The Effect of Valerian Extract on Sleep Polygraphy in Poor Sleepers: A Pilot Study

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Summary

The effect of acute and repeated treatment (seven days) with a valerian extract (Valdispert forte®, 405 mg t.i.d.) on objective and subjective measures of sleep was studied. Polysonmography was conducted in 14 elderly poor sleepers on three nights, at one-week intervals (N0, N1, N2). N0 was an adaptation night, N1 and N2 the first and last night under treatment. Six subjects received placebo and eight subjects valerian. Subjects in the valerian group showed an increase in slow-wave sleep (SWS) and a decrease in sleep stage 1. Density of K-complexes was increased under active treatment. There was no effect on sleep onset time or time awake after sleep onset. REM sleep was unaltered. There was also no effect on self-rated sleep quality. We hypothesize that valerian increases SWS in subjects with low baseline values.

Introduction

In the present pilot study we investigated the effect on subjective and objective measures of sleep of an aqueous alkaline dried extract prepared from Radix Valerianae officinalis L.

Animal studies with either isolated constituents such as the sesquiterpenes valerenic acid and valerone or with whole root extracts have shown various behavioral effects. A reduction of locomotion has repeatedly been demonstrated, as well as an increase in the duration of narcosis induced by barbiturates (Wagner et al., 1980; Hendricks, 1985; Rücker et al., 1978; Leuschner et al., in press). Leuschner et al. (1993) concluded that the extract has a moderate sedative activity and only weak anticonvulsive properties.

In humans, sleep-promoting effects have been reported in different controlled studies to assess subjective sleep quality (Leathwood et al., 1982; Kamm-Kohl et al., 1984; Bader and Borbély, 1985; Lindahl and Lindwall, 1988). There are only a few studies which used objective methods to measure sleep by electrophysiological recordings (Leathwood and Chauffard, 1985; Gessner and Klasser, 1984; Balderer and Borbély, 1985; Dressling et al., 1992). The results of these polysomnographic studies are inconclusive. While a shortening of sleep latency was reported by Leathwood and Chauffard (1985), this effect was not confirmed by Balderer and Borbély (1985) or Dressling et al. (1992). However, in the Balderer and Borbély study there was a slight decrease of sleep onset time and wake time after sleep onset. A reduction of wake time was also observed by Dressling et al. There are indications from two studies that poor sleepers benefitted more from treatment, either according to subjective (Leathwood et al., 1982) or objective (Dressling et al., 1992) measures of sleep quality.

Since results from the literature are inconclusive, a pilot study was planned with subjective and objective assessment variables of sleep to generate hypotheses for further controlled studies with valerian.

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Methods

Experimental design and procedure

The study was performed according to a double-blind, placebo-controlled parallel-group design with 14 subjects. Eight subjects were randomly assigned to the verum group, six to the placebo group. Sleep was measured subjectively (sleep questionnaires and sleep diary) and objectively (polysomnography). Polysomnographic recordings were performed at weekly intervals.

Each subject spent one adaptation night (N0) and two study nights (N1 and N2), each one week apart, in the sleep laboratory for polysomnographic recording. During the whole study period (N0 to N2) subjects documented the timing, duration, and quality of sleep by means of a sleep diary and evening and morning questionnaires. In the evening, subjects filled in the VIS-A questionnaire (Olt, 1986) which assesses daytime activity and mood. In the morning, the SF-A questionnaire (Görtelmeyer, 1988) was used. The items of the morning sleep questionnaire were combined into five factorially defined dimensions, (1.) sleep quality, (2.) feeling of refreshment after sleep, (3.) mental balance in the evening, (4.) mental exhaustion in the evening, and (5.) psychosomatic symptoms during sleep.

Subjects

Fourteen elderly (mean age: 61.6 ± 6.5 years) female subjects participated in the study. All were poor sleepers and fulfilled at least two of the following three subjective inclusion criteria: (i) sleep latency > 30 minutes, (ii) more than three awakenings per night and inability to go back to sleep within five minutes, and (iii) total sleep time < five hours. Subjects had to have a normal, age-related health status, normal clinico-chemical values, and an uneventful anamnesis. There were not to be any indications of organic or psychiatric causes of the sleep disturbances. Body weight had to be normal ± 15% (weight tables of the Metropolitan Life Insurance Company). Intake of any hypnotics, sedatives, or other CNS active drugs had to be stopped at least two weeks prior to the study. Drug screening for benzodiazepines, barbiturates, amphetamine, and morphine was performed in the pre-study investigation.

