Zopiclone in the Treatment of Insomnia: An Open Clinical Trial†

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Abstract

The purpose of this study was to examine the efficacy and adverse effects of zopiclone in Thai psychiatric patients. Thirty-two insomniac outpatients with a variety of diagnoses participated in this study. Zopiclone at the dose of 7.5-15 mg was administered 15 minutes before bedtime. The sleep-questionnaire items included: 1) sleep induction; 2) duration of sleep; 3) number of awakenings, 4) sleep quality; 5) dream incidence; and 6) condition in the morning. The mean scores of each item were compared by using pair *t*-test. One week after treatment, significant improvement was found in all items, except item 5. In comparison between sleep at 1 week and 3 weeks after treatment, further improvement was still found in the first three items. The adverse effects found were bitter taste, drowsiness, and headache. In conclusion, zopiclone is an effective hypnotic with few adverse effects.

Insomnia is one of the most encountered problems in clincal practice. In the general population, the prevalence of insomnia is about 10.2 per cent[1]. It is not surprising that sedative-hypnotics have accounted for a substantial fraction of all drug use[2]. However, those taking benzodiazepine hypnotics often suffer adverse effects, for example, tolerance and psychomotor impairment.

Zopiclone, a cyclopyrrolone derivative, is a hypnotic which is chemically unrelated to benzodiazepines. It is thought to potentiate GABA-mediated inhibition in the central nervous system[3]. Zopiclone 7.5 mg is at least as effective as triazolam 0.25-0.5 mg, temazepam 20 mg, nitrazepam 5 mg, flunitrazepam 2 mg, and flurazepam 20 mg[4]. Partial agonists of the benzodiazepine

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receptor caused by zopiclone leading to incomplete allosteric effects resulting in less tolerance, dependence, psychomotor impairment, and less severe discontinuation syndromes than full agonists(5,6).

Although many studies have been carried out in Caucasian insomniacs, to our knowledge, no such study has been conducted in Asian patients. The present investigators therefore proposed to examine the efficacy, acceptability, and adverse effects of zopiclone in Asian insomniac patients.

MATERIAL AND METHOD

This study was carried out in an open clinical trial. The subjects were recruited from those psychiatric outpatients with insomnia at Maharaj Nakorn Chiang Mai Hospital. The insomnia was specified by at least 2 of the following symptoms: 1) delay in falling asleep (30 minutes or longer), 2) more than two awakenings a night, 3) waking period at night for one hour or longer, 4) early waking (one hour or more before desired), 5) sleep duration of less than six hours, and 6) morning or daytime drowsiness affected by the lack of sleep. Patients with alcohol or drug dependence, pregnancy, breastfeeding, or suspected pregnancy were excluded from the study.

Regarding the medication, all subjects started with 7.5 mg zopiclone 15 minutes before bedtime. During the first week, the dose of zopiclone could be increased to 15 mg if needed. The concomitant medications allowed during the study were lithium, high-potency neuroleptics, nonsedating antidepressants, and anticholinergic agents. The concurrent use of benzodiazepines, sedating antidepressants, other hypnotics, and antihistamines was prohibited.

In evaluating the patients' sleep, the investigators requested all subjects to fill out the sleep questionnaire designed for this study. In all six items, the scores were rated from 0 to 4. The lower scores indicated the poor characteristics of sleep while the higher scores revealed a good sleep pattern. The sleep questionnaire comprised of 6 items which were: 1) sleep induction time (very long time to very short time), 2) duration of sleep (very short time to very long time), 3) number of awakenings (very often to not at all), 4) sleep quality (very bad to good), 5) dream incidence (often-vividly to not at all), and 6) condition in the morning (very bad to very good). In each subject, the sleep evaluations were completed at entry, 1 week after treatment, and 3 weeks after treatment. The mean scores of each item were statistically compared by the use of pair *t*-test. The patients were also requested to record the adverse effects found during the study.

RESULTS

Thirty-two patients participated in this study. After 1 week of treatment, one patient withdrew from the study because of intolerance to the bitter taste. The data of this patient was not included in the analysis of this study.

Fifteen males and 17 female patients took part in the present study. The mean age of the patients (SD) was 41.2 (14.6) years. The mean dosage of zopiclone (SD) was 8.47 (0.56). Most of the patients were diagnosed as schizophrenia, reaction to stress, or adjustment disorders. Details of the diagnoses and the number of subjects in each diagnosis are presented in Table 1 (see Table 1).

The mean scores of all six items obtained at entry, 1 week after treatment, and 3 weeks after treatment were compared by the use of pair *t*-test (see Fig. 1).

After 1 week of treatment, significant improvement of sleep was found on the items of sleep induction time, duration of sleep, number of awakenings, sleep quality, and condition in the morning. Comparison to the sleep at 1 week after treatment, further improvement at 3 weeks after treatment was also found on the first three items.

Table 1. The ICD-10 diagnoses and number of subjects in each diagnosis.

