Abstract

Recent news suggests that several patients have suffered from hepatitis due to large doses of green tea as well as the green tea extracts found in nutritional supplements. Diagnosis of chemically induced liver damage is a diagnosis based on elimination, it is imperative to diagnose this form of hepatitis quickly as patients who stop consumption of green tea usually return to normal with time. Adverse events due to dietary and herbal supplements have been on the rise over the last 20 years. This project uses a case study to explore the growing problem of supplement-induced injury and reviews the pertinent literature to establish the scope of the problem here in the United States.

GREEN TEA TOXICITY: A CASE STUDY AND LITERATURE REVIEW

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Abbreviations

Computerized Tomography (CT), Gamma-Glutamyl Transferase (GGT), Prothrombin Time (PT), Partial Thromboplastin Time (PTT), Food and Drug Administration (FDA), Dietary Supplement Health and Education Act (DSHEA), Drug-Induced Liver Injury (DILI), Dietary Supplements Information Expert Committee (DSI EC), Upper Limit of Normal (ULN), Aspartate Aminotransferase (AST), Alanine Aminotransferase (ALT), United States Dollars (USD), United

States (US), Epicatecin (EC), Epigallocatechin (EGC), Epicatechin-3-Gallate (ECG), and Epigallocatechin-3-Gallate (EGCG).

Objectives

Green tea, as well as other supplements, have become increasingly popular and with this increase in popularity have come issues with regulation and a subsequent increase in toxic events. This paper will utilize a case study to facilitate discussion of dietary supplements such as green tea, specifically it will highlight the legislative history that has led to a lack of oversight, the approximate number of people effected by adverse reactions to botanicals in general and green tea extracts more specifically, finally it will discuss the proposed mechanism of action that can lead to liver damage.

Introduction

People are aware of the risks for heart attack associated with supplements labeled as fat burners or energy boosters, however many are not aware that green tea and its extracts are suspected to be a contributing factor in liver damage among users of these products. Recent news suggests that several patients have suffered from hepatitis due to a high intake of either green tea or green tea extract. Diagnosis of chemically induced liver damage is a diagnosis based on elimination, having a thorough patient history and the proper testing is critical in achieving good patient outcomes. Patients presenting with this type of injury would show results indicative of hepatitis, coupled with a negative result for a viral or bacterial cause. It is imperative to diagnose this form of hepatitis quickly as patients who stop consumption of green tea and green tea containing products usually return to normal within three months to one year.

Prolonged exposure has led to liver cirrhosis severe enough to require transplantation for recovery and in one case has resulted in the death of the patient.

Methods and Materials

The case study presented here is based on a news story published in the September 24, 2015 edition of The Telegraph. A 16 year old from England was diagnosed with acute hepatitis after consuming 3 cups of green tea daily for three months.[1] The research herein is based on this report as well as other published papers examining the safety of over the counter herbal products used for weight loss.

Case Study

A 20-year-old female presented to the ER complaining of dizziness, nausea, and general malaise. Physical examination of the patient showed some slight jaundice of the skin and eyes, as well as swelling in the right upper quadrant of the abdomen. Patient history showed no recent travel outside the country, no prescription medications, and the woman denied the use of alcohol or illegal drugs. She had visited her doctor a few days before complaining of dizziness, nausea, malaise, and some pain in her abdomen and lower back, but at the time of initial complaint there was no jaundice and the liver was not swollen upon palpation. Her doctor believed these symptoms to be the result of a urinary tract infection and prescribed broad-spectrum antibiotics. The patient came to the ER when symptoms continued to worsen. Urine and blood were collected, liver function tests and a hepatitis panel were ordered. The results of the chemical

testing were abnormal and indicated possible liver damage so a CT scan and biopsy were ordered.

