examination was unremarkable. Her initial serum aspartate aminotransferase was 710 IU/L, alanine aminotransferase (ALT) was 1972 U/L, alkaline phosphatase was 58 U/L, total bilirubin was 3.8 mg/dL, and international normalized ratio was 1.0. An evaluation for acute hepatitis A, B, C, and E, liver imaging, and anti-nuclear and anti–smooth muscle antibodies were all negative. A liver biopsy obtained on hospital day 5 showed severe acute hepatitis with cholestasis, apoptotic hepatocytes, and a periportal infiltrate with eosinophils.[3] The serum ALT and bilirubin levels normalized by day 38 of follow-up and remained normal thereafter (Fig. 1). The DILIN causality score was 1 (definite), and her

Abbreviations: ALT, alanine aminotransferase; CDC, Centers for Disease Control and Prevention; DILIN, Drug-Induced Liver Injury Network; DMAA, 1,3-dimethylamylamine; FDA, US Food and Drug Administration; HDS, herbal and dietary supplement; OEP, OxyELITE Pro; RUCAM, Roussel-Uclaf Causality Assessment Method.

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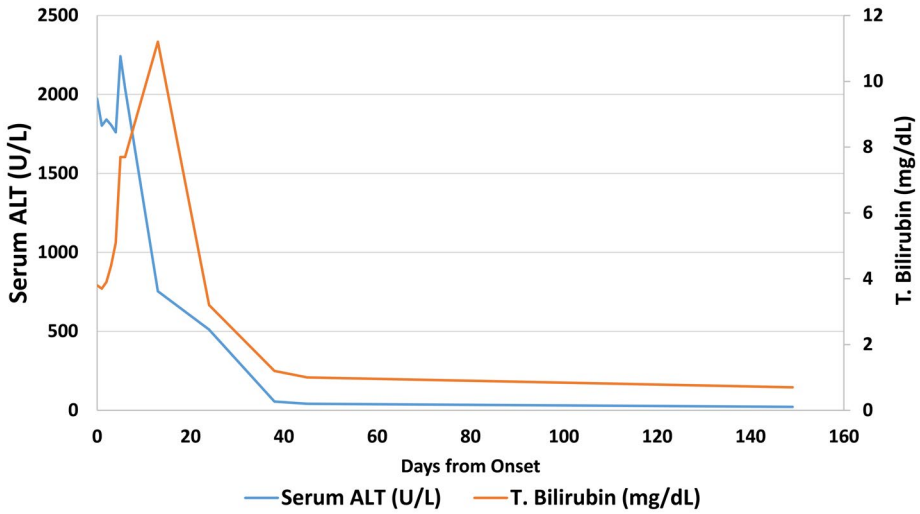

FIG 1 Serum ALT and total bilirubin (T. bilirubin) levels in a 31-year-old Korean woman who experienced severe acute hepatocellular injury attributed to OEP.[3] The improvement in total bilirubin levels lagged behind that of the serum ALT levels, but both had normalized by day 38 of follow-up.

Roussel-Uclaf Causality Assessment Method (RUCAM) score was 7 (probable).

HDS USE IN THE UNITED STATES

HDS product use is substantial and increasing, with nearly 50% of adult Americans reporting use of an HDS product.[8] HDS products are most commonly taken by non-Hispanic whites, women, and those older than 40 years with higher levels of education.[8] The general public perceives HDS products as being safer to take than conventional medications because they are frequently derived from plants and other "natural" products, and are widely available in retail outlets without a prescription. However, HDS products require no evidence of safety nor efficacy testing prior to marketing per the Dietary Supplement Health and Education Act of 1994. In addition, manufacturers are not required to follow good manufacturing process standards; therefore, HDS products are essentially regulated as food products. Investigations of manufacturers are only undertaken when there are complaints of suspected adverse events or concern for possible contaminants or adulterants.

Use of HDS products is very common among athletes and other individuals attempting to lose weight or to stay physically fit. For example, recent data suggest that 69% of active duty military personnel use at least one HDS product, and 22% report using more than three per day.[9] The extensive use of these products is, in part, due to the marketing of such supplements to promote numerous health and performance benefits (e.g., enhanced energy and strength) and nonspecific "structure" and "function" claims.

