The Effect of Galantamine on Sleep Quality in Thai Alzheimer's Disease Patients

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Objective: *To study the effect of Galantamine on sleep quality in Thai Alzheimer's disease (AD) patients with or without cerebrovascular disease.*

Material and Method: *A 6 month,multicenter, open-label, uncontrolled trial was undertaken in 75 mild to moderate Alzheimer's disease patients with or without cerebrovascular disease. Eligible patients received a flexible-dose of Galantamine 16 or 24 mg/day for 24 weeks. The Pittsburgh Sleep Quality Index (PSQI) with self-analysis questionnaires were used to evaluate sleep quality. Analyses were based on the intent-to-treat population.*

Results: *Seventy-five eligible patients with mild to moderate Alzheimer's disease with or without cerebrovascular disease (male:female = 32:43, age range 74.5 $\pm$ 0.9) were included and 58 patients (79%) completed the present study. The global PSQI scores showed some improvement over baseline (week 0 = 5.10 $\pm$ 3.08, week 4 = 4.37 $\pm$ 2.48, week 8 = 4.65 $\pm$ 2.71 week 24 = 3.70 $\pm$ 2.12) but were not yet statistical significant. In contrast, most of each component scores such as sleep quality, sleep latency, sleep duration, sleep disturbances, sleep medication, and daytime dysfunction except sleep efficiency, showed significant differences from baseline after week 8. Moreover, there were no significant differences in global PSQI and component scores between mild and moderate stages of Thai AD patients or between men and women patients.*

Conclusion: *The result of the present study may be consistent with Galantamine being safe and can maintain good sleep quality for mild to moderate Thai AD patients with or without VaD. Galantamine doses of 16-24 mg/day were well tolerated.*

Keyword: *Galantamine, Sleep, Side effect*

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Alzheimer's disease is the most common cause of dementia in the elderly. Cerebrovascular disease and vascular dementia (VaD) is a chronic disease that results from reduced cerebral blood flow to nerve cells and can occur together with AD in a condition called "mixed dementia". There is considerable evidence suggesting that as in AD the central cholinergic system is impaired in VaD.

Sleep problems are commonly found in AD and mixed dementia, and became worsen when the

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disease progresses (Bliwise et al, 1992[2], McCurry et al, 1999[11]). The problems include waking up during nighttime, less rapid eye movement (REM) and slow wave sleep (Moe et al, 1995[12], Reynolds el al, 1985[14]). Sleep-wake cycle disturbances are often found in AD, affecting up to 44% of patients in study group (Vitiello and Boroson, 2001[21]). The prevalence of sleep disturbances in AD is expected to increase (Hebert et al, 2003[7], Wimo et al, 2003[23]).

Moreover, disturbed day/night behavior and the sundown syndrome are also major problems during moderate stages of disease. Nighttime wakefulness, particularly when combined with agitation, hallucinations, and wandering, is a major management problem for caregivers and often leads to early institutionalization of AD patients (Vitiello et al, 1992[21]).

The Acetylcholine esterase inhibitor (AChEI) therapy may have benefits on sleep. Galantamine is a novel drug used for treatment in AD patients. It has a dual benefit mechanism; allosterically modulates nicotinic acetylcholine receptors (Schrattenholz et al, 1996[19]) and enhances cholinergic function by reversibly and competitively inhibiting acetylcholinesterase (Lilienfeld and Prays, 2000[9]).

The increase in acetylcholine plays a critical role in promoting REM sleep. It seems to be a subtly balanced neuroregulatory system, the sleep organizing and regulation apparatus (SORA) that controls timing and transitions among wakefulness, REM sleep, and non-REM (NREM) sleep (Koella, 1984[8]). On the basis of previous studies, Galantamine may provide benefits on cognition and sleep qualities. However, no studies have been conducted in Thai patients before.

Therefore, the authors studied the effects of galantamine on sleep quality among Thai Alzheimer's disease patients with or without cerebrovascular disease (CVD) by using the Pittsburgh Sleep Quality Index (PSQI).

Material and Method

Patients

Men and women with the diagnosis of possible AD who met the clinical criteria of National Institute of Neurological Disease and Communicative Disorders and Stroke and AD Related Disorders Association (NINCDS/ADRDA) (Blacker et al, 1994[1]), or with possible Vascular dementia (VaD) according to the National Institute of Neurological Disease and Communicative Disorders and Stroke and AD Related Disorders Association and the Association Internationale pour la Recherche et l'Enseignement en Neuroscience (NINCDS/AIREN) with the modified Hachinski scale given a score of 4 or higher were included in the present study. They also documented with CT or MRI scan less than 12 months before entry to the trial.

Eligible patients showed presence of mild or moderate dementia as evidenced by a Thai Mental State Examination (TMSE; Folstein et al, 1975[5]) score of 10-24 and a score of[3] 12 on the standard cognitive subscale of the AD Assessment Scale (ADAS-cog; Galasko, 1997[6]). The onset of disease had to be between the ages 40 and 90. Patients must be able to perform certain activities of daily living.

