

CAM/Drug-Induced Hepatotoxicity: Implications in Viral Hepatitis

Mohammad K. Parvez, Mohammed S. Al-Dosari

Mohammad K. Parvez, Mohammed S. Al-Dosari, Department of Pharmacognosy, King Saud University College of Pharmacy, Riyadh 11451, Saudi Arabia

Correspondence to: Mohammad K. Parvez, PhD, Assistant Professor, Department of Pharmacognosy, King Saud University College of Pharmacy, PO Box 2457, Riyadh 11451, Saudi Arabia.

Email: khalid_parvez@yahoo.com

Telephone: +966-1-4675132 Fax: +966-1-4677254

Received: July 10, 2015 Revised: July 23, 2015

Accepted: July 28, 2015

Published online: January 17, 2016

ABSTRACT

In recent times, complementary and alternative medicine (CAM) has gained much popularity in the treatment of various chronic diseases. However, CAM/drug-related hepatotoxicity is a serious public health problem where over- or misdiagnosis is a common phenomenon. For example, the initially assumed drug-induced liver injury was actually due to hepatitis E. In clinical practices, casualty assessment of suspected hepatotoxicity is hampered by the lack of a standardized approach that requires simplicity of the methodology. This could be best achieved by the combination of clinical judgment and a liver-specific causality assessment algorithm issued by the Council for International Organizations of Medical Sciences (CIOMS). Therefore, patients with chronic hepatitis should be counseled and screened by physicians on potential risks associated with CAMs and dietary supplementations.

© 2016 ACT. All rights reserved.

Key words: Complementary and alternative medicine; Hepatotoxicity; Viral hepatitis; Acute liver failure; CAM-drug interaction

Parvez MK, Al-Dosari MS. CAM/Drug-Induced Hepatotoxicity: Implications in Viral Hepatitis. *Journal of Gastroenterology and Hepatology Research* 2016; 5(1): 1921-1923 Available from: URL: <http://www.ghrnet.org/index.php/joghr/article/view/1555>

INTRODUCTION

Complementary and alternative medicine (CAM) has gained much popularity and is preferentially used for various chronic diseases, worldwide^[1,2]. Compared to a single chemically-characterized drug, CAM is a mixture of phytochemical constituents present in the herbal extract. Although CAM is generally thought to be safer than conventional drugs, there are many reports about hepatotoxicity and other adverse effects of some common herbal products or dietary supplements^[1,3]. CAM/drug-related morbidity is therefore, a serious public health problem with broad implications for clinicians, the pharma industries and health regulatory agencies. In CAM/drug-induced liver injury, over- or misdiagnosis is a common phenomenon^[4-7]. Of ample such reports, the initially assumed drug-induced liver injury was actually due to hepatitis E virus (HEV) infection^[5,6]. Similarly, in a recent assessment of initially suspected CAM-induced liver injury, correct diagnoses were missed in about 50% cases^[7]. Recently, the importance of CAMs as a cause of liver injury has been reported in a retrospective study wherein about 10% of cases were attributed to dietary supplements and 7% to Chinese herbal drugs^[8]. Therefore, CAM-induced liver pathogenesis should be considered as a neglected disease that requires special attention. Presently, potential genetic risk factors and biomarkers, including micro-RNAs are being investigated to explain molecular basis of CAM/drug-related liver diseases^[9-11]. Though these data are valuable and provide promising insights, they contribute little to correct and timely diagnosis. Owing to unavailability of the best approach in clinical practices, the physician needs a pragmatic guideline

to quickly evaluate suspicious cases of liver injury and reach a conclusive diagnosis.

HEPATOTOXICITY OR LIVER INJURY

The Council for International Organizations of Medical Sciences (CIOMS) defines liver injury as increase in serum aminotransferases (ALT/AST) and/or alkaline phosphatase (ALP) levels of at least 2-fold of the upper limit of normal (2N)^[12]. Though serum γ -glutamyltranspeptidase (γ GT) alone is not an appropriate parameter for assessing liver cell injury^[13,14], it is recommended to rule out isolated increases of ALP due to bone rather than hepatobiliary disease. The lower threshold of ALT above 2N may include nonspecific liver enzyme elevations and requires more stringent exclusion of causes unrelated to CAMs and drugs^[14]. An ALT cut-off of 5N may not be applicable to some types of chronic liver injuries, such as methotrexate liver fibrosis or nodular regenerative hyperplasia. Misdiagnosis and/or misinterpretation is however, possible in some forms of acute liver injury by valproate- or fialuridine-induced mitochondrial toxicity^[14].

