Aqueous Extract of Valerian Reduces Latency to Fall Asleep in Man

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Abstract: A group of 8 volunteers suffering from mild insomnia received a placebo, 450 mg or 900 mg of an aqueous extract of valerian root in a double-blind, repeated measures, random-order design. Subjective sleep ratings were assessed by questionnaire and movements were recorded throughout the night with wrist-worn activity meters. Using the first period of 5 consecutive minutes without movement as a criterion of sleep onset, there was a significant decrease in sleep latency with 450 mg valerian compared to placebo (15.8 ± 2.2 min vs 9.0 ± 1.5 min; paired *t* = 3.37; *p* < 0.01). The higher dose of valerian produced no further improvement in sleep latency.

Introduction

In a recent study on 128 volunteers we showed that an aqueous extract of valerian root improved subjective ratings for sleep quality and sleep latency but left no “hangover” the next morning. The improvements in sleep latency and sleep quality were especially marked in people who considered themselves to be habitually poor sleepers (11). In an electroencephalographic (EEG) study, however, we found no significant decrease in objective measures of time to fall asleep (10). The participants in the latter study were predominantly good sleepers, so it is quite probable that their normal sleep latencies were too short for valerian to produce a detectable improvement (the latencies were 6.4 ± 1.4 min with placebo and 4.7 ± 1.0 min with valerian). The main reason we used good sleepers for the EEG study, however, we found no significant decrease in objective latencies; doubling this dose led to no further improvement.

Materials and Methods

1. Test samples

Air-dried coarse-ground valerian root (rhizoma Valeriana officinalis L. Dixa S. A., St. Gallen, Switzerland) was ground, mixed with deionised water, heated to 60° C for 15 min, homogenised and centrifuged. After re-extraction of the sediment, the combined supernatant fluids were concentrated and dried (11). From 6 kg of starting material we obtained 1.94 kg of powder, which (to make the valerian less hygroscopic, and to improve powder flow) was mixed with an equal amount of MD 05 maltodextrin. The placebo was finely ground brown sugar.

The test and placebo powders were sealed into capsules (Parke-Davis snap-fit bicolour opaque #0, Schaller Pharmaceuticals, Renens, Switzerland) such that each capsule contained 225 mg of valerian extract.

2. Activity meters

The wrist-worn activity meters were adapted from a design of Colburn (5), developed by Borbély (2). Each meter weighed 93 g, measured 50 × 30 × 30 mm, and was fitted with a digital watch face. Movements were detected by a piezo-electric accelerometer linked via an amplifier and an analogue-digital transducer to a counter, and thence to a 1024 ×
3. Experimental design

A group of 8 volunteers, 5 men and 3 women, mean age 45 years (range 33–59), who all complained that they usually have problems getting to sleep, were recruited from among the research staff and their families. Before being enrolled in the experiment, each volunteer received an explanation as to the aim of the study and gave informed consent.

We used a double-blind, repeated measures, random order experimental design with samples administered in the order shown in Table I.

Table I. Order of administration of test samples

<table>
<thead>
<tr>
<th>Day</th>
<th>Volunteer</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>C C C C A B C A C</td>
</tr>
<tr>
<td>2</td>
<td>B C A B C B B C</td>
</tr>
<tr>
<td>3</td>
<td>C C C C A A A B</td>
</tr>
<tr>
<td>4</td>
<td>A A A B A C C A</td>
</tr>
<tr>
<td>5</td>
<td>Weekend</td>
</tr>
<tr>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>8</td>
<td>A B C C C A C C</td>
</tr>
<tr>
<td>9</td>
<td>B B C B B A A B</td>
</tr>
<tr>
<td>10</td>
<td>A C B A A A C B</td>
</tr>
<tr>
<td>11</td>
<td>B A A A B B B B</td>
</tr>
<tr>
<td>12</td>
<td>Weekend</td>
</tr>
<tr>
<td>13</td>
<td>14</td>
</tr>
<tr>
<td>15</td>
<td>B B B A A B B A</td>
</tr>
<tr>
<td>16</td>
<td>C A B C B C A C</td>
</tr>
<tr>
<td>17</td>
<td>A A B C C B B A</td>
</tr>
<tr>
<td>18</td>
<td>A B A B C C C A</td>
</tr>
</tbody>
</table>

This design has three advantages: first it mimics the “occasional” sedative consumption typical of poor sleepers who do not resort to powerful tranquillizers. Second, it is more complex than the straight crossover design (i.e. with 1 week on each treatment) which reduces the risk that volunteers will detect the different treatments other than by sensing their effects on sleep. Thirdly, the design allows us to detect any carry-over effects if they occur.

