Regulatory Toxicology and Pharmacology 59 (2011) 1–7

Contents lists available at ScienceDirect

Regulatory Toxicology and Pharmacology

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

Commentary

Regulatory causality evaluation methods applied in kava hepatotoxicity: Are they appropriate?

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ARTICLE INFO

Article history:
Received 20 July 2010
Available online 18 September 2010

Keywords:
Kava
Kava hepatotoxicity
Herbal hepatotoxicity
Drug-induced liver injury
Herbs induced liver injury
Hepatotoxicity
Toxic liver disease
Toxic liver injury
Causality assessment

ABSTRACT

Since 1998 liver injury has been assumed in some patients after the use of kava (*Piper methysticum* G. Forster) as an anxyolytic herbal extract, but the regulatory causality evaluation of these cases was a matter of international and scientific debate. This review critically analyzes the regulatory issues of causality assessments of patients with primarily suspected kava hepatotoxicity and suggests recommendations for minimizing regulatory risks when assessing causality in these and other related cases. The various regulatory causality approaches were based on liver unspecific assessments such as ad hoc evaluations, the WHO scale using the definitions of the WHO Collaborating Centre for International Drug Monitoring, and the Naranjo scale. Due to their liver unspecificity, however, these causality approaches are not suitable for assessing cases of primarily assumed liver related adverse reactions by drugs and herbs including kava. Major problems emerged trough the combination of regulatory inappropriate causality assessment methods with the poor data quality as presented by the regulatory agency when reassessment was done and the resulting data were heavily criticized worldwide within the scientific community. Conversely, causality of cases with primarily assumed kava hepatotoxicity is best assessed by structured, quantitative and liver specific causality algorithms such as the scale of the CIOMS (Council for International Organizations of Medical Sciences) or the main-test as its update. Future strategies should therefore focus on the implementation of structured, quantitative and liver specific causality assessment methods as regulatory standards to improve regulatory causality assessments for liver injury by drugs and herbs including kava.

1. Introduction

Herbal hepatotoxicity is a rare but potentially life-threatening disease and requires special attention for both treating the affected patients and ascertaining a sound diagnosis (Seeff, 2007; Navarro, 2009). Of particular importance is the early suspicion and collection of all relevant data of the case under consideration to facilitate subsequent causality assessment (Teschke and Bahre, 2009). As difficult as it may be to unequivocally establish drug-induced liver injury of conventional synthetic drugs, it is even more difficult to implicate herbal products for the many reasons such as product purity, product contamination and adulteration (Borrelli and Ernst, 2008; Health Canada, 2010). In addition, causality evaluation may be confounded by various inconsistencies and factors such as lack of a temporal association; missing definitions of the adverse reaction; inappropriate treatment modalities with high product doses and prolonged use; missing challenge and dechallenge data; alcohol consumption; alternative diagnoses; comorbidity; and coadministration with other synthetic drugs, herbal drugs and dietary supplements containing a variety of other herbs as mixture (Teschke et al., 2009a,b). Other challenging issues commonly recognized are poor qualities of data primarily collected by the treating physicians (Teschke et al., 2009b) and inadequate regulatory data presentation (Liss and Lewis, 2009). Taking these limitations into account, various open questions remain as to whether the use of an herb was really causally related to any liver disease.

Herbal hepatotoxicity by the use of the anxiolytic herb kava (pepper family Piperaceae, *Piper methysticum* G. Forster) is a particular challenging issue (Schmidt et al., 2005; WHO, 2007). Thorough analyses are available as reviews regarding its clinical aspects (Teschke, 2010a) and pathogenetic factors (Teschke, 2010b). The present review will focus on the regulatory shortcomings of data presentation and causality evaluation which are of common interest with respect to pharmacovigilance considerations.

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doi:10.1016/j.yrtph.2010.09.006

2. Regulatory data presentation

Expectations are high when a regulatory agency issues a withdrawal of an herbal drug such as kava from the market and presents the pharmacovigilance data of the cases (BfArM, 2002), especially when problems of toxic liver disease presumably associated with kava extracts have to be discussed regarding causal relationship, role of solvents for aqueous, ethanolic and acetonic extracts, kava raw material, comedication, dosage and duration of intake, impurities, and adulteration (WHO, 2007; Teschke, 2010a,b). There was worldwide interest and analysis, and the general conclusion was reached that the data quality of the regulatory presented cases with primarily suspected kava hepatotoxicity was poor and inappropriate (Denham et al., 2002; Schulze et al., 2003). Despite international criticisms and the requests of various scientific groups to provide additional data (Denham et al., 2002; Teschke et al., 2003; Schmidt et al., 2005), the regulatory agency failed to follow these suggestions (BfArM, 2005). No major regulatory attempts have been made to present, for instance, results concerning exclusion of non kava and non drug causes (Teschke et al., 2003), although these and other data have basically been available and were published later on with thorough analyses in scientific journals (Teschke et al., 2008a; Teschke and Wolff, 2009; Teschke, 2010a). The regulatory information of the patients was also selective, incomplete and thereby inadequate (Teschke and Wolff, 2009). It therefore appears that the regulatory data presentation in general was disappointing for the scientific community (Denham et al., 2002; Schulze et al., 2003; Teschke et al., 2003; Schmidt et al., 2005; Teschke and Wolff, 2009).

