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''OxyElite Pro'' Induced Fulminant Hepatotoxicity

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Abstract

Around 35% of adults or more are overweight according to a report by Global Health Observatory (GHO). In the absence of proven medical therapeutics, the use of dietary supplements to effect weight loss has increased and under much less scrutiny by regulatory agencies like the U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA). For many, these approaches represent apparent alternatives to failed attempts at weight loss with the use of more conventional approaches [1]. Hepatotoxicity from supplements is a growing problem while the internet facilitates obtaining these agents across national regulatory boundaries.

OxyElite Pro capsules are sold as a dietary supplement for weight loss and ''super thermogenic'' agent (Figure1A & B). According to the manufacture, the proposed mechanism of action is 'fat burning via the contained ingredients which are: Rauwolfia Canescens, Thyroxine (T4) and Triiodothyronine (T3), Bauhinia Purpurea Trypsin Inhibitor (BPLTI), Bacopa monnieri, Geranium which contains a powerful constituent known as 1,3-Dimethylamylamine (DMAA), Cirsium Oligophyllum, and Caffeine'. A more recent formula of OxyElite Pro released in late 2012 contained a new ingredient, Aegeline.

We describe a case of acute liver failure in an otherwise young healthy female after taking the newer OxyElite Pro formula to lose weight.

Keywords: OxyElite Pro, Hepatotoxicity, acute liver failure, fulminant, herbal induced liver injury

Figure 1: a- ''OxyElite Pro'' capsules photos from the patient
b- ''OxyElite Pro'' package and supplement facts

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Case Presentation

In March, 2013 a previously healthy 34 year old woman with no past medical or surgical history presented to her General Practitioner (GP) with progressive fatigue, new-onset jaundice and dark urine over the previous three weeks. This was associated with right upper quadrant pain for one day before presentation. Initial laboratory testing showed an Alanine Transaminase (ALT) 1347 IU/L, Aspartate Transaminase (AST) 766 IU/L, Alkaline Phosphatase (ALP) 135 IU/L, Total Bilirubin (TB) 83 umol/l.

Given the biochemical evidence of an acute hepatitis, aetiologies including acute viral causes were initially sought and were negative. One week later she felt very unwell and was referred to a local hospital with poor appetite, lack of energy and worsening of jaundice where further testing ensured. On examination, her vital signs were normal and her Body Mass Index (BMI) was 31.2 kg/m2. She was icteric but without stigmata of chronic liver disease and the initial neurological and abdominal examinations was normal, notably without signs of hepatic encephalopthy. Repeat liver enzymes were more elevated with an ALT of 1184 IU/L, TB was 422 umol/l, ALP of 113 IU/L. Importantly, the Prothrombin Time (PT) was elevated at 23.7 seconds (9.6-11.8 sec) with an INR of 2.2. Extensive laboratory investigations were negative or normal for viral, metabolic and autoimmune causes of acute hepatitis. Initial copper studies showed low caeruloplasmin and high 24 hour urinary copper, 1.2 umol/24 hrs (reference rage <1.0 umol/24 hrs) however slit lamb examinations by two independent ophthalmologists were negative for Kayser-Fleisher rings. Liver imaging studies including ultrasonography with Doppler interrogation and MRI were normal. The patient was given empiric high dose parenteral corticosteroids for 5 days with no significant improvement. The patient was not confused but developed definite asterixis consistent with grade 2 hepatic encephalopathy and was urgently transferred to the National Liver Transplant Unit for an expedited liver transplantation evaluation.

On closer questioning, it transpired that she had been taking a herbal remedy -OxyElite Pro – as a weight loss supplement. The patient had purchased the supplement on-line from an American company which has separate retail websites across Europe including the UK, Ireland, The Netherlands, Germany, France, Italy and Spain. Her average weekly intake was 8 tablets over the previous one year.

However, she had recently purchased a bottle of OxyElite Pro with the new formula in March 2013 from the same source and took the new supplement for about 2 weeks before her initial presentation. The patient did not use or ingest any other potentially hepatotoxic substances. She was not on any prescription medications or herbal supplement apart from OxyElite Pro. Indices of synthetic function continued to deteriorate with an INR and Total Bilirubin (TB) that continued to rise up to 2.6 and 643 u mol/l respectively though aminotransaminases started to slowly decline (figure 2 {A-C}). The patient underwent a trans-jugular liver biopsy which showed inflamed portal tracts expanded by a moderate mixed infiltrate consisting of lymphocytes, neutrophils, & eosinophils. Plasma cells were not conspicuous. There was a slight increase in portal tract fibrosis together with interface hepatitis. The lobules showed moderate to severe pan lobular inflammation with broad areas of lobular necrosis, parenchymal collapse and ductular reaction. Bile plugs were present within hepatocyte canniculi. The histologic findings were consistent with a severe acute hepatitis (Figure 3 {A-C}).

