Indian Journal of Gastroenterology (January–February 2018) 37(1):5–7
https://doi.org/10.1007/s12664-018-0820-6

EDITORIAL

Ayurvedic and herbal medicine-induced liver injury: It is time to wake up and take notice

Harshad Devarbhavi[1]

Received: 29 December 2017 / Accepted: 4 January 2018 / Published online: 8 February 2018

Sir William Osler, the renowned physician and one of the founding professors of Johns Hopkins Hospital once remarked, "the desire to take medicine is perhaps the greatest feature which distinguishes man from animals." A number of prescription drugs used by mankind, including but not limited to antibiotics and antiviral agents, anesthetics, antihypertensives, and analgesics, have undoubtedly enhanced the quality of life and helped cure many chronic diseases.

Anecdotal reports of the side effects and ineffectiveness of modern or allopathic drugs have led to the false and fallacious belief in the safety and puissance of complementary and alternative medicine (CAM) worldwide. The notion that these compounds are "natural" and "safe" and hence bereft of side effects has contributed to their popularity and widespread use. In the United States of America (USA), the annual expenditure on CAM in 2007 was about a third of the total spent on prescription drugs, which was estimated to be 33.9 billion US dollars [1]. Increased use of CAM has also led to increased concerns about their safety and potential for hepatotoxicity. Although prescription drugs are an important cause of liver injury, the contribution of herbal and botanical medication-induced liver injury has increased over the years and has varied considerably across the world ranging anywhere from 17% in Japan [2], 20% in the USA [3], and 31% in China [4] to 70% in Korea [5]. Furthermore, the incidence of CAM-induced severe liver injury in the USA has almost doubled from 12.4% in the last decade to 21% now [6]. This has resulted in a higher rate of liver transplantation, and a lower transplant-free survival, highlighting the increased morbidity and mortality from these agents [6]. Similar studies are unavailable in India, although final results of the study by the Indian Network of Drug-Induced Liver Injury are awaited.

✉ Harshad Devarbhavi
harshad.devarbhavi@gmail.com

[1] Department of Gastroenterology and Hepatology, St. John's Medical College Hospital, Sarjapur Road, Bengaluru 560 034, India

While CAM in the West is often used for weight loss, body building, or performance enhancement, traditional and alternative forms of medicines in India, China, Korea, and other Asia-Pacific regions are primarily used for treatment of myriad symptoms and syndromes, and at times solely for the purpose of "improving general health or well-being." Comparisons between western medicines and traditional medicines are scarce. One retrospective study from China identified 1985 drug-induced liver injury (DILI) cases (2.05%) among 96,857 patients hospitalized for liver dysfunction from 2009 to 2014 [7]. DILI cases were stratified and compared between traditional Chinese medicines (TCM) vs. Western medicines (WM). The investigators observed a significantly greater number of females ingesting TCM vs. WM (71% vs. 51%). Hepatocellular injury (88% vs. 62%) and severe disease leading to mortality (4.8% vs. 2.8%) were also higher in the TCM group [7]. The lower probability score on causality assessment due to multiple ingredients and/or polypharmacy attests to the challenge of ascribing causality to a specific agent [7].

The use of Ayurvedic herbal medicines (AHM) dates back to ancient times, as far back as 3000 years ago. They are widely advertised and promoted as natural products and hence considered safe. Aside from anecdotal case reports, large series or studies of hepatotoxicity from AHM are lacking in India. Reports of hepatotoxicity from the use of AHM procured from local stores or on the internet have been published or presented. Given that a vast majority of the population in India is exposed to AHM for centuries, the "reported" lack of adverse reports is both misleading and intriguing. Nevertheless, medical providers, particularly gastroenterologists and hepatologists, will attest to its occurrence as patients seek medical care only when they develop severe liver disease. A major reason for the unsubstantiated lack of hepatotoxicity is the uncertainty in ascribing causality, especially when using multi-ingredient and often unlabeled products and when all other causes of liver disease have not been meticulously ruled out (Fig. 1). The lack of investigational and

Fig. 1 Multi-ingredient Ayurvedic formulations from a patient who developed severe liver injury (twice) with re-challenge. The culprit ingredient is difficult to impute among them

financial resources, the inability to obtain comprehensive medical history due to patient ignorance or reluctance to divulge pertinent information, and the relative unfamiliarity of CAM products among mainstream health care providers often lead to a missed diagnosis.

In this context, the article by Philips et al. published in this issue of the *Journal* is of major significance [8]. It adds to the growing body of knowledge in the area of AHM-induced liver injury by reporting the clinical, laboratory, liver biopsy findings, toxicological profile, and outcome in 34 patients exposed to AHM. In their study which spans over less than a year, 94 patients with severe liver injury who presented to outpatient clinics or emergency rooms were observed to be exposed to AHM. After excluding patients with other contributing causes of liver dysfunction, 2.3% of the cases were ascribed to AHM. The investigators reviewed the clinicopathologic features of 27 patients and analyzed the levels of heavy metal and highly volatile organic compounds (hVOC) of 47 and 17 AHM formulations respectively from 33 patients. The primary reason for AHM use was for relief of "digestive issues." About two thirds of the patients had other co-morbidities. Other unique features in this patient population included the presence of liver fibrosis in 21 out of 27 patients, and the presence of autoantibodies in the remaining six patients (implying the possibility of a drug-induced autoimmune-like hepatitis which is a novel finding). Mortality was 22% (6/27 patients), and some patients with liver fibrosis and steatosis also had evidence of hepatic decompensation such as hepatic encephalopathy and ascites. This observation supports a diagnosis of acute-on-chronic liver failure (ACLF) in this subset of patients. This observation is very relevant in that it lends further support to the finding of the ACLF APASL research consortium (AARC) where CAM or AHM was the second most common cause of drug-induced ACLF [9].

