

Original Article

Review for Herbal Drug and Drug-Induced Liver Injury

Bong-Ky Park, Chang-Gue Son

Liver - Immunology Research Center of Oriental Medicine College, Daejeon University

Objectives: This study aimed to review the general features of drug induced liver injury (DILI) and the important factors in consideration of herbal drugs and DILI.

Methods: We reviewed general aspects of DILI such as classification, inducible factors, diagnosis methods, prevention, and the status of herbal drug-associated DILI via literature.

Results: Besides the drug itself, genetic and environmental factors affect hepatic toxicity. There is a lack of definitive diagnoses of DILI by drugs, including herbal remedies. The possibility of herbal drug-associated DILI is exaggerated, and majority of herbal drug-derived hepatic injury could be easily prevented if Oriental doctors pay attention to this issue.

Conclusion: This study can provide Oriental doctors an overview and be helpful in minimizing the episodes of hepatotoxicity in use of herbal drugs.

Key Words : Drug-induced liver injury, herbal drug, traditional Korean medicine

Introduction

The liver primarily metabolizes drugs, and they reveal therapeutic functions before being eliminated in the form of urine or bile juice¹⁾. Sometimes their metabolites can induce various types of liver injuries, including acute hepatic failure, which is life threatening. Drug-induced liver injury (DILI) is defined as that any drug destroys the hepatic cells or alters normal liver function.

The incidence of DILI has been increasing in Japan; 88 cases during 1944-1953, 231 cases during 1954-1963, and 2,534 cases during 1964-1973 decades respectively²⁾. DILI is the most frequent cause of acute hepatic failure in America³⁾. In Korea, one report presented that the second main reason for

acute hepatitis, by drugs or chemicals, was 20% of cases, compared with the first cause, hepatitis type B, which was 30%⁴⁾.

The expanding use of herbal drugs worldwide raised the consideration of risk of hepatic toxicity from herbal products. There are many reports which seem to exaggerate the reality of herbal drug-induced liver injury in Korea. Two Western doctor groups reported that from 27.9% to 44.7% of patients hospitalized with toxic liver disorder were related with herbal remedies^{5,6)}. On the contrary, there are clinical-based data strongly supporting the safety of herbal drugs, which presented no adverse effects and even benefit hospitalized patients prescribed them^{7,8)}. However, the important fact is that the worry about herbal drug-associated liver injury is increasing

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• Correspondence to : Chang-Gue Son

Liver and Immunology Research Center, Daejeon Oriental Hospital of Daejeon University,
22-5 Daehung-dong, Jung-gu, Daejeon, 301-724, Republic of Korea.

Tel : +82-42-257-6397, Fax : +82-42-257-6398, E-mail : ckson@dju.ac.kr

among general population⁹).

This study aimed to review the definition of drug-induced liver injury, the method of diagnosis and its limitation, data for herbal drug-associated hepatic toxicity, and the preventive strategy. Therefore, we wished to provide information helpful to minimize the risk herbal drug-related liver injury.

Methods

In order to analyze data on herbal drug-induced liver injury, all articles focused on both herbal drug and liver injury were collected via public medical databases including STAR-society (<http://society.kisti.re.kr>), Korean Traditional Knowledge Portal (<http://www.koreantk.w.k>), KISTI (<http://www.ndsl.kr>), Korean Oriental Medical Society (<http://intl.koms.or.kr>), Korean Society for Oriental Internal Medicine (<http://www.oim.or.kr>), Korean Association for the Study of the Liver (<http://www.kasl.org>), and Korea Society of Gastroenterology (<http://www.gastrokorea.org>). In addition, data for incidence of DILI among different countries was derived from PubMed (<http://www.ncbi.nlm.nih.gov/pubmed>).

Thirty-nine reports were finally selected and reviewed carefully to retrieve the information for inducible factors, classification, diagnosis methods and prevention of herbal drug-induced liver injury.

Results and Discussion

1. Definition and classification of drug-induced liver injury

Drug-induced liver injury (DILI) is any type of liver injury that occurs due to medications. CIOMS (Council for International Organization of Medical Sciences) consented the criteria for DILI in Paris in 1989, which was defined as the elevation of at least one marker among aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase

(ALP), total bilirubin, or direct bilirubin over two-fold the upper limitation of the normal range¹⁰. The terms “drug-induced hepatitis” or “drug-induced necrosis” are generally used in a case verified by histological examination. If the value is between one-fold to two-fold, it is called “abnormality of liver tests” instead of hepatic injury¹¹.

DILI is classified as acute or chronic liver injury, where 90% of DILI is acute¹². Acute DILI can be divided into one of three patterns according to ALT/ALP ratio, total bilirubin, and direct bilirubin¹³. Hepatocellular type is defined as ALT > three-fold or an ALT/ALP ratio ≥ 5 . Cholestatic type is defined as an increase in serum ALP > two-fold or by an ALT/ALP ≤ 2 . Mixed type is that the ALT/AP ratio is between 2 and 5. Chronic DILI includes parenchymal injury, cholestasis, vascular lesion, and generation of tumors^{11,13}. Additionally, there are predictable injuries by intrinsic hepatotoxins and non-predictable injuries by non-intrinsic hepatotoxins. These classifications are important to predict the clinical course and prognosis¹⁴.

