May 19, 2013

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 3275-review.docx).

Title: Green Tea Extract: A Potential Cause of Acute Liver Failure

Authors: Shreena S. Patel, MD, Stacey Silver, MPH, RD/LD, Debra L. Kearney, MD, Garrett Phillips, MD, and Beth A. Carter, MD

Name of Journal: World Journal of Gastroenterology

ESPS Manuscript NO: 3275

The manuscript has been improved according to the suggestions of reviewers:

1. Format has been updated
2. Revisions have been made according to the suggestions of the reviewers:
    A. Reviewer No. 02438659:
        - **Because of different concentrations of green tea extract, the green tea extract is not equal to green tea. Thus the contents which may comprehend the hepatotoxicity attributable to green tea, should be clearly changed to blame the green tea extract:**
            - It is indeed the green tea extract, and in particular the EGCG within the extract, that has been the most evident in leading to liver injury and failure. I have revised the manuscript to ensure that statements referring to liver injury are used with “green tea extract” and statements referring to views of the lay-public are used with “green tea.”

    B. Reviewer No. 00158730:
        - **It would be helpful to make a table of the Laboratory studies including the follow-up labs:**
            - I have revised the manuscript to include a table of laboratory studies at admission, hospital day number 15, at discharge, and at follow-up. Peak/ nadir lab values suggesting impending liver failure are still stated within the text.
        - **Are any of the other herbals consumed associated with hepatotoxicity? Could the combination of these herbals be the cause of the liver failure or is it definitely only the green tea extract? May wish to acknowledge there is no definitive proof that green tea extract alone was the etiologic agent responsible for the liver failure**
            - A literature search was conducted of all supplements consumed and

included research of the individual ingredients within each of the supplements. Although likely to be multi-factorial in nature, current data was most convincing for green tea extract hepatotoxicity. I have revised the manuscript to include statements to this effect and have included references, where data exists (since as indicated in our discussion there is quite a lack of research of herbal supplements in the U.S.), to support these statements.

C. Reviewer No. 00182114:

- **According to your clinical data (P.6),abnormal datas are AST(2106 U/L),ALT (2984 U/L),CB (12.9MG/DL) ,UB (1.9 MG/DL) and INR 1.3. According to the criteria of acute liver failure, prothrombin time is prolonged by 4-6 seconds or more (especially INR>1.5). According to above data, I think that this case is not belong to acute liver failure. But this case is belong to acute liver injury. Would you please comment me the diagnosis of acute liver failure in this case.?**
    - Yes, we agree. Because no encephalopathy ensued in our patient, an INR greater than or equal to 2.0 is required to strictly fit the definition of liver failure. Accordingly, we have changed the text to read “acute impending liver failure” rather than “acute liver failure.” Given that the patient had decreased Factor 7 levels and worsening synthetic function of the liver, we feel “acute impending liver failure” is a fair representation of his clinical condition.
- **In the majority of acute liver failure there is widespread hepatocellular necrosis beginning in the centrizonal distribution and progressing towards portal tracts. Zone 1(periportal),Zone 2(midzonal) and Zone3 (centrilobular) necrosis occur in acute liver failure. In page 8, histological examination of the livers showed pathology characteristic of inflammatory infiltrates, cholestasis, steatosis and necrosis. What kinds of Zone is this case belong?**
    - The histology provided includes liver Zones 1-3 as injury was pan-lobular. Yet as seen in the slides, injury was most prominent in Zone 1. I have revised the manuscript text to include this.
- **In page 6, the patient had a liver biopsy on hospital day 5. What kind of route do you perform liver biopsy., echo guide liver biopsy or transjugular route ? From my impression, most of liver failure are performed via the transjugular route due to coagulopathy. Please comment to me.**
    - The liver biopsy was ultrasound-guided. Biopsy was done prior to INR

reaching 1.5. It is our hospital's policy to conduct all biopsy via ultrasound guide for an INR of 1.5 or less.

