ANNALS of Hepatology

LETTERS TO EDITOR

April-June, Vol. 10 No.2, 2011: 239-240

Elevated acetaminophen level: Could it be a red herring?

Cheryl Dale,* Kathy L. Denesyk,** Natasha Chandok*

* Multi-organ Transplant Program, Division of Gastroenterology, London Health Sciences Center, University of Western Ontario, Canada.
** Pharmacy Department. London Health Sciences Center, Ontario, Canada.

Dear Editor:

A 34 year old woman, previously healthy and on no medications or supplements, presented with a 5 week history of fatigue and jaundice. She denied alcohol or illicit drug use. She had no encephalopathy or ascites, and transaminases were 8 times normal, gamma-glutamyl transpeptidase 9 times normal, alkaline phosphatase 3 times normal, INR 1.7 (normal 0.9-1.1), MCV 97 fL (normal 80-98 fL) and bilirubin and conjugated bilirubin both above upper limit of detection (570 and 180 umol/L, respectively; normal 3.4-17.1 and < 5.1 umol/L, respectively). Viral and autoimmune serologies, liver imaging, pregnancy screen, slit lamp exam, and urine copper studies were negative. Liver biopsy revealed severe active steatohepatitis with no fibrosis. Blood acetaminophen level was 5 times the therapeutic limit by colorimetric assay. She received N-acetyl cysteine (NAC) while awaiting a confirmatory assay for acetaminophen with gas chromatography/mass spectrometry (GC-MS) that was negative. She later admitted to consuming 50 units of alcohol daily in the week prior to the onset of her illness, and she gradually improved with abstinence from alcohol.

Patients with a history of drug and alcohol misuse are not always forthcoming in providing an accurate account of what they ingested. Furthermore, patients with severe liver injury may withhold aspects of their psychological or addiction history due to embarrassment or fear of denial of liver transplantation should it be required. Health care practitioners must strive to establish a trusting rapport with a patient, and seek corroborative histories.

Given this patient's clinical presentation, a toxicology screen was pertinent. The diagnosis of acetaminophen hepatotoxicity was appropriately questioned in this case given the subacute rather than acute clinical presentation, and transaminases less than 20 or more times the upper limit of normal, which is more typical with acetaminophen hepatotoxicity when associated with the degree of synthetic dysfunction experienced by this patient. NAC should not be delayed or withheld in any patient with suspected acute acetaminophen induced hepatotoxicity, given prospective data showing its efficacy in reducing hepatotoxicity and mortality when administered within 8 and up to 24 hours of ingestion.[1]

Many laboratories utilize colorimetric assays as the initial test to determine acetaminophen concentrations because it is generally reliable, rapid and inexpensive. This methodology relies on detection of indophenol, which is an end product of the hydrolysis reaction of acetaminophen.[2] The change in absorbance determined by colorimetry is directly proportional to the quantitative acetaminophen level in the plasma.[2] However, clinicians should be aware of the limitations of colorimetric assays for acetaminophen, namely that profound hyperbilirubinemia (total bilirubin > 170-400 umol/L), can yield a false positive acetaminophen level.[2-4]

When the diagnosis of acetaminophen induced hepatotoxicity is questionable, confirmatory testing using GC-MS analysis should be performed. GC-MS involves extraction of acetaminophen from a urine sample following acetylation, dilution with water and saline, and an organic phase with dichloromethane/acetone followed by measurement subsequent to aspiration and evaporation.[5] No false positive acetaminophen levels have been reported in the literature with GC-MS.

Acetaminophen is the most common cause of acute liver failure in North America.[3] The im-

Correspondence and reprint request: Natasha Chandok, MD, MPH, FRCPC
Division of Gastroenterology. University of Western Ontario
339 Windermere Road. London, Ontario. N6A 5A5 Canada
Fax: 519-663-3858
E-mail: Natasha.Chandok@lhsc.on.ca

Manuscript received: January 05, 2011.
Manuscript accepted: January 27, 2011.

plications of misdiagnosing the etiology of acute liver failure can have dire consequences, including missed opportunities to provide life saving treatment, genetic counseling or prognostic information for patients and their families.

Clinicians should be aware of the limitations of colorimetric assays for acetaminophen in the setting of hyperbilirubinemia.

ABBREVIATIONS

- **ALF:** Acute liver failure.
- **ALT:** Alanine aminotransferase.
- **AST:** Aspartate aminotransferase.
- **GC-MS:** Gas chromatography-mass spectrometry.
- **NAC:** N-Acetyl cysteine.

CONFLICT OF INTEREST OR FINANCIAL DISCLOSURES

None for all authors.

REFERENCES

1. Smilkstein MJ, Knapp GL, Kulig KW, Rumack BH. Efficacy of oral N-acetylcysteine in the treatment of acetaminophen overdose. Analysis of the national multicenter study (1976 to 1985). *N Engl J Med* 1988; 319(24): 1557-62.
2. Diagnostics R. Acetaminophen cobas. Indianapolis. In: Roche Diagnostics; 2009, p. 1-3.
3. Polson J, Wians FHJr, Orsulak P, Fuller D, Murray NG, Koff JM, et al. False positive acetaminophen concentrations in patients with liver injury. *Clin Chim Acta* 2008; 391(1-2): 24-30.
4. Beuhler MC, Curry SC. False positive acetaminophen levels associated with hyperbilirubinemia. *Clin Toxicol (Phila)* 2005; 43(3): 167-70.
5. Brooks KE, Smith NB. Versatile, efficient system for extracting drugs from urine for gas chromatographic/mass spectrometric analysis. *Clin Chem* 1989; 35(10): 2100-3.