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Case Report

Fatal kavalactone intoxication by suicidal intravenous injection

Raimo A. Ketola [a,*], Jenni Viinamäki [a], Ilpo Rasanen [a], Anna Pelander [a], Sirkka Goebeler [b]

[a] University of Helsinki, Faculty of Medicine, Department of Forensic Medicine, P.O. Box 40, FI-00014 University of Helsinki, Finland
[b] National Institute for Health and Welfare (THL), Department of Forensic Medicine, P.O. Box 30, FI-00271 Helsinki, Finland

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ABSTRACT

Kavalactones are a group of compounds found in kava, a beverage or extract prepared from the rhizome of the kava plant (*Piper methysticum*). Traditionally kava extracts have been used for their anxiolytic and sedative properties. Sales of kava extracts were severely restricted or prohibited in European countries in 2002 following several cases of serious hepatotoxicity. Here we report a case where high concentrations of kavalactones and ethanol were detected in post mortem femoral blood. An injection needle with a 10-mL syringe containing 7.5 mL of slightly yellowish liquid was found next to the victim, and there were numerous needle prints on both lower arms following the venous tracks. No evidence of other cause of death was found in the medico-legal investigation. The case was therefore classified as suicide using an injection of kavalactones intravenously together with alcohol poisoning.

1. Introduction

Kavalactones are a group of compounds found in kava, a beverage or extract prepared from the rhizome of the kava plant (*Piper methysticum*) [1]. Kava extracts have been used for many centuries among South Pacific islanders for their anxiolytic and sedative properties [2,3]. These properties are due to kavalactones, which are pyrone- or dihydropyrone-containing components (Fig. 1). The six kavalactones methysticin, 7,8-dihydromethysticin, kavain, 7,8-dihydrokavain, yangonin, and desmethoxyyangonin, account for approximately 96% of the total kavalactones [4]. Commercial products are usually ethanol or acetone extracts, while traditional extracts used in the South Pacific have been water extracts. These extracts as well as kava products in the form of tablets or capsules in therapeutic use are meant to be administered orally, while extracts for intravenous injection are not marketed. The German Commission E recommended dosages of kavalactones of 60–120 mg/day for no longer than 3 months without medical evaluation [5]. Sales of kava extracts were severely restricted or prohibited in European countries in 2002 following several cases of serious hepatotoxicity [6].

The toxicity of kavalactones is due partly to inhibition of CYP P450 enzymes, especially CYP2C9, 2C19, 2D6, and 3A, which can affect the metabolism of other products or drugs, thus possibly forming toxic metabolites [7]. On the other hand, kava products have been found to increase the expression and activity of CYP1A1 after repeated administration with large doses [8]. This indicates that kava products have a potential for drug interactions with other products or with drugs that are metabolized by the CYP450 enzymes. Other possible indirect causes of toxicity are the ability to inhibit cyclooxygenase enzymes COX-1 and COX-2 [9] as well as glutathione depletion [10]. Kavalactones may cause hepatic stress if not mediated by glutathione, and are usually metabolized in the liver by lactone hydrolases [11]. Kavalactones can also be phototoxic as they form radical oxygen species under UV irradiation, which, in turn, can result in lipid peroxidation and DNA damage [12]. Other speculations on the origin of hepatotoxicity of kava cite pipermethystine [13], flavokavain B [14] or mold hepatotoxins [15–18] found in kava extracts, although no clear results have yet been obtained. Kavalactone pharmacophores and their effect on several drug targets as well as the toxicokinetics of kava have recently been reviewed [19,20]. These show that kavalactones can induce toxicity and hepatotoxicity via several routes, such as blockade of voltage-gated sodium ion channels, reduced excitatory neurotransmitter release from blockade of calcium ion channels, enhanced ligand binding to F-aminobutyric acid (GABA) type A receptors, reversible inhibition of monoamine oxidase B, inhibition of cyclooxygenase, and reduced neuronal reuptake of dopamine and noradrenaline.

* Corresponding author. Tel.: +358 2941 27487; fax: +358 9 454 4117.
E-mail address: raimo.ketola@helsinki.fi (R.A. Ketola).