D. Reviewer No. 00070897:

- **Before the onset of liver injury, this patient took Applied Nutrition? Green Tea Fat Burner，Whey protein，GNC Mega Men? Sport, and l Nopal (Cactus) at the same time, how to determine the liver damage is caused by the green tea extract, rather than the other substance? What is the composition of Applied Nutrition? Green Tea Fat Burner, in addition to the green tea extract, is there any other substances that may have hepatotoxicity?**
    - A literature search was conducted of all supplements consumed and included research of the individual ingredients within each of the supplements. Although likely to be multi-factorial in nature, current data was most convincing for green tea extract hepatotoxicity. I have revised the manuscript to include statements to this effect and have included references, where data exists (since as indicated in our discussion there is quite a lack of research of herbal supplements in the U.S.), to support these statements.
- **Over the weight loss period, this patient lost 56 pounds. Rapid weight loss may create serious risks. The liver damage of this patient may be caused by rapid weight loss?**
    - There is literature to suggest that rapid weight loss can alter AST and ALT values, but such alterations are typically transient and mild in nature. References: Gasteyger C et al *Am J Clin Nutr* 2008, Friis R et al *J Clin Gastroenterol* 1987. Our patient's transaminitis was severe in nature and likely due to more than just weight loss.
- **How the patient is treated?**
    - Treatment included initiation of oral Vitamin K 5 mg daily on hospital day 2, Ursodiol on hospital day 3, both of which were continued until after three - week follow-up visit. He also received intravenous fluids with a 5% dextrose content, initiated one week after admission and discontinued one week prior to discharge. I have revised the manuscript to include this.

E. Reviewer No. 00054969:

- **I note that the authors did not test for hepatitis E virus serology? (while tests were carried out for CMV, EBV and adenovirus). Is HEV an uncommon cause of acute liver injury in the USA?**
    - Serologies for Hepatitis E were not performed given that the prevalence of Hepatitis E is not significant in the U.S. and given that the patient denied

recent travel outside of the U.S. I have revised the manuscript to include this.

- **Is the warning label on green tea extract suggested by US pharmacopeia mandatory or is it just a suggestion? A review article by Bunchorntavakul and K. R. Reddy on herbal and dietary supplement hepatotoxicity in alimentary pharmacology and therapeutics (Aliment Pharmacol Ther 2013; 37: 3–17) suggested otherwise.**
    - The warning by the U.S. pharmacopeia was a suggestion. I have revised the manuscript to include the phrase “not mandated” following the original statement of “suggested” to clarify.

F. Reviewer No. 00503401:

- **The attribution of an acute liver failure to green tea should be justified. Namely, prior to administration to the hospital the patient received four dietary supplements. Consequently, the possibility that the liver damage was caused by another substance cannot be excluded.**
    - A literature search was conducted of all supplements consumed and included research of the individual ingredients within each of the supplements. Although likely to be multi-factorial in nature, current data was most convincing for green tea extract hepatotoxicity. I have revised the manuscript to include statements to this effect and have included references, where data exists (since as indicated in our discussion there is quite a lack of research of herbal supplements in the U.S.), to support these statements.
- **Consider a table depicting in details the patients laboratory parameters (on admission, during hospital stay, on discharge, post-hospitalization follow up).**
    - I have revised the manuscript to include a table of laboratory studies at admission, hospital day number 15, at discharge, and at follow-up. Peak/ nadir lab values suggesting impending liver failure are still stated within the text.
- **Does the patient history remarkable only for obesity? Provide brief information about patients’ occupation, family history and alcohol consumption.**
    - The patient’s history was only remarkable for obesity. He is a 16 yr old high-school student with no history of alcohol consumption, recent travel, or sick contacts. I have revised the manuscript to include this.
- **Was markers of hepatitis E performed, if not, provide a comment**

- Serologies for Hepatitis E were not performed given that the prevalence of Hepatitis E is not significant in the U.S. and given that the patient denied recent travel outside of the U.S. I have revised the manuscript to include this.

- **The total bilirubin level is 14.8 mg/dL. Was the jaundice evident only on face and sclera?**
  - Jaundice was most prominent in the face and sclera, but yes was also present on chest and upper extremities. I have revised the manuscript to include this.
- **Describe liver physical examination**
  - The liver on physical exam was hard to appreciate given that the patient was still overweight at the time of presentation. I have revised the manuscript to include this.
- **Provide radiology data (US/CT)**
  - I have revised the manuscript to include radiological exam of the liver done on admission (ultrasound done, no CT).

3. References and typesetting were corrected.

We appreciate the reviewers' comments and thank you again for your consideration for publication of our manuscript in the *World Journal of Gastroenterology*.

Sincerely,

Shreena S. Patel, MD
Baylor College of Medicine
Department of Pediatrics
6621 Fannin St. Suite A170
Houston, TX 77030, United States
sspatel3@texaschildrens.org
Telephone: 832-822-1076