A POSTMARKETING SURVEILLANCE STUDY OF ZOPICLONE IN INSOMNIA

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ABSTRACT

Zopiclone, a novel cyclopyrrolone compound has recently become available for the treatment of insomnia in Singapore. Pharmacodynamic and pharmacokinetic studies have shown it to be an effective hypnotic with a good safety profile and minimal side-effects.

The efficacy of Zopiclone was studied in a group of patients with insomnia (n=40). The study group comprised patients with and without a psychiatric diagnosis. About two-thirds (65%) of the patients had been on hypnotics previously without relief of the insomnia.

There was improvement in the various sleep parameters studied: sleep latency, sleep duration, night awakening, sleep quality, dreams, "day-after" effects. The drug was well-tolerated and only four patients experienced minor side-effects.

Keywords: *Zopiclone, non-benzodiazepine hypnotic, insomnia.*

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INTRODUCTION

Zopiclone is a new third generation hypnotic which is available for the pharmacotherapeutic management of insomnia. It belongs to the Cyclopyrrolone group of compounds and is chemically unrelated to existing hypnotics and tranquillisers (see Fig 1 a, b and c). Zopiclone is sometimes referred to as a non-benzodiazepine hypnotic. Therapeutic trials comparing it with various benzodiazepines have shown it to be as effective as the benzodiazepine but better tolerated and without the side-effects frequently associated with benzodiazepines use such as residual sedation, anterograde amnesia and rebound insomnia[1, 2]. Zopiclone does not cause dependence. It was introduced in Singapore in 1991 and although extensively studied in other populations, there is only one local study.

Zopiclone binds at GABA macromolecular receptor complexes in the central nervous system. Pharmacokinetic studies have revealed that it has a safe profile. It is rapidly absorbed when given orally, has a half-life of 6.5 hours and the optimal does is 7.5 mg[3, 4]. There is no accumulation on repeated administration and no major variation in pharmacokinetics with increasing age. Side-effects are infrequent; some patients have complained of bitter taste and dry mouth[5].

This report is from an on-going postmarketing surveillance study in Woodbridge Hospital on the efficacy of Zopiclone in patients who complain of insomnia. The study looks at the subjective effects of short-term (one week) Zopiclone use.

Fig 1a - First Generation Barbiturates

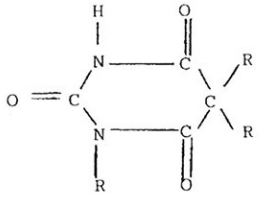


Fig 1b - Second Generation Benzodiazepines

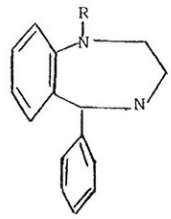
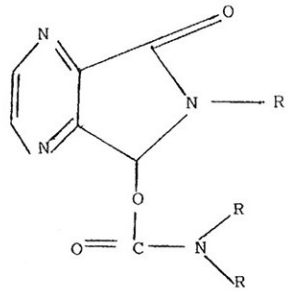


Fig 1c - Third Generation Cyclopyrrolones



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METHODOLOGY

Selection of Patients

Patients with subjective complaints of insomnia were selected from among inpatients and outpatients at Woodbridge Hospital. They had experienced one of the following for at least one month:

(a) sleep latency of 30 minutes or more,
(b) frequent nocturnal awakenings (two or more) without a known cause and difficulty falling asleep again,
(c) premature early waking,
(d) subjective feeling of insufficient sleep.

The minimum age for inclusion into the study was twenty years. None of the patients were on concurrent hypnotic treatment. Those who were on hypnotic treatment were weaned off the hypnotic at least a week before entering the study. Some of the patients were on neuroleptics and medication for medical problems such as diabetes and

hypertension. We ensured that no changes were made in the doses of the other medication for one week prior to study entry and during the one week study period. All patients were physically well.

The sample unlike other studies included psychotic and neurotic patients. However those who were acutely disturbed or depressed were not included. Also excluded were those in whom insomnia was secondary to drug or alcohol abuse. This was an uncontrolled open study. Informed consent was taken before the patients were entered into the study.

Drug Regimen

Zopiclone 7.5mg was given nightly for seven days.

