Application of fragrance in discontinuing the long-term use of hypnotic benzodiazepines


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Summary An evaluation was made of the usefulness of fragrance application in discontinuing the long-term use of hypnotic benzodiazepines in primary insomniacs with low-dose dependence. Based on the results of pentobarbital sleep time in rats, we made a new fragrance consisting primarily of sandalwood (35%), juniper berry (12%), rose (8%) and orris (6%). This mixed fragrance was found to prolong the pentobarbital sleep time in rats. A total of 42 outpatients with low-dose dependence on hypnotic benzodiazepines, all of whom met DSM-IV criteria for primary insomnia, participated in the study. In advance, all subjects attempted to reduce the doses of drugs gradually (25% reduction a week if possible) and 29 subjects who had failed to do so all participated in the study on the application of fragrance. A gradual tapering of hypnotic benzodiazepines (25% reduction a week if possible) was attempted while sniffing the fragrance in bed. The application of fragrance reduced the doses of hypnotic benzodiazepines in 26 of 29 subjects and 12 subjects did not require any drug for sound sleep. The present study indicated that a kind of fragrance may prove effective as an alternative to hypnotic benzodiazepines.

Introduction

Benzodiazepines as hypnotics are permitted for short-term use (NIH, 1984; Maczaj, 1993), whereas the long-term use may only have the purpose of suppression of rebound or withdrawal symptoms (Lader, 1999). Kupfer and Reynolds (1997) recommended that if hypnotic medication was used, especially in treating chronic insomnia, its use needed to be limited to 3–4 weeks, as there is no efficacy or safety data for any longer time periods. There are, however, a significant number of patients with insomnia who use

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Fragrance; Hypnotic benzodiazepines; Dependence; Insomnia; Gradual taper

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medication for protracted periods (Ohayon and Caulet, 1996; Simon et al., 1996; Ancoli-Israel and Roth, 1999).

The specific concerns about the long-term treatment of chronic insomnia with benzodiazepine hypnotics include residual daytime effects such as sedation, memory impairment, falling, respiratory depression, rebound insomnia, medication abuse, tolerance development, dose escalation, dependency with withdrawal difficulties, and an increased risk of death (Kramer, 2000). Insomnia is the most frequent withdrawal symptom after developing dependence on hypnotic benzodiazepines. Poor sleep, which includes rebound insomnia (Lader, 1992) for a few days following discontinuation of the hypnotics, forces subjects to recommence the hypnotics (Ashton, 1994). A tapering schedule (Greenblatt et al., 1987) or halving the dose for a week before discontinuing (Lader and Freck, 1987) has been shown to reduce the risk of rebound insomnia, but we know from our clinical experience that it’s not the way to success. One-third of long-term benzodiazepine users have difficulty in stopping the medication (Lader, 1994). Among general practice patients, 80% who tried to stop using their benzodiazepines reported worse symptoms (Hohagen et al., 1993). Alternatives to hypnotic benzodiazepines such as cognitive therapy (Hackmann, 1993) and relaxation (Sloan et al., 1993) are applicable only under limited conditions.

Olfaction can influence various vital behaviours in mammalian species (Alberts and Galef, 1971) and we postulated that an application of sensory input may be useful in combination with such alternatives or by itself. We have already reported that fragrance is useful in the treatment of depression (Komori et al., 1995). In the present study, some fragrances were screened by pentobarbital-induced sleep time. The duration of sleep induced by intraperitoneal pentobarbital injection is an indicator of central nervous system (CNS) depressant action of a psychotropic agent administered prior to pentobarbital (Sharp et al., 1994). Using this method, several fragrances have been proven to exert a depressant effect on CNS in mice (Tsuchiya et al., 1991). Such effects of fragrances, however, are confirmed only in rodents but not yet in humans. In the present study, we made a new mixed fragrance based on the results of pentobarbital-induced sleeping time and modulated to suit most preferences of human smell. The aim of present study was to evaluate the usefulness of fragrance application in discontinuing the long-term use in primary insomniacs with low dose dependent on them.

Materials and methods

Animals

Male Wistar rats, 12 weeks old, were purchased from SLC (Shizuoka, Japan) and used throughout the experiments. All rats were housed in cages in a quiet room and given access to pelleted diet and water ad libitum. Room temperature was controlled (20 ± 2 °C) and lights were on between 6.00 am and 6.00 pm. The experimental protocol was approved by the Ethics Review Committee for Animal Experimentation of Mie University Graduate School of Medicine.

Exposure to fragrances

The apparatus for fragrance application, as described previously (Komori et al., 2003), consisted of an air cylinder, flow meter, glass tube covered with a mantle heater (maintained at approximately 100 °C) and a chamber (height 14 cm, diameter 25 cm). All these components were connected by tubes in this order. One rat was placed in the chamber. For fragrance application, the volatile fragrance liquid was injected into the glass tube at 0.1 ml/h using an infusion pump. The odorized air was delivered into the chamber by driving air through the glass tube. The flow rate was kept at 2.0 l/min using a flow meter.