History

In 1994 the FDA passed the Dietary Supplement Health and Education Act (DSHEA) in an attempt to regulate the market on products that were considered neither foods nor drugs. This act provided guidelines for manufactures producing products intended to enhance dietary intake.[2, 3] In 1994 there were approximately 4000 supplements available for purchase in the United States, as of 2014 this number had rocketed to 90,000 products[2] and is valued at over $60 billion USD.[4] Products regulated under the 1994 act have to meet certain standards; they must meet good manufacturing practice guidelines, may not contain substances that are known hazards, and any new product that was not marketed before 1994 requires premarket notification. These rules are meant to protect the public, however there are many loopholes that allow practices harmful to the consumer such as no limits on concentration, no required safety trials, and no rules on which ingredients are combined (so long as all of them meet the above standards).[2] In addition adulterated products containing unproven ingredients regularly make it onto the market and good manufacturing practices are often ignored. The FDA can challenge companies that are not in compliance but the product may still be sold until the courts side with the FDA.[2]

With regards to plant-based products, studies have detected the presence of heavy metals and other contaminants; one such study showed that of 44 herbal products from 12 different companies, “59% of tested botanical supplements contained plant species not listed on the label.”[2, 4] A study conducted in 2013 “assayed 97 herbal dietary supplements implicated in human hepatotoxicity for catechins”,[5] catechins are the active ingredient in green tea; of these 97 products 73 claimed to not contain either green tea extract or catechins. Of these 73 products, 29 contained catechins regardless of what the labeled ingredients were.[5] If it is possible to get samples of the products suspected in causing a toxic event, testing could reveal possible etiological agents and eliminate others. Without this there is no guarantee as to what the actual causative agent was. In addition, proper identification of dangerous products is key to getting them off the market faster.

Scope

It is estimated that in the United States, between the years 2004 and 2013 there were "more than 23,000 emergency department visits annually... for adverse events associated with dietary supplements. Such visits commonly involved cardiovascular adverse effects from weight-loss or energy herbal products among young adults, unsupervised ingestion of micronutrients by children, and swallowing problems associated with micronutrients among older adults."[6] Geller et al feel that the number of visits due to herbal supplementation is likely higher than the estimated 23,000 per year, as "physicians may not identify adverse events associated with supplements as often as they do those associated with pharmaceuticals".[6] Compounding the problem of establishing a true number of supplement injuries is that the “the primary mechanism

for monitoring supplement safety is a voluntary reporting system… An Office of the Inspector General report revealed that fewer then 1% of all (adverse events) are reported"[2]. So the true scope of these supplement-based injuries is still unknown.

With regards to liver damage due to herbal supplements, as of 2008 drug-induced liver injury (DILI) was cited as the cause in 13% of all reported cases of acute liver failure.[7] A survey of these cases found that 9% of the patients diagnosed with DILI received their injuries from dietary supplements.[7]

Greater scrutiny is being shown to the herbal supplement market then ever before and investigations into the toxic effects of some of these herbal preparations is expanding. The first true stirrings of concern over green tea came in 2003 when the French and Spanish governments banned the green tea based weight loss supplement Exolise.[8] The ban was put into effect after thirteen patients reported liver toxicity from Exolise.[8] The US Pharmacopeia Dietary Supplements Information Expert Committee (DSI EC) responded with a systemic review of the safety of green tea extracts.[8] The study covered the period of 1996-2007 and examined 216 case reports involving green tea products. Thirty-four of these reports concerned liver damage. The result of this survey was to label green tea extracts as a Class 2 dietary supplement. Class 2 supplements are "articles for which the DSI EC is unaware of significant safety issues that would prohibit monograph development when the article is used and formulated appropriately, provided there is a warning statement in the labeling section".[8] The recommended warning statement would have had to read "(t)ake with food. Discontinue use and consult a healthcare practitioner if you have a liver disorder or develop symptoms of liver trouble such as abdominal pain, dark urine, or jaundice".[8] This decision was made in early 2008; in June of 2008 the DSI EC decided

to defer approval of this labeling.[9] Then in February 2009 the US Pharmacopeia changed its classification system from a 4 class system to a two class system and green tea was downgraded to a class A substance, "Class A: Admitted into the Compendia: Articles for which the available evidence does not indicate a serious risk to health or other public health concern that precludes inclusion of a quality monograph into the compendia".[10] The previous four-class system allowed the FDA to have some leeway in regulating products that can, under certain circumstances, be harmful. Products that fell into a grey area, like green tea, could be required to carry a warning label alerting consumers of possible ill health effects while also preventing further burden to the manufacturers. This new two-class system limits the ability to regulate potentially harmful botanicals by marking dietary supplements as either harmful or not harmful.