Spontaneous signaling programs carried out by regulatory agencies are usually based on accumulated reports that meet a case definition, sometimes referred as signal generation. In recent years much work is being done on the use of data mining methods for signaling, procedures that are independent of content, solely based on statistical disproportionality. The use of these regulatory causality methods may be helpful in the field of herbal pharmacovigilance, but evidence was not presented that these methods had actually been applied for regulatory assessment in cases of suspected kava hepatotoxicity (BfArM, 2002). Prior to pharmacovigilance assessment, however, an exhaustive evaluation of each individual case is required, since quality of causality assessment is more important than quantity of poorly assessed cases (Teschke et al., 2009c).

3. Ad hoc causality assessment

In 2002, the regulatory ban of kava was based not only on poor data but also on a narrative causality assessment, suggesting obviously some kind of an ad hoc causality approach by guilt by association (BfArM, 2002). There is no question that the use of an ad hoc causality assessment method for cases with liver injury is highly debatable, since this approach is inaccurate and lacks liver specificity (Kaplowitz, 2001; Teschke and Wolff, 2009).

Various items are usually considered essential for this type of assessment but certainly open for discussion (Table 1); in particular, there is no universally accepted description given for this method or its usage. Having ruled out nondrug causes, a distinction of a probable, possible, and unlikely causality is often used (Kaplowitz, 2001). A probable causality is usually assigned when the manifestation of liver disease, temporal association, and dechallenge response fit the typical signature of the drug in question. A possible causality is assigned when one of these parameters is not typical, the drug is not known to cause the reaction, or so rarely that it is difficult to distinguish from background, or an alternative cause is less or equally plausible. An unlikely causality is assigned when most of the features are atypical or an alternative cause is more plausible. Obviously, this simple distinction between levels of probability of assigning causality cannot be accurately and reproducibly applied to every case and is likely to foster disagreement among experts. In practice, this ad hoc approach is attempting to give a "yes, no, or may be" answer to a diagnosis without a gold standard. It has been pointed out that in the absence of liver specific causality assessment methods there has been no sound basis for determining the likelihood that an episode of hepatitis represents a drug-related reaction (Lee, 2003; Gunawan and Kaplowitz, 2004; Maddrey, 2005. The inaccuracy of the ad hoc causality approach is highlighted by a high rate of diagnoses missed upon assessment, and the correct diagnoses became evident upon subsequent thorough analysis including also quantitative assessment methods (Aithal et al., 1999). Missed diagnoses were not restricted to primarily suspected drug-induced liver injury (Aithal et al., 1999; Andrade et al., 2006; García-Cortés et al., 2008; Teschke et al., 2008b) but included also herbal hepatotoxicity (Teschke et al., 2008a, 2009a,b). Under these conditions, a patient with an incorrectly diagnosed disease is inappropriately being treated, whereas the real existing disease lacked a specific treatment in time; this delay may result in a deleterious outcome.

Table 1
Ad hoc causality assessment.

Items
1. Signature of clinical manifestation
2. Latency period
3. Dechallenge
4. Definitive exclusion of alternative causes
5. Risk factors
6. Alcohol
7. Other diseases
8. Track record of the drug

Details are derived from Kaplowitz (2001), Gunawan and Kaplowitz (2004), and Maddrey (2005).

Not presenting any criteria used for the assessing method is quite unusual for a regulatory agency (BfArM, 2002) and was unexpected but possibly explained by the poor data quality (Teschke and Wolff, 2009). Under the latter conditions, the initial causality assessments of scientific groups have also been achieved only on an ad hoc basis (Denham et al., 2002; Teschke et al., 2003; Schmidt et al., 2005), in accordance with other regulatory agencies such as the MCA (Medicines Control Agency) or EMA (European Medicines Agency, formerly EMEA) (Teschke et al., 2003; Schmidt et al., 2005; Teschke and Wolff, 2009). In all patients with primarily suspected kava hepatotoxicity, the regulatory assessment yielded various levels of causality categories for kava: causality was highly probable, probable, probable/possible, and possible in 2, 14, 2, and 7 patients, respectively (BfArM, 2002; Teschke et al., 2008a), despite shortcomings regarding regulatory data presentation, selection and major deletions (Teschke and Wolff, 2009). Based on identical regulatory presented case data and identical ad hoc causality assessments, the high regulatory causality ranking for kava was not reproducible; rather than low graded causality was suggestive, and this in only a few patients, as evaluated by MCA, EMEA, and various scientific groups (Denham et al., 2002; Schulze et al., 2003; Teschke et al., 2003; Schmidt et al., 2005; Teschke and Wolff, 2009). As expected, the combination of poor data quality with inappropriate causality assessment methods led to unacceptable results. In accordance with this impression is the high rate of diagnoses missed by the regulatory ad hoc assessment of patients with primarily assumed kava hepatotoxicity (Teschke et al., 2008a; Teschke, 2010a). It is clear that missed diagnoses are in no way acceptable, neither for the section of pharmacovigilance nor for physicians treating patients with primarily assumed liver injury