SlimQuick™ - associated hepatotoxicity in a woman with alpha-1 antitrypsin heterozygosity

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INTRODUCTION

Green tea (Camellia sinensis)-associated hepatotoxicity is reported. However, the presence of alpha-1 antitrypsin MZ phenotype as a predisposing factor to green tea-associated drug-induced liver injury (DILI) is unknown. A previously healthy woman with alpha-1 antitrypsin MZ phenotype who took SlimQuick™, an herbal supplement containing green tea extract, developed severe hepatotoxicity requiring corticosteroid treatment. Green tea-associated hepatotoxicity is reviewed and alpha-1 antitrypsin MZ phenotype as a predisposing factor to green tea-associated DILI is discussed. Liver biopsy demonstrated marked inflammation with necrosis suggestive of toxic injury with diffuse alpha-1 antitrypsin globule deposition on immunostaining. Corticosteroid therapy resulted in rapid clinical improvement. Alpha-1 antitrypsin MZ phenotype may increase vulnerability to herbal hepatotoxicity.

Key words: SlimQuick™; Green tea, Hepatotoxicity; Drug-induced liver injury, Alpha-1-antitrypsin MZ phenotype

INTRODUCTION

Green tea obtained from the leaves of Camellia sinensis is thought to improve health due to antioxidant and anti-carcinogenic effects.[1-4]. Nonetheless, green tea has pro-oxidant effects, primarily due to epigallocatechin-3-gallate (EGCG).[2,3]. Lambert et al.[5] reported dose-dependent hepatotoxicity in mice associated with pro-oxidant effects of high-dose EGCG. Hepatotoxicity associated with green tea extracts that contain high concentrations
of EGCG is being reported\(^6\)–\(^9\). Due to hepatotoxicity, Exolise\(^{®}\) (Arkopharma, Carros, France), a weight-loss supplement was withdrawn from the market in France and Spain\(^9\). Exolise\(^{®}\) contained EGCG\(^6\)–\(^9\). The Drug-Induced Liver Injury Network indicated that in 6 of 28 cases of hepatotoxicity secondary to herbal and dietary supplements, green tea extract was the major component of the supplement\(^6\)–\(^9\). Fong et al\(^8\) reported 8 patients who developed drug-induced liver injury (DILI) due to Hydroxycut\(^{®}\), 3 of whom required liver transplantation. The authors concluded that green tea was likely the major ingredient in Hydroxycut\(^{®}\) resulting in severe liver injury\(^8\).

We report a young woman who developed severe hepatotoxicity while taking SlimQuick\(^{™}\) (Distributed by Wellnx Life Sciences, Wilmington, DE), an herbal weight-loss product containing green tea extract. This is important because we identified an often overlooked predisposition to DILI; the alpha-1 antitrypsin MZ phenotype\(^9\).

**CASE REPORT**

A 24-year-old white woman presented to her primary care physician with complaints of dark urine, acholic stools, right upper quadrant pain and progressive fatigue. She reported taking two caplets of SlimQuick\(^{™}\) orally on an empty stomach 6 h apart twice per day for three months to improve energy for marathon training. She took no other dietary supplements or medications except for oral tetracycline 500 mg/d orally for eleven months to improve energy for marathon training. She stopped both drugs eight days after the symptoms began. Desiccated thyroid (50 mg/d) was initiated. All laboratory parameters rapidly improved within one week of therapy (Figure 1). Prednisone was tapered over 4 wk and stopped. On follow-up, the patient’s liver tests were normal and she was asymptomatic.

**Figure 1** Two months earlier, our patient had normal serum alanine aminotransferase, alkaline phosphatase and total bilirubin (baseline). The peak total bilirubin level lagged 19 d behind the peak ALT and ALP levels. There was striking improvement in serum aminotransferase and total bilirubin levels after initiation of prednisone (50 mg/d). Laboratory values remained normal after prednisone therapy was discontinued. ALT: Alanine aminotransferase; ALP: Alkaline phosphatase.
DISCUSSION

The major ingredient in SlimQuick™ caplets is green tea extract (Camellia sinensis leaf) containing 135 mg of EGCG. EGCG has pro-oxidant effects that can cause hepatotoxicity when administered at high doses\(^1\).\(^2\)\(^3\).