Given the presence of asterixis and coagulopathy, the patient was evaluated and listed in an expedited manner for orthotopic liver transplantation for Fulminant Liver Failure (FLF). However, the patient remained alert, fully oriented, and the asterixis resolved after 4 days. The total bilirubin peaked at 872 u mol/l

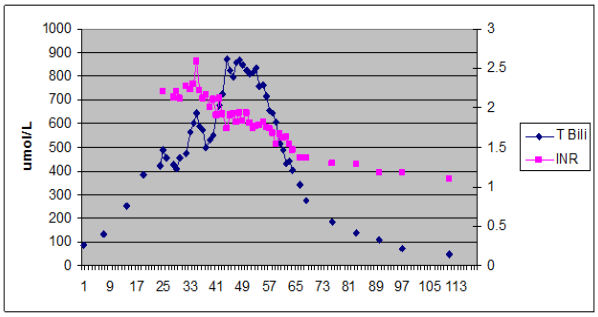

Figure 2a: T bili: Total bilirubin
INR: International normalized ration

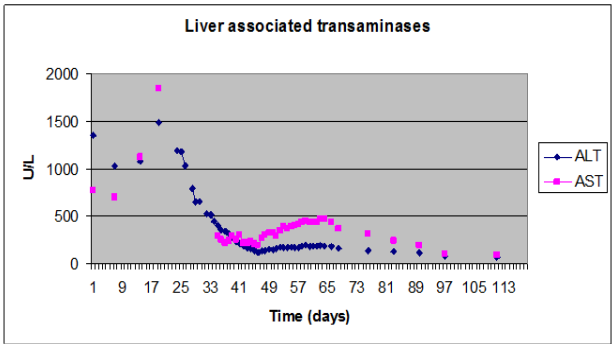

Figure 2b: ALT: Alanine transaminase
AST: Aspartate transaminase

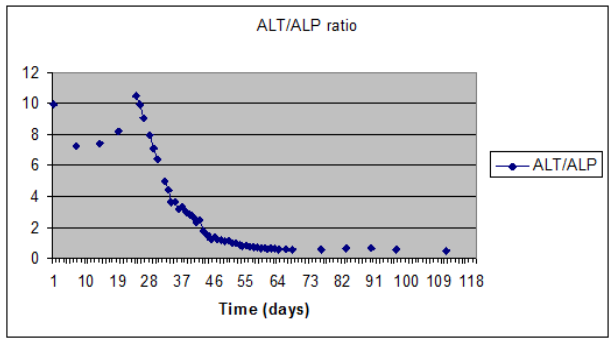

Figure 2c: ALT: Alanine transaminase
ALP: Alkaline phosphatase

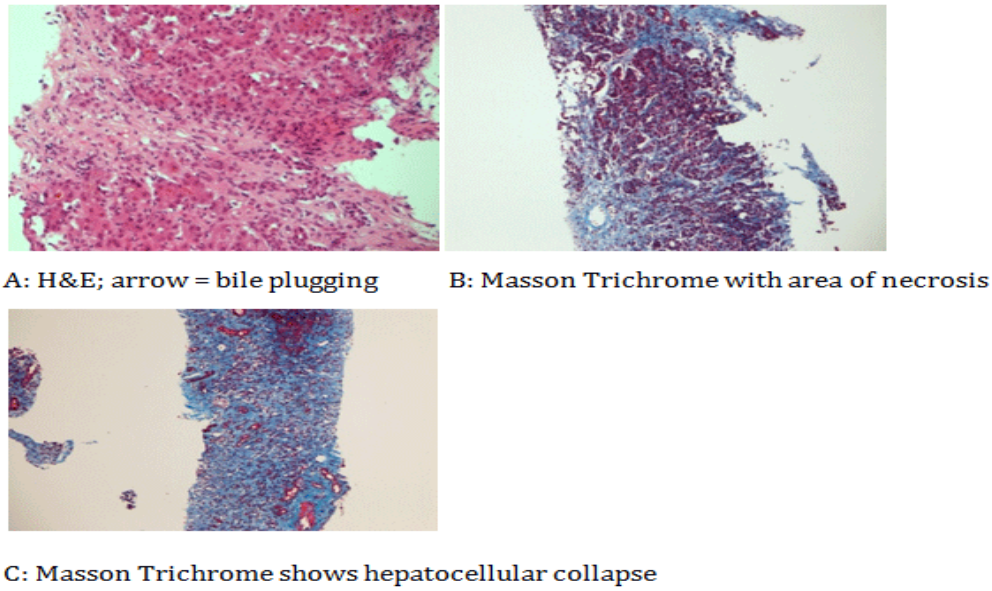

Figure 3: Histologic features with H&E and Masson Trichrome stains

after six weeks of her initial presentation but the INR improved to 1.74. Hepatic synthetic function continued to slowly improve over the subsequent 4 weeks. In outpatient follow-up, the patient's aminotransaminases, TB and INR normalized after 7 months from her initial presentation. She has continued to avoid all complementary and alternative mediations.

Discussion

In the context of rising obesity rates and the perception of ineffective conventional medical therapeutics, patients increasingly are turning to complementary and alternative remedies for weight reduction. Coupled to easy, often internet-based availability and presumed safety, there is a lack of robust or consistent regulatory evaluation for safety and efficacy by national and international regulatory authorities [2-6].

We report the first case in Europe to our knowledge of fulminant liver failure due to the supplement OxyElite Pro. Causality is supported by the extensive negative testing for other causes of acute liver injury and the temporal relationship between administering the new OxyElite Pro formula and her presentation. Moreover, the histologic findings are supportive of a severe acute drug-induced liver injury. Twenty nine cases of acute hepatitis and liver failure were reported in Hawaii, USA. Twenty four (83%) reported using OxyELite Pro during the 60 days before illness onset. Twelve patients (41%) reported use of this supplement with no other dietary supplement, and 12 (41%) reported use of both OxyElite Pro and at least one additional dietary supplement. Their median age was 33 years (range: 16–66); 14 (48%) were male. The most commonly reported symptoms included loss of appetite, light-coloured stools, dark urine, and jaundice. Median laboratory values reported at the peak of