

Hepatic injury due to traditional aqueous extracts of kava root in New Caledonia

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Traditional aqueous kava extracts were the most probable cause of hepatitis in two patients presenting with markedly elevated transaminases and hyperbilirubinemia. A consequent survey of 27 heavy kava drinkers in New Caledonia showed elevated gamma glutamyl transferase in 23/27 and minimally elevated transaminases in 8/27. We conclude that not only commercially available, but also traditionally prepared kava extracts may rarely cause liver injury. The increased activity of gamma glutamyl transferase in heavy kava consumers in the presence of normal or minimally elevated transaminases is probably not a sign of liver injury, but rather reflects an induction of CYP450 enzymes. *Eur J Gastroenterol Hepatol* 15:1–4 © 2003 Lippincott Williams & Wilkins

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Introduction

New Caledonia is an island in the South Pacific where consumption of the psychoactive aqueous extract from kava root (*Piper methysticum* Forst.f.) is common. Kava also represents a major export good and therefore plays an important social and economic role for Pacific islanders [1]. A previous study from Australia reported adverse health effects associated with chronic heavy kava consumption, such as malnourishment, haematuria, blood cell dyscrasia, shortness of breath accompanied by elevated p-waves on a resting electrocardiogram and complaints of poor health [2]. Plasma levels of gamma glutamyl transferase (GGT) were also greatly increased in kava users, but no cases of acute liver injury were identified in this study. In Europe, hepatitis and fulminant hepatic failure in relation to acetonic or ethanolic extracts of kava that are used for sleep and anxiety disorders have recently been reported [3–8] and led to regulatory actions. Hepatotoxicity related to the aqueous kava extract has not been documented, and the mechanism of kava hepatotoxicity is unknown.

Case reports of kava-related hepatitis

The study was approved by the pharmacist–inspector of the Direction des Affaires Sanitaires et Sociales de Nouvelle-Calédonie. All volunteers and also the patients presented in the case reports were informed and gave their written informed consent for the study and publications of results.

Case 1

A 59-year-old female patient of oceanian origin started drinking traditional kava prepared with tap water and dried kava root imported from the islands of Vanuatu. Four weeks later she presented with icterus, transaminases elevated 18 and 14 times the upper limit of normal (aspartate amino transferase, 671 U/l; normal, <37 U/l; and alanine amino transferase, 568 U/l; normal, <40 U/l), a prolonged thromboplastin time (Quick value, 62%; normal, 70–120%) and an eosinophilia of 10%. Total bilirubin was not measured until 2 weeks after the initial presentation, when it was 30.7 µmol/l (normal <17 µmol/l). Abdominal ultrasound showed no dilatation of the bile ducts, and the titres for anti-nuclear and anti-DNA antibodies were minimally elevated (1/128 and 1/20). Hepatitis serology was positive for anti-HBc immunoglobulin (Ig)G antibodies but negative for HBs antigen and antibodies against HBs, hepatitis A and hepatitis C. The patient did not consume any alcohol. Long-term medication included lisinopril, phenobarbital and fenofibrate, which had all been taken for several months or years. Initially all drugs and kava drinking were stopped, but the formerly taken drugs were then re-started. Drinking kava was not re-started and the patient recovered, and laboratory values normalized over the following 3 months.

Case 2

A 55-year-old female patient of oceanian origin started drinking traditional kava in a quantity of about 4 cups per evening, corresponding to approximately 18 g kava-

lactones per week. Five weeks later, she presented with fatigue, icterus and transaminases and total bilirubin elevated 42 and 13 times the upper limit of normal, respectively (aspartate amino transferase, 1569 U/l; alanine amino transferase, 1666 U/l; total bilirubin, 220 μ mol/l). Abdominal ultrasound showed no dilatation of the bile ducts. Antinuclear antibodies were minimally positive (1/40), autoantibodies against LKM and smooth muscle were negative. Hepatitis serology was positive for anti-HBc and anti-HBs IgG antibodies, but negative for anti-HBc IgM and hepatitis A IgG antibodies and HBs antigen. Intake of other drugs and alcohol was denied. Drinking kava was consequently stopped and the patient recovered and laboratory values normalized over the following 3 months.

Consequent genotyping of these two patients did not indicate CYP2D6 poor metabolizer status.

