



ELSEVIER

Fitoterapia 70 (1999) 221–228

---

---

**FITOTERAPIA**

---

---

## Tolerability and efficacy of valerian/lemon balm in healthy volunteers (a double-blind, placebo-controlled, multicentre study)

A. Cerny<sup>a</sup>, K. Schmid<sup>b,\*</sup>

<sup>a</sup>*Inselspital, University Hospital, Bern, Switzerland*

<sup>b</sup>*PharmaPart AG, Weberstrasse 10, Postfach 8669, Zürich 8036, Switzerland*

Received 25 August 1998; accepted 2 December 1998

---

### Abstract

This clinical study was conducted to evaluate the tolerability and efficacy of a new galenic formulation of a herbal sleeping aid, a valerian/lemon balm combination, to treat minor sleep disorders. The study was performed according to a randomised, placebo-controlled, double-blind, parallel group, multicentre design with healthy volunteers. Primary parameters were the assessment of the overall tolerability and the incidence of adverse events. Secondary parameters included laboratory tests, physical examination and assessments of well-being and sleep quality. The preparation proved to be well tolerated by most subjects (93% of the participants in the valerian/lemon balm group and 91% in the placebo group). There was no statistically significant difference concerning the frequency of adverse events between the two treatment groups (valerian/lemon balm 29%, placebo 28%) and no serious adverse events were reported. No significant changes were seen in regard to laboratory tests, physical examination and rating of well-being. In contrast, the valerian/lemon balm group revealed a significantly higher quality of sleep (33%) compared to the placebo group (9%),  $P$ -value = 0.04. In conclusion, these results indicate that this valerian/lemon balm formulation is well tolerated. © 1999 Elsevier Science B.V. All rights reserved.

*Keywords:* *Valeriana officinalis*; Valeriana; *Melissa officinalis*; Lemon balm; Herbal remedies; Insomnia

---

\* Corresponding author. Tel.: +41-1-299-4949, fax: +41-1-299-4950, e-mail: [pharmapart@access.ch](mailto:pharmapart@access.ch)

## 1. Introduction

Insomnia is a common problem among the general population in the Western world. In Germany, for instance, up to 18% of the population occasionally suffer from some kind of sleeping problem [1]. Approximately 7% of Germans complain about frequent problems in falling asleep or sleeping through the night. Of these, 44% use hypnotics on a regular basis. The preferred choice and most widely used are the benzodiazepine receptor agonist type drugs (benzodiazepines, cyclopyrrolones, imidazopyridines) and barbiturates. The use of these drugs, however, is generally not indicated for individuals who are affected with minor sleeping disorders. Their adverse effect profile (rebound and ‘hang-over’ effects, reduced concentration and efficiency during the day, modification of the various phases of sleep) and the danger of physical addiction require a careful and restricted usage of these drugs.

In search of alternatives, interest has been shifted to herbal sedatives [2], which have been used in folk medicine as mild sleeping aids for centuries. The use of such herbal preparations, however, is still controversial, as their efficacy and tolerability has not yet been scientifically established.

As phytopharmacology, a predominantly empirical science, is now on its way to becoming an established medicinal science [3], systematic research to demonstrate effects, efficacy and safety of herbal remedies in man is highly desirable.

The last years have produced a number of controlled, double-blind studies which demonstrated the efficacy and tolerability of some single compound preparations containing valerian (*Valeriana officinalis*) [4–7], kava-kava (*Piper methysticum*) [8–10], or St John’s wort (*Hypericum perforatum*) [11–13]. For other preparations, e.g. lemon balm (*Melissa officinalis*), or the combination of valerian/lemon balm or valerian/hops (*Humulus lupulus*) data are still scarce [1]. The present study was designed to determine the safety of a new galenic formulation of a valerian/lemon balm preparation and to provide indications of its efficacy (as far as possible in healthy volunteers not suffering from insomnia).

