Acute liver failure caused by ‘fat burners’ and dietary supplements: A case report and literature review

Y Radha Krishna MBBS1, V Mittal MD1, P Grewal MD1, MI Fiel MD2, T Schiano MD1

Globally, people are struggling with obesity. Many effective, non-conventional methods of weight reduction, such as herbal and natural dietary supplements, are increasingly being sought. Fat burners are believed to raise metabolism, burn more calories and hasten fat loss. Despite patient perceptions that herbal remedies are free of adverse effects, some supplements are associated with severe hepatotoxicity. The present report describes a young healthy woman who presented with fulminant hepatic failure requiring emergent liver transplantation caused by a dietary supplement and fat burner containing usnic acid, green tea and guggul tree extracts. Thorough investigation, including histopathological examination, revealed no other cause of hepatotoxicity. The present case adds to the increasing number of reports of hepatotoxicity associated with dietary supplements containing usnic acid, and highlights that herbal extracts from green tea or guggul may not be free of adverse effects. Until these products are subjected to regulatory testing by the United States Food and Drug Administration (FDA), herbal remedies continue to be a popular weight loss and related health products. Because they are not subject to regulatory testing by the United States Food and Drug Administration (FDA), herbal remedies continue to be a popular choice due to their perceived safety and easy availability. Among the more popular remedies are the ‘fat burners’. These supplements are advertised to work by increasing thermogenesis and the basal metabolic rate, thus, mimicking exercise. Despite the common perception that these natural supplements are free of side effects, some are associated with severe toxicities including hepatotoxicity.

Several slimming aids and herbal medications associated with severe hepatotoxicity have been reported in the literature. The list is long, and examples of a few are the following: Chaso, Onshind, Senmomotounou (Japan); Green tea extracts (e.g. Exolise [Arkopharma-France]); Hydroxycut (Iovate, Canada); The Right Approach (Pharmanex-USA); LipoKinetix (Syntrax, USA); Ma Hung; Pure usnic acid; Kombucha mushroom; Teucrium chamadrys (germander); Teucrium capitatum; and Teucrium polium (golden germander) (1-4).

The present report describes a case of acute liver failure in a young healthy female taking herbal supplements containing usnic acid, green tea and guggul tree extracts.

Key Words: Dietary supplements; Hepatotoxicity; Liver failure; Liver transplantation

CASE PRESENTATION

A previously healthy 28-year-old female bodybuilder with no risk factors for liver disease presented to her local emergency centre with fatigue, malaise, inability to exercise and new-onset jaundice. Her symptoms worsened over a span of one week before hospitalization. Initially, she was confused, and over two days became obtunded and eventually required intubation for airway protection before her transfer to The Mount Sinai Medical Center (New York, USA) for liver transplant evaluation. The patient was a professional bodybuilder taking a multi-ingredient, nonstimulant health supplement and fat burner (Somalyz and Lipolyz, Species Nutrition, USA). Somalyz contains usnic acid (4 mg), propionyl-L-carnitine (167 mg), phosphatidylcholine/phosphatidylethanolamine (50 mg), gamma-aminobutyric acid (667 mg) and vitamin E (27 IU) per capsule. Lipolyz contains usnic acid (12 mg), propionyl-L-carnitine (500 mg), green tea extract (300 mg), guggulsterone Z and guggulsterone E (10 mg), cyclic adenosine monophosphate (2 mg) and vitamin E (20 IU) per capsule (Table 1). She was taking one to two capsules of Somalyz at bedtime and one capsule of Lipolyz with meals three times a day as recommended for one month before illness. Her other medications included over-the-counter calcium and fibre supplements, and caffeinated tablets.