Philips et al. additionally reported higher than permissible levels of arsenic and mercury in the AHM formulations which were significantly associated with mortality [8]. They also identified the presence of hVOC in 70% of samples and reported scientific links to liver injury. Higher levels of arsenic, mercury, and lead in Ayurvedic drugs were reported earlier by Saper et al. in a seminal paper [10].

Philips and colleagues should be commended for systematically compiling the data in their study as there is little information available regarding AHM producing DILI, although case reports of DILI from AHM were anecdotally reported or presented before. While high levels of arsenic and mercury have been found in AHM, they have been hitherto associated with extrahepatic toxicity and hence the active ingredients that caused hepatotoxicity are still at large unknown.

Unacceptably high levels of metals and hVOC suggest contamination or adulteration during the production or delivery process and needs to be investigated by regulatory bodies. More recently, Navarro and colleagues from the Drug-Induced Liver Injury Network (DILIN) reported that mislabeling of ingredients was rampant, occurring in more than 50% of the products tested particularly in weight loss and body building supplements [11]. A similar finding is reproduced in this study reported by Philips et al. in the *Journal*. Philips et al. study is a timely reminder of the hepatotoxic potential of at least some AHM.

What can we learn from the already published studies to help minimize the adverse effects of AHM?

(I) It is time to get rid of the wrongly held notion that alternative systems of medicines have no side effects. Acknowledgement of this fact is imperative and should not be held off any further for lack of publication of more studies. The Chinese were early to acknowledge and recognize the association of hepatotoxicity with traditional Chinese medicine (TCM) [7] and measures were implemented to identify the culprit ingredient and publish reports comparing hepatotoxicity between different systems of medicine. A similar line of action should be implemented in India. (II) More research and controlled studies are needed to better clarify the efficacy and safety of CAM for the countless diseases they are claimed to benefit. (III) Regulatory oversight should be instituted for all such products akin to what is employed for the modern/western/allopathic medicines. (IV) Health care providers should be mandated to report to regulatory agencies of instances of adverse effects from CAM so that remedial measures including restriction/termination of products can be undertaken. (V) There should be a greater collaboration between health care providers of different systems of medicine for a

better understanding of the medications used for various diseases, including their propensity to produce adverse effects. And finally, to paraphrase William Osler, "one of the first duties of the physician is to educate the masses not to take medicines" particularly for trivial ailments.

Compliance with ethical standards

Conflict of interest HD declares that he has no conflict of interest.

References

1. Nahin RL, Barnes PM, Stussman BJ, Bloom B. Costs of complementary and alternative medicine (CAM) and frequency of visits to CAM practitioners: United States, 2007. Natl Health Stat Report. 2009;30:1–14.
2. 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;39:427–31.
3. Navarro VJ, Barnhart H, Bonkovsky HL, et al. Liver injury from herbals and dietary supplements in the U.S. Drug-Induced Liver Injury Network. Hepatology. 2014;60:1399–408.
4. Zhao P, Wang C, Liu W, et al. Causes and outcomes of acute liver failure in China. PLoS One. 2013;8:e80991.
5. Suk KT, Kim DJ, Kim CH, et al. A prospective nationwide study of drug-induced liver injury in Korea. Am J Gastroenterol. 2012;107:1380–7.
6. Hillman L, Gottfried M, Whitsett M, et al. Clinical features and outcomes of complementary and alternative medicine induced acute liver failure and injury. Am J Gastroenterol. 2016;111:958–65.
7. Zhu Y, Niu M, Chen J, et al. Hepatobiliary and pancreatic: comparison between Chinese herbal medicine and Western medicine-induced liver injury of 1985 patients. J Gastroenterol Hepatol. 2016;31:1476–82.
8. Philips CA, Paramaguru R, Joy AK, Antony KL, Augustine P. Clinical outcomes, histopathologic patterns and chemical analysis of ayurveda and herbal medicine associated with severe liver injury—a single center experience from South India. Indian J Gastroenterol. 2018; 37: https://doi.org/10.1007/s12664-017-0815-8.
9. Devarbhavi H, Choudhury A, Reddy V, et al. Acute on chronic liver failure secondary to drugs: causes, outcome and predictors of mortality. J Hepatol. 2016;64:232A.
10. Saper RB, Phillips RS, Sehgal A, et al. Lead, mercury, and arsenic in US- and Indian-manufactured Ayurvedic medicines sold via the Internet. JAMA. 2008;300:915–23.
11. Navarro VJ, Khan IA, Avula B, Verma M. The frequency of herbal and dietary supplement mislabelling: experience of the Drug Induced Liver Injury Network. Hepatology. 2017;66:149A.