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Kava ichthyosis: a nitric oxide synthase inhibition?

L'ichtyose due au kava : une inhibition des nitric oxyde synthases ?

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Abstract – Purpose: Kava is a traditional Pacific beverage made from the root of *Piper methysticum*. It is mainly used for its sedative properties due to lipophilic lactones called kavalactones. Various preparations or medications made from this plant can be purchased via the internet. Kava action mechanisms include cell membrane stabilisation, inhibition of intracellular Ca^{2+} increase and enzyme inactivation. Chronic or heavy kava consumption results in the skin taking on a scaly aspect. Biologically, an isolated increase in serum gamma-glutamyltransferase is apparent. Cases of sudden death after heavy kava sessions have occurred in Australia, and nine cases in New Caledonia were reported by our forensic laboratory during the 2000–mid-2013 period. No clear explanation has been given. We describe the possible action mechanism. **Methods:** We monitored 116 heavy kava drinkers. A multiple-probe drug cocktail was used on six other volunteers, all heavy and chronic kava drinkers, before and after kava abstinence to carry out CYP450 phenotyping. **Results:** The heavy chronic drinkers showed an isolated increase in GGT without any biological or clinical abnormality other than scaly skin. With the multiple-probe drug cocktail an inhibition of the CYP1A2 isoenzyme was demonstrated. In kava dermatopathy a lack of epithelial nitric oxide production leading to an increased S-nitroso-glutathione degradation by the epithelial gamma-glutamyltransferase should be considered. **Conclusions:** As there are close structural and functional similarities between nitric oxide synthase (NOS) and CYP1A2, and as we have formerly demonstrated that kava inhibits CYP1A2, an inhibition of NOS in chronic kava drinkers must be studied to see if ichthyosis can be explained, and if high blood GGT level is a reflection of epithelial cell GGT activity. Furthermore, a decrease in NO bioavailability can cause myocardial and vascular dysfunctions and hypercoagulability, leading to acute coronary syndrome or ischemic stroke. This mechanism should be explored in cases of “post-kava session sudden death”.

Key words: Kava, abuse, ichthyosis, GGT, sudden death, NO synthase

Résumé – Objectifs : Le kava est une boisson traditionnelle faite à partir du rhizome de *piper methysticum*. Il est principalement consommé pour ses propriétés sédatives dues à des lactones lipophiles appelées kavalactones. Des préparations variées à base de kava peuvent aussi être commandées sur Internet. Les mécanismes d'action du kava comprennent une stabilisation membranaire, une inhibition de l'élévation du Ca^{2+} intracellulaire et des inactivations enzymatiques. Après une consommation chronique et importante on note cliniquement un aspect écaillé de la peau. Du point de vue biologique on observe une augmentation isolée de gamma-glutamyltransférase sérique. Des cas de mort subite après consommation de kava sont survenus en Australie, et neuf cas sont survenus en Nouvelle-Calédonie durant la période de 2000 à mi-2013. Aucune explication satisfaisante n'a été apportée et nous décrivons le possible mécanisme d'action de ces effets délétères. **Méthodes :** Nous avons réalisé le suivi clinique et biologique de 116 gros buveurs de kava. De plus, un cocktail multimédicamenteux pour phénotypage CYP450 a été administré à six autres volontaires, buveurs chroniques de kava, avant et après abstinence de kava. **Résultats :** Les buveurs de kava montraient une augmentation isolée de GGT sérique sans autre anomalie biologique ou clinique qu'une peau écaillée. La sonde multimédicamenteuse a mis en évidence une inhibition des enzymes du CYP1A2. Dans la dermatopathie liée au kava, un défaut de production épithéliale de monoxyde d'azote conduisant à une augmentation de dégradation de S-nitroso-glutathion par la gamma-glutamyltransférase épithéliale doit être considéré. **Conclusions :** Comme il existe des similitudes structurales et fonctionnelles entre la nitrique oxyde synthase (NOS) et le CYP1A2, et étant donné que nous avons montré précédemment que le kava inhibait le CYP1A2, une inhibition de la NOS chez les buveurs chroniques de kava devrait être étudiée afin de pouvoir expliquer le phénomène d'ichtyose et de confirmer si l'élévation isolée de la GGT

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sérique est le reflet de l'activité GGT des cellules épithéliales. De plus, une diminution de la biodisponibilité du NO peut causer des dysfonctionnements cardiovasculaires pouvant entraîner un syndrome coronarien aigu ou un accident vasculaire cérébral ischémique. Un tel mécanisme devrait être étudié dans les morts subites survenant au décours d'une consommation de kava.

