

REVIEW

Toxicity of kava pyrones, drug safety and precautions – a case study

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Summary

Kava pyrones have been sold in Germany as OTC anxiolytics until June 2002, when all preparations with a kava pyrone content of more than 10^{-4} of a homeopathic stock solution were withdrawn. Other countries in which kava pyrones have been used as anxiolytics, namely GB and the USA, have not followed suit. Kava pyrone anxiolytics have been positively reviewed by the Cochrane Collaboration; also newer German clinical studies have indicated pharmacological anxiolysis at the recommended doses. To use the first choice of treatment, psychotherapy, for all uncomplicated cases of pathological fear does not appear to be realistic. Current data about kava pyrone toxicity are unclear. Judging from the few well documented cases of kava pyrone hepatotoxicity (appr. 2 out of 36) in Germany and Switzerland, an immunologically mediated idiosyncratic mechanism appears to be most likely, especially at higher doses, whereas a direct toxic mechanism is much less likely. No direct results are available for the incidence of kava pyrone-related adverse drug effects. From spontaneously reported cases the incidences of adverse drug reactions cannot be obtained, a rough estimation indicates the incidence of hepatotoxicity to be comparable to those of benzodiazepines. Taken together, the withdrawal of kava pyrone-based anxiolytics appears to be an ill founded over-reaction given the lack of superior therapeutic alternatives. Neither the case evaluations presented by the BfArM (Bundesamt für Arzneimittel und Medizinprodukte = Federal Office for Drugs and Medical Products) nor the complete rejection of proof for therapeutic efficacy of kava pyrone anxiolytics are scientifically well founded.

Key words: kava pyrones, anxiolytics, adverse drug reaction, hepatotoxicity, risk evaluation

■ Introduction

Fear is a symptom which can range from normal reaction to foreign stimuli to severe pathological fear attacks. The incidence of pathological fear is high, it was estimated by Linden et al. (1996) to occur in 8,5% of all outpatient care patients. According to other authors (Buller and Legrand, 2001; Connor et al. 2001) attacks requiring treatment occur in 20–30% of the general population. These estimates are supported by the high sales figures for anxiolytics in all industrialized countries.

Psychotherapy is the accepted method of choice for fear attacks. Nevertheless, in most light attacks anxiolytics are prescribed (often additionally). A lot of fear patients also treat themselves with OTC drugs or drugs prescribed by their family physician. For the indication anxiolysis plant extract based drugs (hops-, hypericum-preparations) and chemical compounds (antidepressants like amitriptylin, buspirone, benzodiazepines) are registered in Germany.

■ Clinical efficiency

Clinical testing of anxiolysis has been problematic since it is a parameter which cannot easily be quantitated. This results in a high rate of placebo responders (30–50% in anxiolysis studies; Buller and Legrand, 2001); even when clinical studies with proven anxiolytics are repeated, equivocal or negative results are not uncommon. Consequently, only a few drugs have undisputed anxiolytic effects and have been positively reviewed, e.g. by the Cochrane collaboration (Pittler and Ernst, 2002).

Besides sedatives and antidepressants clinical studies of anxiolytic effects have also been published for kava pyrone preparations. The pharmacological mechanism of kava pyrone anxiolysis is not yet known. A meta analysis of clinical studies by Pittler and Ernst (2000) indicates the superiority of 150 mg/die kava pyrones over placebo. This analysis is confirmed by newer studies and reviews, which support a relationship between kava pyrone dose and anxiolysis (Lehrl and Wölk, 2002; Malsch and Kieser, 2001; Bilia et al. 2002). As a result, anxiolysis by kava pyrones has been positively evaluated by the Cochrane collaboration (Pittler and Ernst, 2002). Against this, other authors criticise the lack of a cogent pharmacological effect of kava pyrones (de Smet, 2002). However, with clinical parameters like fear with a high placebo rate and quantitation difficulties it is hard to clearly demonstrate pharmacological effects (Buller and Legrand, 2001).

