Journal of Ethnopharmacology 143 (2012) 884–888

Contents lists available at SciVerse ScienceDirect

Journal of Ethnopharmacology

journal homepage: www.elsevier.com/locate/jep

A prospective study on the safety of herbal medicines, used alone or with conventional medicines

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ARTICLE INFO

Article history:
Received 26 March 2012
Received in revised form
14 July 2012
Accepted 15 August 2012
Available online 25 August 2012

Keywords:
Safety
Drug-induced liver injury
Adverse drug reaction
Herbal medicine

ABSTRACT

Ethnopharmacological relevance: Along with increase of herbal medicine use worldwide, the safety of traditional herbal medicines frequently becomes a medical issue.
Aim of the study: This study aimed to investigate the incidence of herbal medicine-induced adverse effects on liver functions.
Subjects and methods: A prospective study was performed with 313 inpatients (87 male and 226 female) receiving herbal prescriptions during hospitalization. The patients were classified into two groups based on their treatments: one group received herbal medicines only (57 patients), and another received herbal and conventional medicines concurrently (256 patients). All patients were given liver and renal function tests at the start of hospitalization (baseline) and at approximately 2-week intervals thereafter, until discharge.
Results: Six of the 313 patients showed abnormal liver function without related clinical symptoms (1.9%, 95% CI 0.38–3.41); none of the patients in the herbal group had abnormal result in liver function tests (0% of 57 patients) while all six had received a combination of herbal and conventional medicines (2.3% of 256 patients, 95% CI 0.46–4.14).
Conclusion: Our findings indicate that herbal drugs used alone are relatively safe, but the risk for adverse reactions may increase when herbal and conventional drugs are taken concurrently.

1. Introduction

Herbal medicines have been both prescribed for and taken by patients in Asia thousands of years and are generally considered to be safe on the basis of anecdotal evidence (Ye and He, 2010). These days the market for the herbal medicines is growing rapidly worldwide since the virtues of herbal medicines are being recognized (Bent and Ko, 2004). However, many doctors and scientists are expressing doubts about the safeness of herbal medicines owing to lack of scientific data and compositional analyses that support the its effect as well as stability (Bent, 2008).

Drug-induced liver injury (DILI) is the most critical adverse drug reactions (ADRs) because they affect the primary organs that detoxify and excrete drugs (Harvey et al., 2006). Few studies have been published concerning herbal medicine-induced liver and renal injury. One retrospective study reported the incidence of herbal medicine-induced liver injury as approximately 0.1% in Japan (Mantani et al., 2002). However, the number of studies regarding herbal medicine toxicity is limited, and their quality is poor because of their retrospective nature which makes it difficult to determine an accurate incidence rate of DILI.

On the other hand, many patients adopt both herbal and conventional medicines for single and multiple health problems during the same period. This situation creates an urgent requirement for investigations into the interactions between herbal and conventional medicines (De Smet, 2007; Izzo and Ernst, 2009). One study estimated the incidence of liver enzyme elevations as approximately 0.9% among 1507 subjects who had taken Chinese medicines with conventional drugs in Germany (Melchart et al., 1999) while another study presented the prevalence 0.56% of DILI during concurrent use of herbal and conventional medicines in Korea (Kim et al., 2011). However, these previous studies were conducted retrospectively, and it is well known that the ADR incidence rates observed in retrospective studies are lower than those found in prospective studies (Bagheri et al., 2000).

This study aimed to investigate the DILI incidence rate for traditional herbal medicines, taken alone or in combination with conventional medicines, among inpatients at two hospitals affiliated with Daejeon University using a prospective design.

2. Methods

2.1. Subjects and study design

A total of 313 patients (87 male and 226 female) who were hospitalized in two Oriental Hospitals of Daejeon University,

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http://dx.doi.org/10.1016/j.jep.2012.08.016

Daejeon, Korea from August 2008 to October 2010 were enrolled in this study. This study included the patients who received herbal medicine for at least 10 day during their hospitalization. The exclusion criteria were as follows: a life expectancy of less than 12 months (by judgment of the patient's doctor); current or previous liver diseases including carrier status of hepatitis virus, renal disease, or autoimmune disease; and abnormal baseline results on liver or renal function tests on hospitalization. All patients received herbal medicines, and in addition some patients received conventional medicines, according to disease and symptoms. Each herbal medicine was prepared as a traditional decoction of multiple herbal formulae.

All patients (313 patients) were divided into two groups; one group received herbal medicine only (herbal group, 57 patients) and the other received herbal and conventional medicine concurrently (combined group, 256 patients). The total incidence rate of DILI and the separate incidence of two groups were investigated. This study followed guidelines of the Declaration of Helsinki and Tokyo. Informed consent was obtained from each patient, and the Ethical Committee of Daejeon University Hospital approved the study protocol.

