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Kava Treatment in Patients with Anxiety

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In several clinical trials, mainly conducted with a dose of 300 mg kava extract per day, kava has been employed successfully for the treatment of anxiety disorders.

The goal of the placebo-controlled double-blind outpatient trial was to obtain more information on the dosage range and efficacy of a kava special extract WS 1490 in patients with non-psychotic anxiety. 50 patients were treated with a daily dose of 3 × 50 mg WS 1490 during a 4-week treatment period followed by a 2-week safety observation phase.

In the active treatment group, the total score of the Hamilton anxiety scale (primary efficacy variable), showed a therapeutically relevant reduction in anxiety versus placebo (more than 4 points). In the secondary variables studied, HAMA 'somatic and psychic anxiety' subscales, the Erlangen anxiety, tension and aggression scale (EAAS), the brief personality structure scale (KEPS), the adjective checklist (EWL 60-S) and clinical global impressions scale (CGI), a trend in favour of the active treatment was detectable. WS 1490 was well tolerated and showed a safety profile with no drug-related adverse events or post-study withdrawal symptoms.

It can be concluded that the applied 150 mg WS 1490 per day is an effective and safe treatment of non-psychotic anxiety syndromes in the described population. Copyright © 2004 John Wiley & Sons, Ltd.

Keywords: kava; clinical trial; herbal medicine; anxiety; efficacy.

INTRODUCTION

In general, the use of psychotropic herbs has increased and many patients take such medication because of the favourable adverse event profiles. In particular, public interest in *Kava kava*, the roots of the oceanic plant *Piper methysticum*, has been augmented as demonstrated by an increase in recent reviews about this topic (Mack, 1999; Pepping, 1999). The pharmacologically active ingredients of the root are a group of substances known as kava lactones or pyrones which have been found to have significant anxiolytic, tranquillizing, anticonvulsive and analgesic effects via non-opiate pathways (for review see Singh, 1992). CNS effects seem to be mediated by several mechanisms. Studies have been contradictory regarding its GABA-receptor-binding capacity (Jussofie *et al.*, 1994; Davies *et al.*, 1992). However, a major mechanism in anticonvulsive, analgesic and centrally muscle relaxing effects is assumed to be the blockage of voltage-gated sodium and calcium channels (Schirrmacher *et al.*, 1999; Friese and Gleitz, 1998; Gleitz *et al.*, 1995) which thus suppresses the release of endogenous glutamate (Gleitz *et al.*, 1996). Additional psychotropic effects may be due to influences on neurotransmitter metabolism by blocking of MAO-B (Uebelhack *et al.*, 1998), the activation of mesolimbic dopaminergic neurons or effects on 5-serotonin levels (Baum *et al.*, 1998).

In several clinical studies a statistically significant superiority of the special kava extract WS 1490 compared with placebo has been shown (Kinzler *et al.*, 1991; Warnecke, 1991; Woelk *et al.*, 1993; Volz and Kieser, 1997; Heinze *et al.*, 1994) using doses of 300 mg per day. A similar therapeutic efficacy for lower doses is to be expected according to the German Commission E monograph, which recommends a daily dose of 70 to 120 mg kava lactones per day (Commission E monograph, 1990). Therefore, more detailed information about a lower dose of our kava special extract WS 1490 was sought. This extract, which is standardized to 70% kava lactones, contains only the naturally present (+) enantiomers. In a special extraction process these lipid-soluble kava lactones have been enriched leading to a standardized extract with good oral bioavailability (Biber *et al.*, 1992; Johnson *et al.*, 1991). In an effort to define better a safe and effective dosing for patients, investigation of a low dose of the WS 1490 preparation was envisaged for this study by testing the efficacy and tolerability of 3 × 1 capsule of 50 mg kava special extract WS 1490† versus placebo in patients with non-psychotic anxiety.

SUBJECTS AND METHODS

The study was designed, performed and evaluated in accordance with the Principles of Proper Conduct of Clinical Studies with Medicinal Products, the GCP guidelines and the Declaration of Helsinki of 1975 revised as of 1983. The randomized, placebo-controlled, double-blind study was conducted over a treatment period of 4 weeks in 50 patients (39 women and 11 men), aged 51–90 years (mean age 76 years). The sex distribution was similar in each of the two groups.

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† WS 1490 is contained in Laitan ® (Dr Willmar Schwabe GmbH & Co., Germany).

