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Risk of Liver Injury associated with Green Tea Extract in SLIMQUICK® Weight Loss Products: results from the DILIN Prospective Study

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Abstract

Introduction—Herbal and dietary supplements (HDS) have been increasingly recognized as a cause for acute liver injury[1, 2]. HDS products frequently contain numerous ingredients, and are marketed under various product names. A perusal of marketed weight loss products indicates that green tea extract is a common ingredient in many. We aimed to describe the course and outcome of six patients who developed liver injury attributed to SLIMQUICK® weight loss products.

Methods—Patients with suspected drug induced liver injury were enrolled in a prospective study of the Drug-Induced Liver Injury Network (DILIN) and causality was assessed by a panel of hepatologists. During the period under study, 6 of 1091 cases of liver injury were attributed to a SLIMQUICK® product and were assigned causality scores of probable, highly likely, or definite.

Results—Six cases of acute liver injury attributed to SLIMQUICK® products were enrolled in the DILIN prospective study between 2007 and 2011. All were women aged 22 to 58 years. Two had a normal body weight and four were mildly obese (body mass index 22.9 to 32.2 kg/m^2). All were taking SLIMQUICK® products for weight loss and no patient reported prior use. Laboratory tests revealed a hepatocellular pattern of injury, with initial alanine aminotransferase (ALT) levels above 1000 U/L in all but one patient. Three patients were hospitalized and one underwent

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Compliance with Ethical Standards:

Conflicts of interest: Elizabeth Zheng has no conflicts of interest that are directly relevant to the content of this study. Simona Rossi has no conflicts of interest that are directly relevant to the content of this study. Robert Fontana has no conflicts of interest that are directly relevant to the content of this study. Raj Vuppalanchi has no conflicts of interest that are directly relevant to the content of this study. Jay Hoofnagle has no conflicts of interest that are directly relevant to the content of this study. Iklhas Khan has no conflicts of interest that are directly relevant to the content of this study. Victor Navarro has no conflicts of interest that are directly relevant to the content of this study.

successful liver transplantation. No patients died of liver injury. GTE and/or its component catechins were listed among the ingredients for 5 of the 6 products.

Conclusions—SLIMQUICK® products can lead to severe acute hepatocellular liver injury, which may result in transplantation. Given the frequency of GTE as a component in weight loss products, this ingredient should be studied further as a possible cause for liver injury.

Introduction (1)

Broadly speaking, dietary supplements are products intended to supplement the diet. As delineated in the current regulatory framework for dietary supplements, the Dietary Supplement Health and Education Act (DSHEA) of 1994, they may include vitamins, minerals, an herb or other botanical, or an amino acid. Clinicians have come to use the term Herbal and Dietary Supplements (HDS) to include multi-ingredient products often marketed under names that may not describe their actual ingredients. The HDS as well as single ingredient dietary supplements have been reported to cause hepatotoxicity severe enough to lead to hospitalization and, in rare instances, liver transplantation. Examples of HDS that have been implicated in liver injury include Hydroxycut[3] and OxyElite Pro.[4] While the mechanisms for injury remain unknown, the majority of patients with liver injury from weight loss products present with a hepatocellular pattern of injury.[5] SLIMQUICK® products, marketed for weight loss, have also been implicated in several cases of liver injury enrolled into the Drug Induced Liver Injury Network (DILIN).

The DILIN enrolls patients with suspected liver injury from drugs and dietary supplements into its Prospective Study.[6] Recent results from the first 1257 patients enrolled in the DILIN prospective study revealed that liver injury was attributed to HDS in 16% of cases; SLIMQUICK® products were among the supplements implicated in HDS associated liver injury.[7]

Different products of varying formulations are marketed under the SLIMQUICK® product label. Like other weight loss supplements, many SLIMQUICK® products contain green tea extract (GTE), which has been advertised on its website as a key ingredient responsible for “boosting metabolism” and “burning fat.”[8] Although GTE has been shown to have thermogenic properties, it has also been implicated in liver injury in both *in vitro* and *in-vivo* studies.[9,10] Several clinical reports provide compelling evidence for GTE's toxic potential in humans.[11,12]

In this report, we describe the clinical characteristics of hepatotoxicity associated with six cases enrolled into the DILIN in which injury was attributed to SLIMQUICK® products. It should be noted that these cases were included in the initial description of the DILIN's HDS experience with hepatotoxicity.[1] However, the SLIMQUICK® cases were not the focus of that or other publications as clinical characteristics were not presented at the level of detail as in this current paper.[13]