Concurrent to the US Pharmacopeia review, Italian researchers also ran their own literature review. This study covered the years 1999-2008 and was followed by an update in 2015 covering the years 2008-2015, this later review was, in part, a response to the 2009 Hydroxycut recall and also due to continued cases of hepatotoxity from green tea appearing in the literature.[9, 11, 12] A total of 53 cases were isolated, 34 from 1999-2008, and 19 from 2008-2015. In 8 of these 53 cases green tea leaves were implicated, the remainder of the cases were from green tea extracts or multicomponent supplements. Among the 53 cases of hepatotoxicity there was 1 death and four transplants, all five of these cases involved the use of multi component supplements of which green tea extract was a listed ingredient.[11, 12] There were 7 known cases of positive rechallenge in which the patient showed improvement and when they began taking the product again the symptoms returned.[11] One patient, who reported consuming an "extract infusion" had a previous diagnosis of steatosis.[12] Of the cases reporting

liver enzyme levels, it should be noted that ALT was 3.6 - 96 times the upper level of normal (ULN), AST was 4.9-99 times the ULN, and if present ALP could be 5.5 times the ULN.[12] Considering that in 2013 the United States imported 217 million kg of tea,[13] having a reported incidence of 53 cases in 16 years (or 3.3 cases per year), is not a high yield injury, however it highlights how much we do not know about the impact of herbal products on the human body.

Results of Patient Testing

Tests performed at the time of the patients ER visit showed that the hepatitis testing for anti-HAV IgM, HBsAg, and anti-HCV was negative. Urinalysis only showed the normal levels of bacteria expected in female patients with no casts, crystals, leukocytes, or red blood cells. Liver enzyme levels were markedly increased but alkaline phosphatase and GGT were normal indicating that while the liver was experiencing injury, the bile ducts seemed to be functioning properly, the presence of both bilirubin and urobilinogen in the urine confirms that the patients jaundice was due to liver damage and not bile duct obstruction or hemolytic disease.[14] PT and PTT were performed to assess the extent of the damage to the liver. PT was only slightly elevated and PTT was normal indicating that the patient was suffering from early liver damage. CT scan and biopsy showed evidence of liver cirrhosis, and no bacterial cysts could be seen. No obvious cause of the cirrhosis could be determined. See table 1 for a summery of the test results. Upon further probing from the emergency room staff, the woman admitted that she had been drinking at least 3 cups of green tea a day in order to stimulate weight loss, she had continued to drink it after her initial doctors visit. The patient was advised to discontinue use of the tea.

Test	Results at time of first check up: day 1	Results at time of admittance to ER: Day 4	Follow up: Day 20	Follow up: Day 60	Normal Values
Gram Stain of Urine	Negative for pathogens	Negative for pathogens	N/A	N/A	Negative for pathogens
Antigen and Antibody Tests for Viral Hepatitis		Negative	Negative	N/A	Negative
ALT		1999	1001	30	Females 12mo-60yr: 7-35 U/L
AST		2500	1400	32	Female Adults: 13-35 U/L
Alkaline Phosphatase		170	75	75	Females 20-29: 70-260
GGT		15	16	15	Females 20-24: 4-27 U/L
Albumin		4.2	3.7	3.7	Adults: 3.5-4.2 g/dL
Conjugated Bilirubin		12.5	15.0	0.0	<0.2 mg/dL
Unconjugated Bilirubin		1.8	2.0	0.3	<1.1 mg/dL
Urine Bilirubin		1+	Negative	Negative	Negative
Urine Urobilinogen		2+	Negative	Negative	Negative
PT		16.5 sec	13.8 sec	13.5	11-16 sec
PTT		29 sec	30 sec	28	25-35 sec

Table 1: Patient lab values over time. Normal results based on Tietz Guide to Laboratory tests and patient values based on case studies found in Mazzanti et al.[12, 15]

Mechanism

In the United States there has been an explosion of attention to antioxidants for improved health. Green tea in particular has become increasingly popular due to its purported antioxidant properties. It appears that the very property that has made green tea so popular is also the likely culprit in cases of hepatotoxicity. The proposed mechanism for hepatotoxicity from green tea has

been fairly well researched with most of the studies being published in 2005 and 2006, the most applicable recent research being a study from 2009 and a review from 2011. Much of this research has shown that low to moderate doses of green tea are safe, but despite this evidence injuries are still occurring indicating that more investigation should be considered.