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The inclusion criteria were the presence of non-psychotic anxiety (DSM-III-R criteria: agoraphobia, specific phobia, generalized anxiety disorder and adjustment disorder with anxiety) with a total HAMA score of >18 and a score >12 in the multiple choice vocabulary test (MWT-B). Each patient provided a declaration of informed consent.

The exclusion criteria were severe psychic illnesses such as endogenous depression, organic and schizophrenic psychoses, psychopathologies and suicidal tendencies. Patients with sleep apnoea and cerebral ataxia were excluded from the study. Severe liver, kidney, lung or cardiovascular disease, neoplasm, and known drug, alcohol and medication abuse likewise led to exclusion. Patients receiving treatment that could interfere with the absorption, metabolism or potentiation (barbiturates, benzodiazepines) of kava and that could not be discontinued were excluded, as were patients incapable of filling out the self-rating scales or of cooperating. Patients with myasthenia gravis, acute poisoning with centrally sedative drugs or alcohol, or primary hypotension (systolic/diastolic pressure less than 90/60 mmHg) were not allowed to participate. Inclusion and exclusion criteria were checked by the clinical investigator and verified by the monitor during source data control.

Primary efficacy variable. The Hamilton anxiety scale (HAMA) (CIPS, 1981) allows an anxiety state to be evaluated in terms of 14 groups of emotional and somatic symptoms. The total HAMA score was determined upon inclusion in the run-in phase, at the start of treatment and after 2, 3 and 4 weeks of treatment.

Secondary efficacy variables. The HAMA subscales with the dimensions 'somatic' and 'psychic anxiety' were applied. Additionally, the Erlanger anxiety, tension and aggression scale (EAAS) (CIPS, 1981), a self-rating scale with 15 items for determination of situational anxiety and tension, was used. Supplementary tests such as the brief personality structure scale (KEPS) (Weidenhammer and Burkard, 1987), a self-rating scale for the objective assessment of the strength of the personality dimensions 'neuroticism', 'extroversion', 'dominance' and 'control' in terms of 48 items, and the adjective checklist (EWL 60-S) (CIPS, 1981; Janke and Debus, 1977), a self-rating scale comprising 60 adjectives for determination of current wellbeing, were employed. Finally, the clinical global impressions (CGI) (CIPS, 1981), a three-item scale for assessment by a rater, was used for risk–benefit evaluation. The assessment was done by the physician, who evaluated successively the severity of the illness, the recovery course, and the therapeutic efficacy (intended drug effect). With the exception of the CGI, which was carried out in weeks 1 and 4 of the treatment phase, the patients were investigated and questioned every week, i.e. five times altogether.

The 4 week treatment phase was preceded by a 1 week run-in phase without study medication. The patients were randomized to the treatment (active treatment or placebo) in blocks of 10 using a computer-generated random scheme. During the treatment phase the patients received 3×50 mg capsules/day of the special extract WS 1490, a monoextract from the dried root of the kava plant, standardized to 70% kava lactones and containing 30% of ancillary substances that promote its absorption, or placebo capsules, which were identical into appearance, smell and taste. Concomitant medication with other psychotropic substances such as antidepressants, major tranquillizers, psychostimulants and anxiolytics was not allowed. The treatment phase was followed by a 2 week follow-up period with documentation of any withdrawal symptoms.

Safety of the test substance was investigated by performing laboratory tests at the start and end of treatment, by daily blood pressure and heart rate measurements, and by documenting all adverse events during and up to 2 weeks after termination of the treatment phase.

Sample size determination and evaluation. As the assumption of normality was not justified for the primary efficacy variable HAMD total score, a non-parametric analysis with the U-test (Bühning and Trenkler, 1978) was specified in the protocol. A trial size of 50 patients was calculated to achieve a power of 90% at a type I error rate of $\alpha = 5\%$ assuming a stochastic superiority of the verum group of 0.74 (Noether, 1987). In confirmatory analysis, the values of the primary efficacy variable after 4 weeks and 2 weeks of treatment were to be tested. Assuming that the treatment effect would at least not decline over the course of treatment, this sequence of testing was stipulated in the protocol for the corresponding null hypotheses. The first hypothesis was to be tested at a level of $\alpha = 5\%$, and only if this hypothesis could be rejected, the second hypothesis could be tested at the same level. Application of this test procedure for *a priori* ordered hypotheses assures control of the multiple level $\alpha = 5\%$ (Maurer *et al.*, 1995). Evaluation was performed according to the intention-to-treat principle. Missing values were to be replaced by the last available value (last observation carried forward). The secondary variables were analysed descriptively.