Methods (2)

Initiated in 2004, the DILIN Prospective Study is an ongoing cohort study of patients with drug induced liver injury (DILI). Briefly, patients eligible for enrollment must have met minimal laboratory criteria that included a serum AST or ALT >5 times the upper limit of normal (or pretreatment baseline if baseline levels were elevated) on two separate consecutive occasions. Alternatively, subjects with serum alkaline phosphatase levels >2 times the upper limit of normal (or baseline if the baseline level was abnormal) on two consecutive occasions may have qualified. In addition, subjects who developed a serum total bilirubin of greater than 2.5 mg/dL or an INR above 1.5 in the absence of a competing cause of hyperbilirubinaemia or hypoprothrombinaemia, respectively, were eligible. The details of eligibility, initial evaluation, and enrollment procedures have been described in a previous publication.[14] In addition, other causes of liver injury were excluded and all participants were asked to return six months after enrollment to document recovery.

To assess causality, a panel of DILIN investigators independently assigned an overall score from 1 (definite) to 5 (unlikely), reflecting the likelihood that liver injury was caused by a drug or supplement.[14] Each case is graded as definite (>95% likelihood), highly likely (75-95%), probable (50-74%), possible (25-49%), or unlikely (<25%) DILI. This causality scale, based on consensus expert opinion , has been adopted by the DILIN and when compared to other approaches such as the Roussel Uclaf Causality Assessment Model (RUCAM), the former was more likely to generate a score supportive of DILI.[15] In cases where more than one agent is implicated, each medication or product is separately scored for the likelihood that it was responsible for injury. SLIMQUICK®products were implicated in six cases, and all had an overall causality score of probable (3), highly likely (2), or definite (1). All SLIMQUICK® cases that were enrolled in the DILIN have been included in this series.

Demographics and other clinical variables were extracted. Ingredients of implicated SLIMQUICK® products were ascertained from the actual product label or via on-line information and are shown in the supplementary material.

Results (3)

Among the 1257 cases enrolled in the DILIN Prospective Study between September 2004 and May 2013, 1091 were reviewed and adjudicated and 899 subjects were determined to have causality scores of definite, highly likely, or probable.[7] In 6 of the 1091 cases, a SLIMQUICK® product was implicated, with the likelihood of it being the responsible agent adjudicated as probable in one, highly likely in three, and definite in two instances.

The demographic and clinical features of the patients are shown in Table 1. Characteristics such as race were self-reported as white, black or African-American, Asian, Hispanic, or other/multiracial. The patients presented between 2007 and 2011 at four different medical centers with no evidence of clustering by year or locale. All 6 were women who ranged in age from 22 to 58 years (mean = 40.6 years). Comorbidities included hypertension and diabetes, though not all patients had significant chronic illnesses. All were taking

SLIMQUICK® products in powder or capsule form for weight management and no patient reported prior history of use. Two had a normal body weight and the remainder were overweight or mildly obese; body mass index (BMI) ranging from 22.9 to 32.2 (mean = 29.0). The duration of consumption of a SLIMQUICK® product to the onset of injury ranged from 12 to 66 days (mean = 32 days) and the duration of use ranged from 6 to 66 days.

Five patients had symptoms of liver injury, typically fatigue and nausea. Four patients had jaundice, two had pruritus, and one had abdominal pain. Fever and rash occurred in two patients but none had documented eosinophilia. Laboratory tests showed a hepatocellular pattern of injury, with alanine aminotransferase (ALT) levels above 1000 U/L in all but one patient and alkaline phosphatase concentration less than twice elevated in all. Three patients were hospitalized and one underwent successful emergency liver transplantation after developing jaundice, ascites, and hepatic encephalopathy. There were no deaths among the patients and the remaining five recovered from acute injury.

Patient 2 was enrolled in the DILIN for a similar episode of liver injury two years previously, following the use of another multi-ingredient GTE containing weight loss product, DEXATRIM. As listed in Table 1, two patients took other products within two months of DILI onset. Green tea extract and/or its component catechins were listed among the ingredients for five of the six implicated products.

Discussion (4)

These cases accrued by the DILIN suggest that SLIMQUICK® products can lead to acute hepatocellular liver injury, which can be severe enough to warrant liver transplantation. The injury was typically self-limiting, resolving within a few weeks of stopping treatment. Because GTE is a major component of most SLIMQUICK® products and, on its own, has been linked to cases of liver injury with a similar clinical presentation and course, it is suggested that this constituent was the major cause of injury.