Benzodiazepines, buspirone, antidepressants and others are also used as anxiolytics. The mode of action of benzodiazepine anxiolysis is thought to rely on their sedation and lowering of general activity. Newer *in vivo* (Benson 1998; Löw, 2000) studies ascribe the anxiolytic effect to activation of the GABA_A-alpha₂-receptor subtype (reviewed in Möhler et al. 2002) but subtype specific benzodiazepines have to be developed. Antidepressants likely act by modulating serotonergic activity. Both benzodiazepines and antidepressants have been reviewed positively for severe fear attacks by the AKdÄ (Arzneimittelkommission der deutschen Ärzteschaft [German physicians drug commission] 1999). Their use in slight fear attacks is not commented upon.

■ Adverse drug effects by kava pyrones

Characteristic skin changes have been reported from Polynesia and Australia after long term usage of high doses of aqueous kava root extracts. Herbal extracts for pharmacological usage are made by ethanol or acetone extraction, their composition differs from aqueous extracts. The spontaneous reporting system for adverse

drug reactions (ADR) in Germany and Switzerland has received reports of a variety of symptoms in association with kava pyrone intake over the last 15 years (Table 1). Most of these symptoms can mechanistically be explained by allergic or idiosyncratic reactions, especially itching, exanthema and cutaneous allergic reactions. Hepatic ADR usually appear as serum enzyme elevations. With a similar incidence central nervous ADR have been reported, and less cases of gastrointestinal ADR. Most cases were incidental and mild; a total of 5 cases with severe to lethal ADR in connection with kava pyrone intake has been published separately (Brauer et al. 2000; Escher et al. 2000; Kraft et al. 2001; Russmann et al. 2001; Saß et al. 2000; Strahl et al. 1998).

Judging the causality between drug intake and observed toxicity is always difficult; for hepatotoxicity in timely association with kava pyrone intake reviews have differed in some cases. Except for the BfArM (Bundesamt für Arzneimittel und Medizinprodukte = Federal agency for drugs and medical products, German federal authority) all authors conclude that in most cases, including most published cases, causality can only be suspected but is not proven (Anon, 2002; Schulze and Siegers, submitted; Teschke, 2002). Sufficient proof of causality has been provided in only one

Table 1. Adverse drug reactions reported in connection with kava intake. All cases of kava pyrone ADR were evaluated for type of ADR (n = 36). The list includes multiple reporting, for reports with more than one ADR both effects are listed. Additionally, six observations of mild kava pyrone effects from clinical studies were included.

Adverse drug effect	Total (1986–2001)
<i>Central nervous system:</i> drug abuse, agitation, fear, paradox reaction, pain	18 cases
headache	5 cases
<i>Gastrointestinal:</i> diarrhea, dyspepsia, nausea	13 cases
<i>Liver:</i> cholestasis, icterus	11 cases
increased liver enzymes	14 cases
liver failure	4 cases
<i>Allergy:</i> urticaria, conjunctivitis, rash and/or itching	27 cases
asthma	1 case
edema	4 cases
allergic shock	2 cases
Stevens Johnson syndrome	3 cases
<i>Other:</i> urine retention	1 case
impaired vision	9 cases
angina pectoris	3 cases
hyperglykemia	1 case
<i>Diverse</i>	3 cases

published, well documented and investigated case (Russmann et al. 2001). In vitro tests documented lymphocyte proliferation in response to kava pyrone addition, indicating a T-lymphocyte mediated mechanism to be probably responsible for this case of kava pyrone hepatotoxicity.

Among the reported cases no dose response relationship can be seen for kava pyrone related hepatotoxicity (Fig. 1), although this has been postulated by some reviewers (e.g. BfArM 2002). The absolute number of ADR reports for the recommended dose range (<100 mg/day kava pyrones, 11 cases) is nearly as high as the number of cases with intake of higher amounts (>150 mg/day, 14 cases). Besides these, in 11 cases no dose range has been reported. Although daily doses can only be roughly estimated for drugs taken over a longer time, the case distribution over the dose range is hardly compatible with a toxic, dose dependent mechanism for kava pyrone hepatotoxicity.

Until now, no hints for a dose dependent hepatotoxicity at low doses have been published from animal experiments or from patient observations (Connor et al. 2001). For rats a *no observed adverse effect level* (NOAEL) of 24 mg/kg has been reported, for dogs 20 mg/kg, equivalent to 1500–1800 mg for a 75 kg patient. In mice, a single dose of 500 mg/kg kava pyrones induce histological signs of liver damage (G. Friedman, personal communication, no NOAEL given). In vitro studies using rat hepatocytes indicate a toxic threshold of 50 µg/ml kava pyrones (BfArM 2002, ref. 18, unpublished study by Gebhardt). Since no pharmacokinetic parameters for kava pyrones have been published, this concentration cannot be converted to doses.