Assessment

The patients had to complete a Sleep Questionnaire on the day of entry into the study and one week later. The six-item questionnaire assessed qualitative aspects of sleep and included the following items:-

(1) sleep latency
(2) sleep duration
(3) night awakening
(4) sleep quality
(5) dreaming
(6) "day-after" effects

The patients were also given a Sleep Diary to complete after the first night and after one week. At the end of one week, patients were questioned about side-effects and also asked to evaluate the drug on a five-point scale (from excellent to bad). The subjective assessment of the drug was of importance in this study and is significant particularly as insomnia is after all a subjective complaint of inability to sleep.

RESULTS

All forty patients who were entered (as of September 1992) completed the one-week study. The age and sex distribution are shown in Table I. The majority were below fifty years of age. There were 21 males (52.5%) and 19 females (47.5%). The mean age of the group was 36.5 years. Twenty-two (55%) of the patients had a psychiatric diagnosis, 18 (45%) did not. The type of psychiatric diagnosis is shown in Table II. Eighteen (45%) of the patients were on other medication and these are listed in Table III. Twenty-six patients (65%) had been on benzodiazepine hypnotics previously with no improvement of their insomnia.

The duration of sleep disturbance in the patients varied from as short as one month to the longest of fifteen years. The patients attributed various causes such as stress, social problems, work-related problems. The characteristics of the sleep disturbance the patients experienced are shown in Table IV. Most of the patients experienced more than one of the disturbances. Twenty-five patients (62.5%) experienced insomnia every night and fifteen patients (37.5%) complained of it a few times per week.

The results of the questionnaire are presented in graph form and indicate clearly the subjective changes following short-term use of the drug (Fig 2 to 7). In all the six graphs on sleep efficiency parameters studied, there is a clear shift to the left after a week's use of Zopiclone, indicating a general improvement and a reduction in the complaints. It is important to note that there was one patient who found improvement only in quality of sleep but had no change in the other items. Significantly this patient's Sleep Diary revealed that he was

Table I - Distribution of patients by age and sex

Age	Male	Female
20 - 29	7	3
30 - 39	6	6
40 - 49	7	8
50 - 59	0	1
60 & above	1	1

Table II - Psychiatric diagnosis (n = 22)

Diagnosis	No. of Patients
Schizophrenia	7
Affective disorder	4
Neurosis	9
Personality disorder	1
Stress reaction	1

Table III - Additional medication taken by patients (n = 18)

Medication	No. of Patients
Antipsychotics	7
Antidepressants	7
Medical drugs	4

Table IV - Characteristics of sleep disturbances experienced by patients

Sleep disturbance	No. of Patients
Difficulty falling asleep	32
Awakening at night	21
Premature early waking	6
Insufficient sleep	19

Fig 2 – Sleep latency before and after one week of Zopiclone 7.5 mg o.n.

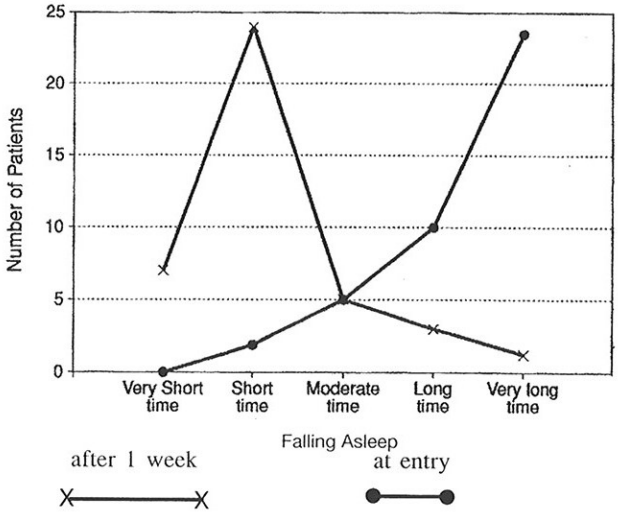


Fig 3 - Sleep duration before and after one week of Zopiclone 7.5 mg o.n.