SlimQuick™ caplets also contain other ingredients including rhodiola (Rhodiola rosea), chastetree (Vitis agnus castus), Juniper (Juniperus communis), soy (Glycine max), Asian ginseng (Panax ginseng), Japanese knotweed (Polygonum cuspidatum) extracts, brown seaweed (Fucus vesiculosus), dandelion (Taraxacum officinale), yerba mate (Ilex Paraguariensis), uva-ursi (Arctostaphylos uva ursi), phytosterols (Glycine max), l-theanine, caffeine, vitamins D, K, B6 and B12, folate, and calcium. Boehm et al\(^4\) reviewed 51 studies, including 27 case-control, 23 observational and 1 randomized controlled trial related to green tea consumption and concluded that drinking 3 to 5 cups of green tea per day provided at least 250 mg catechins per day and might be considered safe. We calculated that our patient was exposed to green tea extract that contained catechin in amounts higher than these suggested safe levels. Moreover, she was also directed to take it while fasting. This augments the likelihood of hepatotoxicity in animals and fasting humans achieve 5-fold higher catechin concentrations compared to fed controls\(^5\)\(^6\). Lambret et al\(^7\) reported moderate to severe hepatic necrosis in 60% and mild necrosis in 40% of mice treated with two oral doses of 750 mg/kg EGCG per day.

We performed an Ovid Medline search that extended from 1948 until October 22, 2010 by combining key words “drug-induced liver injury” or “hepatotoxicity” and both common and scientific names of herbal ingredients of SlimQuick™. We also searched the Natural Medicines Comprehensive Database\(^8\) for hepatotoxicity associated with any ingredients of SlimQuick™ other than green tea extract. Based on our search, we identified only two herbal ingredients in SlimQuick™ other than green tea extract associated with hepatotoxicity in animals or humans. Nowak et al\(^9\) reported a radiographer exposed to hydroquinone fumes who developed toxic hepatitis. Hydroquinone is a component of uva ursi\(^10\). However, Nowak et al\(^9\) associated toxic hepatitis with hydroquinone fumes, not an herbal medicine, uva ursi\(^10\)\(^11\). McGee et al\(^12\) associated mate tea with veno-occlusive disease due to pyrroliziding alkaloids detected in small quantity in tea samples. However, they failed to detect pyrroliziding alkaloids in mate tea sold locally\(^13\). Our patient’s liver histopathology was inconsistent with veno-occlusive disease. In addition, the latency period of 12 wk, peak laboratory values and histopathological findings are more compatible with Exolise® and Hydroxycut® hepatotoxicity\(^14\)\(^15\).

Besides taking a hepatotoxic weight-loss supplement, our patient was also heterozygous for alpha-1 antitrypsin deficiency. There remains considerable debate regarding the importance of the alpha-1 antitrypsin MZ phenotype\(^16\)\(^17\).\(^18\)\(^19\). Graziadei et al\(^16\) suggested that the alpha-1 antitrypsin MZ phenotype might be a risk factor for chronic liver disease or liver failure. Rakela et al\(^19\) showed that subjects with the alpha-1 antitrypsin MZ phenotype might develop liver disease later in life compared to subjects with the alpha-1 antitrypsin ZZ phenotype.

Given our patient’s baseline normal liver function, most likely the presence of alpha-1 antitrypsin MZ phenotype increased her vulnerability to severe hepatic cellular injury. Tetracycline-induced liver injury was excluded as an offender based on the histopathology, leaving SlimQuick™ as the likely hepatotoxic agent. To our
knowledge, this is the first report of herbal drug-associated DILI in the context of the alpha-1 antitrypsin MZ phenotype. This demonstrates the importance of seeking underlying susceptibility to hepatic injury in previously healthy subjects who develop DILI.

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