Mots clés : Kava, abus, ichtyose, GGT, mort subite, NO synthase

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1 Introduction

Kava is a traditional Pacific beverage made from the root of *Piper methysticum*. It is mainly used for its sedative properties due to lactones called kavalactones. Various preparations can be purchased via the internet. The kavalactones are highly lipophilic and after oral absorption rapidly go into the central and peripheral nervous system where they have a stabilising effect on the neuronal membrane [1] and cause a decrease in intracellular Ca^{2+} , modifying the nervous influx transmission and the activation of numerous enzymes.

After chronic and heavy consumption of kava, dryness of the consumers' skin becomes apparent, which can turn into ichthyosis, which in some cases can be severe (figures 1–3). In our experience, it is reversible within two or three weeks of giving up kava. Some suggestions have been made to explain this phenomenon [2], but none have been verified. Biologically, an isolated increase in serum gamma-glutamyltransferase is classically observed [3]. In addition, we report nine cases of sudden death following a kava session; such cases have also been reported in Australia [4].

2 Methods

After a clear explanation and written consent, clinical evaluation and biological parameters were studied in 116 heavy and chronic kava drinkers from New Caledonia and the Futuna Islands (where the local authorities gave their approval) who showed only an isolated increase in gamma-glutamyltransferase activity (GGT) – other biological parameters being in the normal range – without any sign of liver function alteration or ultrasonography abnormalities. This isolated elevation is present in our study in 60% of the heavy or chronic kava drinkers and returns to normal values after giving up kava, suggesting hepatic enzymatic induction [3].

To verify if the kava beverage has an action on CyP450 enzymes, we used a multiple-probe drug cocktail in six New Caledonian volunteers; heavy kava drinkers who agreed to completely stop kava consumption for one month [5]. Full written consent was obtained and the pharmacist-inspector of the Direction of sanitary and social affairs of New Caledonia (DASS-NC) approved it. The multiple-probe drug cocktail used permitted us to do phenotyping of CYP3A4, CYP2D6, CYP2E1, CYP2C9 and CYP1A2 by measuring the metabolite/parent drug ratio before and after one month of kava abstinence [6].

In New Caledonia, over a period of thirteen years (2000–mid-2013), we identified nine cases of sudden death



Fig. 1. Ichthyosis in a Melanesian kava drinker (photo: YB).



Fig. 2. Ichthyosis in a Melanesian kava drinker (photo: YB).



Fig. 3. Ichthyosis in a Melanesian kava drinker (photo: YB).

(with no obvious causes) following kava consumption. Upon discovery of a corpse, consumption of kava may be detected incidentally during toxicological screening performed by the forensic laboratory as part of the search for causes of death.

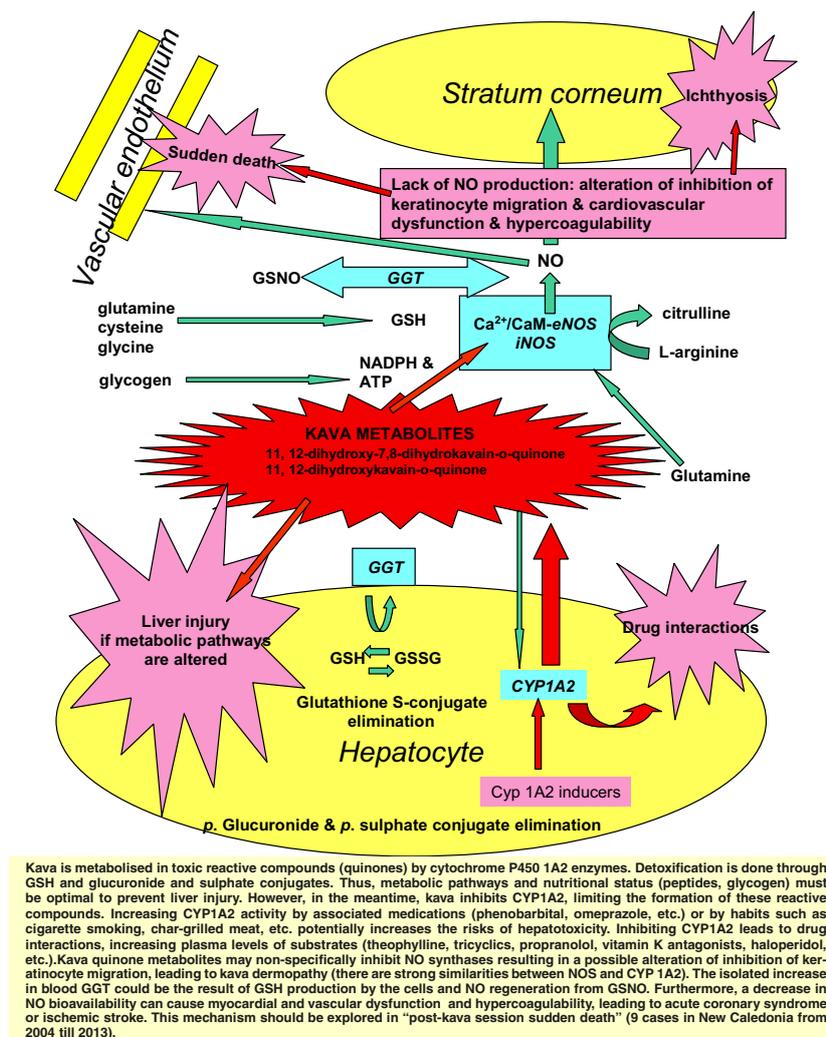


Fig. 4. Hypothetical action mechanism and deleterious consequences.