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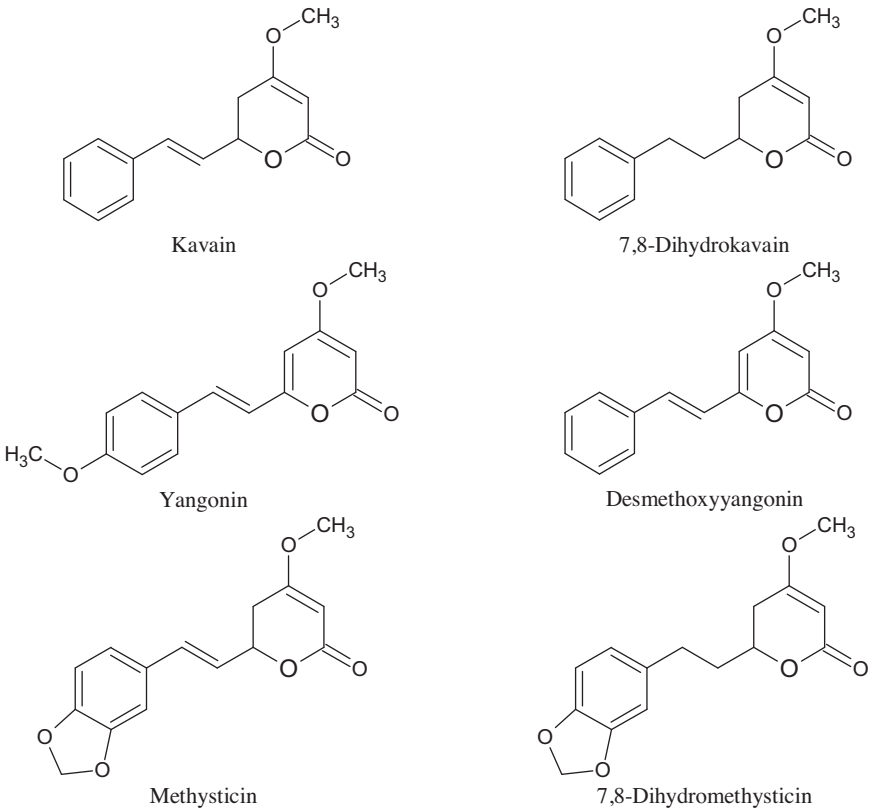

Fig. 1. Chemical structures of the major kavalactones.

Pharmacokinetics studies with rats *in vivo* showed that in intravenous (i.v.) dosing the half-life of kavain ($T_{1/2}$) was 0.63 h, which is very short and about half of that in oral dosing [6] and much shorter than with rat liver microsomes, which ranged from 5.7 to 13.9 h for different kavalactones [21]. However, in human clinical studies the $T_{1/2}$ value in oral dosing has been much longer, about 9 h [22]. Nevertheless, it shows that the maximum plasma concentration (C_{max}) can be obtained immediately, and that the rate of elimination from plasma is fairly rapid. Another important fact obtained in the study by Mathews et al. [6] was that the C_{max} in i.v. dosing was three times higher than in oral dosing, even though the kavain dosage was much less (about 7 mg/kg in i.v. dosing compared to about 97 mg/kg in oral dosing). This means that if extracts containing high concentrations of kavalactones meant to be taken orally are infused i.v. there can be a sudden increase of kavalactone concentrations in plasma, causing acute intoxication.

The pharmacokinetic and pharmacodynamic interactions of kava with other substances were reviewed by Anke and Ramzan in 2004 [1] and with ethanol by Li and Ramzan in 2010 [23]. These reviews show that there are reasonable grounds to suggest that a metabolic interaction of kava with, say, alcohol might be a possible mechanism of kava hepatotoxicity. Based on the review by Clouatre in 2004 [24] the risk of acute intoxication by ingestion of kava beverage or extracts (whether water, acetone, or ethanol extracts) is rather small. However, there is no mention of i.v. injection of extracts and its possible acute effect on health or toxicity.

A major survey of clinical case reports was conducted by the World Health Organization (WHO) in 2007 [25]. Based on this, 93 case reports were identified in which seven patients died and 14 patients had liver transplants. Eight cases were found to have a close association between the use of kava and liver dysfunction because the patients recovered on withdrawal of kava and no other plausible cause of the liver problems was identified. Fifty-three cases were classified as having a possible relationship, but they could not be fully assessed due to insufficient data or other potential causes of liver damage. Five cases had a positive effect, as the patient improved on withdrawal of kava, but worsened with reintroduction. Most of the other case reports could not be evaluated due to lack of sufficient information. In a critical review of clinical cases it was concluded that the major risk factors in the use of kava products are overdose, prolonged treatment, and co-medication with synthetic drugs which might cause hepatotoxicity [26]. The same conclusion was drawn from the analysis of 26 case reports [27]. To our knowledge there are no publications reporting acute poisoning or suicides using kavalactones.

This study reports the first time that acute poisoning has been encountered in i.v. injection of kava extract together with ethanol, caffeine, and salicylate intake.

2. Experimental

2.1. Case details

A young man (age 36) was found dead in his bathroom. He was sitting on the floor, and next to his left hand there was an injection needle with a 10-mL syringe containing 7.5 mL of slightly yellowish liquid. There were two ties around his right upper arm, and numerous needle prints on both lower arms following the venous tracks. Several suicide notes were found in the apartment. No other people were involved, and we have no information on the time interval between the times of dosing and death. The victim had suffered from long-term depression and had acted suicidally before. He had been in psychiatric care for depression, but not in