Survey of heavy kava drinkers

A cohort of 27 heavy kava drinkers was recruited from New Caledonian kava bars. They gave their written informed consent to provide a blood sample for determination of liver enzymes and answered a question-

naire regarding demographic information, kava consumption and general health.

Results are summarized in Table 1. All subjects had regularly been drinking kava for at least 5 years with a mean intake equivalent to about 32 g kavalactones per week or approximately 70 mg/kg per day [9]. Twelve out of the 27 subjects also reported drinking alcohol. Eighteen smoked tobacco and nine smoked cannabis. Three subjects had transaminases above 1.5 times the upper limit of normal. Twenty-three subjects showed an increase of GGT, which tended to increase with higher intake of kavalactones as shown in Fig. 1 (Spearman rank coefficient for correlation $R = 0.48$, $P = 0.01$). Fifteen subjects had ichthyotic or dry skin. Alkaline phosphatase and bilirubin were normal in all subjects, none of them showed symptoms of liver disease and all were in good general health. Four subjects markedly reduced their kava consumption and showed a normalization of skin changes and GGT at a follow-up visit 1 month later.

Discussion

In the two presented patients, the failure to identify other causes of liver injury, the time interval from the

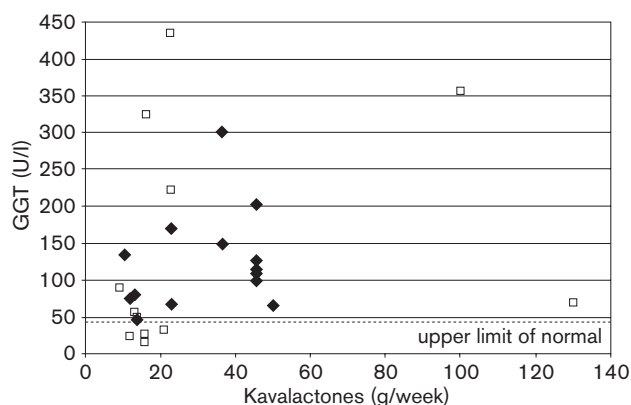
Table 1 Clinical and laboratory data of 27 chronic heavy kava drinkers

Subject	Sex	Age (years)	Ethnic origin	Estimated kava consumption (cups per week/grams of kavalactones per week)	ASAT (< 37 U/ml)	ALAT (< 40 U/ml)	GGT (< 43 U/ml)	Alcohol (drinks per week)	Skin	Medication
1	Male	31	Caucasian/oceanian	200/130	28	28	69	7	Dry	None
2	Male	39	Oceanian	154/100	76	83	356	5	Normal	Melanesian medications
3	Female	50	Oceanian	77/50	34	46	65	0	Dry	None
4	Female	43	Oceanian	70/46	25	27	126	0	Dry	None
5	Female	43	Oceanian	70/46	19	19	99	0	Ichthyosis	Diltiazem
6	Male	44	Oceanian	70/46	27	31	109	0	Dry	None
7	Male	47	Oceanian	70/46	29	27	201	0	Ichthyosis	Linisopril + hydrochlorothiazide
8	Female	42	Oceanian	70/46	24	31	114	0	Normal	None
9	Female	43	Oceanian	56/36	39	29	149	0	Dry	None
10	Male	43	Oceanian	56/36	31	33	147	0	Ichthyosis	None
11	Female	45	Caucasian/oceanian	56/36	39	78	300	0	Normal	None
12	Male	39	Oceanian	35/23	40	54	435	4	Dry	Salbutamol inhaler
13	Male	42	Caucasian	35/23	23	26	67	0	Normal	None
14	Male	26	Oceanian	35/23	39	31	222	10	Dry	None
15	Male	31	Oceanian	35/23	23	32	169	0	Dry	None
16	Male	39	Caucasian	32/21	20	35	32	8	Normal	None
17	Male	32	Oceanian	25/16	43	34	324	4	Dry	None
18	Male	48	Caucasian	24/16	18	27	27	8	Normal	None
19	Female	30	Oceanian	24/16	22	21	15	5	Dry	None
20	Male	36	Caucasian	21/14	48	93	49	9	Normal	None
21	Male	41	Black	21/14	18	24	46	0	Normal	None
22	Male	52	Caucasian	20/13	16	25	80	0	Normal	Perindopril
23	Male	53	Caucasian	20/13	20	23	56	10	Dry	None
24	Male	30	Caucasian	18/12	19	30	75	0	Normal	None
25	Male	35	Caucasian	18/12	15	23	24	1	Normal	None
26	Female	27	Oceanian	16/10	21	26	43	0	Dry	None
27	Male	41	Caucasian	14/9	21	20	89	10	Normal	Atorvastatine

ASAT, aspartate amino transferase; ALAT, alanine amino transferase; GGT, gamma glutamyl transferase.