PHENOTYPE OF OEP HEPATOTOXICITY

OEP is an HDS product that contains several herbal constituents, caffeine, yohimbine, and other ingredients, including the sympathomimetic drug 1,3-dimethylamylamine (DMAA), in earlier formulations prior to 2013. The nature of OEP-induced liver injury was first brought to light when an outbreak of severe, acute hepatocellular injury with jaundice was reported in seven previously healthy military personnel taking OEP or a newer "Super Thermo" formulation of the product[6] (Table 1). DMAA has been previously implicated in serious nonhepatic adverse events such as acute myocardial infarction.[10] In March 2013, OEP products containing DMAA were removed from the marketplace by the manufacturer (USP Labs, Dallas, TX), and some had synthetic aegeline added to them. Aegeline is an alkaloid from the bael tree, *Aegle marmelos*, that has been used in Ayurvedic medicine for centuries. An epidemiological investigation by the US Food and Drug Administration (FDA) and Centers for Disease Control and Prevention (CDC) identified 36 cases of acute hepatitis associated with the use of various OEP formulations including the Super Thermo formulation. In September 2013,

TABLE 1. CASE SERIES OF SEVERE ACUTE HEPATOCELLULAR LIVER INJURY ATTRIBUTED TO OEP

	US Military[6] (N = 7)	CDC[5] (N = 44)	DILIN[3] (N = 7)
DILI onset dates	Prior to 2014	April to November 2013	August 2011 to December 2013
Location	Southern California	Hawaii	Continental United States
Median age, years	24	33	36
Female sex, %	42	57	86
Asian/Pacific Islander, %	Not reported	25*	43
Median peak ALT, U/L	1980	1740	2250
Median peak total bilirubin, mg/dL	6.7	9.4	13
Outcomes, %			
Hospitalized	100	39	86
Liver transplant	28	5	28
Death	0	2	0
Concomitant HDS, %	42	68	71

*Fifty-seven percent were two or more races, including Asian, Pacific Islander, and/or Caucasian.

the manufacturer of OEP removed the formulations of OEP containing aegeline from the marketplace.[4] A follow-up report from the CDC and other health authorities demonstrated that the incidence of OEP hepatotoxicity markedly declined after 2014.[5]

The clinical features of OEP hepatotoxicity consisted of nausea and anorexia with a median peak serum ALT and total bilirubin values of 1740 U/L and 9.4 mg/dL, respectively.[5] Liver biopsies showed acute hepatitis suggestive of a toxic injury. One of the 44 patients died, and 2 others underwent emergency liver transplantation. Among the patients who recovered, many had a prolonged course with a few developing autoimmune hepatitis-like features managed with steroids.[4] During the same time period, the DILIN database reported 7 cases of liver injury attributed to OEP following a median duration of use of 18 weeks (range: 5-102 weeks).[3] All of the patients presented with an acute hepatocellular injury, leading to liver transplantation in two patients. Other cases have been reported from the continental United States and in active duty military personnel.[6,7] Although there was an overrepresentation of Asian-Pacific islanders with OEP hepatotoxicity, confirmatory studies demonstrating a genetic or ethnic predisposition are lacking.

CAUSALITY ASSESSMENT IN HDS HEPATOTOXICITY

Causality assessment in drug- and HDS-associated hepatotoxicity is complex and evolving due to the lack of a confirmatory, objective biomarker that is specific for DILI.[2] Currently, most study groups use expert opinion or standardized instruments such as the RUCAM. Causality assessment methods take into consideration the temporal association between product intake and DILI onset, improvement with drug discontinuation, exclusion of competing causes, and comparison of the laboratory, clinical, and histological phenotype of the case with what has previously been reported with that agent.[11] Immunoallergic and autoimmune features are uncommon with most instances of HDS hepatotoxicity, but latency is usually within 6 months of exposure. Causality assessment in HDS cases is further confounded by the fact that many patients take more than a single HDS product simultaneously, and the specific chemical ingredients and blends of botanicals used in HDS preparations may vary substantially between lots and over time.[2] A recent analysis from DILIN demonstrated a high level of discrepancy between the listed label ingredients of HDS products and those confirmed by using highly sensitive and specific liquid chromatography and mass spectroscopy methods.[12]