Subjects in the verum group (n = 8) and in the placebo group (n = 6) showed a similar age distribution (mean age: 62.0 ± 6.8 years vs. 61.3 ± 6.7 years).

Drug

Valdispert® forte (405 mg t.i.d.) or placebo was administered for eight consecutive days. A single coated tablet contains 135 mg dry extract of valeriana radix. The drug is an aqueous alkaline dried extract prepared from Radix Valerianae officinalis L., which grows in Western Europe. Valenic acid is used as indicator. The drug: extract ratio is 5–6:1.

The dose of 405 mg valerian (three coated tablets) was administered for the first time one hour before polygraphic sleep recording in the second laboratory night (N1). In the following seven days, 405 mg valerian was taken three times per day at mealtimes.

Sleep recording and analysis

Sleep was recorded polysomnographically (4 EEG, 2 EMG, 4 EOG; I ECG) on nights N0, N1 and N2 between 10:30 p.m. and 6:30 a.m. Analysis was done visually according to the criteria of Rechtschaffen and Kales (1968).

The following parameters were recorded: time in bed (TIB), total sleep time (TST), sleep period time (SPT), sleep efficiency index (SEI = TST/TIB x 100), sleep latencies, and sleep stages in minutes and percentages of TST. In addition, the density of sleep spindles and K-complexes was visually evaluated from two five-minute segments of stage 2 sleep which were selected from the first and the second half of each sleep record by a person otherwise not involved in the study.

Statistics

For the target variables, descriptors of the empirical distributions were computed (Min, max, median, first and third quartile, mean and standard deviation). In accordance with the hypothesis-generating intention of the study, the two treatment groups were compared on each of the three laboratory nights by means of dual-sample Wilcoxon rank-sum tests. To analyze the changes from N0 to N1 and N2, and from N1 to N2 within each treatment group, single-sample Wilcoxon signed-rank tests were used. Based on findings in the literature and empirical knowledge from traditional herbal medicine, an increase in sleep quality was expected. Therefore single-sided tests were used. For both tests the exact distributions were calculated. No α-adjustment was performed and all tests had to be interpreted on a descriptive level.

Results

Sleep duration, latencies, and stages

Homogeneity of the two treatment groups was tested with the polysomnographic data from the adaptation night (N0). At baseline, the groups differed significantly in sleep period time. SPT was shorter in the verum group (358.5 ± 45.9 min) than in the placebo group (437.3 ± 12.8 min) (p = 0.0426, Table 1). There was also a nonsignificant difference in sleep efficiency, which was lower in the verum group than in the placebo group (70.5 ± 9.8% vs. 78.1 ± 7.8%). Finally there was a remarkable difference in sleep latency which was defined as the time between lights-off and the first epoch of stage 2 sleep. Sleep latency was longer in the verum group (48.6 ± 29.5 min) than in the placebo group (21.8 ± 14.1 min; p = 0.0593). Thus, the groups were not homogenous for some essential sleep parameters in the first laboratory night.

After acute administration of the study medication (night 1) the two treatment groups differed in none of the sleep parameters. Between N0 and N1 the group treated with valerian presented an increase in TST from 319.3 ± 48.1 minutes to 367.4 ± 55.1 minutes (p = 0.0391). Slow-wave sleep (SWS, sum of S3 plus S4) increased between N0 (7.7 ± 6.3%) and N1 (13.2 ± 7.4%). For S4 the difference between N0 and N1 was significant (N0: 1.2 ± 2.1%, N1: 3.0 ± 3.6%; p = 0.0469). It was also possible to demonstrate the effect of valerian on SWS after repeated administration, i.e., when N2 was compared with the previous nights. Stage 3 increased from N0 to N2 (N0: 6.5 ± 4.3%; N2: 10.2 ± 1.5%; p = 0.0273). In addition, the sum of S3 and S4 increased between N0 (7.7 ± 6.3%) and N2 (12.5 ± 3.0%) (p = 0.0273), SWS increased in each single subject of the group treated with valerian.

