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Suspected Herbal Hepatotoxicity

Requirements for Appropriate Causality Assessment by the US Pharmacopeia

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Abstract

The aim of this current opinion report is to discuss relevant issues of regulatory causality assessment methods related to initially suspected herb-induced liver injury (HILI).

Herbal hepatotoxicity represents a major clinical, regulatory and public challenge since its diagnosis may be difficult to be established, requiring a sophisticated approach that includes a liver-specific and validated causality assessment method. In cases of primarily suspected HILI, however, problems emerged when the US Pharmacopeia (USP) published results with causality assessments of liver disease cases. In these studies, herbal drugs and herbal dietary supplements were considered as causative products based on causality attribution by a shortened version of the Naranjo scale. However, the Naranjo scale is not liver specific and not validated for liver toxicity, and these shortcomings also apply to its shortened and thereby modified version. Consequently, these results were questioned and considered invalid, requiring re-evaluation with a liver-specific causality assessment method validated for hepatotoxicity, such as the scale of the Council for International Organizations of Medical Sciences (CIOMS) or its validated update. In essence, the USP and other regulatory agencies should apply validated liver-specific causality assessment methods rather than liver unspecific and not validated assessment methods in suspected HILI cases.

Herbal extracts are used as dietary supplements or herbal drugs worldwide and perceived as effective and safe.[1] It is poorly recognized, however, that herbal extracts may also cause adverse effects, including rare hepatotoxicity in analogy to synthetic drugs,[1,2] with a great overlap in the clinical presentation, disease spectrum, and causality assessment in herb-induced liver injury (HILI) and drug-induced liver injury (DILI) cases.[1] HILI cases are to be differentiated not only from DILI[2-4] but also from other widespread liver diseases to ensure the appropriate causality assessment and therapy.[4,5]

1. Essential Elements for Assessing Herb-Induced Liver Injury Cases

Key criteria for the confirmation of drug and herbal hepatotoxicity are appropriate time associations, dechallenge and involuntary re-exposure

reactions, as well as thorough exclusion of alternative causes, according to various items as listed in table I.[4-7] Among these are infections, for instance, by hepatitis A, hepatitis B, hepatitis C, hepatitis E, cytomegalovirus, Epstein-Barr virus, herpes simplex virus and varicella zoster virus.[4] In addition, specific laboratory parameters, abdominal ultrasound, and/or magnetic resonance cholangiography (MRC) should exclude rare liver diseases such as genetic and autoimmune disorders, and biliary obstruction. Considering these aspects, establishing the diagnosis of HILI may be crucial and represents a particular clinical and regulatory challenge,[4,5] with major problems that emerged when the US Pharmacopeia (USP) assessed HILI cases.[2,8-10]

2. US Pharmacopeia Standards

Expectations were high when the USP evaluated data of spontaneous cases and case reports of assumed herbal hepatotoxicity.[8,9] However, the validity of the results was fundamentally questioned because the applied causality assessment method was considered inappropriate as a result of its lack of liver specificity.[2,10] This challenge was unexpected because following its foundation in 1820, the USP has gained worldwide reputation because of its comprehensive evaluations of adverse event reports (AERs) associated with dietary supplements, including herbal products.[1] In the past, the USP has provided standards that were subsequently also adopted by other countries; uncertainty now has emerged about the reliability of causality assessment methods, at least for hepatic AERs.

3. Regulatory Use of the Naranjo Scale

In its reports on the assessment of suspected herbal hepatotoxicity, the USP used the not liver specific, not validated for hepatotoxicity Naranjo method, and its further not validated modification with only five of the original ten items.[8,9] For general AERs assessment, the original Naranjo scale may have its merits,[5] but because of its organ unspecificity, this method is not suitable for causality assessments of HILI cases (table II).[2,4,5,10,11]

Table I. Essential criteria required for causality assessment in cases of suspected herb-induced liver injury[a]

