Quetiapine for Primary Insomnia: A Double Blind, Randomized Controlled Trial

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Objective: *To evaluate the clinical efficacy of Quetiapine 25 mg for the treatment of primary insomnia.*
Material and Method: *A randomized, double-blind, placebo-controlled clinical trial was conducted. Patients with DSM-IV-TR defined primary insomnia were asked to record a sleep diary one week prior to treatment, followed by 2 weeks of nightly treatment with either Quetiapine 25 mg or placebo. The primary outcomes were total sleep time (TST), sleep latency (SL), daytime alertness and functioning and sleep satisfaction; side effects were recorded as secondary outcome. Data were collected between January 2007 and December 2007, at Srinagarind Hospital of Khon Kaen University.*
Results: *Thirteen patients completed the present study (mean age 45.95 years old; range 25-62). Quetiapine group increased mean TST by 124.92 minutes and 72.24 minutes in the placebo group. Mean SL was reduced by 96.16 minutes in the Quetiapine group and 23.72 minutes in the placebo group. Statistical significance was not reached between both groups. In the Quetiapine group two patients reported side effects of dry lips, dry tongue and morning drowsiness.*
Conclusion: *The present study is the first study to evaluate the effect of Quetiapine in primary insomnia in a randomized controlled trial. Quetiapine at 25 mg at night did show a trend for improvement of TST and reduced SL in primary insomnia with few side effects but not reaching statistical significance. A study with a larger sample size is needed to demonstrate its efficacy.*

Keywords: *Insomnia, Primary insomnia, Quetiapine, Sleep*

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Insomnia is among the most common concerns in clinical practice[1]. Numbers of studies have assessed the prevalence of insomnia. The findings vary, depending mostly on the criteria used for insomnia and the population studied. Data from the National Institutes of Health Epidemiologic Catchment Area (ECA) study, approximately 10-15% of adults in the United States suffer from chronic insomnia and 25-35% has transient or occasional insomnia[2,3]. In European countries insomnia occurred in 19% of the population[4]. Only one study from Thailand reported the prevalence of 46.3% in elderly[5].

From the Diagnostic and Statistical Manual of Mental Disorders, Fourth edition Text Revision (DSM-IV-TR) criteria, primary insomnia is characterized by the predominant complaint of difficulty initiating or maintaining sleep, or of non-restorative sleep, for at least 1 month. This sleep disturbance should not be caused by another diagnosable sleep disorder or mental disorder[6]. Primary insomnia accounts for 12-15% of patients with chronic insomnia. The essential features are conditioned arousal in response to efforts to sleep and negative expectations about sleep[7]. Because insomnia is a subjective complaint, polysomnography is the only method that provides a comprehensive measurement of sleep but it is expensive and unpractical. The use of subjective assessment methods such as self report questionnaires and sleep logs are more often used in clinical studies[8,9].

Primary insomnia treatments include both pharmacological and non-pharmacological modalities. Pharmacotherapies aim to reduce morbidity and prevent complications. Medication should be given for short-term management. Benzodiazepines and sedating antidepressants are commonly used.

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Benzodiazepines may cause tolerance, dependence and weakness in the elderly. Other drugs which have been used as hypnotics are antihistamines, muscle relaxants, anticonvulsants and antipsychotics[10,11]. Non-pharmacological treatments consist of patient education and behavioral therapy such as sleep hygiene, relaxation therapy and sleep restriction therapy[11].

Quetiapine is a dibenzothiazepine derivative, rapidly absorbed after oral administration and half-life of approximately seven hours, predominantly metabolized by cytochrome P450 3A4[12], has antagonist effects on serotonin, dopamine, histamine and adrenergic receptors. Antagonist action to histamine (H_1) receptor is the main cause of sedation. Quetiapine is approved by FDA for treatment of schizophrenia and mood disorders.

Extensive off label use of Quetiapine have been prescribed for treatment of depression, agitation, anxiety and insomnia. Numbers of studies favor Quetiapine for treating insomnia. Cohrs et al in a study of normal subjects, found Quetiapine 25 and 100 mg significantly improved sleep induction and continuity, increases in total sleep time, sleep efficiency and sleep quality[13]. In Parkinson's Disease without psychotic symptoms, Juri et al suggested that Quetiapine is a safe and effective treatment of insomnia in Parkinson's Disease patients[14]. A pilot study of Quetiapine in primary insomnia found sleep improvement after 2 weeks of receiving low dose Quetiapine[15]. No randomized controlled trial has been done on primary insomnia patients.

The present study aimed to evaluate sleep efficacy of Quetiapine in primary insomnia patients.