On evaluation at The Mount Sinai Medical Center, there were no stigmata of chronic liver disease. Blood work revealed a total

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TABLE 1
Composition of dietary supplements taken by the patient

<table>
<thead>
<tr>
<th>Lipolyz*</th>
<th>Dose</th>
<th>Active ingredient†</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin E</td>
<td>20 IU</td>
<td>Vitamin E</td>
<td>27 IU</td>
</tr>
<tr>
<td>Propionyl-L-carnitine</td>
<td>500 mg</td>
<td>GABA</td>
<td>667 mg</td>
</tr>
<tr>
<td>Green tea extract</td>
<td>300 mg</td>
<td>Propionyl-L-carnitine</td>
<td>167 mg</td>
</tr>
<tr>
<td>Usnic acid</td>
<td>12 mg</td>
<td>Phosphatidylcholine</td>
<td>50 mg</td>
</tr>
<tr>
<td>Guggulsterone Z and guggulsterone E</td>
<td>10 mg</td>
<td>phosphatidylethanolamine</td>
<td></td>
</tr>
<tr>
<td>C-Amp</td>
<td>2 mg</td>
<td>Usnic acid</td>
<td>4 mg</td>
</tr>
<tr>
<td>Capsule composition</td>
<td></td>
<td>Melatonin</td>
<td>1 mg</td>
</tr>
<tr>
<td>Gelatin</td>
<td></td>
<td>Gelatin</td>
<td></td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td></td>
<td>Magnesium stearate</td>
<td></td>
</tr>
<tr>
<td>Rice flour</td>
<td></td>
<td>Rice flour</td>
<td></td>
</tr>
</tbody>
</table>

*Species Nutrition, USA; †Per capsule. C-Amp Cyclic adenosine monophosphate; GABA Gamma-aminobutyric acid

serum bilirubin level of 62.08 mmol/L (normal range 1.71 mmol/L to 20.5 mmol/L), a direct bilirubin level of 47.88 mmol/L (1.71 mmol/L to 13.6 mmol/L), a serum alanine aminotransferase level of 1220 U/L (1 U/L to 53 U/L), a serum aspartate aminotransferase level of 577 U/L (1 U/L to 50 U/L), an alkaline phosphatase level of 111 U/L (30 U/L to 110 U/L), a gamma-glutamyl transferase level of 125 U/L (8 U/L to 35 U/L), an international normalized ratio of 2.6 and a serum creatinine level of 53.04 µmol/L (44.2 µmol/L to 106.2 µmol/L). Her hematological markers, electrolyte levels, metabolic profile, amylase levels and lipase values were unremarkable.

Etiological workup included the following: negative viral serology (hepatitis A virus immunoglobulin M, hepatitis B virus surface antigen and core antibody, hepatitis C virus antibody [polymerase chain reaction assay], cytomegalovirus DNA and Epstein-Barr virus immunoglobulin M); negative sulphis rapid plasma regain; negative autoimmune markers (antinuclear antibody, antiliver kidney muscle antibody, antimitochondrial antibody and antismooth muscle antibody); and normal serum gamma globulins. Extensive toxicology screening was negative, with no features of acetaminophen toxicity (acidosis, high lactate or renal failure). She had normal levels of ferritin, ceruloplasmin and alpha-1 antitrypsin. A pregnancy test was negative. A computed tomography scan of her abdomen revealed a normal size liver with a patent portal vein, hepatic artery, hepatic vein and biliary anatomy. Her spleen was normal and no ascites was noted.

The patient's encephalopathy worsened and she remained unresponsive. A computed tomography scan of her head was normal. An intracranial pressure monitor was placed, which measured an intracranial pressure of 19 mmHg and a cerebral perfusion pressure of 10.5 mmHg. She developed acute liver failure within one month of commencing Usnic acid (Pure Usnic acid, Industrial strength; AAA Services, USA) 500 mg/day for two weeks (7).

Several previous reports described liver failure associated with the use of LipoKinetic, a multi-ingredient preparation containing usnic acid (6-8). In 2002, Favreau et al (6) reported on seven patients who developed acute hepatitis after using LipoKinetic. This dietary supplement contains sodium usonate, norephedrine, yohimbine, 3,5-diiodothyronine and caffeine; both usnic acid and ephedra alkaloids have been associated with severe hepatotoxicity. LipoKinetic withdrew the product from the market.