The quantification of kavalactones was performed in kava beverages obtained from several New Caledonian kava bars by high-performance liquid chromatography as previously described [9] (1 cup \approx 70 ml \approx 650 mg kavalactones). Alkaline phosphatase and bilirubin values were measured in all chronic kava users and were normal in all subjects.

Fig. 1



Plasma levels of gamma glutamyl transferase (GGT) versus intake of kavalactones in 27 heavy kava drinkers: (◆) no history of concomitant alcohol use, (□) history of concomitant alcohol use.

onset of kava consumption to presentation with symptoms and the resolution of the biochemical abnormalities after abstinence from kava strongly argue for the consumption of aqueous kava extract as the cause of liver injury. Thus, the similar clinical presentation in previously reported cases associated with commercial ethanolic and acetic extracts of kava suggests a hepatotoxic potential of kava regardless of its dose and mode of preparation. The mechanisms leading to liver injury are not known and may involve a metabolic and/or an allergenic idiosyncrasy. An allergenic component is suggested by the apparently low incidence, the latency time of several weeks in these and previously reported cases, the eosinophilia in case 1 and by a positive lymphocyte transformation test [10] in one previous case [6]. In contrast to Caucasian patients [6], CYP2D6 poor metabolizer status was not identified as a risk factor.

The survey of heavy kava drinkers revealed the well-known skin changes (also known as kava dermatopathy [11]) and an increase in GGT as the only abnormalities associated with kava, two observations that were also reported in a previous survey of heavy kava users in an Australian Aboriginal community [2]. However in contrast to this previous study, we did not observe a generally poor health status in heavy kava users. A comparison with our study may be limited by different methods and the unknown amount of ingested kavalactones in the Australian study subjects, but a possible explanation for this discrepancy might be confounding social factors and concomitant diseases in the Aboriginal community. GGT activity increases with induction of CYP450 enzymes [12] and is thus not a specific marker of liver injury, particularly in the absence of other symptoms and signs of liver disease. Indeed, in

mice fed 100 mg/kg kavalactones per day for 11 days (an amount comparable with the consumption of heavy kava users in New Caledonia) we found no signs of liver injury on histology, but did find a significantly increased liver weight of 1.72 ± 0.08 g versus 1.29 ± 0.07 g (95% confidence interval, 0.20–0.67 g; $P < 0.005$) (mean \pm standard error and 95% confidence interval on the difference, P value of student's t test) and CYP450 content per liver [13] of 14.1 ± 1.6 nmol versus 9.0 ± 1.0 nmol per liver (95% CI, 0.8–9.4 nmol per liver, $P < 0.05$), as compared with control animals ($n = 6$ per group, unpublished data from our laboratory). Previous studies have identified hydroxylated kava metabolites in humans [14] and have shown that kavalactones interfere with CYP450 enzymes *in vitro* [15], suggesting that kavalactones are substrates of CYP450. As suggested by the present data, kava consumption may induce CYP450 and thus increase the risk for drug interactions when consumed with other drugs.

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Conflicts of interest

None declared.

Authors' contributions

Stefan Russmann: animal experiment, data interpretation, clinical and causality evaluation, coordination of genotyping, literature review and writing of the manuscript. Yann Barguil: planning and execution of cohort study of heavy kava drinkers in New-Caledonia, data acquisition and reporting of three kava related cases of hepatitis, data interpretation, editing of the manuscript. Pierre Cabalion and Marina Kritsanida: recruitment of heavy kava drinkers and editing of the manuscript.

Daniel Duhet: quantification of kavalactones and editing of the manuscript. Bernhard H. Lauterburg: design of animal experiment, data interpretation, hepatological evaluation and editing of the manuscript.

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