Material and Method

The present study was conducted in the psychiatric outpatient department at Srinagarind Hospital of Khon Kaen University. The study period was from January to December 2007. Patients between 16-65 years diagnosed with primary insomnia who met the DSM-IV-TR criteria were asked to join the present study.

Patients were excluded from the study if they:

1) had other psychiatric diagnosis;

2) were receiving any medication or drugs that could cause sedation;

3) were patients with other medical diseases which are orthostatic hypotension, liver disease, thyroid disease, heart disease, history of seizure or cognitive impairment;

4) were pregnant;

5) were unable to record sleep log, answer questionnaires or refused to join the present study.

The sample size was calculated by STATA program. The expected number of samples was sixteen. Patients were randomized by blocks of four to either Quetiapine or placebo group. The present study was approved by the Khon Kaen University Ethics Committee.

Possible side effects were explained and informed consent was obtained before recruitment. Other drugs that cause sedation were not allowed during the present study. Participants were asked to complete questionnaires and the visual analog scale. Sleep log or sleep diary was used to record total sleep time, sleep latency, number of awakenings. Sleep log is a self report tool, participants were asked to record exact time they went to bed, fall asleep and wake up. Sleep log sensitivity was 72.73-97.56% (mean 86.71%) and specificity was 92.85-99.68% (mean 97.04%)[16]. Mean total sleep time change was compared between Quetiapine and placebo group.

Side effects were reported after the intervention. Participants who completed the study reported side effects found.

The patients took home the sleep log and recorded their sleep pattern for one week. After that participants were randomized to either Quetiapine or placebo group. Sleep log was recorded for another two weeks. Patients then returned the sleep log, the visual analog scale and reported on any side effects.

Placebo was prepared at the Faculty of Pharmaceutical Science of Khon Kaen University; it was made identical in color, size and shape to commercially available Quetiapine tablet.

Data analysis

Statistical analysis used was Independent Sample t-test with statistical significance at $p < 0.05$ and calculated by SPSS version 11.5.

Results

The flow diagram of the present study is presented in Fig. 1. A total of 25 individuals were screened. Of these nine were not randomized because they failed to meet the entry criteria of the present study. The remaining 16 patients were randomized and 13 completed the double blind period. Three patients discontinued from the present study, one in the Quetiapine group due to emerging of other medical problems before intervention (one patient was

diagnosed with vertigo), two in the placebo group due to lack of efficacy.

Mean age of the present study sample was 45.95 years (range 25-62). There were more women than men in both groups. No significant differences in demographic characteristics between the two treatment groups were observed. Baseline demographic data is shown in Table 1.

Baseline sleep characteristics in the Quetiapine group were more severe than in the placebo group. Total sleep time during baseline was 222.55 minutes in the Quetiapine group compared to 289.64 minutes in the placebo group. The result of increased total sleep time was found in both groups, 124.92 minutes increase in the Quetiapine group and 72.24 minutes in the placebo group. No statistical significance was found between the groups ($p = 0.193$). Sleep latency was 162.65 minutes versus 71.16 minutes in Quetiapine and the placebo group respectively. Sleep latency was reduced by 96.16 minutes in the Quetiapine group and 23.72 minutes in the placebo group. There was no statistical significance between the groups ($p = 0.07$). Participants in the placebo group reported slightly better sleep quality and day time functioning at baseline. Sleep satisfaction was measured by patient scoring on visual analog scale (VAS). Although the differences in satisfaction score in the Quetiapine group were greater at 18.33 and in placebo group 12.17, no statistical significance ($p = 0.505$) was reached. Side effects found in the Quetiapine group were dry lips dry tongue and day time drowsiness. No side effect was reported in the placebo group.

Discussion and Conclusion

The objective of the present study was to evaluate the efficacy of Quetiapine 25 mg in comparison with placebo in patients with primary insomnia for a short period of two weeks using sleep log and patient self report.

Treatment with 25 mg of Quetiapine daily for 2 weeks showed a trend towards improvement in total sleep time, decreased sleep latency, increased sleep satisfaction and improved daytime functioning compared to the placebo. Increasing the sleep time for 2 hours in insomniacs can make an important difference in their quality of life even if no statistical significance was found. Sleep latency was reduced more than four times compared to placebo and nearly reached statistical significance.