During the afternoon of each test day the 8 activity meters were checked and, at about 16.00 h, initialized. The meters, the capsules (identified only by a code number), and questionnaires were then distributed. Each volunteer put on an activity meter and, one hour before retiring to bed, took the capsules. The time of “lights out” was noted and, the next morning the volunteer completed a sleep questionnaire and delivered the activity meter to the laboratory. The contents of the meter were then read into the computer, and the cycle was repeated.

Analysis of the results

Individual and mean activity counts were plotted using an HP 3000 computer and software developed in our laboratory. The statistical treatment was simple. The specific hypothesis being tested was that valerian would decrease sleep latency. We first checked for the absence of overt “carry-over” effects of one treatment night to the next. Then, using the first period of 5 minutes without movement as a criterion for sleep onset, we calculated the mean sleep latency for each treatment for each volunteer. Using the paired Student’s “t” test, we checked the probability that valerian produced a decrease in sleep latency.

Results

All the volunteers finished the study and there were no problems of compliance with the experimental protocol nor were there any reports of side effects of the treatments.

One of the 8 activity meters broke down on 6 of the 12 nights so results for that person were eliminated from the study. Another meter functioned unreliably on 2 nights (1 placebo night and one night with 900 mg valerian), and a third broke down on a single night (900 mg valerian). For these two volunteers results for the remaining 3 nights for the particular treatment were included in the analysis.

Effects of valerian on sleep latency

Fig. 1 shows mean activities throughout the night for the 3 treatments, synchronised to start 1 hour before “lights out”, for the 7 subjects with usable results. The first point to note is the relatively high activity during the 20 minutes following “lights out” on the placebo nights which contrasts with the rapid disappearance of movement after 450 or 900 mg of valerian. Second, for the rest of the night, activity levels were similar for all 3...
groups. Third, sleep latency after 450 mg valerian was so short that it is not surprising that an increase in the dose to 900 mg led to no further improvement.

Using the first period of 5 consecutive minutes without movement after "lights out" as a criterion of sleep onset, we calculated sleep latencies for the 3 treatments for each volunteer. As Table II shows, valerian (450 mg) produced a significant decrease in this measure of time to fall asleep; increasing the dose to 900 mg led to no further improvement.

The correlation between sleep latency (measured with the activity meters) and perceived sleep latency (measured by questionnaire) was calculated for each person and for each treatment. The mean correlation coefficient (r) was 0.52 ± 0.23 (SEM) – a value significantly higher than zero and very close to that found in studies comparing subjective and EEG measures of sleep latency (13).

We also checked for "carry-over" effects by comparing sleep latency and sleep quality on the placebo nights which followed nights with either (a) no treatment at all; (b) placebo; (c) 450 mg valerian or (d) 900 mg of valerian. As Table III shows, for these parameters at least, there was no evidence for "carry-over" of valerian effects to the next night.

In addition to testing the specific hypothesis that valerian would decrease sleep latency, we also measured total sleep time, the number of minutes with 1 or more movements during the night, and the total number of movements during the night.

These results are summarized in Table IV, and show that valerian had no significant effect on total sleep time, nor did it influence the number of minutes with movement nor the total number of movements. Valerian produced more stable sleep than placebo during the first quarter of the night (p < 0.05). There were no significant changes in activity during the rest of the night.

Subjective ratings

In addition to the activity meter measures, we also asked the volunteers to complete a sleep questionnaire each morning. The results are summarized in Table V which shows that the subjective ratings for sleep latency mirror the results from the objective ratings but the technique is less sensitive in that improvements in sleep latency, as measured with the activity meters, reached a statistical significance of p < 0.01; with subjective ratings p < 0.1.