In contrast to the increase in SWS, the percentage of stage 1 sleep decreased under valerian, from 16.4 ± 5.2% (N0) to 14.2 ± 2.9% (N1) and further to 11.9 ± 2.5% (N2). The difference between N0 and N2 was significant (p = 0.0273) for the valerian group, while there was no systematic change in the amount of S1 sleep in the placebo group: 17.1 ± 3.1% (N0), 18.8 ± 9.5% (N1), and 15.9 ± 7.3% (N2). There was also a slight but systematic increase of S2 sleep between N1 (54.1 ± 8.2%) and N2 (58.6 ± 6.2%; p = 0.0391) in the valerian group. In the placebo group there was only a significant reduction of movement time (MT), which indicates a decrease of large body
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Tab. 1: Sleep parameters (mean ± SD) for the three polysomnographic recordings. NO: adaptation night, N1: night after first drug administration, and N2: night after one week treatment.

<table>
<thead>
<tr>
<th>Sleep parameter</th>
<th>valerian (n = 8)</th>
<th>placebo (n = 6)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NO</td>
<td>N1</td>
</tr>
<tr>
<td>TIB [min]</td>
<td>463.7 ± 19.1</td>
<td>474.3 ± 7.4</td>
</tr>
<tr>
<td>SPT [min]</td>
<td>385.5 ± 45.9</td>
<td>423.4 ± 45.0</td>
</tr>
<tr>
<td>TST [min]</td>
<td>319.3 ± 48.1</td>
<td>367.4 ± 55.1</td>
</tr>
<tr>
<td>SEI [%]</td>
<td>70.5 ± 9.8</td>
<td>78.6 ± 10.7</td>
</tr>
<tr>
<td>SOL [min]</td>
<td>48.6 ± 29.5</td>
<td>31.2 ± 19.1</td>
</tr>
<tr>
<td>REM lat. [min]</td>
<td>180.7 ± 77.2</td>
<td>161.9 ± 71.9</td>
</tr>
<tr>
<td>Wake [min]</td>
<td>133.3 ± 43.3</td>
<td>99.3 ± 47.7</td>
</tr>
<tr>
<td>S1 [min]</td>
<td>52.1 ± 18.1</td>
<td>51.6 ± 11.0</td>
</tr>
<tr>
<td>S2 [min]</td>
<td>188.4 ± 37.8</td>
<td>197.1 ± 32.6</td>
</tr>
<tr>
<td>S3 [min]</td>
<td>20.5 ± 12.5</td>
<td>38.4 ± 19.0</td>
</tr>
<tr>
<td>S4 [min]</td>
<td>3.5 ± 5.7</td>
<td>10.7 ± 12.8</td>
</tr>
<tr>
<td>REM [min]</td>
<td>52.3 ± 21.1</td>
<td>67.5 ± 29.1</td>
</tr>
<tr>
<td>MT [min]</td>
<td>2.4 ± 1.4</td>
<td>2.3 ± 1.6</td>
</tr>
</tbody>
</table>

Tab. 2: Mean number (± SD) of sleep spindles and K-complexes in 10-Minute samples of stage 2 sleep. Mean values and standard deviations are represented for nights NO, N1, and N2 and both treatments.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>sleep-spindle density</th>
<th>K-complex density</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NO</td>
<td>N1</td>
</tr>
<tr>
<td>Valerian</td>
<td>55.9 ± 19.3</td>
<td>55.1 ± 18.3</td>
</tr>
<tr>
<td>Placebo</td>
<td>75.3 ± 15.2</td>
<td>70.7 ± 21.9</td>
</tr>
</tbody>
</table>

movements, from NO (0.9 ± 0.4 %) to N1 (0.2 ± 0.3 %) (p = 0.0156) and N2 (0.4 ± 0.3 %; p = 0.0313).

Sleep spindles and K-complexes

As mentioned in the methods section above, the phasic EEG-features spindles and K-complexes were analyzed in samples from each polysomnographic recording. The mean values and standard deviations of these two parameters are shown in table 2. The two treatment groups were not significantly different in respect to spindle or K-complex density on any of the three nights. For sleep spindles, there were also no systematic intragroup differences across the three nights whereas K-complex density increased in the valerian group from NO to N1 (p = 0.0313) and from NO to N2 (p = 0.0469), while there was no difference between N1 and N2. In the placebo group, there was no difference in K-complex density in any combination of nights.

Subjective Sleep Parameters

Neither in the evening or morning questionnaires, or in the entries in the sleep log did any of the subjective sleep parameters show changes which might be related to the study medication. Thus, these data have not been presented in detail here.

Discussion

The results from this pilot study suggest that valerian has selective effects on non-REM sleep. The most obvious change was an increase in SWS on both treatment nights. This effect could be seen in every single subject. Between the second night under treatment and the adaptation night, there was a decrease in stage 1 sleep, and from the first to the second night under treatment stage 2 sleep increased. All these changes are linked to NREM sleep, while REM sleep was unaltered. In contrast, the number of the different sleep stages under placebo did not change with the exception of movement time which was reduced on nights 1 and 2 compared to adaptation night 0.