## 2. Experimental

### 2.1. Experimental design and procedure

The study was performed according to a randomised, placebo-controlled, double-blind, parallel group, multicentre design. It was coordinated by a CRO and carried out at three different hospital units and three general practices in Switzerland.

Primary endpoints were the assessment of the overall tolerability of the preparation on a 5-point rating scale (excellent, good, moderate, acceptable and unsatisfac-

tory) and the incidence of adverse events (AE). Secondary endpoints were laboratory parameters, physical examination, sleep quality and well-being.

At enrolment, inclusion and exclusion criteria were checked; demographics, medical history, smoking and drinking habits were recorded, and informed consent was obtained. A short physical examination and laboratory tests were performed. The volunteers were asked to rate their well-being and their sleep quality on a 100 mm visual analogue scale (VAS). At the second visit, the physical examination, the laboratory tests and the rating of well-being and sleep quality were repeated. In addition, compliance and adverse events were assessed.

Physical examination parameters examined were blood pressure, pulse and weight. Laboratory parameters tested were: haemoglobin, RBC, WBC and platelets, creatinine, alkaline phosphatase, ALT (SGPT), AST (SGOT),  $\gamma$ -GT, sodium and potassium.

## 2.2. *Subjects*

This study was carried out with healthy volunteers of both genders, 20–70-year olds. ‘Healthy’ was defined as fit for work and absence of a serious disorder, which might interfere with the evaluation of the safety of the test drug (e.g. renal insufficiency, hepatic dysfunction, cardiovascular, disease, or psychic disorder) or known abnormal values of the laboratory tests.

Further exclusion criteria were drug and alcohol abuse, concomitant treatment with other drugs, including herbal sedatives, interfering with the evaluation of the test drug; known hypersensitivity to any of the ingredients of the study drug; pregnancy, lactation, women of childbearing potential who did not use an established contraceptive; and participation in another study within the last 30 days.

## 2.3. *Ethical approval*

The study was conducted in accordance with international GCP regulations and the Declaration of Helsinki of the World Medical Association. Approvals of ethical committees and regulatory authorities were obtained before starting volunteer recruitment. Prior to enrolment, each volunteer received an explanation as to the aim and risks of the study and gave his/her written informed consent.

## 2.4. *Drug and treatment*

The test drug [coated tablets of valerian/lemon balm (Songha Night<sup>®</sup>, Pharmaton Natural Health Products, Bioggio/Lugano, Switzerland)] contained 120 mg valerian extract (extr. valerianae e. rad. spir. sicc. 4.5:1) and 80 mg lemon balm extract (extr. melissae e. fol. sicc. 5:1). The comparator placebo visually matched the test drug.

The volunteers were instructed to take three tablets daily, in one dose, 0.5 h before bed-time. The total daily dose for volunteers in the valerian/lemon balm

group was thus 360 mg valerian and 240 mg lemon balm. The treatment duration was 30 days.

### 2.5. Statistical methods

Categorical data were analysed by using the  $\chi^2$  test, continuous data were analysed by the Student's *t*-test. *P*-values < 0.05 were considered significant.

## 3. Results

### 3.1. Subjects and treatment

Ninety-eight healthy volunteers (58 women and 40 men) were enrolled in this study (Table 1). Mean age of the volunteers in the valerian/lemon balm group was 33.4 (S.D. 12.5) years, mean age of the volunteers in the placebo group was 34.8 (S.D. 11.7) years. By 2:1 randomisation, 66 were allocated to the valerian/lemon balm group, and 32 to the placebo group.

All participants were included in the tolerability evaluation: 97% of the valerian/lemon balm group and 94% of the placebo group showed good/acceptable compliance. One volunteer in the placebo group stopped taking the medication early because of nausea and insomnia, which was considered drug-related. Two volunteers in the valerian/lemon balm group discontinued because of lacking efficacy, and nausea and sleep disturbances, respectively.