With the larger dose (900 mg) of valerian, the volunteers reported feeling more sleepy (p < 0.05) the next morning than with placebo. This suggests that, with a high enough dose, valerian may leave a "hangover" effect the next morning, similar to some benzodiazepines and barbiturates (7).
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Table V. Subjective ratings of sleep for the 3 treatments

<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo</th>
<th>Valerian (450mg)</th>
<th>Valerian (900mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep quality</td>
<td>5.0 ± 0.3</td>
<td>5.8 ± 0.3+</td>
<td>5.2 ± 0.3</td>
</tr>
<tr>
<td>Sleep latency</td>
<td>4.9 ± 0.4</td>
<td>4.3 ± 0.3</td>
<td>4.9 ± 0.3</td>
</tr>
<tr>
<td>Sleepiness the next morning</td>
<td>5.1 ± 0.4</td>
<td>5.8 ± 0.3+</td>
<td>5.4 ± 0.2</td>
</tr>
<tr>
<td>Sleep latency</td>
<td>4.6 ± 0.5+</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1. 9 point scale: higher score = better sleep quality
2. 9 point scale: higher score = longer sleep latency
3. 9 point scale: higher score = greater sleep depth
4. 9 point scale: higher score = better form (less sleepiness)
* worse than placebo (p < 0.05) paired “t”-test
+ better than placebo (p < 0.1) paired “t”-test.

Discussion

The specific hypothesis being tested in this experiment was that extract of valerian root, taken by people who suffer problems in getting to sleep, will decrease the time required for them to settle down to sleep. The results confirm that hypothesis. As, however, the method of measurement (activity meters) and the sedative (valerian) used are both rather unusual, it is worth discussing their relevance to more conventional methods and drugs.

The effectiveness of hypnotics is usually tested using a combination of electroencephalographic (EEG) and subjective sleep measures. EEG allows accurate measures of sleep latency, total sleep time and night awakenings, and is particularly useful to ensure that the hypnotic dose does not disrupt normal sleep electrophysiology. On the other hand, it is invasive in that the volunteer must come to the sleep laboratory, sit for 20 minutes while face and scalp electrodes are fitted, and then, flossed with wires, sleep in a strange bed. It is not surprising that EEG itself can interfere with sleep (4), or that people with mild insomnia are unenthusiastic about submitting to it (10).

Questionnaire studies are easier to set up and can be run on a large scale. They are extremely important because, as Oswald (12) has pointed out, whatever the results of objective studies, if the patient does not feel that he or she slept better, the hypnotic is useless. Questionnaire studies are also useful in identifying which group of people are most sensitive (11).

Activity meters have the particular advantage that they allow objective measurements of movement during the night (thus allowing accurate estimates of sleep latency, sleep time and night awakenings) but they do not disrupt the normal life of the patient or volunteer. The results of this and our two earlier studies (10, 11) underline the utility of combining the three techniques.

We found no evidence of “carry-over” of the different treatments from one night to the next (see Table III), which is not surprising in that the effects of smaller doses of valerian appear to be confined to the early part of the night (10, 11).

The present study also showed that there was a significant but unremarkable correlation between the questionnaire and the activity meter estimates of sleep latency. This correlation is similar to values found in comparisons between EEG and subjective evaluations (13) and tends to confirm that subjective estimates of sleep latency are quite reliable.

Although all the volunteers complained that they normally have long sleep latencies, activity meter measures suggest that even with placebo the average time to stable sleep was less than 20 minutes. Again, this fits well with other studies showing that insomniacs usually sleep better than they think they do (9).

The 450 mg dose of valerian decreased average sleep latency in all subjects (Table II) and, as Fig. 1 shows, sleep latency was so short that it is not surprising the higher dose produced no further improvement. The changes were, however, quite small (i.e. sleep latency decreased by, on average, 7 minutes) and it should be stressed that they were detectable only because the activity meters summed movements over short time periods (~ 1 min). With the 7.5 minute interval typically used by Borbély (1, 2) this decrease in sleep latency simply would not be seen.

The results using questionnaires (Table V) mirrored the objective measures but did not reach the same level of statistical significance. This is not surprising in that the technique is less sensitive and larger populations are usually required before clear-cut results are obtained (7, 11).