3 Results

No induction was noticed, but a significant inhibitory effect for CYP1A2 with the kava beverage was found [6]. The GGT blood levels of the volunteers, originally twice the upper normal value ($N < 43$ UI/L), returned to normal after the abstinence period, as did the appearance of the skin. Kava consumption or non-consumption was verified by high-performance liquid chromatography of the volunteers' urine and hair according to the methods previously described [7, 8].

It has been demonstrated that insufficient NO production is responsible for keratinocytes hyperproliferation, leading to ichthyosis [9]. To see if kava dermopathy could be due to a lack of NO production, as a first step, a NO defect resulting from a lack of substrate or the impossibility of the epithelial cells producing enough Ca^{2+} to activate NO synthesis had to be excluded. So, as kava does not inhibit NMDA receptors [1], we decided to try to increase intracellular Ca^{2+} by giving oral glutamate to kava drinker volunteers. Arginine was also given *per os* as a substrate for NO synthesis (2.5 g arginine-glutamate twice daily for twenty days to two volunteers who continued their kava consumption; this dosage being classically used

as antiasthenic medication without any side effects) without a marked improvement of the skin's appearance. Then arginine-glutamate was mixed in cold cream (6%) and administered locally twice daily for seven days, using the same volunteers, without any marked success.

In the nine cases of sudden death, the blood toxicological screening performed by high-performance liquid chromatography highlighted the presence of kavalactones, in significant concentrations in most cases, and showed recent use of kava (within minutes or a few hours before death). The search for drugs was negative for all the cases; trace amounts of cyamemazine were found in one case, and one case had a low alcohol blood level (0.45 g/L). No autopsies were carried out but clinical information was obtained in six cases (*i.e.*: heavy smoker, severe hypertension, sleep apnoea, cardiac arrhythmias, asthma, family history of sudden death).

4 Discussion (figure 4)

NO is synthesised from l-arginine in two steps, catalysed by nitric oxide synthase (NOS; EC 1. 14. 13. 39) and there is

a catalytic relationship between NOS and cytochrome p450. In addition, the gene structure of both enzymes shows that the C-terminal domain of NOS is identical to the CYP450 protein. There are three forms of NOS: epithelial (eNO), neuronal (nNO) and inducible (iNO). The latter is synthesised under particular circumstances (stress induced by aggression) and is calcium-independent. The former two types are normally expressed and are calcium-dependent enzymes. In the tissues, NO is stored in S-nitroso-glutathione (GSNO). *In vitro*, GGT metabolises GSNO, resulting in the separation of NO, and it has been shown that GGT controls the rate of NO production from GSNO by T cells [10].

In kava dermopathy, possible NOS non-specific inhibition by kava, resulting in an alteration of the inhibition of keratinocyte migration, has never been studied. Moreover, a recent publication highlighted a suppression of iNOS by flavokavain [11]. In NOS inhibition, the metabolism of GSNO by GGT is increased, leading to an elevation of keratinocyte GGT activity. Thus, the elevated GGT blood level in heavy kava drinkers could be the result of an increased GSNO metabolism to destock NO.

A decrease in NO bioavailability may cause myocardial and vascular dysfunctions and hypercoagulability, leading to acute coronary syndrome or ischemic stroke [12]. The involvement of such a mechanism in worsening a pre-existing cardiovascular disease in “post-kava session sudden death” should be explored.

5 Conclusion

In chronic kava drinkers, kava ichthyosis and the isolated high GGT blood level could be explained by the described mechanism related to NO.

In order to confirm this “NO deficiency” hypothesis, the dosages of NO and the NOS activity of various tissues (*i.e.*: vascular endothelium, epithelium) of heavy kava consumers should be examined. An induction of CYP1A2 by a vegetable diet (Brussels sprouts, broccoli, etc.) could be tried to reverse possible NOS inhibition and high GGT blood levels; but as some kava-related toxic compounds (quinones) are probably synthesised by the CYP1A2 isoenzyme, inducing CYP1A2 under a kava regimen could be hazardous (possible hepatotoxicity).

We strongly recommend that people suffering from known vascular or cardiac dysfunctions drink kava in moderation and that they maintain a balanced diet.

Conflicts of interests. No competing interest.

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