### 3.2. Tolerability rating

The overall tolerability was rated on a 5-point rating-scale by questioning the volunteers after 30 days of treatment. In general, the preparation was very well tolerated (Fig. 1): 97.0% of participants in the valerian/lemon balm group and 96.9% of participants in the placebo group reported acceptable to excellent tolerability. Only 3.0% and 3.1%, respectively, of the volunteers considered the

Table 1  
Synopsis: demographic data (Mean, S.D.)

Volunteers	Valerian/ lemon balm	Placebo
Total	66	32
Females	38	20
Males	28	12
Mean age (years)	33.4 (12.5)	34.8 (11.7)
Mean weight (kg)	66.8 (11.8)	65.6 (9.3)
Mean height (cm)	173.0 (10.5)	170.8 (9.0)

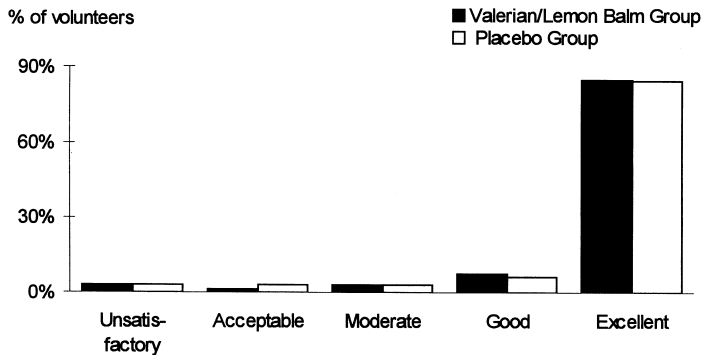


Fig. 1. Rating of tolerability after 30 days of treatment valerian/lemon balm vs. placebo.

overall tolerability as unsatisfactory. There was no statistically significant difference in tolerability between the two treatment groups ( $P = 0.76$ ).

### 3.3. Adverse events

Twenty-eight (28.6%) volunteers reported adverse events. The proportion of volunteers reporting adverse events was similar in both treatment groups: 28.8% in the valerian/lemon balm group and 28.1% in the placebo group. Sleep disturbances and tiredness were the two most frequent adverse events. Their frequencies were similar in the two treatment groups valerian/lemon balm vs. placebo (12% vs. 13%) and (11% vs. 13%), respectively. No severe adverse events were reported during this study.

### 3.4. Laboratory tests and physical examination

The mean values of blood pressure, pulse rate, body weight and laboratory test results at the beginning and the end of the study did not change throughout the study and there were no statistically significant differences between the two treatment groups (Table 2).

### 3.5. Sleep quality

When questioned during the second visit 33.3% of the volunteers in the valerian/lemon balm group and 9.4% in the placebo group reported an improvement in sleep quality ( $P = 0.04$ ) (Fig. 2). This, however, was not reflected by the analysis of the results from the visual analogue scale of sleep quality (0–100 mm). It revealed only a slight but not statistically significant improvement in sleep quality in both treatment groups over the 30 days treatment period, valerian/lemon balm from 74 mm (S.D. 23) to 76 mm (S.D. 23) and placebo from 77 mm (S.D. 19) to 79 mm (S.D. 19).

Table 2

Results of haematology and blood chemistry tests (Mean, S.D.)

