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Review

Suspected black cohosh hepatotoxicity—Challenges and pitfalls of causality assessment

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ABSTRACT

Objectives: Black cohosh (BC) is a herbal drug or herbal dietary supplement used for treatment of menopausal symptoms. Recently, however, reports have appeared about the occurrence of rare toxic liver disease in an assumed relationship with the use of BC.
Methods: We have analyzed and reviewed the data of all 69 reported cases with suspected BC hepatotoxicity. Causality for BC was assessed utilizing the scale of the original structured quantitative Council for International Organizations of Medical Sciences (CIOMS), or the main-test as its updated form.
Results: With the hepatotoxicity specific causality assessment methods, there was an excluded, unlikely, unrelated or unassessable causality for BC in 68 of 69 cases with liver disease. One patient had a possible causality for BC and a symptomatic cholelithiasis with confounding variables of fatty liver of unknown etiology; unknown BC brand including possible herbal mixture; unknown daily BC dosage; and an unassessable duration of BC usage. In general, the cases of the 69 patients were poorly documented. Confounding variables were: failure to identify the BC product; use of herbal mixtures with multiple ingredients in addition to BC; co-medication with synthetic drugs and dietary supplements including herbal ones; missing temporal association between BC use and development of liver disease; not specified modalities of BC treatment; failure of dechallenge after BC discontinuation; pre-existing liver diseases; insufficiently excluded other liver diseases; presence of alternative liver diseases.
Conclusions: The analysis of 69 cases shows little, if any, supportive evidence for a significant hepatotoxic risk of BC.

Contents

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1. Introduction

The diagnosis of idiosyncratic hepatotoxicity by drugs and dietary supplements (DDS) continues to be a challenge for clinical hepatologists [1–6]. It is well recognized that for the diagnosis of DDS hepatotoxicity a diagnostic biomarker is not available [5]. The diagnosis may therefore only be established when other liver diseases have been excluded [2,5]. However, even in a clinical setting of liver diseases, this diagnostic approach is not always successful. And in up to 30% of patients with acute liver failure its cause remains undetermined [7–10]. The way to prove or disprove the diagnosis of DDS hepatotoxicity is therefore cumbersome and characterized by challenges and pitfalls.

Recent interest has emerged regarding the question whether the use of black cohosh (BC) may cause idiosyncratic hepatotoxicity [11–22]. BC is the synonym for *Actaea racemosa* and *Cimicifuga racemosa*, and its rhizome and roots are raw materials for herbal drugs and herbal dietary supplements to treat menopausal symptoms. In few published case reports with liver disease causality for BC has been suggested [11–19]. Spontaneous reports were also presented to regulatory agencies [20–22]. For all these cases, additional information was provided and questions were raised [23–41]. Causality for BC was declined for most cases using a systematic quantitative causality assessment method specific for the evaluation of DDS hepatotoxicity [21,39,40]. A possible causality for BC was proposed in other poorly documented cases using a not hepatotoxicity specific method [22]. It is generally agreed, however, that in the suspected cases poor data quality and various other confounding variables prevail [21,22,39–41]. These circumstances certainly complicate a sound quantitative causality assessment.

In the present review we focus on the available evidence regarding causality for BC in patients with liver disease.

2. Challenging evaluation of suspected BC hepatotoxocity

Ascertaining causality for BC in patients with liver disease requires a step-by-step approach. First of all, documentation of the used BC product and of treatment modalities is essential. Missing data may lead to the conclusion that causality of the case is not assessable [21,22,39,40]. Second, criteria for liver disease in assumed connection with the use of BC have to be defined, based on actual data of liver values [39]. In the final stage, a structured quantitative causality method specified for DDS hepatotoxicity is mandatory [21,39,40]. This includes various items such as temporal course of the liver values and exclusion of other, BC unrelated causes [5].

Reviewing the cases with presumed BC hepatotoxicity, in all three key areas of interest shortcomings are evident. These are the basis of a world-wide discussion [21,22,39–41].