Diagnosis	No. of subjects
F20-29 Schizophrenia, schizotypal and delusional disorders	8
F20.X Schizophrenia	7
F22.0 Delusional disorder	1
F30-39 Mood (Affective disorders)	7
F31.X Bipolar affective disorders	2
F32.X Depressive episode	1
F33.X Recurrent depressive disorders	1
F34.1 Dysthymia	3
F40-48 Neurotic, stress-related and somatoform disorders	16
F43.X Reaction to severe stress, and adjustment disorders (e.g. acute stress reaction, adjustment disorders)	16

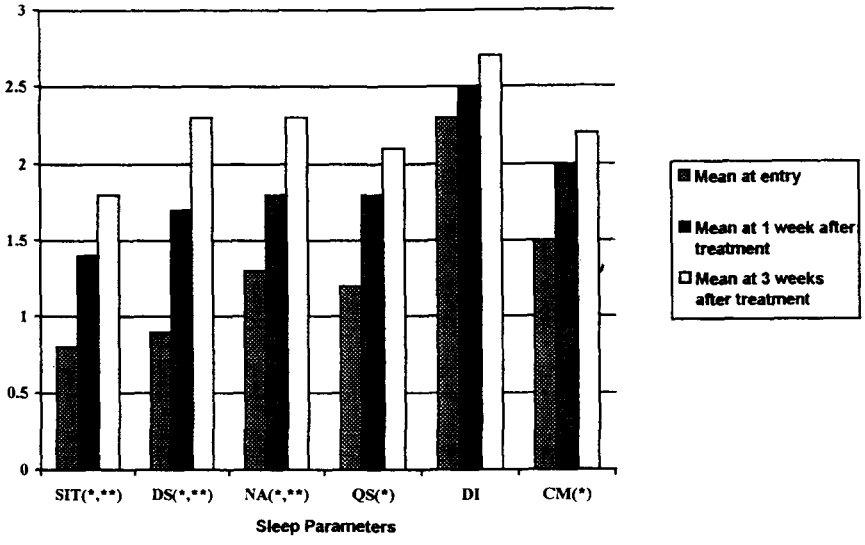

Fig. 1. Mean differences of each sleep item at entry, at 1 week after treatment, and at 3 weeks after treatment

SIT = sleep induction time;
DS = duration of sleep;
NA = number of awakening;
QS = quality of sleep;
DI = dream incidence;
CM = condition in the morning.
*** = significant difference between at entry and 1 week after treatment ($p < 0.05$);**
**** = significant difference between at 1 week and 3 weeks after treatment ($p < 0.05$).**

Other than the intolerable bitter taste in one patient, tolerable bitter taste was also found in two patients. In the other two patients, one patient complained of drowsiness, while the other one reported the problem of headache.

DISCUSSION

The results of this study confirm the sedative-hypnotic effect of zopiclone presented in several studies in Caucasian patients. The early improvement of sleep could be seen on a variety of sleep parameters including sleep induction time, duration of sleep, number of awakenings, sleep quality, and condition in the morning. Also, after 3 weeks of treatment, further improvement could be found on some sleep parameters which included sleep induction time, duration of sleep, and number of awakenings. The benefits of zopiclone found in this study appear to be consistent with the conclusions in a previous review[7].

Bitter taste, the most prevalent adverse effect in this study, was reported by Pull et al (1983)[8]. Interestingly, this adverse effect is quite rarely seen in other hypnotics. The entity of adverse effects in this study included bitter taste, drowsiness, and headache is not much different from the study of Momose[9].

In conclusion, as in the studies in Caucasians, the results of this study confirm the efficacy and acceptability of zopiclone in Asian patients with insomnia. Zopiclone at the dosage of 7.5-15 mg at bedtime is an effective, fast-acting, and well tolerated hypnotic for psychiatric patients. Further studies in a randomized double-blind design should be carried out to compare the efficacy and adverse effects of zopiclone with other hypnotics.

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โซปิโคลนในการรักษาอาการนอนไม่หลับ : การทดลองทางคลินิกแบบเปิด

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การศึกษาวิจัยนี้มีจุดประสงค์ที่จะตรวจสอบประสิทธิผลและผลไม่พึงประสงค์ของยา zopiclone ในผู้ป่วยจิตเวชไทย ผู้ป่วยนอกจิตเวชจำนวน 32 รายซึ่งมีปัญหาการนอนไม่หลับจากโรคทางจิตเวชที่แตกต่างกันได้เข้าร่วมในการศึกษาวิจัยนี้ ผู้ป่วยเหล่านี้รับประทาน zopiclone ในขนาดยา 7.5–15 mg ราว 15 นาทีก่อนนอนทุกคืน แบบสอบถามเกี่ยวกับการนอนประกอบด้วยหัวข้อต่อไปนี้ คือ 1) การเหนี่ยวนำให้หลับ, 2) ระยะเวลาการนอน, 3) จำนวนครั้งของการตื่น, 4) คุณภาพของการนอน, 5) ความถี่ของการฝัน และ 6) สภาพภายหลังการตื่นนอน คะแนนเฉลี่ยของแต่ละหัวข้อได้ถูกนำมาเปรียบเทียบโดยใช้ pair *t*-test ผลการศึกษาพบว่า หลังการรับประทานยา 1 สัปดาห์ ผู้ป่วยมีการหลับดีขึ้นในทุกหัวข้อยกเว้นหัวข้อที่ 5 ในการเปรียบเทียบการนอนหลังการรับประทานยา 1 สัปดาห์กับการนอนหลังการรับประทานยา 3 สัปดาห์พบว่า ผู้ป่วยมีลักษณะการนอนที่ดีขึ้นใน 3 หัวข้อแรก ผลข้างเคียงที่พบคือ อาการขมปาก, ง่วงนอน และปวดศีรษะ โดยสรุป ยา zopiclone เป็นยานอนหลับที่มีประสิทธิผลดีและมีผลไม่พึงประสงค์บางประการ

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