Severe acute hepatitis attributed to the Herbal and Dietary Supplement OxyELITE Pro

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Abbreviations
BMI    Body mass index
DILIN  Drug induced liver injury network

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Introduction

Herbal and dietary supplements (HDS) 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 into the ongoing US Drug Induced Liver Injury Network (DILIN) registry study (1,2). Herein, 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 BMI was 33.8 kg/m², scleral icterus was present but the remainder of her exam was unremarkable. Her initial serum AST was 710 IU/L, ALT 1972 U/L, alkaline phosphatase 58 U/L, total bilirubin 3.8 mg/dl and INR was 1.0. An evaluation for acute hepatitis A, B, C, and E, liver imaging and antinuclear 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

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levels normalized by day 38 of follow-up and remained normal thereafter (Figure 1). The DILIN
causality score was 1 (Definite) and her Rousell- 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
over 40 with higher levels of education.(8) The general public perceive HDS products as being safer to
take than conventional medications since 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 and 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 3 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 non-specific “structure” and “function”
claims.

**Phenotype of OxyELITE Pro 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 7 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 non hepatic 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 FDA and CDC identified 36 cases of acute hepatitis associated with
the use of various OEP formulations including the SuperThermo formulation. In September of 2013, the
manufacturer of OEP removed the formulations of OEP containing aegiline from the marketplace. 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. Amongst the patients that recovered, many had a prolonged course with a few
developing autoimmune hepatitis-like features managed with steroids. 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 to 102 weeks) (3). All of the patients presented with an acute hepatocellular
injury leading to liver transplantation in 2 patients. Other cases have been reported from the
continental United States and in active duty military personnel. 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 to what has previously been reported with that agent (11).
Immuonoallergic 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 both 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 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 is advisable and recommended (2).

References


**Figure 1.** Serum ALT and total bilirubin levels in a 31 year old Korean female who developed severe acute hepatocellular injury attributed to OxyELITE Pro (Ref #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.
Table 1 - Case series of severe acute hepatocellular liver injury attributed to OxyELITE Pro.

<table>
<thead>
<tr>
<th></th>
<th>US military (ref #6) N=7</th>
<th>CDC (ref #5) N=44</th>
<th>DILIN (ref #3) N=7</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DILI onset dates</strong></td>
<td>Prior to 2014</td>
<td>April – Nov 2013</td>
<td>Aug 2011- Dec 2013</td>
</tr>
<tr>
<td><strong>Location</strong></td>
<td>Southern California</td>
<td>Hawaii</td>
<td>Continental US</td>
</tr>
<tr>
<td><strong>Med Age (yrs)</strong></td>
<td>24</td>
<td>33</td>
<td>36</td>
</tr>
<tr>
<td><strong>Female (%)</strong></td>
<td>42%</td>
<td>57%</td>
<td>86%</td>
</tr>
<tr>
<td><strong>Asian/ Pacific Islander (%)</strong></td>
<td>NR</td>
<td>25% *</td>
<td>43%</td>
</tr>
<tr>
<td><strong>Med peak ALT (U/L)</strong></td>
<td>1980</td>
<td>1740</td>
<td>2250</td>
</tr>
<tr>
<td><strong>Med peak total bilirubin (mg/dl)</strong></td>
<td>6.7</td>
<td>9.4</td>
<td>13</td>
</tr>
<tr>
<td><strong>Outcomes</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Hospitalized (%)</td>
<td>100%</td>
<td>39%</td>
<td>86%</td>
</tr>
<tr>
<td>Liver transplant (%)</td>
<td>28%</td>
<td>5%</td>
<td>28%</td>
</tr>
<tr>
<td>Death (%)</td>
<td>0%</td>
<td>2%</td>
<td>0%</td>
</tr>
<tr>
<td>Concomitant HDS (%)</td>
<td>42%</td>
<td>68%</td>
<td>71%</td>
</tr>
</tbody>
</table>

NR = Not reported  * 57% were > two races including Asian, Pacific Islander, and/ or Caucasian

Table 2: Results of OxyELITE Pro Product ingredient analysis *

<table>
<thead>
<tr>
<th></th>
<th>OEP Pro Super Thermogenic Capsules</th>
<th>OEP Pro- Super Thermo Capsules</th>
<th>OEP Pro Super Thermo Powder</th>
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<table>
<thead>
<tr>
<th>Availability</th>
<th>Thru July 2013</th>
<th>Late 2012 – Oct 2013</th>
<th>Thru July 2013</th>
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<tbody>
<tr>
<td>Caffeine per serving</td>
<td>100 mg</td>
<td>135 mg</td>
<td>125 mg</td>
</tr>
<tr>
<td>Daily recommended amount</td>
<td>119.5 mg per serving</td>
<td>140 mg per serving</td>
<td>1058 mg per scoop</td>
</tr>
</tbody>
</table>

- Adapted from data presented in Ref #5