Perhaps the case that most convincingly implicated GTE was patient 2 who had a previously documented episode of acute liver injury that followed ingestion of another GTE-containing supplement, DEXATRIM. The two episodes of hepatotoxicity were similar in course and outcome except for latency, which was shorter with the second episode. These features strongly suggest a common ingredient to which the patient was inadvertently re-exposed. As observed previously in similar cases, this is consistent with a positive rechallenge test in which the patient was exposed to GTE for a second time, allowing for a more confident diagnosis of DILI.[16]

Green tea extract is a commonly used weight loss supplement that is derived from the unfermented leaves of the Chinese tea tree, *Camellia sinesis*. Both green and black tea leaves come from *C. sinesis*, though unlike green tea, black tea is oxidized and fermented. GTE contains several polyphenolic flavonols and catechins, the most abundant of which is epigallocatechin gallate (EGCG). EGCG has been purported to possess anti-obesity properties through its activity of inhibiting lipogenic enzymes in micromolar

concentrations.[17] Pharmacokinetic analysis of green tea and its different catechins, particularly EGCG, has been explored in humans. A prior study revealed that after drinking approximately two cups of green tea, or 195mg of EGCG, only a small percentage of plasma EGCG was detected, however considerable differences were observed among individuals.[18]

The potential weight loss benefits of GTE have been explored in a recent human study, though with unexpected results. In a randomized controlled trial, 92 overweight or obese women were treated with 500 mg of GTE or placebo three times daily for twelve weeks (equivalent of 856.8 mg of EGCG or approximately 12 mg/kg daily). Weight and BMI decreased in both groups but was not significantly different in the GTE or placebo group.[19] The GTE group had no significant adverse events and serum ALT levels remained normal.

Despite its purported benefits, several animal and human studies have shown that GTE has some degree of toxic potential. For instance, in mice, single oral doses of EGCG above 750 mg/kg caused elevations in serum ALT levels and reduced survival rates.[20] Less injury was seen with multiple doses of 500 mg/kg suggesting a threshold dose effect of toxicity. The estimated equivalent doses of EGCG in humans were 30 to 90 mg/kg daily which equates to 10-32 cups of green tea. This is well above the usual recommended dose of GTE in weight loss supplements, though without chemical analysis, it is not possible to determine the exact amount of GTE in each supplement. The liver injury in mice caused by high doses of GTE appeared to be the result of oxidative stress and hepatocellular apoptosis.[9,10] Such injury would be reflected in an hepatocellular pattern of injury.

Liver injury associated with weight loss products containing GTE has also been described in humans in numerous published case reports.[11,12] Many such reports are summarized and can be found on livertox.nih.gov, an online database that features a case registry and provides clinical information on prescription and nonprescription medications as well as herbal and dietary supplements that have been attributed to liver injury.[21] Ours is the largest compilation to date providing details of liver injury attributed to the multi-ingredient products under the SLIMQUICK® label as a cause.

A compelling report implicating GTE as a hepatotoxin described a 37-year-old woman who developed acute, icteric hepatocellular injury approximately 4 months after starting a weight loss supplement containing green tea (“The Right Approach”). Other causes of acute liver injury were excluded and she recovered after stopping the HDS. One year later she presented with a similar pattern of hepatic injury, a month after restarting the same weight loss supplement.[12] Two additional cases of suspected hepatotoxicity specifically linked to SLIMQUICK® has been reported.[22,23] The clinical features of those cases were similar to those described in this current report as summarized in Table 2.

Although our report provides evidence of liver injury attributable to SLIMQUICK®products, most of which contain GTE, the question remains if this herbal extract and its component catechins were the sole culprits, or if injury was the result of contaminants or other herbal ingredients in the SLIMQUICK® products. There is also the possibility of product mislabeling, making it more difficult to identify the culprit ingredient or ingredients. The

unavailability of product consumed by all patients, or even the dose consumed, prevents us from addressing this limitation.

Aside from a dose response relationship with injury, one must consider that liver injury from GTE may be idiosyncratic in nature rather than direct and dose related as occurs in mice. Additionally, behavioral factors such as fasting and recent weight loss, which may augment the hepatotoxic potential of GTE, could not be adequately assessed. However, as shown in dogs, the consumption of catechins in the fasting state as compared to the fed state leads to higher pharmacological exposure.[24]

Given the pattern of injury among these six cases and the scientific background to support its toxic potential, GTE is a reasonable candidate for the causative agent of injury from SLIMQUICK® products. More confident attribution of injury to GTE will result from further exploration of a dose relationship with injury, careful chemical analysis of the actual products implicated in injury, and demonstration of similar injury resulting from other GTE containing products.