There were various shortcomings in the design of the study which restrict the interpretation of the results. Due to the small sample sizes, the sleep data of the valerian and placebo groups were not balanced on the adaptation night. Sleep period time was greater, and sleep latency tended to be shorter in the placebo group. Due to the pilot character of the study, only a minimum number of polygraphic sleep recordings were performed. For this reason a true baseline is missing and changes within each treatment group had to be evaluated by comparing the recordings from nights 1 and 2 with those from the adaptation night. Even allowing for these limitations, there were various signs of a consolidation of NREM sleep under the acute and repeated administration of the valerian preparation. This finding is in contrast with that of Balderer and Borbely (1985) who were unable to detect any significant changes in objective sleep parameters after a single application of 900 mg.
of an aqueous extract of valerian root. One of the main differences between both studies is the selection of subjects. While Balderer and Borbély investigated sleep in young subjects with normal sleep quality, our sample consisted of elderly subjects with disturbed sleep. It is conceivable that changes in NREM sleep, and especially an increase in SWS, under treatment with valerian can only be demonstrated if NREM sleep is disturbed and SWS reduced. This view concurs with the results of Dressling et al. (1992), who found an increase in sleep efficiency and SWS not in the whole sample, but only in a subgroup of poor sleepers. The results of a study by Geßner and Klasser (1984), who observed a reduction of S4 as a result of treatment with a valerian preparation, are not comparable, since these authors used an automatic scoring procedure for S4, with uncertain validity.

While Leathwood et al. (1982), Balderer and Borbély (1985), and Lindahl and Lindwall (1989) observed a positive effect of different preparations of valerian on subjective sleep quality, our subjects did not notice any effect of the trial medication on subjective sleep quality, sleep onset time, or other rated sleep parameters. Since study designs, subject characteristics, dosage, and the content of study drugs differed essentially, it is too early to explain the clear divergences in outcome between the different studies.

If it were possible to replicate the main result of the present study, namely an increase in SWS, this would indicate a different mode of action between valerian and benzodiazepine-type hypnotics. The latter substances reduce EEG slow-wave activity (Achermann and Borbély, 1987), while they increase sleep-spindle activity and reduce the number of K-complexes (Kubicki et al., 1988). In the present study, we found no change in the density of sleep spindles under valerian treatment, but an increase in K-complex density. This increase in K-complexes could be caused by the same mechanism which is responsible for the increase in SWS, since both phenomena depend on the synchronizing activity of cortical neuronal structures (Declerck et al., 1993). Naitoh et al. (1982) proposed an antagonistic dynamic relationship between mechanisms which generate sleep spindles and those responsible for the production of vertex sharp waves, K-complexes, and delta waves in the sleep EEG. If valerian induces the latter type of EEG effects, this pattern might possibly correspond to its clinical effect, which may be tranquilizing rather than sedating, as Holm et al. (1980) suggested.

A putative tranquilizing effect of valerian has been studied with various pharmacodynamic models in humans. As early as 1939, von Werz and Homann demonstrated that acute administration of valerian extract attenuated caffeine-induced deterioration of psychomotor performance. Later, von Bracken and Weidemann (1953) reported a dose-dependent effect of valerian on critical flicker fusion (CFF). Since the effect was strongest at the lowest dose, the authors concluded that valerian has tranquilizing rather than sedating properties. This interpretation was supported by results of Broerens (1969). In a more recent study, Stephan (1980) used different psychological tests to study the effect of one week of treatment with one of two dosages of a valerian extract or placebo. In none of the perceptual and concentration tests was there a difference between active treatment and placebo. Thus the authors concluded that valerian did not cause sedation.

We conclude from the present results and those from the literature that valerian has a mild tranquilizing quality. Under certain conditions, which have still to be explored, sleep quality may improve. In those subjects who have low amounts of SWS, valerian seems to induce an increase of SWS and to reduce stage 1 sleep. It is worth speculating whether there is a link between the putative tranquilizing action of valerian and its effect on slow-wave sleep.

References


![Fig. 1 Percent of sleep stages S1, S2, S3, S4, REM, and wakefulness (W) within total sleep time (TST). Distributions for nights 0, 1, and 2 under valerian (left side) and placebo (right side)](image-url)