2.2. Case identification

All patients were given liver function tests on the day of admission (baseline) and were tested repeatedly at intervals of approximately 2 weeks, until discharge. The liver function tests (LFTs) included measurements of total bilirubin, direct bilirubin, aspartate transaminase (AST), alanine transaminase (ALT), alkaline phosphatase (ALP), and gamma-glutamyl transferase (GGT). Liver injury was judged according to the established CIOMS laboratory criteria (Benichou, 1990). Liver injury was determined when one of following criteria was satisfied: (1) direct bilirubin level of more than twice the upper limit of normal (ULN); (2) ALT level of more than twice the ULN; or (3) total bilirubin, AST, or ALP level of more than twice the ULN and another of these levels above the ULN. The reference ranges of those biochemical parameters were justified as follows; 0.3–1.2 mg/dL for total bilirubin, 0.1–0.3 mg/dL for direct bilirubin, 0–40oIU/L for AST, 0–40/IU/L for ALT, 30–120LIU/L for ALP, and 0–64 IU/L for GGT, respectively.

2.3. Type of DILI

Liver injuries were classified into three types according to the CIOMS laboratory criteria (Benichou, 1990). The hepatocellular type was indicated when the ALT level was more than twice the ULN or when the ratio of the ALT serum activity to the ALP serum activity (R) was ≥ 5. The cholestatic type was indicated when the ALP level was more than twice the ULN or when R was ≤ 2. The mixed type was indicated when $2 < R < 5$.

2.4. Causality assessment for individual drugs

The Roussel uclaf causality assessment method (RUCAM) was used to quantify the strength of the association between liver injury and each medication (Danan and Benichou., 1993). Medicines (both herbal and conventional) with a RUCAM score of ≥ 3 points were determined to be suspected injury-causing medicines.

2.5. Statistical analysis

First, the total incidence rate of DILI was determined, and then compared between two groups (herbal group *vs.* combined group) based on treatment: A frequency test was used to analyze the patients' characteristics. An independent t-test was used to quantify the statistical significance by gender, age, hospital day, and patient group. In addition, Pearson's correlation coefficient was performed with respect to age and duration of hospital stay. A P-value < 0.05 was considered to indicate statistical significance. All statistical analyses were performed with SPSS (SPSS® 18.0KO. for Windows; SPSS, Inc., Chicago, IL, USA).

3. Results

3.1. Subjects' characteristics

The patients' characteristics are summarized in Table 1. The median age of the 313 patients was 51 years (53 and 51 years for 87 males and 226 females, respectively). According to the International Classification of Diseases-10 (World Health Organization (WHO), 2007), the leading causes of admission were diseases of the circulatory system (27.8%), neoplasm (24.6%), and diseases of the musculoskeletal system (21.1%), followed by diseases of the nervous system (12.8%), symptoms (7.3%), and diseases of the digestive system (5.4%). The herbal group comprised 57 patients (18.2%) who were treated with herbal medicines only, and the combined group consisted of 256 patients (81.8%) who received both herbal and conventional medicines during their hospital stays.

The median age of the herbal group was younger than that of the combined group (44 *vs.*54 years). The median hospital stay was 26 day for total group while herbal group was shorter (24 day) than combined group (27 day). The herbal group mainly included patients with diseases of the musculoskeletal system, whereas the combined group included all patients with diseases

Table 1
Patient characteristics

Characteristics	Sub-class of patients	Total number (%)	Herbal group* number (%)	Combined group[a] number (%)
	Total subjects	313 (100)	57 (18.2)	256 (81.8)
Gender	Male	87 (27.8)	17 (29.8)	70 (27.3)
	Female	226 (72.2)	40 (70.2)	186 (72.7)
Age	Median (range)	51 (5–85)	44 (15–72)	54 (5–85)
Hospital stay	Median (days)	26	24	27
Cause of admission (according to ICD-10)	Circulatory system	87 (27.8)	0 (0)	87 (34.0)
	Neoplasm	77 (24.6)	16 (28.1)	61 (23.8)
	Musculoskeletal system	66 (21.1)	27 (47.4)	39 (15.2)
	Nervous system	40 (12.8)	1 (1.8)	39 (15.2)
	Digestive system	17 (5.4)	4 (7.0)	13 (5.1)
	Symptoms	23 (7.3)	9 (15.8)	14 (5.5)
	Others	3 (1.0)	0 (0.0)	3 (1.2)

* Herbal group was treated with herbal drug without conventional medicine.
[a] Combined group was treated with both herbal and conventional medicine.