ACUTE LIVER FAILURE

Acute liver failure, also known as fulminant hepatic failure is described as a syndrome characterized by the rapid development of liver damage (80-90% of hepatocytes), decreased hepatic metabolizing of enzymes and drugs. Though it is less common than chronic liver failure, can further lead to serious complications such as encephalopathy and coagulopathy. While hepatitis viruses are among the most common causes of acute liver failure in developing countries, CAM/drug intoxication by kava, ephedra, skullcap, pennyroyal and acetaminophen etc. predominates in the USA and Europe^[15-17].

CAM-DRUG INTERACTIONS IN VIRAL HEPATITIS

In CAM-induced hepatotoxicity, a major concern is the knowledge and awareness while considering using CAM that whether or not drug-CAM interactions may exist and could impact the therapy. Garlic extracts, grapefruit juice, and gember have been already reported to interact with drug-metabolizer gene cytochrome P₄₅₀ 3A4 (CYP3A4)^[18]. St. John's wort, a common CAM used for the treatment of depression, is a known inducer of CYP3A4^[19]. In recent years, a substantial increase of reports on efficacies of natural- or phytoproducts against hepatitis B and C viruses (HBV and HCV) has been published^[20]. The issue of CAM-drug interaction becomes even more complicated with the addition of new herbal medications for the treatment of chronic hepatitis C. Notably, CYP3A4 is also the primary metabolizer of many antiviral drugs, including the inhibitors of HCV protease (Telaprevir, Boceprevir and Simeprevir) and reverse-transcriptase (Sofosbuvir). Since, St. John's wort is also a potent inducer of intestinal P-glycoprotein, it may lead to altered absorption and therefore, reduced therapeutic effect of Sofosbuvir^[21].

In addition to drugs, several herbal flavonoids such as apigenin, quercetin, kaempferol and green tea catechins, interact with drug uptake transport proteins of the organic anion-transporting polypeptides (OATP) family^[22]. Silymarin, a purified extract from milk thistle, is a popular herbal supplement that is used by approximately one-third of patients with chronic liver disease including hepatitis C. Very recently, interaction of silymarin, silybin A,

silybin B and silychristin with OATAP has been described^[22]. Also, concomitant use of silymarin is contraindicated with Simeprevir because of possible hepatotoxicity^[23]. Glycyrrhizin, the main active component of licorice, is another widely used therapeutic against hepatitis C. Due to its widespread, multifaceted use, potential drug interactions of glycyrrhizin have recently gained attention showing its effects on drug-metabolizing enzymes (CYP3A and PXR) and efflux transporters^[24].

CONCLUSION

In clinical practices, causality assessment of suspected hepatotoxicity is hampered by the lack of a standardized approach that requires simplicity of the methodology. This could be best achieved by the combination of clinical judgment and a liver-specific causality assessment algorithm issued by CIOMS. Moreover, patients with chronic hepatitis should be counseled and screened by physicians on potential risks associated with CAMs and dietary supplementation

CONFLICT OF INTERESTS

The authors declare that they do not have conflict of interests.

REFERENCES

- Eisenberg DM, Davis RB, Ettner SL, Appel S, Wilkey S, Van Rompay M, Kessler RC. Trends in alternative medicine use in the United States, 1990-1997: results of a follow-up national survey. *JAMA*. 1998; **280**: 1569-1575.
- Vickers A. Recent advances: complementary medicine. *BMJ*. 2000; **321**: 683-686.
- Gupta NK, Lewis JH. Review article: The use of potentially hepatotoxic drugs in patients with liver disease. *Aliment Pharmacol Ther*. 2008; **28**: 1021-1041.
- Aithal GP, Rawlins MD, Day CP. Accuracy of hepatic adverse drug reaction reporting in one English health region. *BMJ*. 1999; **319**:1541.
- Dalton HR, Fellows HJ, Stableforth W, Joseph M, Thurairajah PH, Warshow U, Hazeldine S, Remnarace R, Ijaz S, Hussaini SH, Bendall RP. The role of hepatitis E virus testing in drug-induced liver injury. *Aliment Pharmacol Ther*. 2007; **26**: 1429-1435.
- Davern TJ, Chalasani N, Fontana RJ, Hayashi PH, Protiva P, Kleiner DE, Engle RE, Nguyen H, Emerson SU, Purcell RH, Tillmann HL, Gu J, Serrano J, Hoofnagle JH; Drug-Induced Liver Injury Network (DILIN). Acute hepatitis E infection accounts for some cases of suspected drug-induced liver injury. *Gastroenterology*. 2011; **141**:1665-1672. e1-9.
- Teschke R, Schulze J, Schwarzenboeck A, Eickhoff A, Frenzel C. Herbal hepatotoxicity: suspected cases assessed for alternative causes. *Eur J Gastroenterol Hepatol*. 2013; **25**:1093-1098.
- Takikawa H, Murata Y, Horiike N, Fukui H, Onji M. Drug-induced liver injury in Japan: An analysis of 1676 cases between 1997 and 2006. *Hepatol Res*. 2009; **39**: 427-431.
- Chalasani N, Björnsson E. Risk factors for idiosyncratic drug-induced liver injury. *Gastroenterology*. 2010; **138**:2246-2259.
- Larrey D, Faure S. Herbal medicine hepatotoxicity: a new step with development of specific biomarkers. *J Hepatol*. 2011; **54**: 599-601.
- Grant LM, Rockey DC. Drug-induced liver injury. *Curr Opin Gastroenterol*. 2012; **28**: 198-202.
- Teschke R, Wolff A, Frenzel C, Schwarzenboeck A, Schulze J, Eickhoff A. Drug and herb induced liver injury: Council for International Organizations of Medical Sciences scale for causality assessment. *World J Hepatol*. 2014; **6**: 17-32.
- Aithal GP, Watkins PB, Andrade RJ, Larrey D, Molokhia M, Taki-