		Visit 1 (Day 0)	T	Visit 2 (Day 30)	T
<i>Haematology</i>					
Haemoglobin (g dl <sup>-1</sup> )	V/LB	14.3 (1.7)	0.228	14.3 (1.5)	0.004
	Placebo	14.4 (1.5)		14.3 (1.5)	
Red blood cells (10E12 l <sup>-1</sup> )	V/LB	4.7 (0.5)	0.219	4.7 (0.5)	-0.068
	Placebo	4.7 (0.5)		4.7 (0.4)	
White blood cells (10E9 l <sup>-1</sup> )	V/LB	6.3 (1.7)	0.339	6.3 (1.8)	1.340
	Placebo	6.5 (1.6)		6.9 (2.0)	
Platelets (10E9 l <sup>-1</sup> )	V/LB	254.1 (54.0)	-1.136	250.6 (50.5)	0.679
	Placebo	241.7 (48.9)		242.9 (56.5)	
<i>Blood chemistry</i>					
Potassium (mmol l <sup>-1</sup> )	V/LB	4.2 (0.7)	-0.966	4.0 (0.4)	0.348
	Placebo	4.1 (0.4)*		4.1 (0.4)	
Sodium (mmol l <sup>-1</sup> )	V/LB	142.0 (3.1)	0.963	141.6 (3.3)	0.439
	Placebo	142.6 (2.5)		141.9 (2.9)	
Creatinine (μmol l <sup>-1</sup> )	V/LB	85.5 (18.1)	-1.59	85.0 (15.6)	-1.123
	Placebo	81.7 (10.4)		81.7 (14.2)	
Alk. phosphatase (IU l <sup>-1</sup> )	V/LB	57.2 (17.9)	0.281	56.0 (16.9)	-0.993
	Placebo	54.0 (15.9)		59.8 (19.2)	
ALT (SGPT) (IU l <sup>-1</sup> )	V/LB	10.0 (13.6)	-0.505	20.2 (11.2)	0.612
	Placebo	18.8 (10.1)		20.2 (10.4)	
AST (SGOT) (IU l <sup>-1</sup> )	V/LB	20.6 (6.5)	0.612	20.8 (7.5)	0.686
	Placebo	19.7 (5.7)		18.6 (9.7)	
Gamma-GT (IU l <sup>-1</sup> )	V/LB	16.5 (12.2)	0.831	16.3 (12.8)	-1.150
	Placebo	14.6 (9.9)		13.4 (9.3)	
<i>Vital signs</i>					
Blood pressure Systolic (mmHg)	V/LB	118.5 (13.4)	0.526	119.9 (12.3)	0.874
	Placebo	116.9(14.2)		117.3(14.2)	
Diastolic (mmHg)	V/LB	71.9 (8.3)	0.385	72.7 (8.9)	0.371
	Placebo	71.3 (8.0)		71.9 (9.9)	
Pulse rate	V/LB	70.8 (9.3)	-0.034	72.0 (10.5)	-0.611
	Placebo	70.8 (9.3)		70.7 (8.9)	

V/LB = Valerian/Lemon Balm.

V/LB: N = 66; Placebo: N = 32 (\*Placebo: N = 31).

### 3.6. Well-being

After 30 days of treatment, 85% of the valerian/lemon balm group and 81% of the placebo group rated their general well-being as unchanged. The difference was not statistically significant ( $\chi^2 = 2.388$ ,  $P = 0.303$ ).

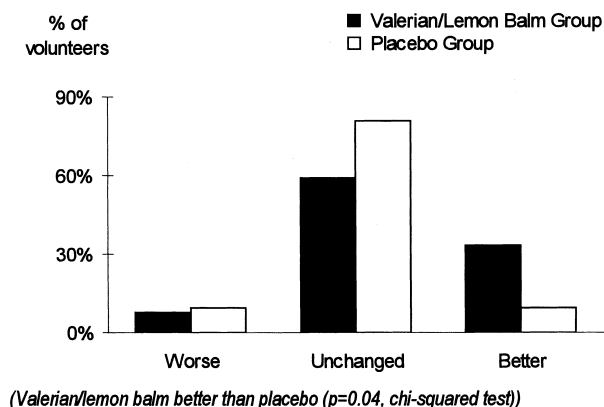


Fig. 2. Rating of sleep quality after 30 days of treatment valerian/lemon balm vs. placebo.

#### 4. Discussion and conclusion

The studied valerian/lemon balm combination product was well tolerated over the 30 day study period. The results obtained from physical examination, haematology and blood chemistry tests confirm the subjective tolerability rating by the volunteers. These results are in accordance with previously published reports. In an open user study with 2395 patients suffering from psycho-physiological disorders, who were treated with a combination of valerian and lemon balm, 96% rated the tolerability as good or very good [14], and a placebo controlled double-blind study with a standardised combination drug containing valerian and lemon balm in patients with minor insomnia reported excellent tolerability of the preparation [2].

