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Kava hepatotoxicity: Regulatory data selection and causality assessment

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ABSTRACT

Background: Kava hepatotoxicity in 20 patients from Germany has been debated worldwide following a regulatory ad hoc causality assessment and ban of kava, an anxiolytic herbal remedy obtained from the rhizome of *Piper methysticum* Forster.
Aims: We assessed causality with a quantitative structured causality analysis in all 20 cases of patients with liver disease, presented by the German regulatory agency that assumed a causal relationship with the use of kava extracts.
Methods: The quantitative scale of CIOMS (Council for International Organizations of Medical Sciences) in its updated form was employed for causality assessment and quality evaluation of the regulatory data presentation.
Results: The regulatory information is scattered and selective, and items essential for causality assessment, such as exclusion of kava independent causes, were not, or only marginally, considered by the regulator. Quantitative causality assessment for kava was possible ($n = 2$), unlikely ($n = 12$), or excluded ($n = 6$), showing no concordance with the regulatory ad hoc causality evaluation.
Conclusion: The regulatory data regarding kava hepatotoxicity is selective and of low quality, not supportive of the regulatory proposed causality; but instead, is an explanation of the overall causality discussions of kava hepatotoxicity. We are proposing that the regulatory agency reports data in full length and reevaluates causality.

1. Introduction

Causality assessment of toxic liver disease by chemical drugs, herbal remedies and dietary supplements is a major challenge for health organisations and regulatory agencies [1–5]. Their databases commonly contain a substantial body of spontaneous reports which may be used for regulatory measures, even though different levels of causality are evident and data varies from one study to the other. For instance, causality could not be established in cases of drug-induced liver disease reported to the database of the WHO (World Health Organization) [1], was suggested by EMEA (European Medicine Agency) in only 4 out of 40 cases with liver disease in an assumed relationship with the treatment by black cohosh [2] but subsequently discussed [3], and was proposed by the German regulatory agency in 20 out of 38 patients with assumed hepatotoxicity by kava [4] but immediately debated as being flawed [5].

Kava hepatotoxicity has attracted great interest worldwide [5–24], since the use of kava was considered previously as safe and devoid of major side effects [5–9]. Kava (*Piper methysticum* G. Forster) is a perennial shrub native to islands of the South Pacific [6]. Its rhizome contains various psychoactive kavapyrones [5,14] and is used for preparation of aqueous, ethanolic and acetonic extracts [9]. Whereas aqueous kava extracts serve as beverages for informal social occasions and traditional ceremonials in most South Pacific islands [5,9], ethanolic and acetonic kava extracts are considered as herbal anxiolytic remedies [6] with proven efficacy according to a systematic Cochrane review [19].

Based on ad hoc causality assessments kava was declared by the German regulatory agency as being hepatotoxic in 20 patients from Germany, and a regulatory ban of kava extracts followed [4]. In face of the ongoing discussions regarding the quality of both the regulatory data presentation and the subsequent causality assessment [5–24], we have analysed the available published regulatory data and submitted these to a structured quantitative causality evaluation. We found that the regulatory data as published was selective and of low quality, and did not substantiate the regulatory causality assessment, but instead explained the overall discussions.

2. Patients and methods

The study consisted of 20 patients from Germany with liver disease declared by the German regulatory agency (BfArM, Bun-

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desinstitut für Arzneimittel und Medizinprodukte, Bonn) on an ad hoc basis, to be all causally related to the treatment by ethanolic and acetonic kava extracts [4]. Regulatory evaluation ranged from certain and probable, to possible causality. The individual data of each patient was presented online by the regulatory agency, and were now analysed regarding quality required for a sound causality assessment. Basically, the original regulatory data of patients with assumed kava hepatotoxicity were subjected to both a thorough ad hoc evaluation and a structured quantitative causality assessment.

In the initial stage, the ad hoc causality evaluation was cumbersome due to regulatory data shortage and incomplete signals provided by spontaneous reports [18]. Since the regulatory data appeared scattered and selective [4], additional details were asked for as outlined before [18]. When appropriate, the authors of published case reports [20–23], the involved pharmaceutical companies [18], and others [16,24] were kindly requested to supplement the regulatory presented data and to assure completeness as far as possible [18]. Most of the additional data including medical reports were provided to us by the reporting hospital physicians and the primary care physicians through the involved manufacturers. Thereby, a comparison of the ad hoc causality evaluation was attempted regarding the original regulatory data alone with those supplemented by additional features.