- kawa H, Hunt CM, Wilke RA, Avigan M, Kaplowitz N, Bjornsson E, Daly AK. Case definition and phenotype standardization in drug-induced liver injury. *Clin Pharmacol Ther.* 2011; **89**: 806-815.
- 14 Teschke R, Schmidt-Taenzer W, Wolff A. Spontaneous reports of assumed herbal hepatotoxicity by black cohosh: is the liver-unspecific Naranjo scale precise enough to ascertain causality? *Pharmacoepidemiol Drug Saf.* 2011; **20**: 567-582.
- 15 Larson AM. Diagnosis and management of acute liver failure. *Curr Opin Gastroenterol.* 2010; **26**: 214-21.
- 16 Larson AM, Polson J, Fontana RJ, Davern TJ, Lalani E, Hynan LS, Reisch JS, Schiødt FV, Ostapowicz G, Shakil AO, Lee WM; Acute Liver Failure Study Group. Acetaminophen-induced acute liver failure: Results of a United States multicenter, prospective study. *Hepatology* 2005; **42**(6): 1364-72.
- 17 Krishna YR, Mittal V, Grewal P, Fiel MI, Schiano T. Acute liver failure caused by 'fat burners' and dietary supplements: A case report and literature and literature review. *Can J Gastroenterol.* 2011; **25**(3): 157-60.
- 18 Bunchorntavakul C, Reddy KR. Review article: herbal and dietary supplement hepatotoxicity. *Aliment Pharmacol Ther.* 2013; **37**: 3-17.
- 19 Wang Z, Gorski JC, Hamman MA, Huang SM, Lesko LJ. The effects of St John's wort (*Hypericum perforatum*) on human cytochrome P450 activity. *Clin Pharmacol Ther.* 2001; **70**: 317-326.
- 20 Liu J, Manheimer E, Tsutani K, Gluud C. Medicinal herbs for hepatitis C virus infection: a Cochrane hepatobiliary systematic review of randomized trials. Toxicity of complementary therapies: An eastern perspective. *J Clin Pharmacol.* 2000; **40**: 451-456.
- 21 Approval of Sovaldi (sofosbuvir) tablets for the treatment of chronic hepatitis C. Available from: <http://www.fda.gov/forconsumers/byaudience/forpatientadvocates/ucm377920.htm>.
- 22 Köck K, Xie Y, Hawke RL, Oberlies NH, Brouwer KL. Interaction of silymarin flavonolignans with organic anion-transporting polypeptides. *Drug Metab Dispos.* 2013; **41**: 958-65.
- 23 Olysio (simeprevir) for the treatment of chronic hepatitis C in combination antiviral treatment. Available from: <http://www.fda.gov/ForConsumers/ByAudience/ForPatientAdvocates/ucm377234.htm>
- 24 Feng X, Ding L, Qiu F. Potential drug interactions associated with glycyrrhizin and glycyrrhetic acid. *Drug Metab Rev.* 2015 May; **47**(2): 229-38.

Peer reviewers: Limin Chen, PhD, Professor, Institute of Blood Transfusion (IBT), Chinese Academy of Medical Sciences (CAMS), Peking Union Medical College (PUMC), Chengdu, Sichuan, China; Aydin Seref Koksak, Associate Professor, Türkiye Yüksek İhtisas Education and Research Hospital, Department of Gastroenterology, Ankara, Ankara, Turkey.