RESULTS

Although the two groups showed no relevant structural differences in concomitant diseases, there were differences in previous medication. The number of patients receiving centrally active substances before the start of the study was twice as high in the active treatment group (six patients on active treatment, three patients on placebo). With one exception, however, all impermissible concomitant drugs were stopped punctually. All study participants took the study medication as stipulated in the protocol. The investigation dates were as planned.

The total HAMA score at baseline was similar in both groups. For the primary variable and the intention-to-treat evaluation, a tendency of superiority over the course of treatment with WS 1490 (Table 1) was observed.

Five patients (three on active treatment, two on placebo) with a total HAMA score <18 were included in the study. These erroneous inclusions, together with the very early dropouts on active treatment (three patients), strongly influenced the intention-to-treat evaluation and therefore a per protocol analysis was also performed. In this explanatory approach, a statistically

Table 1. HAMA total score

	Intention-to-treat analysis			Per-protocol analysis		
	WS 1490 (*n* = 25)	**Placebo (*n* = 25)**	***p*-value *U*-test one-tailed**	**WS 1490 (*n* = 18)**	**Placebo (*n* = 20)**	***p*-value *U*-test one-tailed**
Before treatment	25.6 (21.6; 29.5)	27.6 (23.8; 31.5)	0.36[a]	26.6 (23.9; 29.3)	29.9 (26.2; 33.5)	0.18[a]
After 2 weeks of treatment	18.8 (14.8; 22.8)	21.0 (17.3; 24.7)	0.1	17.9 (15.4; 20.4)	22.2 (18.6; 25.8)	0.03
After 4 weeks of treatment	14.8 (10.5; 19.1)	16.8 (13.3; 20.4)	0.1	12.4 (10.1; 14.7)	17.1 (13.6; 20.6)	0.03

[a] Two-tailed.
Mean of HAMA total score with 95% confidence interval for the intention-to-treat and the per-protocol analysis respectively.

significant and clinically relevant advantage of 4.7 points in favour of the WS 1490 treatment was found after 4 weeks ($p = 0.03$) (Figure 1).

For the secondary variables HAMA subscales 'somatic anxiety' and 'psychic anxiety', a statistically significant advantage of the active treatment was detectable ($p = 0.03$ and $p = 0.04$, respectively). The effect of the test substance on each of these two separate dimensions was the same as on the total score. A trend in favour of the active treatment was also found in all other secondary variables, but none reached significance.

On item I (severity of illness) of the clinical global impressions (CGI) scale, the number of patients graded 'at least markedly ill' after 4 weeks was twice as high on placebo compared with WS 1490: 28.6% (6 out of 22 patients) in the active treatment group versus 54.6% (12 out of 21 patients) on placebo ($p = 0.08$, chi-square test) (Figure 2). At the beginning of therapy 64% (16 out of 25 patients) had been rated 'at least markedly ill' in both treatment groups.

Adverse events over the course of the study were seen in three patients, two of whom were in the active treatment group. In one patient in the active treatment group, the general condition deteriorated on account of pleuro pneumonia. Another patient in the active treatment group was excluded on account of existing pulmonary fibrosis and a resulting deterioration in condition. One patient on placebo who developed nausea, retching, restlessness and sleeplessness dropped out of the study after 3 days. No adverse events related to the study medication were observed.

A total of seven patients dropped out (four on active treatment, three on placebo). Besides the three dropouts due to an adverse event, four patients (two in each treatment group) withdrew their consent to participation. None of the patients showed withdrawal symptoms in the follow-up phase.

The laboratory tests at the start and end of the study revealed no pathological changes in blood count (haemoglobin, haematocrit, erythrocytes, leukocytes, platelets), enzyme values (ALT, AST, gamma-GT and alkaline phosphatase), total bilirubin, glucose, cholesterol or triglycerides. Cholesterol actually fell from an initially elevated level to within the physiological range (≤240 mg/dL) in five active treatment patients and showed an improvement within normal limits in a further four active treatment patients.