Durazo et al (7) reported on a healthy 28-year-old woman who developed acute liver failure within one month of commencing usnic acid (Pure Usnic acid, Industrial strength; AAA Services, USA) 500 mg/day for two weeks (7).

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Usnic acid has been shown to uncouple oxidative phosphorylation in a murine model, with resultant loss of mitochondrial respiratory control and inhibition of ATP synthesis. A direct hepatotoxic effect analogous to carbon tetrachloride-induced liver toxicity has also been described (10). Based on a case report (11) detailing three sisters with acute hepatitis after consumption of a ‘fat burner’ herb containing usnic acid, it was suggested that an inherent susceptibility was present.

Usnic acid is a weak inhibitor of cytochrome CYP2D6 and a potent inhibitor of cytochrome CYP2C19. Based on potent inhibition of CYP2C enzymes, usnic acid has significant potential to interact with other medications (5). Hepatotoxicity due to usnic acid appears to be idiosyncratic and is possibly due to a ‘convergence of risk factors’ (12).

Chinese green tea extracts are derivatives of the leaves of Camellia sinensis, which belongs to the aceae family. Green tea extracts have been marketed as effective weight-loss supplements, and for the prevention and cure of solid tumours. Although there is little scientific evidence supporting the effectiveness of green tea extracts, serious side effects, including acute liver failure, are increasingly being reported (13,14). Similar cases have been reported from France and Spain resulting in the removal of the green tea extract ‘Exolise’ from the market (15). Two cases of fulminant hepatic failure associated with green tea extracts have been reported (16,17). Mitochondrial toxicity...
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Epigallocatechin-3-gallate, a key constituent of green tea extracts, has been demonstrated to cause the formation of reactive oxygen species. The possibility of an allergic reaction to green tea itself has also been reported.

Gum guggul and its constituents are increasingly being used as dietary supplements. Gum guggul is the oleoresin of Commiphora mukul, a plant native to India. Its extracts include compounds known for their hypolipidemic properties — the Z and E isomers of guggulsterone and its regulated guggulsterols. Human exposure to gum guggul most often occurs from ingesting herbal remedies or pharmaceuticals, and from the use of cosmetics. Side effects include skin rashes, irregular menstruation, diarrhea, headache, mild nausea and, with very high doses, liver toxicity. Guggulsterol was associated with acute hepatitis in a 63-year-old woman taking the natural lipid-lowering agent Equisterol (Istituto Farmacoterapico Italiano SpA, Italy), which also contains red yeast rice extract.

Based on the temporal relationship between the use of the dietary supplements and onset of liver failure, literature supporting reports of hepatotoxicity associated with dietary supplements and exclusion of other causes, it is fair to assume that the patient developed fulminant hepatic failure due to dietary supplements. In view of the bulk of the literature, of all the ingredients, usnic acid may have been predominantly responsible for the hepatoxicity. Although usnic acid was the main hepatotoxic agent, its effect was possibly perpetuated by other hepatotoxins, including green tea and gum guggul, also contained in the dietary supplements taken by the patient.

According to the Dietary Supplement Health and Education Act of 1994, dietary supplements are regulated as foods and are not subject to regulation as drugs by the FDA; manufacturers are not compelled to provide safety data to the FDA. However, increasing reports of liver failure due to usnic acid have triggered a regulatory warning and one voluntary product withdrawal (LipoKinetix) (20). Usnic acid is still available and advertised on the Internet as an ingredient in various other dietary supplements and fat burners. Usnic acid, green tea and guggul tree extracts are a few of the many herbal and dietary supplements associated with significant liver injury.

CONFLICTS OF INTEREST: The authors have no financial disclosures or conflicts of interest to declare.

REFERENCES
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