The present finding was similar to the previous findings which found Quetiapine to improve

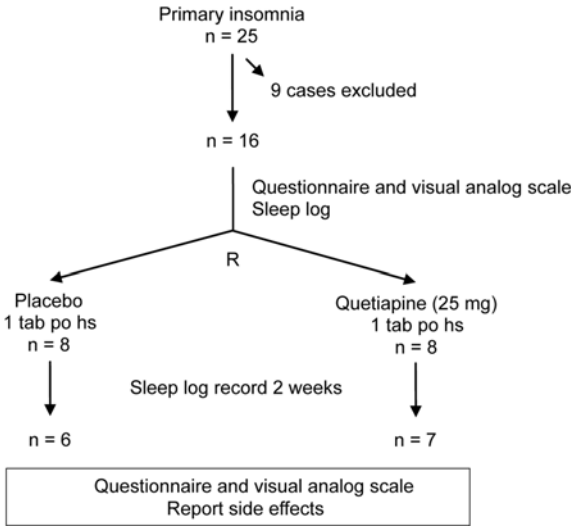

Fig. 1 Flow diagram of the study

Table 1. Baseline demographic data

Demographic data	Placebo (8) n (%)	Quetiapine (8) n (%)
Mean age (years)	47.00	44.89
Range	28-62	25-61
Male	2 (25.0)	1 (12.5)
Female	6 (75.0)	7 (87.5)
Marital Status		
Single	1 (12.5)	3 (37.5)
Married	6 (75.0)	4 (50.0)
Divorced/widowed	1 (12.5)	1 (12.5)
Education		
Primary school	1 (12.5)	2 (25.0)
Secondary + high school	2 (25.0)	1 (12.5)
Bachelor degree	2 (25.0)	3 (37.5)
Higher than bachelor degree	3 (37.5)	2 (25.0)
Occupation		
Government officer	2 (25.0)	5 (62.5)
Employee	2 (25.0)	0
Businessman	0	2 (25.0)
Housewife	3 (37.5)	1 (12.5)
Other (monk)	1 (12.5)	0
Underlying disease (s)		
Yes	4 (50.0)	5 (62.5)
No	4 (50.0)	3 (37.5)
History of hypnotic use		
Yes	6 (75.0)	5 (62.5)
No	2 (25.0)	3 (37.5)
History of substance abuse		
No	8 (100.0)	8 (100.0)
Yes	0	0

Table 2. Treatment results

	Placebo Mean (SD)	Quetiapine Mean (SD)	p-value
Total sleep time (minutes)			
Before treatment	289.64 (67.90)	222.55 (142.93)	
After treatment	361.88 (85.37)	347.47 (100.87)	
Differences between before and after	72.24 (45.02)	124.92 (82.90)	0.193
Sleep latency (minutes)			
Before treatment	71.16 (52.53)	162.65 (129.59)	
After treatment	47.44 (30.38)	66.50 (51.21)	
Differences between before and after	23.72 (26.76)	96.16 (85.51)	0.070
Sleep satisfaction (scored on VAS)			
Before treatment	46.17 (20.00)	41.43 (23.75)	
After treatment	58.33 (23.17)	59.29 (14.56)	
Differences between before and after	12.17 (10.01)	18.33 (19.41)	0.505

VAS = visual analogue scale

sleep. The study on sleep-promoting properties of Quetiapine in normal subjects[13] found at 25 mg could improve sleep induction and continuity. From quality of sleep in Quetiapine treated patients with depression[17] Quetiapine could improve actual sleep time, sleep efficiency and lessen sleep latency. In patients with schizophrenia[18,19] Quetiapine had prolonged sleep latency but no difference in total time spent asleep when comparing quetiapine to placebo. The study on insomnia in patients with Parkinson's disease[14] showed most improvement in sleep latency. In patients with Tamoxifen induced insomnia[20] most patients showed improvement from insomnia and the effect maintained after 6 weeks. One pilot study on Quetiapine in primary insomnia[15] also demonstrated that low dose Quetiapine improved sleep parameters. There were some side effects found with Quetiapine in agreement with the previous studies which include transient hangover effect in the morning[14,15], dry mouth[15], one study found weight gain and dizziness[20].

The present study had some advantages as it was a randomized, double blind trial. The inclusion and exclusion criteria were strictly applied. The present study was not supported by the pharmaceutical company and the authors do not hold any conflict of interest.

Limitations

The present study had certain limitations. First, efficacy was only evaluated for two weeks. Second, the sample size was quite small and with drop-outs the sample size was smaller than expected.

Recalculating the statistical power, statistical significance may be reached if sample size were increased to 17 or more subjects per group. Increasing the dose of Quetiapine, may lead to significance in the treatment of insomnia but could create more side effects. A longer duration of controlled study, including other groups of patients such as psychotic patients with insomnia, should be pursued.

In conclusion, the current study suggests that Quetiapine 25 mg maybe a promising drug for primary insomnia. Additional studies on efficacy of Quetiapine for this complaint are needed.

Disclosure Statement

This study was supported and fully funded by the Faculty of Medicine, Khon Kean University. All authors have no conflicts of interest.