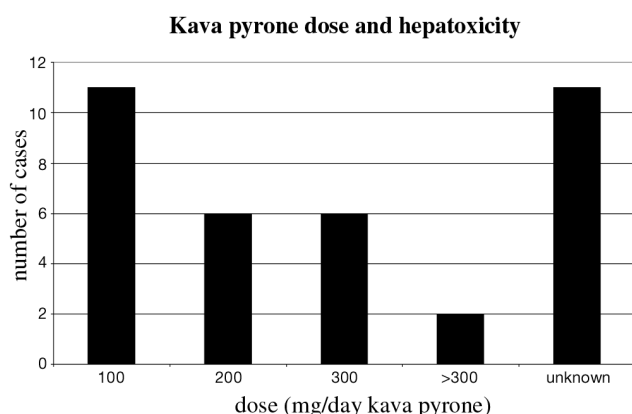


Fig. 1. Dose dependency of kava related adverse drug reactions. For all reported adverse drug reactions ($n = 36$) average kava doses at the time of diagnosis were categorized according to: 60–150 mg/d = 100; 160–250 mg/d = 200; 260–350 mg/d kava pyrone = 300; more than 350 mg/day = >300; unknown: dose of intake not reported.

No mechanistic studies for immune mediated kava pyrone toxicity have been performed in animal experiments. On the other hand, T cell-mediated toxicity by other compounds are not rare; they have been reported and investigated for various drugs like heparin, quinine or chlorheximide. Available patient data support a non-toxic, allergic mode of action for kava pyrones, at least for the hepatotoxicity (Schulze and Siegers, submitted; Teschke, 2002).

■ Incidence of kava-induced hepatotoxicity

No methodologically valid studies for the incidence of kava pyrone ADR have been performed, which is also the case for nearly all plant extracts and most chemically defined drugs with long registration duration. With the lack of good data bases, each estimation of ADR incidences has to be drawn from the few data available from other sources, usually collected for different purposes.

Spontaneous reporting systems are inadequate to estimate incidences. On one hand causality can be accepted confidently only in very few cases. Only time coincidence cannot be accepted as sufficient proof for causality. In spontaneously reported cases, essential data are often missing, necessary in vitro data for the judgment of causality have not been collected or other, similarly acting comedications are not reported. This system also is not exhaustive, second wave reporting after the publication of a severe ADR with a well founded causality due to a specific drug (index case) is a well known phenomenon and results in multiple additional cases. On the other hand, a primary report will only be generated if a physician suspects a causality between an ADR and the intake of a specific drug; this is not routinely the case, especially in common drug reactions like hepatotoxicity, or for common and assumedly safe medications prescribed on a wide scale.

Incidence estimates can only be obtained from unselected data, as routinely are collected in the context of safety studies or the clinical application for new drugs (phase I–III studies). One possibility to ameliorate this lack of data is a calculation based on primary data like the MEDIPLUS data base (IMS Health, Frankfurt/Main, Germany), which was created from approximately 1 500 000 unselected patients and includes a variety of clinical parameter measured during outpatient medical care. This database is large enough to mirror frequencies as they occur in the general population. Together with available sales figures, it is possible to roughly calculate the association frequency between kava pyrone intake and liver dysfunction in outpatients (Table 2). Association does not necessarily imply

causality; a recognized hepatic insult may be related to other risk factors, comedication or life style. In this regard (causality) data from unselected data collections correspond to spontaneous reporting systems. Both systems are inaccurate since both are uncertain in terms of completeness and of causality judgment; however, the better a patient base mirrors the average population the more accurate a (semiquantitative) estimation will be. For this purpose, data from unselected patient collections like MEDIPLUS are far superior to data generated by a spontaneous collection system.