Pentobarbital sleeping time in rats

Pentobarbital sodium (Nembutal, Dainippon Pharmaceutical Co. Tokyo, Japan) was diluted in physiological saline and administered to each rat intraperitoneally at a dose of 50 mg/kg to induce sleep. The anesthetized rat was then placed on its back in the same chamber from which it came before administration of pentobarbital. With the criterion for sleep being loss of righting reflex (Rolland et al., 1991) the sleep time was defined as the time elapsed between the intraperitoneal administration of pentobarbital and the first time that the animal spontaneously righted itself.

Experiment 1

The experiment was performed using nine types of fragrances; jasmine, juniper berry, lavender, lemon, orris, peppermint, rose, sandalwood and lemon. These fragrances were freely available commercial products and purchased from Shiseido (Tokyo, Japan). The control rat was exposed to
pure air. The test was performed in 10 groups of 10 rats each.

**Experiment 2**

Based on the results of Experiment 1, a mixture consisting primarily of sandalwood (35%), juniper berry (12%), rose (8%) and orris (6%) was made. This mixed fragrance was modulated to suit most preferences of human smell. In this experiment, the effect of mixed fragrance on the pentobarbital-induced sleep time was compared with the effects of sandalwood, juniper berry, rose and orris.

**Statistical analysis**

In experiment 1, statistical analysis was performed using Student’s t-test compared with the control. Statistical significance was recognized when \( p < 0.05 \). In experiment 2, the effect of mixed fragrance on the pentobarbital-induced sleep time was compared with the effects of sandalwood, juniper berry, rose, orris and control using one-way ANOVA and Fisher’s test. Statistical significance was recognized when \( p < 0.05 \).

**Human study**

Forty two subjects meeting DSM-IV criteria for primary insomnia participated in this study. All were free of symptoms through use of brotizolam 0.25 mg/day alone (nine subjects) or flunitrazepam 1 mg/day in addition to brotizolam 0.25 mg/day (seven subjects), or brotizolam 0.5 mg/day alone (18 subjects) or flunitrazepam 1 mg/day in addition to brotizolam 0.5 mg/day (eight subjects). Hypnotic benzodiazepines were administered for more than six months in all subjects, since it was difficult to discontinue the drugs or reduce the doses because of the inescapably resultant insomnia.

According to prior approval of the Committee on Human Experimentation of our institution, informed consent was obtained from all subjects following detailed explanation. In advance, all subjects attempted gradual drug taper for four weeks (25% reduction a week, provided the dose resumed the last amount if each subject’s sleep was unsatisfactory). The doses were reduced more or less in three subjects on brotizolam 0.25 mg/day alone, six subjects on brotizolam 0.5 mg/day alone, two subjects on brotizolam 0.25 mg/day and flunitrazepam 1 mg/day and two subjects on brotizolam 0.5 mg/day and flunitrazepam 1 mg/day. The remaining 29 subjects (16 males and 13 females, 38–62y) who could not gradually reduce the doses at all participated in a trial of fragrance. Six subjects were given brotizolam 0.25 mg/day alone, 12 subjects brotizolam 0.5 mg/day alone, 5 subjects flunitrazepam 1 mg/day in addition to brotizolam 0.25 mg/day and six subjects flunitrazepam 1 mg/day in addition to brotizolam 0.5 mg/day.

With the use of the fragrance, all subjects attempted gradual drug taper in the same schedule as described above for 8 weeks. Subjects who had success were observed for 1 year after a taper schedule. During this period, the medication dose could be returned to any level due to poor sleep.

**Results**

**Experiment 1**

Table 1 shows the effects of fragrance inhalation on the sleep induced by intraperitoneal pentobarbital administration in rats. The fragrances that altered the pentobarbital sleep time by more than 5% of the control were lemon (−21%), jasmine (−8%), rose (+16%), sandalwood (+13%), juniper berry (+6%) and orris (+5%). Student’s t-test revealed that both the effects of lemon and rose reached a significance (\( p < 0.05 \)).

**Experiment 2**

The mixed fragrance prolonged the pentobarbital sleep time by 15%. ANOVA followed by a post hoc comparison revealed that the increment was not significant compared to any each component’s effect and was significant only compared to the control (\( p < 0.05 \)).

<table>
<thead>
<tr>
<th>Fragrance</th>
<th>Pentobarbital sleep time (min)</th>
<th>% of control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>68.2 ± 4</td>
<td></td>
</tr>
<tr>
<td>Lemon</td>
<td>53.7 ± 3</td>
<td>−21*</td>
</tr>
<tr>
<td>Jasmine</td>
<td>62.6 ± 4</td>
<td>−8%</td>
</tr>
<tr>
<td>Rose</td>
<td>78.9 ± 5</td>
<td>+16%</td>
</tr>
<tr>
<td>Sandalwood</td>
<td>76.9 ± 4</td>
<td>+13%</td>
</tr>
<tr>
<td>Juniper berry</td>
<td>72.1 ± 4</td>
<td>+6%</td>
</tr>
<tr>
<td>Orris</td>
<td>71.4 ± 4</td>
<td>+6%</td>
</tr>
<tr>
<td>Mixed</td>
<td>78.2 ± 5</td>
<td>+15%</td>
</tr>
</tbody>
</table>

The data show means ± SD. For all data, \( n = 10 \).