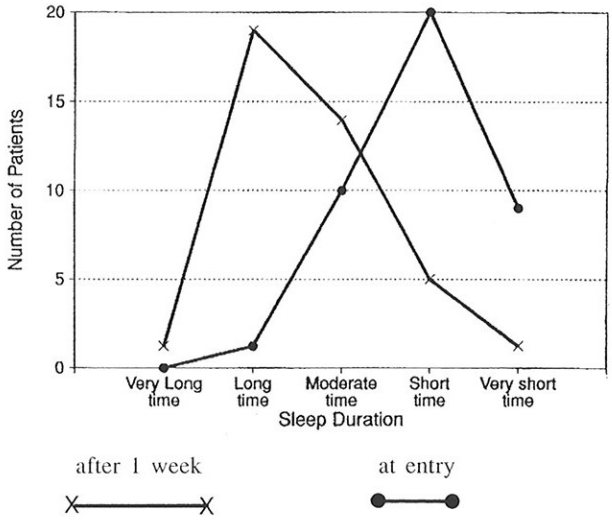


Fig 4 - Night awakening before and after one week of Zopiclone 7.5 mg o.n.

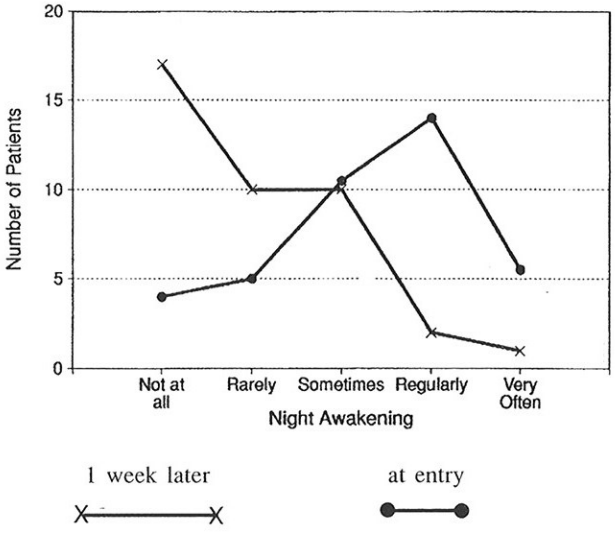


Fig 5 - Quality of sleep before and after one week of Zopiclone 7.5 mg o.n.

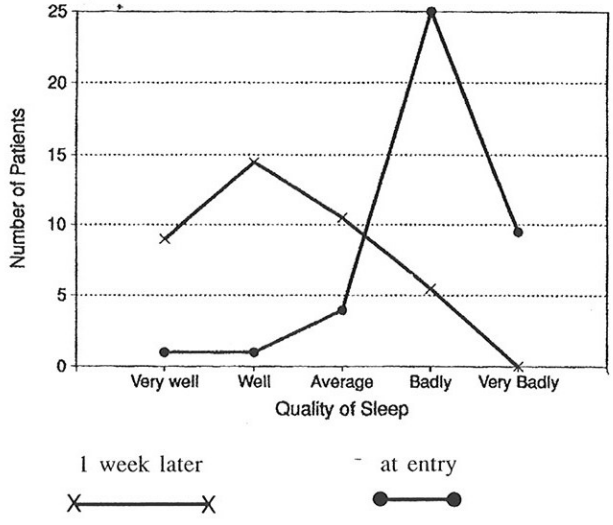


Fig 6 - Dreaming before and after one week of Zopiclone 7.5 mg o.n.