Sex, age, bodyweight, height, alcohol and drug use, past medical history of the patient
Brand name with details of ingredients, plant parts, batch number and expiration date
Name and address of manufacturer
Herb as a drug or an ingredient of an undetermined product
Herb as an ingredient of a polyherbal product
Indication of herbal use with dates of symptoms leading to treatment
Daily dose with details of the application form
Exact date of herb start
Exact date of herb end
Accurate date of symptoms
Accurate date of initially increased liver values
Time on herb
Time to onset of symptoms or increased liver values
Temporal association
ALT value initially including normal range
ALT values during dechallenge at least on days 8 and 30, as well as later on
ALT values during dechallenge to exclude a second peak
Exact date of ALT normalization with actual value
ALP value initially including normal range
ALP values during dechallenge at least on days 8 and 30, as well as later on
ALP values during dechallenge to exclude a second peak
Exact date of ALP normalization with actual value
AST value initially including normal range
Assessment of involuntary re-exposure
Laboratory criteria for hepatotoxicity and its pattern
Liver and biliary tract imaging, colour Doppler sonography of liver vessels
Exclusion of HAV, HBV, HCV, HEV, CMV, EBV, HSV, VZV
Co-medicated synthetic drug(s), herbal drugs, herbal supplements, dietary supplements
Assessment of pre-existing diseases, including liver diseases
Evaluation of alcoholic, cardiac, autoimmune and genetic liver diseases
Consideration of the several hundreds of other liver diseases
Statement regarding actual treatment with corticosteroids or ursodesoxycholic acid
Evidence of prior hepatotoxicity of the suspected herbal product

a Data are derived from various reports on HILI and DILI cases.[4-7] For exclusion of other differential diagnoses, recommendations are given in special reports.[4,5]

ALP = alkaline phosphatase; **ALT** = alanine aminotransferase; **AST** = aspartate aminotransferase; **CMV** = cytomegalovirus; **DILI** = drug-induced liver injury; **EBV** = Epstein-Barr virus; **HAV** = hepatitis A virus; **HBV** = hepatitis B virus; **HCV** = hepatitis C virus; **HEV** = hepatitis E virus; **HILI** = herb-induced liver injury; **HSV** = herpes simplex virus; **VZV** = varicella zoster virus.

No other regulatory agency has employed the Naranjo scale to assess herbal hepatotoxicity; efforts are now necessary to resolve the question of method selection, differences in causality assessment by various methods, and implementation of further steps to prevent the use of invalid causality approaches by others.

4. Shortcomings of the Naranjo Scale

In 1981, when the Naranjo algorithm was published,[11] this scale was designed for evaluation of toxic drug reactions related to general pharmacological drug actions rather than specifically to idiosyncratic reactions such as hepatotoxicity.[4,11] Not relevant for HILI, this scale contains questions regarding drug concentrations and monitoring, dose relationship, including decreasing dose, placebo response, cross-reactivity, and confirmation of the adverse drug reaction (ADR) using unidentified objective evidence.[5,10,11] Lack of liver specificity associated with the Naranjo algorithm was evident by missing a definition of liver injury as an ADR; the lack of clear timeframes of latency period; undefined timeframe for dechallenge; lacking definitions of risk factors; insufficient evaluation of alternative diagnoses; inappropriate assessment of co-medicated drugs and herbs; and lacking definition of a positive rechallenge test.[5,10,11]

This scaling was also considered too insensitive, allowing a possible causality even in the absence of essential data or by virtue of the patient simply having taken the suspected agent,[2,8] and concern has been expressed that a more sophisticated judgement would have been expected from the USP.[2] Most important, the modified Naranjo scale, as used by the USP,[8] did not exclude alternative causes such as genuine autoimmune hepatitis, alcoholic or cardiac hepatopathy, other pre-existing liver diseases, DILI and drug-induced rhabdomyolysis.[8,10] There was also no overt causality for the primarily suspected herb as a hepatotoxin when assessed in additional studies.[10] A recent thorough meta-analysis of randomized controlled clinical trials on black cohosh also confirmed lack of herbal hepatotoxicity.[12] It therefore appears that the Naranjo scale is an invalid tool for causality assessment in patients with primarily suspected HILI.

5. General Aspects of the CIOMS Scale

For causality assessment of assumed HILI cases, the straightforward approach of the Council for International Organizations of Medical Sciences (CIOMS) [table II][4-6] appears to be more appropriate than the Naranjo scale.[5] Of note, the European Medicines Agency[13] and members of the Drug-Induced Liver Injury Network (DILIN)[14,15] also used the CIOMS scale.[6] The original CIOMS scale and its update are structured, quantitative, validated for hepatotoxicity, and liver-specific causality assessment methods to assess cases of suspected HILI and DILI.[4-6,16] They were successfully applied in various reports dealing with epidemiological studies, clinical trials, case reports, case series, regulatory analyses and genotyping studies.[5,10,13-26]

The updated CIOMS scale[4,5] contains all basic items of the original CIOMS scale.[6] For reasons of precision and actualization, a diagnostic update regarding serology and polymerase chain reactions was required and made for infections by specific hepatitis viruses and other hepatotropic viruses, and the existing item of hepatobiliary