Based on MEDIPLUS data kava pyrone preparations and benzodiazepines show a similar hepatotoxic risk of approximately 1 case (all kinds of severity) in the data base per 1 million defined daily doses of kava pyrones or benzodiazepines sold. This number indicates association, not causality, and also includes the background incidence of liver dysfunction without intake of an external causative factor. Based on sales numbers and spontaneous reporting Teschke (2002) calculates 1 reported case per 1 million monthly doses (recommended daily dose is assumed, no data given for benzodiazepines). Both calculations (Schulze and Siegers, submitted; Teschke, 2002) cannot include causality, they only show coincidence of kava pyrone intake and liver insult. Both numbers therefore can only be semiquantitative as indicated by the authors, but allow a rough comparison of the toxic potential of kava pyrones. Calculations from MEDIPLUS data have been dismissed as inaccurate and unreliable by the BfArM based on the reasoning that the true incidence may be as much as 10fold different from any calculated number (BfArM

2002). This fact is not contested and is a good approximation for the limits of these estimations; however, they clearly demonstrate a comparable hepatotoxic potential of benzodiazepines and kava pyrones. No other data are available, and these estimates are the only available numbers that try to quantitate the toxic risk of kava pyrones.

■ Regulatory action by the BfArM

The discussion on kava pyrone toxicity and the regulatory actions taken may be briefly commented upon. After much media hype in 2000 and 2001, preparations with kava pyrone content above D4 from the homeopathic stock solution have been withdrawn in Germany. This withdrawal was instituted after Switzerland had withdrawn registration of only one preparation (Laitan®) in 2000. At this time point the BfArM declared that no immediate action was necessary. A reevaluation based on hearings (Stufenplan) was started much later, i.e. in November 2001. Obviously the hearing results have been prejudiced already at the start. On a meeting in February 2002 the members of the Kommission E (scientific commission to the BfArM for herbal drugs) stated that kava pyrone preparations have a positive therapeutic benefit and saw “no immediate danger from continuing kava pyrone marketing”. The BfArM did not respond to this statement, but mandated an immediate marketing stop for all kava pyrone preparations in June 2002.

It is interesting to look at the causality judgment by the BfArM for spontaneously reported and published cases of kava pyrone hepatotoxicity. Single case evaluations by the BfArM as given in the official supporting document for kava pyrone withdrawal are not consistent with the evaluation undertaken by others, and sometimes not consistent in cases listed twice. In an extensive presentation of 20 cases with severe hepatotoxicity, causality is given as “definitive” or “likely” in 15 of 20 cases. In this context it escaped the authors attention that in one case both reported and published (reported case 1 and publication by Strahl et al. 1998) causality once is given as “likely”, once as “definitive”. Among the 20 cases presented in depth there is at least one more case of double reporting further decreasing the total number of cases investigated.

Hepatotoxicity from other sources receives only scant attention. The evaluation of hepatotoxicity by comedication drugs is questionably at best. The lack of hepatotoxicity by hypericum medication is mentioned a few times and therefore “hypericum cannot contribute to a hepatotoxic ADR”. The strong induction and inhibition of the P450 system and, from this, possible changes in metabolism of other drugs obviously has

Table 2. Association between kava pyrone intake and liver dysfunction. Data from the MEDIPLUS data base (IMS, Frankfurt/Main, Germany) were extracted according to drug prescription/intake and signs of liver dysfunction.

total patient number	1 500 000 pat.
office visit 9/99–8/2000	895 847 pat.
patients with hepatic insult	28 779 pat.
treated with psychoactive drugs	3 075 pat.
treated with anxiolytics	1 212 pat.
	with 1 313 prescriptions
patients with fatty acid degeneration	968 cases
patients with toxic hepatitis	52 cases
hepatotoxicity within < 6 mo. after drug intake	564 cases
fatty acid degeneration and kava prescription	58 cases
and bromazepam	327 cases
and diazepam	284 cases
and oxazepam	299 cases

escaped the attention of the BfArM. This also holds true for the postulated correlation between kava pyrone hepatotoxicity and CYP4502D6 poor metabolizer phenotype (Russmann et al. 2001) which may be imitated by P450 inhibition. Additionally, hepatotoxicity of other drugs with known potential is dismissed or subordinated, or the reported intake of these drugs is questioned (cases 1, 8, 11). This kind of evaluation appears to be arbitrary. Consequently, the IKS (Interkantonale Kontrollstelle für Heilmittel = intercantonal clearing agency for drugs; Switzerland) only judges 2 of 6 severe cases as likely correlated to kava pyrone intake, the BfArM nearly all cases. Other agencies like the Center for Disease Control (CDC, Atlanta, USA) appear to be even more careful; only 2 cases (1 case from the US reporting system, 1 European case) are mentioned as being “obviously caused by kava pyrone intake” (Anon, 2002).