* Significantly differs from the control at \( p < 0.05 \).
Human study

The results of subjects on brotizolam alone are shown in Table 2. For six subjects on brotizolam 0.25 mg/day alone, the use of fragrance reduced the doses in all subjects and three of them ceased to require the drug for sound sleep. For 12 subjects on brotizolam 0.5 mg/day, the use of fragrance reduced the doses of the drug in 11 subjects and 5 of them discontinued the drugs without suffering poor sleep.

The results of subjects on brotizolam and flunitrazepam are shown in Table 3. For five subjects on brotizolam 0.25 mg/day and flunitrazepam 1 mg/day, the use of fragrance reduced the doses of the drugs in four subjects and two of them did not require the drugs for sound sleep. For six subjects on brotizolam 0.5 mg/day and flunitrazepam 1 mg/day, the use of fragrance reduced the doses of the drugs in five subjects and two of them did not require the drugs for sound sleep.

After the taper schedule for eight weeks, some of subjects moreover attempted gradual drug taper. Tables 2 and 3 also shows the results at one year after the taper schedule.

Some subjects succeeded in reducing the doses. In the result, 5 of 6 subjects on brotizolam 0.25 mg/day and 6 of 12 subjects on brotizolam 0.5 mg/day did not require the drugs for sound sleep. The doses of subjects on both brotizolam and flunitrazepam did not show any remarkable change at one year. About half of subjects continued to use the fragrance and the remaining half of subjects discontinued the fragrance without suffering poor sleep and without increasing the doses of hypnotic benzodiazepines.

Discussion

The use of fragrance to get sound sleep has been attempted since ancient times, but to our knowledge, no scientific report is available on this matter. The present study is the first medical report suggesting that a kind of fragrance, the effect of which was verified by the animal experiment, can help insomniacs to get sound sleep.

Insomnia is considered to be often influenced by subjective perception. Efficacy of hypnotics may be amplified by overestimating total sleep time in the drugged state or overestimating sleep onset latency upon withdrawal. This misperception may be derived from an amnesiogenic effect of benzodiazepine (Schneider-Helmer, 1988). It is unclear whether fragrances have such an effect or not. From the subject’s retrospective report, fragrances may possibly function to reduce subject’s anxiety until the onset of sleep despite the slight prolongation of sleep onset. Further study is needed to confirm anti-anxiety effects of fragrances.

Although any psychological influence may contribute to the effects of fragrance, the effects of fragrance were not transient and appear to be consistent with a CNS depressant action found in rodents. Possibly the fragrance used in the present study may be an example and future studies are needed to make more useful blends of fragrance. Moreover, the present study is based on subjective perception and therefore controlled sleep laboratory studies using more subjects should be conducted to confirm the validity of the effects of fragrances.

Chronic insomnia is a fluctuating condition and relapse may occur immediately or after some stressful life event (Lader, 1994). In the present study, about half of subjects continued to use the fragrance and the remaining half of subjects discontinued the

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Effects of fragrance on doses of brotizolam</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects treated with brotizolam 0.25 mg/day</td>
<td>Subjects treated with brotizolam 0.5 mg/day</td>
</tr>
<tr>
<td>At the experiment</td>
<td>1 year after</td>
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<tr>
<td>No effect</td>
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</tr>
<tr>
<td>25% off</td>
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<tr>
<td>50% off</td>
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<td>75% off</td>
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<td>6</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Effects of fragrance on doses of hypnotic brotizolam and flunitrazepam</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects treated with brotizolam 0.25 mg/day and flunitrazepam 1 mg/day</td>
<td>Subjects treated with brotizolam 0.5 mg/day and flunitrazepam 1 mg/day</td>
</tr>
<tr>
<td>At the experiment</td>
<td>1 year after</td>
</tr>
<tr>
<td>No effect</td>
<td>1</td>
</tr>
<tr>
<td>25% off</td>
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<tr>
<td>50% off</td>
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<td>75% off</td>
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</tr>
<tr>
<td>100% off</td>
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</tr>
<tr>
<td>Total</td>
<td>5</td>
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</table>
Fragrance without suffering poor sleep and increasing the doses of hypnotic benzodiazepines.

There is a clinical implication from the results of the present study. Although there are a few effective managements for benzodiazepine hypnotics dependency, the present study implies significance for it. It is shown that non-pharmacological treatments for primary and secondary insomnia are feasible and effective alternatives to the use of benzodiazepines, and that family physicians should consider these when managing older patients with insomnias (Petit et al., 2003). In conclusion, a kind of fragrance may prove effective as an alternative to the hypnotic benzodiazepine.

References