This study was approved by Khon Kaen University Ethics Committee No. i50139 and was registered at Clinicaltrials.gov NCT 00328822.

Oral Presentation of the study was made at the 11th Congress of ASEAN Federation for Psychiatry and Mental Health (AFPMH) on 27th August 2008 at Siam Paragon, Bangkok, Thailand.

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การใช้ยาเควไทอาพีนรักษาผู้ป่วยที่นอนไม่หลับชนิดปฐมภูมิ: การทดลองที่มีการสุ่มและมีกลุ่มควบคุม

กนิดา ทัศนิยม, สุชาติ พหลภาคย์, สมพนธ์ ทัศนิยม, จิราพร เขียวอยู่

วัตถุประสงค์: *เพื่อศึกษาประสิทธิภาพของยาเควไทอาพีนขนาด 25 มิลลิกรัม ในการรักษาผู้ที่มีอาการนอนไม่หลับชนิดปฐมภูมิ*

วัสดุและวิธีการ: *การศึกษานี้ เป็นการทดลองแบบสุ่มที่มีกลุ่มควบคุม และปิดบังทั้งสองด้าน ผู้ที่ได้รับการวินิจฉัยเป็นโรคนอนไม่หลับชนิดปฐมภูมิตามหลักเกณฑ์ของ DSM-IV-TR และผ่านเกณฑ์การจัดกลุ่มตัวอย่าง ได้รับการร้องขอให้บันทึก sleep diary เป็นระยะเวลาหนึ่งสัปดาห์ หลังจากนั้นได้รับการสุ่มเป็นสองกลุ่ม คือกลุ่มที่ได้รับยาเควไทอาพีน 25 มิลลิกรัม หรือ กลุ่มที่ได้รับยาหลอก รับประทานหนึ่งเม็ดติดต่อกันนานสองสัปดาห์ ร่วมกับบันทึก sleep diary ตัวชี้วัดผลการศึกษาได้แก่ ระยะเวลาทั้งหมดที่สามารถหลับได้จริง ระยะเวลาตั้งแต่เข้านอนจนถึงหลับจริง ความสามารถในการทำงานในตอนกลางวัน และผลข้างเคียงที่เกิดขึ้นจากการใช้ยา การเก็บข้อมูล กระทำตั้งแต่เดือนมกราคม ถึง เดือนธันวาคม พ.ศ. 2550 ที่ รพ.ศรีนครินทร์ คณะแพทยศาสตร์ มหาวิทยาลัยขอนแก่น*

ผลการศึกษา: *อาสาสมัครที่เข้าร่วมจนจบการศึกษาทั้งหมด 13 คน (อายุเฉลี่ย 45.95 ปี) กลุ่มที่ได้รับการรักษาด้วยยาเควไทอาพีนมีระยะเวลาการนอนหลับเฉลี่ยได้นานกว่าเดิม 124.92 นาที กลุ่มที่ได้รับการรักษาด้วยยาหลอกนอนหลับได้นานขึ้นเฉลี่ย 72.24 นาที ระยะเวลาตั้งแต่เข้านอนจนถึง เวลาที่หลับได้จริงเฉลี่ยในกลุ่มที่ได้รับการรักษาด้วยยาเควไทอาพีนสั้นลง 96.16 นาที ในกลุ่มที่ได้รับการรักษาด้วยยาหลอกสั้นลง 23.72 นาที ความแตกต่างที่เกิดทั้งสองกลุ่ม เมื่อทำการเปรียบเทียบ ไม่พบความแตกต่างอย่างมีนัยสำคัญทางสถิติ กลุ่มที่ได้รับยาเควไทอาพีนมีรายงานผลข้างเคียงของการใช้ยา ได้แก่ อาการปากแห้งคอแห้ง และอาการง่วงนอนในเวลากลางวัน*

สรุป: *การศึกษานี้เป็นการศึกษาแรกที่ทำการเปรียบเทียบผลของการรักษายาเควไทอาพีน ในผู้ที่มีอาการนอนไม่หลับแบบปฐมภูมิ พบว่ายาเควไทอาพีนในขนาดรับประทานก่อนนอน 25 มิลลิกรัม ทำให้ผู้ที่มีอาการนอนไม่หลับชนิดปฐมภูมินอนหลับได้ง่ายขึ้น และนอนหลับได้นานขึ้นมากกว่ายาหลอก แต่ไม่แตกต่างอย่างมีนัยสำคัญทางสถิติ การศึกษาในอนาคตหากมีกลุ่มทดลองที่มากขึ้นอาจทำให้เกิดนัยสำคัญทางสถิติ ได้จำนวนผู้เข้าร่วมการศึกษาที่มากขึ้นจะช่วยในการยืนยันผลการศึกษา*