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Drug-induced liver injury: A 2-year retrospective study of 1169 hospitalized patients in a single medical center

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ABSTRACT

Background: Although herbal medicines (HMs) are widely used in Asian and Western countries, medicinal information concerning their hepatic toxicity or interaction with conventional medicines (CMs) is sparse.
Purpose: The aim of our study was to estimate the prevalence of drug-induced liver injury (DILI) among total inpatients prescribed HMs or CMs. Furthermore, we noted all medications suspected to be associated with hepatotoxicity in the liver injury group during the period of hospitalization.
Study design: We retrospectively observed medical records of 1169 inpatients in a single medical center from January 2012 to July 2014.
Methods: Based on a database of the 1169 inpatients at a single medical center, we researched the occurrence rate and type of liver injury according to the criteria of the Council for International Organization of Medical Science (CIOMS). We also utilized a simplified Roussel Uclaf Causality Assessment Method (RUCAM) score for probable causality assessment between drugs and liver injury.
Results: Among a total of 1169 inpatients, 13 cases whose baseline LFTs had been in the normal range at admission had abnormal liver parameters at the time of follow-up, and 11 of them (0.94%) were attributed to drugs: 0.43% (5 of 1169) to HMs, 0.43% (5 of 1169) to CMs, and 0.09% (1 of 1169) to combined drug classes. Two of them were found to have liver injury because of pneumonia and sepsis. As for liver injury type, 8 cases were hepatocellular, 2 were cholestatic, and 1 was of mixed pattern. The common causative HMs for hepatotoxicity were *Ephedrae* Herba and *Scutellariae* Radix, while CMs included antidepressants, antihistamines, and antibacterials.
Conclusions: We investigated approximate incidence rates and analyzed suspicious drugs associated with liver damage, which revealed a low frequency of liver injury induced by HMs. However, further study, based on a well-designed, long-term, multicenter prospective study, will be required to determine the safety of HMs.

Introduction

Drugs can have various adverse side effects related to the liver, ranging from mild liver enzyme abnormalities to severe liver injury (Dossing and Sonne 1993; Friis and Andreasen 1992). This incidence of drug-induced liver injury (DILI) accounts for 4–10% of adverse drug events (Friis and Andreasen 1992; Pillans 1996), and has become a challenging issue in the field of medicine. This is due to economic loss in consequence of cessation of drug treatment (Bakke et al. 1995) and potential development to chronic liver disease even after cessation of drug (Andrade et al. 2006). In addition, unclear diagnostic criteria and mechanisms underlying pathology add to the difficulty in resolving the complexities of DILI.

In particular, liver injury in terms of herbal medicines (HMs) has so far been encountered a number of medical disputes. Some studies have reported hepatotoxic effects of HMs suggesting that herbal supplements containing *Ephedrae* Herba had toxicity leading to fulminant hepatic failure (Estes et al. 2003), or have indicated that HMs have caused toxic hepatitis with a high incidence rate (35–68%) (Estes et al. 2003; Wai et al. 2007; Wang et al. 2009). On the other hand, other studies have found liver injury associated with HMs to have a

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotranferase; AST, aspartate aminotransferase; CIOMS, Council for International Organization of Medical Science; CMs, conventional medicines; DB, direct bilirubin; DILI, drug-induced liver injury; EMR, electronic medical records; GGT, gamma-glutamyl transpeptidase; HMs, herbal medicines; KHUKMH, Kyung Hee University Korean Medicine Hospital; LFT, liver function test; RUCAM, Roussel Uclaf Causality Assessment Method; TB, total bilirubin.

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rare occurrence, of less than 1% (Mantani et al. 2002; Melchart et al. 1999). These conflicting reports are indirectly representatives of the various perspectives on the safety of HMs.

Moreover, there are still some concerns that HMs may aggravate liver damage when combined with conventional drugs, although HMs have been recognized as effective and popular remedies in recent times. With respect to concurrent use of HMs and conventional medicines (CMs), the reported percentage of liver injury varies from 0.56% to 14.4% (Kim et al. 2011; Taylor et al. 2006). These results led us to investigate mutual interactions of medications or undesirable side effects, and review a large number of clinical studies and review articles.

Consequently, in this study, we report a retrospective analysis on lists of medicines toxic to the liver among HMs or CMs taken during hospitalization and the approximate prevalence of DILI.

Methods

Subjects

A total of 1169 (511 males and 658 females) patients who were admitted to several departments of Kyung Hee University Korean Medicine Hospital (KHUKMH) between January 1, 2012 and July 31, 2014 were included in our study. They were prescribed HMs or CMs alone or received HMs and CMs concurrently during hospitalization. The inclusion criteria were as follows: (1) hospitalization for at least 7 days, (2) normal range of liver function tests at baseline, (3) conduction of follow-up laboratory data adequate for assessing hepatic injury, (4) prescription of HMs or CMs. Excluded from this study were patients who had evidence of liver injury according to the criteria of the Council for International Organization of Medical Science (CIOMS) based on initial liver function test (LFT) results, or liver-related underlying diseases, such as viral hepatitis, liver cirrhosis, hepatocellular carcinoma, and so on. There were no specific restrictions on age, gender, medical department, or alcohol or smoking history.