illness were: AST 1128 IU/L; ALT 1793 IU/L; ALP 150 IU/L; and TB 215 u mol/l. Two people have undergone liver transplantation and one person has died, according to the Hawaii State Department of Health. The FDA initiated a public health investigation including patient interviews, medical chart reviews, and collection of supplement samples for analysis [7]. The clinical features of our case was similar to cases from Hawaii in terms of ingesting the new OxyElite Pro formula, presentation, laboratory data and histologic findings where available (personal communication, Dr. Marina Roytman, Queen's Medical Center, Honolulu, HI, USA). Recently Foley and colleagues published the first case series of acute liver injury of seven cases in Southern California in which OxyElite Pro was involved. Of note two of them required liver transplantation [8]. The possible culprit agent(s) contained in OxyElite Pro is unknown and hepatotoxicity is presumed to be idiosyncratic based on the temporal association between use of new OxyElite Pro herbal formula and the onset of clinical presentation. The calculated Council of International Organizations of Medical Science/Roussel Uclaf Causality Assessment Method (CIOMS/RUCAM) score in our case was 7 (probable causality). This score has 86% sensitivity and 89% specificity with 93 % positive predictive value and 78% negative predictive value [9].

Rauwolfia Canescens is related to yohimbine, an indole alkaloid from the bark of the African Pausinystalia yohimbe tree and is also found in Rauwolfia root. It is an often used ingredient in many thermogenic products due to its purported ability to antagonize alpha 2-receptors. Yohimbine is widely touted as a remedy for male impotence, but the mode of action is by selective blockade of the presynaptic α2- receptor [10]. Deaths from overdose of yohimbine alone have been reported though FLF reports Page 10 of 17 have not implicated [11]. In a case-series report, dietary supplement 'LipoKinetix' which contains Yohimbine among many other substances was reported to be associated with severe hepatotoxicity including FLF [12]. While

Oxy- Elite Pro also contains T3 and T4, our patient did not exhibit clinical signs of hyperthyroidism, and abnormal liver tests results were not typical of that [13]. Bauhinia Purpurea Trypsin Inhibitor (BPLTI), another component exhibits a wide spectrum of anti-proliferative and pro-apoptotic activities especially on human hepatocellular carcinoma Hep G2 cells including induction of cell apoptosis/necrosis [14].