The objective effects of valerian on sleep latency compare favorably with those of many benzodiazepines and barbiturates. Thus Kales et al. (8) in a comparison of nine commonly used hypnotics including secobarbital (100 mg), Flurazepam (30 mg) and Triazolam (0.5 mg) found that only Flurazepam significantly decreased sleep latency. Other clinical trials have shown small decreases (3) or no change (6) in sleep latency with Flurazepam. Similarly, Hindmarch (7) using subjective rating scales found that amylobarbital (100 mg) and Temazepam (15 mg) produced no significant changes in subjective ratings for sleep latency, sleep quality or morning somnolence. Larger doses of Temazepam shortened sleep latency but also produced a marked increase in morning somnolence. Another benzodiazepine, Nitrazepam (5 mg) shortened sleep latency and improved sleep quality but also increased morning sleepiness. While it is difficult to draw comparisons between these studies, the changes we observe with valerian suggest that it is as effective as small doses of barbiturates and benzodiazepines.

Although we have demonstrated that an aqueous extract of valerian improves sleep latency, we are still in the process of identifying the active component. It is often assumed that the valepotriate esters isolated by Von Eckstedt and Rahman (14) are the active principles but they are insoluble in water, and as the preparation tested here contained only 0.01 % valepotriate, they cannot be excluded as the active hypnotic, at least in aqueous extracts.

In summary, these results show that activity meters used on a group of people specifically chosen because they are poor sleepers provides a sensitive and non-invasive means of testing the effects of mild sedatives. They also show that aqueous extract of valerian root decreases sleep latency in people who have a problem getting to sleep.

References

Studies on the Taiwan Folk Medicine; III. A Smooth Muscle Relaxant from *Onychium siliculosum*, Onitin

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Abstract: The pharmacological properties of onitin, onitinoside and onitisin, three phenolic pterosins, isolated from *Onychium siliculosum* have been investigated. Their predominant effects are to inhibit the contraction of isolated guinea-pig ileum. In these three compounds, onitin is the most potent one. Onitin (1 x 10⁻⁶M) inhibits both the D receptor and M receptor of 5-HT. The antagonism of onitin against histamine is non-competitive.

Introduction

*Onychium japonicum* (Thunb) Kunze and *Onychium siliculosum* (Desv.) C. Chr. (Pteridaceae) are commonly used for remedy of diarrhea, dysentery, abdominal cramps and pyrexia (1, 2, 3) in Formosa. From *Onychium japonicum*, a new diterpene alcohol named onychiol C, C₂₀H₃₀O₄, was isolated, Its pharmacological effects were also reported (4). Since the two herbs are very close in morphology, the authors were interested in whether they were comparable in pharmacologically active components. Three phenolic pterosins – onitin, onitisin, onitinoside – were isolated from *Onychium siliculosum*. This investigation was aimed at the examination of their activities on smooth muscle for better understanding of this herb as an antidiarrhoeic agent.

Experimental

Isolation

*Onychium siliculosum* was collected from Liu-Kuei, Kaohsiung in South Taiwan during the summer season (in July). The ethanolic extract of the powdered whole herb of *Onychium siliculosum* was successively partitioned with CHCl₃, EtOAc and n-BuOH. Subsequent separations of the CHCl₃ and EtOAc extracts were achieved using silica gel column chromatography affording onitin, onitinoside, onitisin for pharmacological tests.

Smooth muscle preparations

Segments of relevant tissues from freshly killed animals suspended in an organ bath containing Tyrode solution at 37°C and bubbled with O₂ (95%) and CO₂ (5%). The peristaltic reflex was initiated by raising the intraluminal pressure of guinea-pig ileum (5, 6). The dose which produced 50% inhibition (ED₅₀) on the contractions evoked by histamine diphosphate or on the pendular movement of rabbit jejunum was estimated (7). The effects of onitin on guinea-pig ileum were tested according to the cumulative technique (8). The calculation of pD₂' was also performed (9).

Gut Movement of the Rabbit

Rabbits weighing 2.0–2.5 kg were anesthetized with α-chloralose (60 mg/kg). A small balloon was inserted into the intestine of the rabbit and movements of the gut were recorded with a volume pressure transducer (LPU-0.1).

Results

A bioactive new compound was isolated and named onitinoside (10) (Scheme 1). The other compounds were identified by comparison with authentic samples as onitin and onitisin (11). Onitin and onitisin were dissolved in 1,2-propylene glycol (PG) for pharmacological tests. In concentrations of 1 x 10⁻⁶M, onitin regularly blocked the peristaltic reflex. The relative potency of onitin, onitisin, onitinoside – were isolated from *Onychium siliculosum*. This investigation was aimed at the examination of their activities on smooth muscle for better understanding of this herb as an antidiarrhoeic agent.