Data collection

After approval for this study from the Kyung Hee institutional review board (KOMCIRB-150608-HR-019), we retrospectively reviewed all serum laboratory data that were collected from KHUKMH inpatient records between January 2012 and July 2014. Our search through individual review of their electronic medical records (EMR) was conducted independently by two investigators to determine whether inpatients met the inclusion and exclusion criteria. LFTs, including total bilirubin (TB), direct bilirubin (DB), alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), and gamma-glutamyl transpeptidase (GGT) at both admission and follow-up were reviewed. Only laboratory results which were executed in KHUKMH were included. The total sorts of HMs and CMs were also collected for this study.

Case evaluation and type of liver injury

According to the CIOMS criteria regarding DILI (Benichou 1990), liver injury is indicated by (a) ALT > 2 X ULN (upper limit of normal range), (b) DB > 2 X ULN, or (c) concurrent increases in AST, ALP, and TB, with one value > 2 X ULN. Liver injuries were categorized as hepatocellular, cholestatic, or mixed type according to the *R* ratio (Table 1) (Benichou 1990), and causality assessment was evaluated using *R*-score by the simplified Roussel Uclaf Causality Assessment Method (RUCAM) (WR and R 2008).

Statistical analysis

Data were expressed as mean ± SD or range for continuous variables, while categorical variables were expressed as percentages.

Table 1
Liver injury type.

R: ratio of (ALT/ ULN of ALT) to (ALP/ULN of ALP)	
Hepatocellular	$R \geq 5$, or (ALT > 2 X ULN and ALP in normal range)
Cholestatic	$R \leq 2$, or (ALP > 2 X ULN and ALT in normal range)
Mixed	$2 \leq R < 5$ and (ALT > 2 X ULN and ALP > ULN)

A paired *t*-test was used for comparisons between admission and follow-up time. All statistical data were analyzed using PASW software 18.0 version (Chicago, IL, USA) and statistical significance was set at $p < 0.05$.

Results

Characteristics of study population, non-injury group, and liver injury group

In this study, a total of 1169 patients (511 males, 658 females) admitted between January 2012 and July 2014 were identified through EMR review. Their average age and mean hospitalization length were 59.62 years and 41.82 days respectively. Hypertension and diabetes mellitus were the two main single diseases, and the leading primary diagnosis was cerebrovascular accident (52.18%), followed by neurological disorder (17.37%), and musculoskeletal disease (10.27%). Among 1169 enrolled patients, 11 had elevated liver enzyme results related to DILI, whose group consisted of 5 males (45.45%) and 6 females (54.55%), but this female predominance is not higher than the result of Idilman et al. (2010) (55.8%) . Meanwhile, the DILI incidence rates of gender were estimated as 0.98% (5 of 511) in males and 0.91% (6 of 658), which result suggested that gender difference might not have a decisive influence on the DILI incidence. With regard to primary diagnosis, cerebrovascular disease was strongly implicated in DILI (81.82%), and hospitalization time in the DILI group (38.27 days) tended to be shorter than in the study population (41.82 days) or non-injury group (41.71 days) (Table 2).

Comparison of LFTs between admission and follow-up

To investigate to an approximate degree whether taking HMs or CMs during hospitalization affects liver function parameters, we analyzed changes in LFTs at admission and follow-up. Our study found significant decreases in mean values of TB, ALP, and GGT at follow-up compared to the initial tests. ALT levels were significantly increased from 18.9 (U/L) up to 21.3 (U/L), and AST levels also rose slightly from 23.7 (U/L) to 23.9 (U/L). These liver enzyme elevations during hospitalization do not seem to indicate toxicity of HMs, because both of the elevated values, 21.3 (U/L) and 23.9 (U/L), were within normal limits (Table 3). However, we need to carefully review the individual drug histories of the liver injury group, regardless of these normal values in paired *t*-test, because these results were confined to rough comparison.

Analysis of causative agents in the liver injury group

The analysis of the hepatic injury group in our study suggested that the major cause of liver injury was the use of drugs (84.6%, 11 of 13), 45.5% of which were HMs (5 of 11), 45.5% of which were CMs (5 of 11), and 9.1% of which consisted of a combination of the two drug classes (1 of 11); other factors related to hepatotoxicity were sepsis and pneumonia, each accounting for 7.7% (1 of 13). Of these 11 DILI patients, the most prevalent pattern observed in the liver injury group was hepatocellular type (8 of 11), followed by cholestatic (2 of 11) and mixed (1 of 11) type.

In a previous study, representative HMs which were suspected to induce liver injury included *Scutellariae* Radix (Itoh et al. 1995),