3. Identification problems of BC products

Products of BC derived from its roots and rhizome are sold as dried plant material and as fluid or dried extracts [21,22]. They are marketed as herbal drugs under regulatory supervision or as unregulated herbal dietary supplements. The quality of the raw material contained in BC dietary supplements may be of some concern due to confusion of *Actaea racemosa* with other *Actaea* species [22]. Among these are *A. podocarpa* (yellow cohosh), *A. cimicifuga*, *A. dahurica*, and *A. heracleifolia*. Adulteration or substitution of BC with ingredients of similar binominal name or similar common name such as blue cohosh has also been reported. Various BC-based dietary supplements are used as polyherbal mixtures (Table 1) [22,39,40], causing problems regarding identification of potentially hepatotoxic ingredients [12,24,25] and subsequent causality assignment [21].

In the majority of cases with suspected BC liver disease, BC as a product was not identified or characterized [22,39,40]. This applies to published case reports (Table 1) [39,40] and to spontaneous reports presented by various regulatory agencies [21,22]. These include the European Medicines Agency (EMEA) [21], the Canadian Adverse Drug Reaction Monitoring Program (CADRMP), the Australian Therapeutic Goods Administration (TGA), and the MedWatch of the US Food and Drug Administration (FDA) [22]. Information regarding daily dosage of the BC product and duration of treatment is lacking in most cases (Tables 1 and 2) [21,22,39,40], with reported daily overdosage in 2 cases [21]. Attributing causality to BC, used at normal daily dosage, may therefore be difficult under these conditions of uncertainty.

4. Qualifying criteria for BC hepatotoxicity

Prerequisite for causality assessment in hepatotoxicity by DDS, including BC, is a clear definition of criteria qualifying for this disease entity. DDS hepatotoxicity requires for its diagnosis values of alanine aminotransferase (ALT) and/or alkaline phosphatase (ALP) to be at least 2*N* (*N* corresponds to the upper limit of the normal range) [5,39,40]. Other values such as aspartate aminotransferase (AST), gamma-glutamyltranspeptidase (GGT), or bilirubin are not considered of diagnostic value in this particular context. DDS hepatotoxicity may exhibit a hepatocellular, cholestatic or mixed form of liver injury. Differentiation of these entities is prerequisite for further causality evaluation [5,39,40,42–44]. Therefore, serum activities of alanine aminotransferase (ALT) and alkaline phosphatase (ALP) are measured on the day the diagnosis of DDS hepatotoxicity is suspected. Each activity is expressed as multiple of the upper limit of the normal range (*N*), and the ratio (*R*) of ALT:ALP is calculated. Liver injury is (1) hepatocellular, when ALT > 2*N* alone or $R \geq 5$, (2) cholestatic when there is an increase of ALP > 2*N* alone or when $R \leq 2$, and (3) of the mixed type when ALT > 2*N*, ALP is increased and $2 < R < 5$. For causality evaluation by quantitative causality assessment methods [5,43,44], each case has to be evaluated separately for BC and co-medicated drugs (CDs). These include synthetic drugs, herbal drugs and dietary supplements. Consequently, results of ALT and ALP have to be available, and a temporal association between BC use and the emerging ALT and/or ALP values is mandatory.

Reviewing the cases with liver disease in primarily assumed causal relationship with the use of BC, there were reports lacking ALT and/or ALP values [21,22,39,40]. These cases were therefore not suitable for causality assessment. Moreover, in other cases there was no clear temporal association between the use of BC and the increase of ALT or ALP [32,34]. Again, this condition excludes a causal relationship between liver disease and BC use in these cases.

5. Pitfalls of ad hoc and liver-unspecific causality assessment for assumed BC hepatotoxicity

An ad hoc causality assessment is initially necessary in all suspected cases of assumed hepatotoxicity by DDS including BC. However, some shortcomings of this approach are evident, especially regarding missed diagnoses [4,5]. These shortcomings are also observed in cases of primarily suspected BC hepatotoxicity (Table 1) [39,40]. It is noteworthy that the published case reports of assumed BC hepatotoxicity commonly used the ad hoc causality approach alone [11–14,16–19]. In only one single case report was the scale of the hepatotoxicity-specific structured quantitative Council for International Organizations of Medical Sciences (CIOMS) additionally applied [15].