

ESCOP Section

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Kava-kava: a lesson for the phytomedicine community

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The recent widespread prohibition of kava-kava (“kava”, *Piper methysticum*) has raised fundamental questions about the regulation of herbal medicines. A remedy with established efficacy and long standing popularity has been withdrawn, with severe damage to the economies of several small Pacific nations, on the basis of uncertain reports linking its consumption to liver damage. No rigorous assessment of the balance of benefit and risk has been produced in support of these measures, nor are there opportunities for a reappraisal of its value in human subjects. The world of phytomedicine has been caught unprepared. Are there lessons to be learnt to avoid such events in the future?

On the 8th November 2001 the German health authority *Bundesinstitut für Arzneimittel und Medizinprodukte* (BfArM) published evidence that suggested an association of kava consumption with liver damage in 24 cases. The media noticed that these included one death and 3 liver transplants. Various countries responded with voluntary or statutory withdrawals of kava products while the German authorities considered the situation. For many months it was expected that they would make kava available by prescription only. However on 14th June 2002 BfArM withdrew the marketing authorisations of all kava and kavain-containing medicinal products including homoeopathic products up to D4. All products had to be taken out of the distribution channels immediately. In the UK the Medicines Control Agency and Committee on Safety of Medicines (MCA/CSM) enacted a formal prohibition in January 2003. In the USA the Food and Drugs Administration (FDA) has not banned kava but it has been largely withdrawn as companies heed their insurers advice that they would be in an impossible position in the event of litigation. Even in Australia, where traditional use of kava is particularly strong, there is a suspension of therapeutic supply.

Kava has therefore largely disappeared in the developed world and it is unlikely that any ethics committee would agree to new human studies to re-assess its benefit and risk. Is there another story?

The debate on the evidence

Detailed review of the original cases published by BfArM, particularly by the German industry and trade associations, suggested that initial impressions were misleading. They came to the conclusion that the existing data on the benefit/risk assessment of kava- and kavain-containing medicinal products did not justify the withdrawal of marketing authorisations. In particular, in most of the reported cases, the causality between kava intake and liver reactions was considered as unclear because further medication was used which might have caused liver toxicity. Furthermore, in many cases, detailed information on the patients’ history, co-medication, consumption of alcohol and further particulars were missing, thus not permitting a sound evaluation of these cases. The German companies had already included risk information in package leaflets and expert information at their own responsibility and considered control through physician prescription as an appropriate solution.

In July 2002, the members of the Commission E, the committee responsible for the evaluation of herbal medicinal products at the BfArM, published their opinion about the withdrawal of kava. They felt that their scientific

competence had been ignored and, contrary to the BfArM's decision, they considered the benefit/risk ratio for patients a positive one.

The herbal sector in the UK submitted their interpretation of the data which argued that pharmacopoeial monographs since the 19th century had defined the drug kava as the whole rhizome or its simple extracts. They argued that there were very few adverse effects arising from this drug as used in the UK, Australia and the Pacific for over a century and that therefore more information was needed about the current reports. They concurred with the opinion of others in Germany and the USA that it would be possible to reduce adverse effects substantially by restricting the use of kava in the case of existing liver disease, concomitant prescription of certain other medication and that this might effectively be managed by label warnings.

Since the BfArM publication there have been the expected new cases as old dossiers were reviewed. At the end of 2002 the MCA/CSM had compiled a total of 68 cases. Of these the association between kava and liver damage was judged to be "probable" in 14 cases (including 3 liver transplants) and "possible" in 30 others. The rest were "unassessable". In justifying their prohibition the MCA/CSM argued that there was no safe basis or dosage even for prescription and that the efficacy evidence related generally to higher than current recommended doses.

Better benefit assessment and risk reduction?

In the kava prohibitions it appears that a particularly harsh assessment of the benefit-risk balance has been applied. The conclusion that there is no efficacy for kava is clearly contentious. A number of placebo-controlled and other clinical studies have demonstrated an improvement of symptoms in conditions of nervous anxiety, stress and restlessness. These have very recently been positively reviewed (Pittler and Ernst 2003) (Loew and Gaus 2002). Applying the evidence base in clinical practice is in any case a pragmatic exercise. Hard data are usually lacking or inappropriate in even the most intensely researched area. Surrogate and secondary evidence is almost always taken into account. In the case of a traditional remedy like kava (a popular mild psychoactive commodity in many parts of the world) there is a substantial secondary evidence data base which could actually be the most appropriate for assessing a treatment widely used in real human populations. However these data have been formally ignored in assessing the benefits of kava. A more appropriate assessment of benefit should be considered in future reviews of the availability of traditional herbal products.

In spite of the prohibitions there is no evidence to suggest that kava or its constituent kavapyrones are essentially toxic. The adverse data are consistent with idiosyncratic drug reactions (IDRs) ie. unpredictable adverse events. Understanding of these phenomena has accelerated in recent years, and some mechanisms have been elaborated. IDRs are most likely to be associated with certain products of drug metabolism in the body. It is already theoretically possible to screen plant products or particular extractives *in vitro* for such metabolites. It should in future be possible to understand better how to reduce their ingestion and impact in vulnerable individuals. The herbal sector should get on with the necessary research effort.

The current prohibitions have not reduced risks anyway. Anxiety conditions are wide-spread disorders which, without treatment, can have more severe psychic and social consequences which could require more medical treatment. With the withdrawal of kava products only chemical substances are available as alternatives, e.g. benzodiazepines, anxiolytics, anti-depressants, and neuroleptics. Yet, these have many side effects including liver toxicity, and benzodiazepines are potentially addictive. In future authorities should make a wider assessment of their decisions.

This has been a sorry tale. It is important that lessons are learnt by both the authorities and the herbal sector so that it is not repeated. The UK ban will be reviewed in two years and the German decision is being formally challenged. Even without the opportunity to conduct new human studies a safe role for kava may still be possible.

References

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