Green tea is known to contain six aromatic compounds; this includes the phenolic acids gallic acid and propyl gallate as well as the catechins Epicatecin (EC), Epigallocatechin (EGC), Epicatechin-3-Gallate (ECG), and Epigallocatechin-3-Gallate (EGCG).[16, 17]

EGCG, ECG, and propyl gallate appear to be the most active in the destruction of hepatocytes.[16, 17] Galati et al were able to show that green tea catechines, in particular EGCG and ECG were the most cytotoxic as was the phenolic acid propyl gallate and that these substances appeared to work in conjunction with each other. Interestingly, phenolic compounds such as propyl gallate were shown to deplete hepatocyte glutathione and glutathione seems to detoxify EGCG. In turn EGCG and ECG, or an intermediary product, induce measurable reactive oxygen species in vitro, the end result being that "EGCG, ECG, EGC, and propyl gallate readily collapsed the hepatocyte mitochondrial membrane potential"[16]. In addition to the previously discussed chemical changes, the resulting damage to hepatocytes was encountered throughout the case studies in the form of inflammation, cholestasis, steatosis, and/or necrosis of the liver.[11]

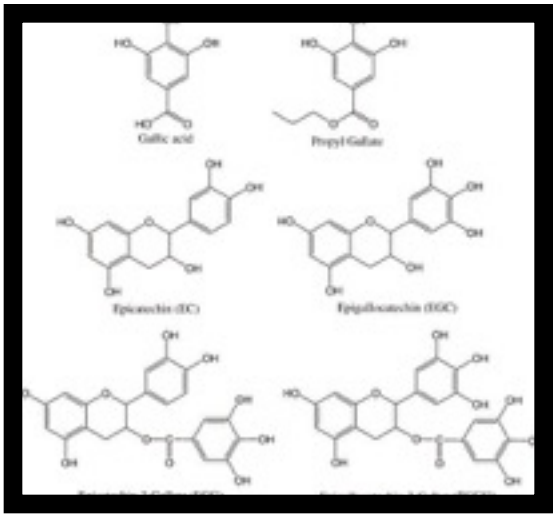

Figure 1: Structure of active compounds in green tea.
Galati et al.

In 2009 Lambert et al performed an in vivo study on mice and found evidence of a threshold dose for cellular damage. They "observed that EGCG caused a does- and time-dependent decrease in the survival of CF-1 mice when given either as a single dose or as multiple once-daily doses. A total dose of 1500 mg/kg i.g. was similarly potent when given as a single dose or as two once-daily doses of 750 mg/kg, i.g." multiple doses of 500 mg/kg daily showed less toxicity.[17] Lambert et al believed that at higher doses the extent of the cellular damage is enough that the body cannot heal enough between dosings leading to a "cumulative toxicity," however they have not yet established enough evidence to fully prove this theory.

While no actual human trials have been performed Lambert et al attempted to scale their results from mouse to human metabolism in order to calculate a possible threshold level. They posit that if a cup of tea were made with 2.5g of green tea leaves in 250 mL of water a person would need to consume 10.5-32 cups of tea in one sitting (30-90 mg/kg).[17] The problem with these numbers is that there have been several cases in which the patient was only consuming 3-6 cups of green tea a day indicating that these numbers do not translate well going from mouse to human models. [1, 17] In regards to green tea extracts, Navarro et al found that in many of the products that they tested for the presence of catechins, the highest estimated daily dose was 40 mg/kg[5] highlighting how easily once can consume doses above the proposed threshold level. Further research in this area would help establish a recommended daily value and could help in reducing injury.