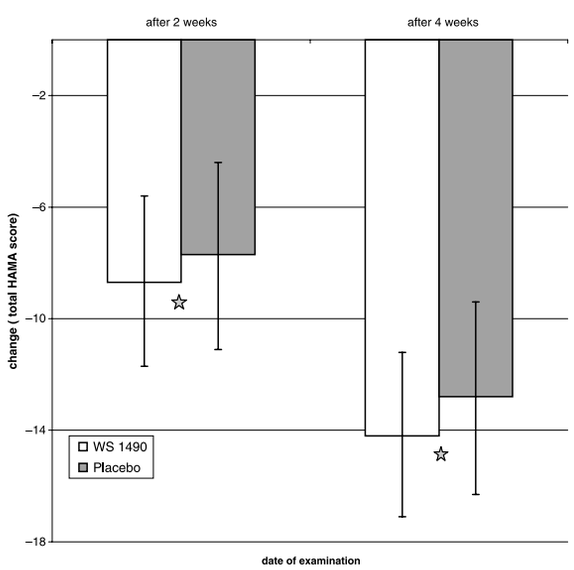

Figure 1. Changes of HAMA total score over the course of treatment versus baseline (per-protocol-analysis, $n = 38$). * Statistically significant finding ($p = 0.03$). Mean values with 95% confidence intervals.

DISCUSSION

Compared with previous studies mainly employing doses of 3 × 100 mg, kava special extract WS 1490 was

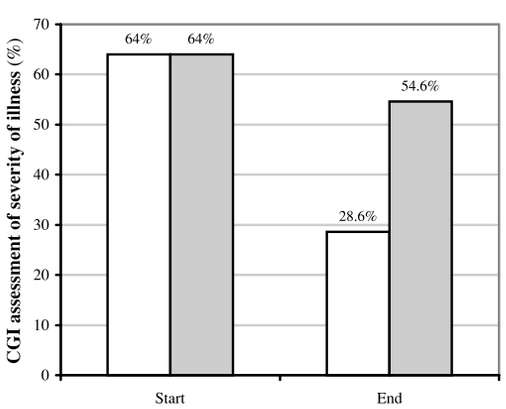

Figure 2. The percentage of patients classified by the clinical global impression (CGI) scale to be 'at least markedly ill' before start of treatment and after 4 weeks of treatment is demonstrated for placebo (■) and kava special extract WS 1490 (□). $P = 0.08$ chi-squared test.

administered at a level of 3×50 mg to test the efficacy of a lower dose. In spite of the placebo effect in both groups, evidence of efficacy at this dose level was visible in the total HAMA score and in the sub scales for 'somatic anxiety' and 'psychic anxiety', which showed comparable clinically and statistically relevant improvements compared with the placebo. The lack of drug-related side effects in this study indicates the advantageous safety profile of WS 1490.

It is recommended to start therapy within the 100–300 mg/day dose range, corresponding to 70–210 mg kava lactones/day. The higher dose has been tested in several clinical studies and proven to be an efficacious treatment for anxiety, with a comparable efficacy to benzodiazepines (Kinzler *et al.*, 1991; Warnecke, 1991; Woelk *et al.*, 1993; Volz and Kieser, 1997; Heinze *et al.*, 1994; Scherer, 1998), whereas the lower dose conforms to the recommendations of the German Commission E monograph. The efficacy of kava extracts for the symptomatic treatment of anxiety in this dose range has been confirmed in a recently published meta-analysis (Pittler and Ernst, 2000). The superiority of kava extracts over placebo was suggested by seven reviewed trials, tested in a dose range of 60–240 mg kava lactones daily.

The HAMA score of the placebo group seemed to be a little bit higher at baseline, but no statistically significant differences ($p = 0.36$) were measured and, since no systematically error could be detected, the groups could be assessed as similar to study start.

Remarkably, in this study, the patients' own subjective assessment of their well-being on the self-rating scales described above demonstrates a clinically relevant improvement compared with placebo suggesting that patients do feel better and obviously tolerate the medication well. Kava shows minimal interaction with other drugs that the majority of the patient population (frequently aged, depressive, and multi morbid) can be expected to take and leads to no impairment of reaction capability and no sedation (Herberg, 1991; Herberg, 1993). When the fact that the treatment of anxiety disorders frequently lasts several weeks or months is taken into account, we conclude that it is of benefit to the patient to administer kava in mild to moderate non-chronic cases before prescribing a synthetic tranquillizer with a marked risk of habituation.

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