Table II. Methods of causality assessments for suspected herbal hepatotoxicity[a]

Methods of causality assessment	Specific criteria of various causality assessment methods				
	Structured	Qualitative	Quantitative	Liver-specific	Liver-validated
• *Ad hoc* approach	No	No	No	No	No
• WHO scale	Yes	Yes	No	No	No
• Naranjo scale	Yes	No	Yes	No	No
• CIOMS scale	Yes	No	Yes	Yes	Yes

a Compilation of details derived from previous reports.[4-6,10,11] CIOMS scale refers to both the original scale[6] and its update.[4,5] Liver-specific and liver-validated criteria reflect hepatotoxicity criteria.

sonography was supplemented by the routinely applied colour Doppler sonography of the liver vessels.[4,5] The CIOMS scale,[6] or better, its updated scale,[4,5,10,17] should be used by the USP in the future, keeping in mind that these two scales may have not only their strengths but also their weaknesses.[17,27]

6. Strengths of the CIOMS Scale

Various reports focused on the strengths of the CIOMS scale[27-31] and its updated version.[4,5,10,17] The CIOMS scale and its update are validated tools for assessing liver toxicity. In particular, the CIOMS scale[6] has been validated for toxic liver injury using the results of cases with a positive rechallenge test.[16] Validation for the updated CIOMS scale with respect to herbal hepatotoxicity[4] was achieved by results obtained with the updated CIOMS scale that were identical to those with the original CIOMS.[10,17-20] For the two scales, special attention is placed on temporal association, latency period, dechallenge with exact time course of liver enzymes, co-medication and specific exclusion of various hepatitis infections, biliary obstruction and cardiac hepatopathy.

Other positive aspects were previously discussed in detail,[5,23,27] and a specific causality algorithm with additional methods for a quick evaluation and exclusion of relevant differential diagnoses was also presented.[4] Overall, reliable and reproducible tools are available, providing objective assessment of complex cases and complete evaluation of the parameters that need to be addressed in cases of suspected HILI.[5,23] By this approach, clinical and regulatory judgement can be improved and made more consistent.[23] In addition, the parameters are transparent because each item is to be listed and scaled ready to be published and open for scientific discussions.[4,5,10,17-20] Therefore, transparency is warranted for each individual case and provided for all items under consideration.

7. Weaknesses of the CIOMS Scale

There are proposals for refinement and discussions on weaknesses of the CIOMS scale and its update,[17,27-29] especially around weights given by international experts from Europe and the US to individual parameters and risk factors such as alcohol and age.[6] These weightings were based on the results of re-exposure tests as the gold standard,[6,16] but valid and evidence-based data to overcome the debated shortcomings, including required revalidation approaches, were not presented.[27-29] The interrater reliability of CIOMS assessment was not a problem in a previous study[30] but was an issue in a recent report.[14] In the latter evaluation, however, various uncertainties were evident, and cases going back to 1994 were included with numerous missing or incomplete medical reports and charts for older cases and high rates (28%) of pre-existing liver disease. Moreover, problems of data presentation by the principal assessor to the external reviewers may have influenced the interrater reliability because the external reviewers received only a subset of the case report forms and had no access to the original data of the cases.[14]

8. Naranjo Scale versus CIOMS Scale

Uncertainty emerges whenever suspected HILI cases are submitted to causality assessment methods that are clearly liver unspecific (table II).[5] This shortcoming applies not only to the Naranjo scale[5,8-10] but also to the *ad hoc* approach and the WHO scale.[5] Because of their liver unspecificity, these three causality assessment methods are also not validated for hepatic AERs (table II).[4] This substantiates that none of these three methods are appropriate for causality assessments of HILI and DILI cases, in contrast to the well-validated CIOMS scale and its update. When characteristics of the Naranjo scale are compared with the CIOMS scale and the updated CIOMS scale, major shortcomings are evident regarding the Naranjo scale (table III). Based also on numerous assessments, there are little, if any, arguments as to why the Naranjo scale should be used any more in cases of liver toxicity.[5,10,17-20,23,25-27,32] Of note, herbal products often represent mixtures of numerous herbs, and each individual ingredient has to be submitted to causality assessment, which is facilitated by the CIOMS scale and its update

Table III. Essential data required for causality assessments by the Naranjo scale and CIOMS scale[a]

