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Herbal hepatotoxicity: Analysis of cases with initially reported positive re-exposure tests

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ABSTRACT

Background: Positive re-exposure tests are diagnostic hallmarks for hepatotoxicity.
Objective: To test validity of positive re-exposures in herb induced liver injury.
Methods: We searched Medline database for cases of herb induced liver injury with positive re-exposures and analysed 34 cases for positive re-exposure test criteria of baseline alanine aminotransferase < 5*N* before re-exposure, and re-exposure alanine aminotransferase ≥ 2× baseline alanine aminotransferase. Re-exposure test was negative, if baseline alanine aminotransferase < 5*N* combined with re-exposure alanine aminotransferase < 2× baseline alanine aminotransferase, or if baseline alanine aminotransferase ≥ 5*N* regardless of the re-exposure alanine aminotransferase including no available re-exposure alanine aminotransferase result.
Results: In 21/34 cases (61.8%), criteria for a positive re-exposure were fulfilled, with negative tests in 6/34 cases (17.6%) or uninterpretable ones in 7/34 cases (20.6%). Confirmed positive re-exposure tests established potential of herb induced liver injury for Aloe, Chaparral, Chinese herbal mixtures, Chinese Jin Bu Huan, Chinese Syo Saiko To, Germander, Greater Celandine, Green tea, Kava, Mistletoe, *Polygonum multiflorum*, and Senna, with up to 4 case reports per herb.
Conclusions: Among 34 cases of herb-induced liver injury with initially reported positive re-exposure tests, 61.8% of the cases actually fulfilled established test criteria and provided firm diagnoses of herb induced liver injury by various herbs.

1. Introduction

Herbal hepatotoxicity or herb-induced liver injury (HILI) is rare and represents a bundle of disorders, each characterised by a specific herb or herbal mixture considered as potentially hepatotoxic [1,2]. Any individual herb with its multiple chemical constituents may target different liver cell types like hepatocytes, Kupffer cells, stellate cells, and perisinusoidal cells and/or different subcellular structures. These conditions likely cause different diagnostic markers for potentially hepatotoxic herbs and injury types with no single marker characteristic for herbal liver damage. The rarity of HILI implies genetic, environmental, and immunological determinants in the pathogenesis of HILI, in analogy to proposed mechanisms for drug induced liver injury (DILI) [3–5]. Though these factors may contribute to stratify the risk of hepatotoxicity in advance in individuals considering the use of herbal products, they likely will not facilitate the actual development of HILI specific diagnostic markers.

NIH LiverTox estimates the prevalence of pre-existing liver disease or abnormal liver enzymes in the serum at 5–20% of the general population [6,7]. In addition to alternative diagnoses, this background is to be considered and differentiated before assuming HILI. Therefore, the clinical assessment of patients with suspected HILI is complex and particularly challenging, the diagnosis commonly based on exclusion of hundreds of competing hepatic and extra hepatic causes [8]. Under these conditions, a reported positive re-exposure test may be most helpful but is rarely available; it is recognised as a signature for the diagnosis of DILI [9]. In analogy, this diagnostic approach may be of benefit in selected cases of suspected HILI.

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We therefore analysed the data quality and validity of positive re-exposure reports in cases of assumed hepatotoxicity by various herbs and herbal mixtures, and evaluated the fulfilment of specific and well established re-exposure test criteria.

2. Patients and methods

2.1. Patients

Case reports of HILI caused by various herbs and herbal mixtures were extracted from the Medline database by searching for "herbal hepatotoxicity" and "herb induced liver injury". The first 100 publications of each category were further analysed.

2.2. Methods

The 200 primarily English language publications included case reports, case series, and review articles, and were searched for HILI cases with a positive re-exposure result. Cases with assumed hepatotoxicity by some Herbalife products were excluded, since they have been analysed and published previously [10]. The study was restricted to cases with herbal use of ≤9 months at first suspicion. Overall, 34 HILI cases with a positive re-exposure test result were identified [11–34] and represented the study group, including publications of additional data and comments for these 34 analysed cases [35–47].

2.3. Criteria for hepatotoxicity

For case analysis, hepatotoxicity criteria were based on alanine aminotransferase (ALT) and/or alkaline phosphatase (ALP) activities of ≥2*N*, with *N* as the upper limit of normal [8,48–51]. In this analysis, upper normal values were taken from the individual publications. Whenever specific *N* values were not available, *N* was considered 40 U/L for ALT and 115 U/L for ALP, in line with recent suggestions [48]. All enzyme activities are expressed in U/L or as multiples of *N*; for comparison, recalculation is provided for both expressions and all 34 cases. In one case, only aspartate aminotransferase (AST) but not ALT values were available, so AST replaced the ALT values, as recommended previously [48].