The BfArM summarizes that “for Kavain containing drugs no proof for its therapeutic benefit, based on current scientific standards and present regulatory practice, has been submitted”; members of the scientific Kommission E conclude at the same time, that “they are convinced by the presented scientific data of the therapeutic effects of kava pyrones” and derive a therapeutic benefit for the patients, in contrast to the BfArM.

Therefore the cost benefit consideration as presented by the BfArM is questionable at least. The Cochrane Collaboration has reviewed anxiolysis by kava pyrones in 2002 and presented evidence for its therapeutic efficiency (Pittler and Ernst 2002). Data collection and evaluation was completed in November 2001. The same authors review kava pyrone anxiolysis in 2000, based on nearly the same clinical evidence. On the other hand, the AKdÄ (1999) states that the efficiency of kava pyrones has not been shown conclusively for severe fear attacks. Therefore it is surprising that neither positive evaluations (Pittler and Ernst, 2000; Pittler and Edzard, 2001) which have been available prior to the BfArM decision in June 2002, nor the statements by the “Cooperation Phytopharmaceuticals” and the Kommission E of the BfArM are mentioned in the BfArM supporting document.

BfArM only briefly mentions current therapeutic alternatives (benzodiazepines, antidepressants, buspirone) and their cost benefit ratio. On one side, reported cases with more or less severe liver damage in connection with benzodiazepin intake are mentioned. On the other hand benzodiazepines are presented as safe alternatives, without supporting proof. Other benzodiazepin ADR like paradox reactions, addiction potential or tolerance are not mentioned. Similarly, antidepressants and buspirone are given as safe alternatives. If a cost benefit consideration is extended to efficiency and

all ADR, the commitment of the BfArM to benzodiazepin and antidepressant but not of kava pyrone efficiency for anxiolytic treatment is not supported by scientific data and meta analysis.

Statements in other countries concerning the hepatotoxicity of kava pyrones always mention the cases reported in Switzerland and Germany. Despite high media attention, only a mere trickle of cases have been found in other countries. As long as it is not shown that drug users in Switzerland and Germany significantly differ from patients in other countries the most likely explanation for this cluster of kava pyrone hepatotoxicity both in time and space is an incorrect causality attribution. This does not imply that kava pyrones are devoid of hepatotoxicity, but case evaluations have to be performed *sine ira et studio*. There is a strong need for ascribing a single culprit especially in severe health problems, but very often a single cause cannot be given. Often enough severe health problems are caused by a mix of contributing factors, or no exogenous culprit can be found; this fact has to be acknowledged in any scientific evaluation of causality.

■ Conclusions

Taken together the impact of scientific advice and literature evaluation by accepted institutions (BfArM Kommission E, Cochrane Collaboration) appears to be limited in this decision of the BfArM. Discrepancies in its rationale are obvious in case evaluations, separate appearance of the same case, judgment of efficiency of therapeutic alternatives and the lack in consideration of regulatory alternatives. The sale of kava pyrone preparations as “prescriptions only” drugs as is the case in Switzerland, or the introduction of mandatory liver function checks and avoidance of other hepatotoxic medications (recommendations of the Kommission E) obviously were not considered. Unfortunately, the mass experiment with anxiolysis by benzodiazepines, antidepressants and buspirone which is now under way will show the true incidence of hepatotoxicity by these alternatives. Other countries like Switzerland, GB, USA prefer to issue patient information and warnings and institute further structured observations with a later reevaluation on a better scientific foundation. Routine treatment of all patients with psychotherapy may be desirable but is neither practical nor affordable.

With the decision to withdraw kava pyrones from the German market the BfArM did not completely follow established scientific judgment. Expert advice should at least be mentioned and discussed in decision and rationale, otherwise scientific committees will become a farce. Also, scientific societies should stick to their

evaluation, “noble silence” here is ill placed. This includes public support for consensus opinions, even in the face of journalistic fashions. It remains to be seen whether decisions by BfArM will be better founded in the next case with a similar mixture of public, political and scientific opinions.

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