Conclusions

We have reported six cases in which SLIMQUICK® products were implicated in liver injury. While SLIMQUICK® products are multi-ingredient, we believe that GTE may be the offending ingredient based upon the frequency of its inclusion as a component and the pattern of liver injury. In an attempt to analyze the phenotypic characteristics of these patients, we observed that with the exception of one case, all patients presented with a hepatocellular pattern of injury, consistent with the type of liver injury observed in those with hepatotoxicity attributed to GTE. However, we cannot confidently ascertain a distinct casual relationship between liver injury and GTE containing SLIMQUICK®products without further chemical analysis of each product and the determination of GTE dosage amount and its relationship with hepatotoxicity.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

DILIN	Drug Induced Liver Injury Network
HDS	herbal and dietary supplements

GTE	green tea extract
BMI	body mass index
ALT	alanine aminotransferase
Alk P	alkaline phosphatase
ANA	antinuclear antibody
SMA	smooth muscle antibody
ECGC	epigallocatechin-3-gallate

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Key Points

Cases of SLIMQUICK® associated hepatotoxicity have been observed and green tea extract has been hypothesized as the ingredient contributing to the hepatocellular pattern of liver injury.

Though there may be an association between green tea extract in SLIMQUICK® and hepatotoxicity, further research to delineate a threshold response related to injury and chemical analysis of SLIMQUICK® ingredients is necessary to establish a more causative relationship.

Table 1

Demographic and Clinical Features

Feature	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Age (years)	58	46	26	22	47	42
Race	African American	White	Hispanic	White	White	African American
Significant Comorbidities	Hypothyroid	Diabetes	None	None	None	Hypertension
BMI (kg/m^2)	25.4	31.0	22.9	32.2	31.4	30.9
Duration of use (days)	30	5	30	7	66	28
Time to DILI Recognition by Physician (days)	48	14	12	21	66	34
Initial ALT (U/L)	446	1018	1384	1732	1329	1020
Initial Alk P (U/L)	239	107	131	123	81	190
Initial R ratio	4.2	26.4	30.2	40.5	30.3	12.5
Initial Bilirubin (mg/dL)	0.6	0.8	5.4	6.4	0.4	9.5
Peak Bilirubin (mg/dL)	0.7	13.8	22.7	11.6	0.6	10.2
ANA/SMA	0/0	0/0	0/1:40	0/1:40	0/0	1:1280/0
Chronic Liver Disease	No	No	No (Transplanted)	Unknown	No	No
Causality Score	Highly Likely	Definite	Probable	Highly Likely	Highly Likely	Definite
Labeled GTE	Yes	Yes	Yes	Yes	No	Yes
Additional dietary supplement use	None	None	Ripped fuel extreme	Ginseng *Gingko biloba*	None	None

R ratio: Patterns of liver injury have been described using the R ratio and is calculated from the ratio of serum ALT to the serum ALP, both expressed as multiples of the ULN. An R ratio ≥ 5 is consistent with a hepatocellular pattern, while an R ratio ≤ 2 indicates a cholestatic pattern, and a mixed pattern can be observed when the R ratio is in between 2 and 5.

ANA: Anti-nuclear antibody

SMA: Anti-smooth muscle antibody

Table 2

Features of previously published case reports of SLIMQUICK® associated hepatotoxicity

Feature	Case 1 - Weinstein et al[22]	Case 2 - Whitsett et al[23]
Age (years)	24	52
Product Form	SLIMQUICK® oral capsules	Liquid SLIMQUICK®
Dosage and Duration of use	2 capsules twice a day for 3 months	Unknown dosage for 2 days
Presenting symptoms	Dark urine, acholic stools, right upper quadrant pain, and fatigue	Vomiting and jaundice
Initial ALT (U/L)	2615	945
Initial Alk P(U/L)	200	210
R ratio	13	4.5
Pattern of injury	Hepatocellular	Mixed
Biopsy Results	Severe inflammatory infiltrate involving both the portal tracts and lobules. The infiltrate included plasma cells, lymphocytes, and neutrophils with prominent eosinophils.	Extensive centrilobular and confluent necrosis with zonal distribution of necrosis favoring drug/toxin-related injury
Chronicity	No	Liver transplantation
Additional facts	Alpha-1 antitrypsin MZ phenotype	Supplement taken while fasting