Bacopa monnieri is another ingredient which has the same mechanism of action as Bauhinia purpurea L and in an animal model, is also suggested to naturally promote production of T4 thyroid hormone when compared to controls [15]. Recently, Teschke and Bahre reported a 64 years old female who developed severe hepatotoxicity after ingestion of Indian ayurvedic herbal products. After a causality assessment using the CIOMS, it was deemed that causality for Bacopa monnieri induced liver injury was probable [16]. Another important ingredient of OxyElite Pro is 1, 3 DMAA. Of note, FDA has sent warning letters to 11 companies over the past year asking them to stop marketing products that contain DMAA in April 2012. To our knowledge, all but one – USPlabs, the company that produces OxyElite Pro, agreed to stop using DMAA in supplements. In April 2013 and after another warning letter from the FDA the USPLabs announces their intention to stop selling DMAA and reformulate OxyElite Pro, stating: "USPlabs stands by the safety and legality of its products containing the dietary ingredient 1, 3-DMAA. We disagree with FDA's position'' [17]. Cirsium oligophyllum (CE) is another component that exhibits lipolysis-promoting activity in subcutaneous adipocytes though there are no reports of hepatotoxicity [18].

Finally, Aegeline or N-[2-hydroxy-2(4-methoxyphenyl) ethyl]-3-phenyl-2-propenamide was introduced to the new formula of OxyElite Pro. This is an alkaloid isolated from Aegle marmelos Correa collected in Yogyakarta Indonesia [19]. It antagonizes the histamine H1 receptor in a competitive manner [20].There are no previous reports suggesting that Aegeline can induce hepatotoxicity. One could also hypothesise the contributions of drug-drug and metabolite-metabolite interactions as aetiology or contributory to the hepatotoxicity of the agent. The pattern of elevated liver associated enzymes in our case was initially hepatitis with ALT/Alkaline Phosphatase (ALP) ratio >5 (range from 6.4-10.5) for the first four weeks of presentation. Then, it evolved into mixed picture that was predominantly cholestatic as the patient's aminotransaminases normalised. The incidence of Drug Induced Liver Injury (DILI) in the general population of the UK has been estimated to be 2.4 /100.000 per year [21]. Remarkably, DILI now accounts for 10-20% of all cases of fulminant and subfulminant liver failure [22, 23]. Epidemiological data of Herbal-Induced Liver Injury (HILI) in Europe is lacking. In Korea, HILI is the most common cause of FLF and accounts for 26% of those cases that required liver transplantation from 2005-2011 [24]. In China, 30 out of 177 cases (17%) of acute liver failure were induced by traditional Chinese medicinal herbs though none of the cohort received liver transplantation [25, 26]. Another study of twenty five patients who developed acute hepatitis following ingestion of herbal preparations and nutritional supplements, polygonum multiflorum thunb reported that 91.6 % had spontaneous recovery with conservative management. Only one patient (4%) died and one patient required liver transplantation [27]. Another prospective nationwide study of DILI reported 270 patients with herbal and dietary supplements related hepatotoxicity in Korea. Most of patients had spontaneous recovery however only two patients died and two required liver transplantation. Although there is no previous data to suggest that Aegeline is the hepatotoxic culprit, our case was supported by a temporal relationship between use of new OxyElite Pro herbal food supplement formula and onset of clinical presentation. In addition, similar cases from Hawaii where patients used the new formula recently resulted in hepatotoxicity. The FDA recent report about many cases of hepatotoxicity induced by OxyElite Pro and histologic findings of severe acute hepatitis supports the diagnosis of OxyElite Pro-induced fulminant hepatic failure. In a warning letter issued to USP Labs LLC of Dallas Texas in October 2013, the FDA informed the company that the dietary supplements OxyElite Pro and VERSA-1 are deemed to be adulterated, and that failure to immediately cease distribution of these products may result in enforcement action by the FDA. In Ireland, the Health Science Authority (HSA) press release on the 18th October 2013 alerted members of the public that OxyElite Pro has been linked to numerous cases of serious liver injuries in the United States (US) and one case in Hong Kong. HSA has warned sellers to stop distribution of ''OxyElite Pro''. We reported this case to the Irish Medicines Board (IMB) in June 2013. In November 2013 The Food Safety Authority Ireland (FSAI) and IMB stated against OxyElite Pro and the advertisement was immediately removed from the online supplier.

Conclusion

Hepatotoxicity from herbal supplements can be difficult to diagnose for many reasons that include the multiplicity of stated ingredients, the presence of substances that are not described on the label, the potential for drug-drug and metabolite-metabolite interactions of the agent. The ability to procure supplements from a variety of internet-based sources, often outside of and/or eluding local regulatory control greatly increases the potential challenges even when reports of toxicity are already circulated in other parts of the world.

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