2. Factors determining drug-induced liver injury

Generally, only a part of the population who was exposed to any drugs shows DILI. The reason is that occurrence of DILI is dependent on three factors. The first factor is characteristics of the drug and its own intrinsic toxicity. The second one is environmental factors such as age, sex, consumption of alcohol, starvation, smoking, and other underlying disorders. The third factor is individual genetic background¹³. In other words, susceptibility to drug-induced hepatotoxicity is influenced by genetic and environmental risk factors besides the drug itself. So, unpredictable, low-frequency, idiosyncratic reactions often occur on a background of a higher rates of mild asymptomatic liver injury¹⁴.

3. Incidence of drug-induced liver injury including herbal drugs

Identifying accurate incidence of DILI is difficult due to the complexity of diagnosis and high frequency of asymptomatic injury. One study reported the incidence of DILI as 1.27 people per hundred thousand in England¹⁵⁾, and 14 people per hundred thousand in France¹⁶⁾. In the United States, 2% of total hepatitis was known as DILI¹⁷⁾. Two studies showed that in Korea 20% and 14.8% among patients hospitalized with hepatitis or acute hepatic disorders were due to DILI^{4,18)}.

The incidence of DILI by herbal drug varies widely according to groups studied, such as no adverse effect vs. 57.9% of hospitalized patients with DILI⁴⁻⁷⁾. This difference might be resulted from bias of study design, and patient' memory-dependant or inappropriate diagnosis¹⁹⁾. There could be data exaggerating the possibilities of liver injury by herbal drug. These unreliable results might be distorting the public reputation of Oriental medicines, including herbal drugs. Recently, a clinical-based observation strongly supported safety of herbal drugs by chasing chemical biomarkers for hepatic function during administration of herbal drugs to 101 hospitalized patients²¹⁾.

4. Diagnostic methods for drug-induced liver injury and its limitation

The definitive diagnosis of DILI is very difficult using biochemical, radiologic, or histopathologic methods due to non-specific features of DILI compared to others¹⁸⁾. Re-challenge of drug is the best known method, but it raises ethical problems. So, the common method of diagnosis of DILI is consideration of circumstance of disorder history and drugs used. This is causality assessment method such as RUCAM scale (Roussel Uclaf Causality Assessment Method) and M & V scale (Maria & Victorino scale)^{20,22,23)}.

Currently, the most common tool is the RUCAM

scale. However, this scale is not a confident method because of its risk of inappropriate diagnosis. This scale gives 2 points if hepatic injury occurs just after administration of the drug, so 3 points corresponding to "possible DILI" can be too easily obtained²²⁾. The RUCAM and M & V scales can make an error especially for herbal drugs because doctors may decide the score depending on verbal report from patients in many cases. Moreover, some groups recently used a modified RUCAM scale which is more sensitive to herbal drug-associated liver injury^{19,24)}.

5. Prevention of herbal drug-induced liver injury

Based on reports by present day data, there are no herbal drugs containing intrinsic hepatotoxins, but some plants such *Dictamnus dasycarpus Turcz*, *Scutellaria baicalensis*, *Viscum album var coloratum*, *Artemisia capillaris Thunb*, *Ulmus macrocarpa Hance*, *Ulmus macrocarpa Hance*, *Psoralea corylifolia L*, and *Houttuynia cordata Thunb* are suspected¹¹⁾. *Artemisia capillaris Thunb* is a representative herbal drug having confirmative evidences of hepato-therapeutic effect from laboratory and clinic²⁶⁾. So these data are not confident to be believed, and they are supposed to be produced as careless data analysis. Moreover, one study by western doctors has listed *Sagunja-tang*, *Yookgunja-tang*, *Samchoolkyunbi-tang*, and *Bojungickgi-tang* as potential candidates for hepatotoxicity²⁷⁾. These formulae are most well known as nontoxic decoctions. There are two assumptions for those contradictions. One could be caused by unintentional distortion of fact due to inaccurate analysis by western doctor groups. Another cause is supposed to be certain factors beside intrinsic toxicity in the prescription.

It is worth noting that many populations may have abnormal level of liver function enzymes before taking herbal drugs²⁷⁾. In that case, just environment and/or genetic factor can induce hepatic injury

without any agent, including herbal drugs. So, to pay intensive attention regarding history of disease; other underlying disease, age, or drug-interaction with western medicine is very important. The half-life of medicine could be retained in patients with liver disease, chronic respiratory failure, lung cancer, or hypothyroidism¹⁾. Moreover, even though a drug is safe for the short term, taking the greatest possible care is necessary in case of retained use over three months^{27,29)}. So, it is strongly recommended to screen the liver function once per month in case of long-term use of herbal drugs. Patients usually notice their uncomfortable symptoms during medication, but sometimes they can be ignored in clinics. Paying attention to the patient's complaints is the most important factor in prevention and early detection of DILI.

Conclusion

Recently, the safety of herbal medicine has become a medical issue, and a negative view of herbal drug-associated safety is increasing. There is somewhat a possibility of exaggeration regarding herbal drug-associated DILI due to unscientific analysis and difficulty of definitive diagnosis of DILI. Nevertheless, minimizing any risk of adverse effects of herbal medicine in practice is strongly demanded, as far as possible. Also, well-organized clinical-based multiple researches for the safety of herbal drugs should be conducted in the Oriental medicine field. This study summarized the elementary knowledge about DILI and various factors determining hepatotoxicity by drugs, including herbal products. We hope that this report is helpful for more comprehensive understanding and prevention of DILI.

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