Details of the individual causality assessment methods	Naranjo scale	CIOMS scale
Accurate timeframe of latency period[b]	No	Yes
Detailed timeframe of challenge	No	Yes
Clear timeframe of dechallenge	No	Yes
Recurrent ALT or ALP increase	No	Yes
Definition of risk factors	No	Yes
Details to exclude alternative diagnoses	No	Yes
Assessment of HAV, HBV, HCV	No	Yes
Assessment of CMV, EBV, HSV, VZV	No	Yes
Liver and biliary tract imaging	No	Yes
Colour Doppler sonography of liver vessels	No	Yes
Assessment of pre-existing diseases	No	Yes
Evaluation of cardiac hepatopathy	No	Yes
Individual score of alternative diagnoses	Yes	Yes
Qualified score of individual co-medication	No	Yes
Scoring of prior hepatotoxicity by the herb	Yes	Yes
Search for unintended re-exposure	Yes	Yes
Definition of unintended re-exposure	No	Yes
Qualified score of unintended re-exposure	No	Yes
Laboratory criteria for hepatotoxicity	No	Yes
Laboratory hepatotoxicity pattern	No	Yes
Liver specific method	No	Yes
Structured, liver-related method	No	Yes
Quantitative, liver-related method	No	Yes
Validated method for hepatotoxicity	No	Yes

a For the Naranjo scale, the respective data are derived from published reports,[4,5,11] and details for the CIOMS scale were presented in earlier reports on the original and the updated scale.[4-6,17-20]

b Latency period indicates time from herb start to symptoms, alternatively to abnormal liver tests.

ALP = alkaline phosphatase; **ALT** = alanine aminotransferase; **CMV** = cytomegalovirus; **EBV** = Epstein-Barr virus; **HAV** = hepatitis A virus; **HBV** = hepatitis B virus; **HCV** = hepatitis C virus; **HSV** = herpes simplex virus; **VZV** = varicella zoster virus.

with their specified items that are not provided by the Naranjo scale.

9. Expert Opinion

Pharmacovigilance is an important issue that requires a sophisticated approach not only by appropriate causality assessment methods but also by various other modalities relevant for HILI cases. For instance, the USP and other pharmacovigilance centres should take advantage of skilled hepatologists as the preferred assessors who are close at the bedside of patients with liver diseases, otherwise unwanted problems may emerge. When the USP assessed cases of HILI, there were, among the 11 or 10 assessors of each study, only two medical doctors,[8,9] with the result that their judgement was heavily debated.[2,10,17,18] Disappointing also is the regulatory information that alternative causes may exist in a number of cases without further specification,[8,9] although all these missed diagnoses were easily diagnosed and named.[10,18] In all cases of suspected HILI, exclusion of other causes is essential because in the course of missed diagnoses the patient is not provided with the appropriate therapy, possibly associated with major health hazards and legal consequences.

There are several reports on the work by DILIN that tries to standardize expert opinion in drug and herbal toxicity.[15,24,33-35] The strengths of this DILIN expert opinion method are the availability and input of the site investigator who obtained the patient's history, performed the physical examination and supervised the data collection.[34] However, according to recent comments and studies,[14,15] there is at present no proof that the opinion of an expert group in addition to the CIOMS assessment may improve the overall causality evaluation. The DILIN expert opinion method has its limitations, which include the lack of generalizability and the low-weighted kappa score for complete agreement among all three reviewers (0.23–0.38).[34] However, it is unacceptable to combine regulatory expert opinion with the Naranjo scale[8–10,18] or the WHO scale.[36-39]

10. Challenges for Regulatory Agencies

Within the frame of an appropriate causality assessment, regulatory agencies should provide transparent and complete case data published point-by-point, ready to be discussed by other scientists without delay, but this kind of data presentation is rarely done.[8,9] Regulatory transparency is also required when, under pharmacovigilance aspects, spontaneous reports related to hepatic AERs are published; only cases with verified causalities

should remain in the system, excluding also duplicates derived from other national or European regulatory databases and the WHO database. This is a general problem since there is no one single database worldwide responsible for all cases of AERs, identified by one individual identification number. Regulatory transparency should also be ascertained by opening the regulatory data files containing only cases with a verified causality level in anonymous form.

11. Conclusions

In essence, for causality assessment of liver injury assumed to be related to herbal extracts, the use of a validated liver-specific assessment method is the appropriate approach rather than the non-organ-specific Naranjo scale, which is not validated for liver toxicity, calling for reconsideration of case analysis and causality reassessment in HILI cases by the USP. Other regulatory measures should be directed to improve pharmacovigilance quality by taking advantage of skilled hepatologists as assessors and by providing data completeness and transparency.

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