2.4. Laboratory liver injury type

The type of injury has to be classified, since damage pattern specification is essential for further evaluation of re-exposure criteria [8,10,49–54] and causality assessment [8,48–51]. To differentiate between the hepatocellular, cholestatic or mixed type of hepatotoxicity, initial serum ALT and ALP activities on the day of HILI hepatotoxicity is suspected must be evaluated. Enzyme activity is expressed as a multiple of *N*, and the ratio (*R*) of ALT/ALP is calculated. Hepatocellular liver injury is assumed if ALT > 2*N* with normal ALP, or *R* value ≥ 5; cholestatic liver injury is assumed if there is an increase of ALP > 2*N* with normal ALT, or *R* value ≤ 2; mixed type liver injury is assumed in all other cases, i.e. ALT > 2*N*, ALP is increased and *R* value > 2 but <5 [8,51].

2.5. Criteria for positive re-exposure tests

Data of all 34 patients with suspected hepatotoxicity and a reported positive re-exposure test result were analysed for specific criteria to verify a positive test. Respective criteria applied in this study were based on the conclusions of International Consensus Meetings in 1988 [53] and 1990 [54], as reviewed previously [51,52] and recently [8,10,49,50]. Test criteria are identical for the hepatocellular and the cholestatic (±hepatocellular) type of injury, except that ALT is the leading parameter for the former condition and ALP for the latter one (Supplementary Table S1). Data transparency and reproducibility of calculations are critical to avoid arbitrary judgements.

In line with previous suggestions [53,54], a baseline ALT (ALTb) activity <5*N* after the first exposure in the course of rechallenge or preferentially restoration and before re-exposure is mandatory to correctly assess re-exposure conditions in cases of the hepatocellular injury type (Supplementary Table S1). Also as essential criterion, the re-exposure ALT (ALTr) value must be at least doubled compared to the baseline ALT (ALTb) value before re-exposure, i.e. ALTr ≥ 2ALTb. Only if both criteria are met, a positive re-exposure result can be assumed. A negative re-exposure test emerges by the combination of ALTb < 5*N* and ALTr < 2ALTb, or for ALTb ≥ 5*N* associated with ALTr ≥ 2ALTb, ALTr < 2ALTb, or a no available ALTr. The re-exposure test is uninterpretable, if ALTb < 5*N* or ALTb was not available, both conditions associated with no available ALTr. The above criteria using ALT values apply only for the hepatocellular injury type; for the cholestatic (±hepatocellular) injury type, ALP instead of ALT is used for the calculations, with identical thresholds (Supplementary Table S1).

2.6. Causality assessment

The data of all 34 cases were submitted to causality assessment using the updated CIOMS scale (Council for International Organizations of Medical Sciences) [8,10,50] and its original form [51,52] with separate scales for the hepatocellular and the cholestatic (±hepatocellular) injury type [8,50]. This scale is structured, quantitative, liver specific, validated for hepatotoxicity and considers all core elements of hepatotoxicity; it was developed by an international expert panel and validated by cases with positive re-exposure tests as gold standard [52]. CIOMS based assessments have shown good sensitivity (86%), specificity (89%), positive predictive value (93%), and negative predictive value (78%). Some reported cases analysed here had been submitted before to the CIOMS scale, others to the methods of Bégaud et al. [55] or Naranjo et al. [56].

3. Results

3.1. Study group characteristics

Specific criteria to accept a re-exposure result as positive are summarised in the Supplementary Table S1. Details relevant for re-exposure assessment are listed for each patient of the study group (*n* = 34) (Supplementary Table S2). The age of the 34 patients ranged from 9 to 78 years (mean 44.7 years). The sex ratio female: male was 5.8:1. The 34 patients originated from Korea (cases 1, 32), Australia (case 2), Canada (cases 3, 19), the United Kingdom (cases 4, 5, 6, 31), the United States (cases 7, 8, 9, 10, 11, 25, 34), Japan (cases 12, 13, 14, 15), France (cases 16, 17, 18, 23, 28), Germany (cases 20, 21, 22, 29, 33), and Spain (cases 24, 26, 27, 30). Outcome was favourable in all patients except one lethal case despite emergency liver transplantation (case 4).

Treatment duration ranged from 1 day to 9 months (mean 2.8 months) at the first exposure, and latency period to symptoms or increased liver values was from 1 day to 6 months (mean 2.5 months) when all 34 cases were considered (Supplementary Table S2). Among 20/34 patients, treatment duration and latency period was identical and in a range between 1 day and 6 months (mean 2.6 months). In other 12/34 cases, treatment duration was considerably longer with a range from 0.3 months to 9 months (mean 3.2 months) as compared to the corresponding latency period ranging from 0.1 month to 5.25 months (mean 2.2 months). In the