For the second evaluation step, the original regulatory data of each patient [4] was submitted item by item to a thorough assessment of the temporal as well as the causal association. The structured quantitative criteria of CIOMS published by Danan and Bénichou [25] were used in its updated form [26]. The CIOMS system was derived from an international concensus meeting of experts who defined various parameters such as time to onset, course of improvement of laboratory data, risk factors, concomitant drugs, searches for nondrug causes, previous information on hepatotoxicity of the drug, and response to re-administration [25]. It provides with each of these parameters a range of scores, and the total score is computed and may be divided into ranges that represent a causality being highly probable, probable, possible, unlikely or excluded. The CIOMS scale has been well validated (sensitivity 86%, specificity 89%, positive predictive value 93%, and negative predictive value 78%) [27] and is universally accepted [28–32]. It has been established by experts originating from France, Denmark, Germany, Italy, UK and USA [25] and was based on the results of rechallenge tests [27] considered as gold standard for the diagnosis of hepatotoxicity by drugs and dietary supplements [25,27]. The scale consists of two parts, one is available for the hepatocellular and the other one for the cholestatic (± hepatocellular) type of acute toxic liver disease. Differentiation by laboratory tests is therefore a requisite for an evaluation [25]. Serum activities of alanine aminotransferase (ALT) and alkaline phosphatase (ALP) are measured on the day drug-induced 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 > 2N alone or $R \geq 5$ (2), cholestatic, when there is an increase of ALP > 2N alone or when $R \leq 2$, and (3) of the mixed type, when ALT > 2, ALP is increased and $2 < R < 5$. When the available laboratory data of the 20 patients were assessed [18], a hepatocellular type of liver disease emerged rather than a cholestatic (± hepatocellular) one.

Finally, with the third step of this study regarding the observed liver disease in assumed causal relationship for kava, various types of evaluation are principally evident: (1) present ad hoc causality assessment for kava, based merely on the original regulatory data; (2) present ad hoc causality evaluation for kava, based on the supplemented original regulatory data; (3) structured causality assessment for kava, based merely on the original regulatory data; and (4) comparison of the present study, using the ad hoc and the updated CIOMS causality assessment, with the data of these 20 patients evaluated by other studies [4,7,16,18,24,33,34]. These comprise the ad hoc assessments for kava by BfArM [4], MCA (Medicine Control Agency) [7,16,24,33], EMEA [16,24,34], and Schmidt et al. [16,24] as well as the structured causality assessment for kava as completed study, using a bundle of information from various sources apart from the regulatory data [18].

Liver histology was available in 14 of 20 cases with a wide range of changes [18]. These include liver cell necrosis alone (cases 5, 7 and 11) and combined with hepatitis (cases 17 and 19), with hepatitis and intrahepatic cholestasis (case 20), with hepatitis and bile duct proliferation (case 1), with hepatitis, intrahepatic cholestastis and bile duct proliferation (case 3), with intrahepatic cholestasis (case 8), or with hepatitis, intrahepatic cholestasis and cholangitis (case 12). Other changes were described such as toxic hepatopathy with hepatic atrophy (case 4), lobular hepatitis (case 10), intrahepatic cholestasis and fibrosis (case 18), and intrahepatic cholestasis with signs of hypersensitivity (case 2).

3. Results

3.1. General characteristics of the study group

The information on all 20 patients is presented and includes age, gender, details of the treatment by kava extracts, co-medication and outcomes (Table 1). The patients were in the age of 23–81 years and mostly females. They had predominantly used ethanolic rather than acetonic kava extracts with often increased daily use of kavapyrones and/or prolonged duration of treatment outside the regulatory recommendations (60–120 mg kavapyrones daily for not longer than 3 months). Outcome was favourable in 13 patients, and in 4 others after LTX, but lethal in 3 patients including 2 subsequently due to LTX.

3.2. Regulatory data presentation and ad hoc causality assessment

In general, the original regulatory information of the 20 patients was selective and thereby inadequate (Table 1). No major regulatory attempt has been made to present, for instance, results concerning exclusion of non-kava and nondrug causes, and the ad hoc causality in most of the cases had to be considered primarily as unassessable for kava (individual data not shown). Although not presented by the regulator, important data substantiating causes independent from kava have been available and are now used together with the regulatory data, for ad hoc causality assessment (Table 1). The ad hoc causality for kava was not assessable in 8 and excluded in 10 patients, possible in one other and highly probable in another one (Table 1). Despite the shortcomings regarding regulatory data presentation, selection and major deletions, the regulatory ad hoc assessment for kava in patients with liver disease described a possible, probable or certain causality in all 20 patients. It therefore appears that the results of ad hoc causality assessments vary substantially, depending on quality of presented information, extent of the data selection and deletion of information essential for a sound evaluation.

3.3. Structured causality assessment

The regulatory data presented for each of the 20 patients were then subjected to a causality assessment for kava using the updated quantitative scores of CIOMS (Table 2). In 18 out of 20 patients the total points ranged from −1 to 2, rendering an excluded or unlikely causality for kava. The remaining 2 patients achieved a total of 3 points each, representing a low level of a possible causality (3–5