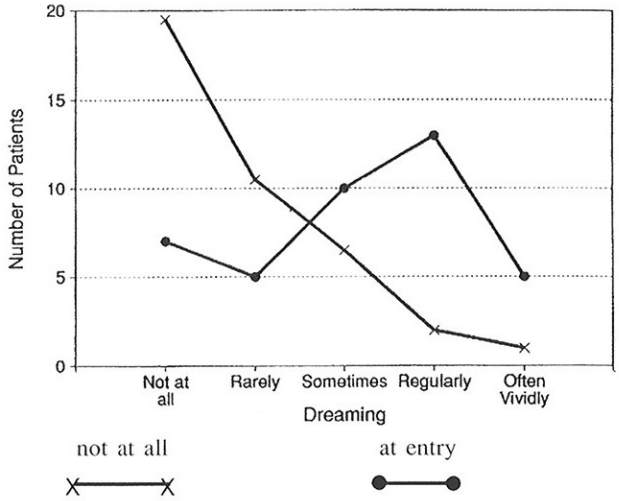
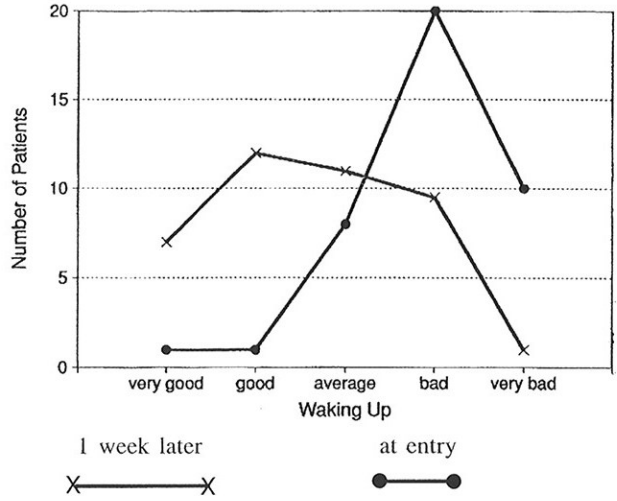


Fig 7 - Effects on waking up before and after one week of Zopiclone 7.5 mg o.n.



actually sleeping more than he claimed. This discrepancy between the objective data and subjective experience of sleep among insomniacs has been observed in many studies. There is always a small group who over-report sleep latency and under-estimate the total amount of sleep time.

There were no occurrences of serious side-effects among the forty patients studied. Four patients complained of minor side-effects; of these, two patients complained of a bitter taste the next morning, one patient experienced thirst and one patient complained of feeling drowsy the morning after. There were no complaints of coordination difficulties or psychomotor impairments.

Patients' evaluation of Zopiclone revealed that more than three-quarters of the study group (34 patients, 85%) rated it as good/fair. Twenty-seven patients (67.5%) preferred taking Zopiclone compared to what they were taking before. Of the ten patients (25%) who did not want to continue taking Zopiclone, cost was a prime consideration. More than three-quarters of the study group (33 patients, 82.5%) reported they felt alert/fairly alert the next morning. Of the remaining patients, none felt drowsy, six felt "fairly drowsy" the next morning, there was no information in one patient. Of the six patients, four were on other medication (three were on other psychiatric medication and one on diabetic treatment).

CONCLUSION

This study shows Zopiclone to be a clinically effective hypnotic producing overall improvements in all the sleep parameters studied. The findings based on subjective reporting are significant in that the insomnia in these patients are aggravated by their psychiatric conditions unlike patients seen for example, in a general practice setting. Furthermore, 65% of the patients were "resistant" to benzodiazepine treatment for their insomnia.

The patients in the study experienced a subjective improvement in sleep latency. A study by Jovanovic and Dreyfus found that sleep latency in patients on Zopiclone was reduced from 97 minutes to 16 minutes[6]. Tsoi has reported a decrease from 45 minutes to 29 minutes in a Singapore study of ten patients on Zopiclone[7]. This effect on sleep latency is constant. Studies have shown that tolerance does not develop even with long-term use[8].

Sleep duration was increased and they experienced less night awakenings. Chaudoir et al showed that awakenings in a group of twenty-five insomniacs on Zopiclone were markedly reduced to just 1 to 1.5 episodes per night[9].

The patients in the study also experienced an improvement in sleep quality. This is mainly because the drug has minimal interference with REM sleep, reduces Stage II sleep and increases deep sleep. There was also less complaints of "morning-after" effects. This is related to the short half-life of 6.5 hours and the absence of active metabolites.

Although there was no specific testing carried out, evaluation with the questionnaire showed no coordination or psychomotor impairment. Compared to benzodiazepines, Zopiclone has little impact on psychomotor performance the next day. Studies done in other centres have shown no impairment in short term memory and no rebound effect on withdrawal[10].

Zopiclone is a safe and well-tolerated hypnotic and side-effects are minimal. Most importantly the patients who used it generally found it effective.

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