Analyses of OEP products looking for adulterants, known hepatotoxicants, and contaminants have failed to identify a known discrete hepatotoxin or unique ingredient in the lots of suspect product[6,7] (Table 2). However, a recent *in vivo* study demonstrated substantial hepatotoxicity and mortality in mice administered OEP-New formulation at 3 to 10 times the mouse equivalent dose, as well as increased up-regulation of the Cd36 gene that is involved in lipid metabolism.[13]

In conclusion, clinicians should have heightened awareness of the potential for inadvertent liver injury associated with the many HDS products that are used by millions of Americans on a daily basis. Reporting of adverse events to the FDA, the product manufacturer, and local health authorities is encouraged, as was done with the recent outbreak of OEP hepatitis, to improve patient outcomes

TABLE 2. RESULTS OF OEP PRODUCT INGREDIENT ANALYSIS

	OEP Super Thermogenic Capsules	OEP Super Thermo Capsules	OEP Super Thermo Powder
Availability	Through July 2013	Late 2012 to October 2013	Through July 2013
Caffeine per serving	100 mg	135 mg	125 mg
Daily recommended amount	119.5 mg per serving	140 mg per serving	1058 mg per scoop
Proprietary blend	Extract of *Bauhinia purpurea* leaf, *Bacopa, Cirsium oligophyllum*, yohimbine bark, DMAA	Extract of *Bauhinia purpurea* leaf, *Hemerocallis fulva*, yohimbine bark aegeline, norcoclaurine HCl	Extract of yohimbine bark, *Eriobotrya japonica*, aegeline, choline bitartrate, norcoclaurine HCl, L-carnitine-tartrate

Adapted from data presented by Johnston et al.[5]

and help identify unsafe products. In light of these findings, further regulations regarding the manufacturing, safety and efficacy testing, and monitoring of HDS products available in the marketplace are advisable and recommended.[2]

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REFERENCES

1) Geller AI, Shehab N, Weidle NJ, et al. Emergency department visits for adverse events related to dietary supplements. N Engl J Med 2015;373:1531-1540.

2) Navarro VJ, Khan I, Björnsson E, et al. Liver injury from herbal and dietary supplements. Hepatology 2017;65:363-373.

3) Heidemann LA, Navarro VJ, Ahmad J, et al. Severe acute hepatocellular injury attributed to OxyELITE Pro: a case series. Dig Dis Sci 2016;61:2741-2748.

4) Roytman MM, Pörzgen P, Lee CL, et al. Outbreak of severe hepatitis linked to weight-loss supplement OxyELITE Pro. Am J Gastroenterol 2014;109:1296.

5) Johnston DI, Chang A, Viray M, et al. Hepatotoxicity associated with the dietary supplement OxyELITE Pro™—Hawaii, 2013. Drug Test Anal 2016;8:319-327.

6) Foley S, Butlin E, Shields W, et al. Experience with OxyELITE Pro and acute liver injury in active duty service members. Dig Dis Sci 2014;59:3117-3121.

7) Klontz KC, DeBeck HJ, LeBlanc P, et al. The role of adverse event reporting in the FDA response to a multistate outbreak of liver disease associated with a dietary supplement. Public Health Rep 2015;130:526-532.

8) Bailey RL, Gahche JJ, Miller PE, et al. Why US adults use dietary supplements. JAMA Intern Med 2013;173:355-361.

9) Lieberman HR, Stavinoha TB, Mcgraw SM, et al. Use of dietary supplements among active-duty US Army soldiers. Am J Clin Nutr 2010;92:985-995.

10) Smith TB, Staub BA, Natarajan GM, et al. Acute myocardial infarction associated with dietary supplements containing 1, 3-dimethylamylamine and Citrus aurantium. Tex Heart Inst J 2014;41:70-72.

11) Rockey DC, Seeff LB, Rochon J, et al. Causality assessment in drug-induced liver injury using a structured expert opinion process: comparison to the Roussel-Uclaf Causality Assessment Method. Hepatology 2010;51:2117-2126.

12) Navarro VK, Avula B, Verma M. Herbal and dietary supplement mislabeling: experience of the Drug Induced Liver Injury Network. Hepatology 2017;66(Suppl. 1):A16.

13) Miousse IR, Skinner CM, Lin H, et al. Safety assessment of the dietary supplement OxyELITE™ Pro (New Formula) in inbred and outbred mouse strains. Food Chem Toxicol 2017;109:194-209.