The reported adverse events, the two most frequent being tiredness and sleep disturbances, were mild and to be expected with this kind of drug. The incidence of AE was relatively high (29%) compared to (3%) reported by Maisenbacher and Podzuweit [14]. This, however, can be explained by the different designs of the two studies. Frequencies of AE are usually considerably lower in open user studies than in controlled double-blind studies. Another indication that the relatively high incidence of AE is dependent on the study design rather than the drug itself is the fact that in this study the frequency and the AE profile in both treatment groups were almost identical. This and the fact that there were no serious or unexpected AE again confirm the good tolerability of the valerian/lemon balm product.

The dose administered (valerian 480 mg, lemon balm 240 mg) proved to be effective and well tolerated. Studies with higher doses of an aqueous valerian extract (900 mg) reported no further improvement of sleep quality but increased sleepiness during the morning [15].

One study administering valerian/lemon balm reported significantly improved sleep quality and well-being after only two weeks' treatment in the valerian/lemon balm group as compared to the placebo group [2]. Similar findings were obtained

by Maisenbacher and Podzuweit [14], where the efficacy was rated as good or very good by 84% of the patients.

In the present study, sleep quality improved significantly in subjects who received valerian/lemon balm, which was surprising as only healthy volunteers not complaining of insomnia participated. The observed effect has to be considered with caution because it was shown only in the assessment of change (which probably is more sensitive) and not in the assessment of actual state by VAS. In addition, efficacy may be different in patients, suffering from sleep disturbances. Thus, it would be interesting to see how effective this preparation would prove in patients suffering from insomnia, where major improvements may be expected.

In conclusion, the studied preparation was well tolerated and results indicate that it improves sleep quality.

### Acknowledgements

The authors would like to express their thanks/gratefulness to the sponsor of the study: Pharmaton SA, Bioggio/Lugano, especially to Dr O. Petrini and Dr W. Meier as well as to all investigating sites who participated in this study: Prof. W. Vetter and Dr J. Koch, Universitätsspital Zürich; Dr R. Jovic, Clin-Pharma Research, Birsfelden; Dr N. Meyer, Winterthur; Dr A. Rinderknecht, Zürich; Dr F. Häfner, Zürich.

### References

- [1] Nachtmann A, Hajak G. *Internist* 1996;37:743–749.
- [2] Dressing H, Köhler S, Müller WE. *Psychopharmakotherapie* 1996;3:123–130.
- [3] Schimmel K. *Therapiewoche* 1984;34:4117–4127.
- [4] Kamm-Kohl AV, Jansen W, Brockmann P. *Med Welt* 1984;35:1450–1454.
- [5] Balderer E, Borbély AA. *Psychopharmacology* 1985;87:406–409.
- [6] Lindahl O, Lindwall L. *Pharmacol Biochem Behav* 1989;32:1065–1066.
- [7] Schulz H, Stolz ?, Müller J. *Pharmacopsychiatry* 1994;27:147–151.
- [8] Kinzler E, Krömer J, Lehmann E. *Arzneim Forsch/Drug Res* 1991;41:584–588.
- [9] Möller H-J, Ulm K, Glöggler A. *Psychiatrie für die Praxis* 17. München: MMV Verlag, 1993:259–266.
- [10] Emser W, Bartylla K. *Neurologie/Psychiatrie* 1991;5:636–642.
- [11] Schulz H, Jobert M. *Nervenheilkunde* 1993;12:323–327.
- [12] Harrer G, Schulz VJ. *Geriatr Psychiatry Neurol* 1994;7:6–8.
- [13] Volz HP, Hänsel R. *Psychopharmakotherapie* 1995;2:61–67.
- [14] Maisenbacher J, Podzuweit H. *Therapiewoche* 1992;42:2140–2144.
- [15] Leathwood PD, Chauffard F. *Planta Medica* 1984;144–148.