A third factor in the toxicity of green tea appears to be the fasting status of the subject. Beginning in 2006 with a study by Isbrucker et al and further studied in 2009 by Kapetanovic et al, research has shown that catechins, when given to dogs, showed a greater ability to cause

hepatocyte damage when the dogs had been fasted versus those that were unfasted.[18, 19] Between these two studies there was a "10-fold difference in maximum tolerated dose between fasted and nonfasted" dogs.[20] Figure 2 is reproduced from Isbrucker et al and shows the plasma concentrations of EGCG in fasted vs. unfasted female Beagle dogs, it highlights how much a fasted state can affect the toxicity of EGCG. When taken together these studies indicate that the likely hood for damage from green tea is greater in those who are consuming it in a fasted state, in large doses, over a prolonged period of time.

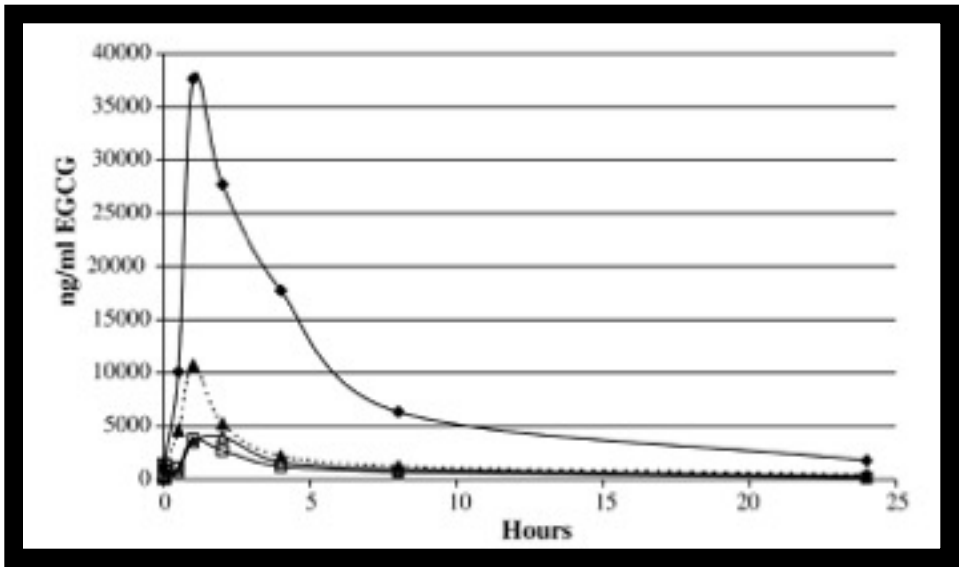

Figure 2: Solid diamonds = fasted dogs 300 mg/kg/day x 14 days, open square = pre-fed 300 mg/kg/day x 14 days. Open triangles = pre -fed 500 mg/kg/day 14 days. Solid triangles with dashed line = pre-fed 500 mg/kg/ day x 28 days. Taken from Isbrucker et. al

Conclusion

When the patient discontinued consumption of the green tea her symptoms abated. The patient returned for check ups at regular intervals. On the follow up exam 20 days later her blood chemistry had begun to come down from its elevated state. A repeat of the viral hepatitis tests were performed and showed that she was still negative for hepatitis A, B and C. By day 60 the patients blood chemistry had returned to normal. This correlates with other patients who have received this type of injury.

Dietary supplements have many purported benefits that are used by manufactures for marketing purposes. Rarely does one see statements on what can happen if these compounds are over consumed, nor is there much research into their safety. Consumption of green tea in moderate amounts, with or after a meal does not often result in injury. Green tea in its brewed form caused only 15% of all the known cases of green tea hepatotoxicity, with the remainder of the injuries being due to products containing the extract. There appears to be more of a concern with regards to green tea extracts and multi component supplements, which often contain higher levels of catechins then natural tea products. Going forward, greater consumer awareness, as well as improved oversight of supplement manufactures can reduce the number of cases of injury, not just from green tea but also from other potentially hazardous supplements. Clinically, greater awareness of the potential health hazards of supplements can lead to improved patient outcomes.

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