Patients were excluded if they had evidence of neurodegenerative diseases other than dementia, uncontrolled epilepsy, significant psychiatric disease, specific coexisting medical conditions, cardiovascular disease, active peptic ulcer disease, clinically significant urinary outflow obstruction, clinically significant hepatic, renal, pulmonary, metabolic, or endocrine disturbances that would be expected to limit the patient's ability to complete the trial. Patients who had used investigator drugs or any drugs to treat dementia or other cognitive impairment within the previous 30 days were also excluded.

Study design

The present study was a multicentre, open-label, uncontrolled trial undertaken in Thailand from January 2002 until December 2003. Patients were assigned to receive flexible-dose of galantamine 16 or 24 mg/day. Treatment with galantamine was initiated at 4 mg twice daily and increased to 8 mg twice daily after 4 weeks. In case that ADAS-cog score is less than 4 points at the evaluation of week 8, the investigator could increase the dose to 12 mg twice daily and based on patient tolerance.

Physical and neurological examinations, psychometric evaluation, laboratory investigations including vital signs were performed at screening, baseline and (together with checks for drug compliance and adverse events) at week 8,12, and 24. CT and MRI were also performed at screening if had not been done in the previous 6 months (Thavichachart et al , 2006[24]).

Assessments

Subjective examination of sleep was examined using the Pittsburgh Sleep Quality Index (PSQI). All patients had to complete the PSQI as a measure of average sleep quality. The PSQI assessed 10 self-assessment questions about their sleep. The questions

included subject sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medication, and daytime dysfunction. The scores ranged from 0 to 21 points, with the lower scores corresponding to better sleep quality. The PSQI was completed at visit 2, 4, 5, and 6 (baseline, week 8, week 12, and week 24 or upon early discontinuation of trial medication). ADASCog to evaluated cognitive function, and the Clinician Interview - Based Impression of Change (CIBIC-plus), to assess over all clinical response including safety and tolerability as well as changes from baseline of physical examination, vital signs, and laboratory values were also assessed.

Statistical analysis

Data from earlier validated Galantamine trial indicated that 64 patients were needed in the study to achieve 80% power (alpha = 0.05) for difference in the score of changes between patients treated with Galantamine between baseline and 6 months[22].

All patients were analyzed for demographic and baseline characteristic data using two-tailed, paired *t*-tests. Analysis efficacy was based on the intent to treat population. Changes in PSQI both global and component scores were assessed by two-way ANOVA and Post hoc analysis were assessed by Pearson Correlation. All statistical tests were interpreted at the 5% significance level.

Results

Seventy-five eligible patients with mild to moderate Alzheimer's disease with or without cerebrovascular disease (male: female = 32:43, mean age 74.5 $\pm$ 0.9) were included and 58 patients (79%) completed the present study.

The baseline characteristics are shown in Table 1. Premature withdrawal was due to nausea, vomiting, weight loss, dizziness, rash, and loss to follow-up.

At baseline, the patients had the mean ADAS-cog score and TMSE score of 21.8 $\pm$ 1.1 and 19.7 $\pm$ 4.2 respectively (Table 1). Fifty-two patients (69%) were classified as mild severity defined by TMSE > 18 and the remaining 23 (31%) were classified as moderate severity (TMSE < 18). The mean daily dose of Galantamine was 21.01 +/3.9 mg/day. There were 28 (47%) patients maintained Galantamine 16mg/day and 31 (53%) patients who maintained Galantamine 24 mg/day at end point.

The Global PSQI scores did not show statistically significant changes throughout the present study (Table 2). But considering each component (except sleep efficiency) such as sleep quality, sleep latency, sleep duration, sleep disturbances, sleep medications, and daytime dysfunction they all showed statistically significant changes from baseline (week 0) 8. Only sleep efficiency had not significantly improvement at week 8. However, one patient had insomnia and trazodone was prescribed to alleviate this problem.

At baseline there were no statistical differences in PSQI scores (Table 3) between men and women. Moreover, there were no statistically significant changes in global PSQI scores (Table 4) and each (Table 5) component between mild and moderate stages in Thai AD patients after being treated with galantamine from week 0-24.

Other efficacy analyses

Improvement of ADAS-cog score over baseline were statistical significant at week 8,12 and 24 (-2.10 +/5.10, -3.53 +/5.4, and -3.34 +/6.8 points respectively; $p < 0.05$). Using the CBIC-plus as a measure of overall global function response to galantamine therapy both groups of patients with mild and moderate severity could maintain or improve their CIBIC-plus scores at the end of the present study. At the present study endpoint, two thirds of the patients (67.8%) reported improvement, 25.4% reported no change, and the remaining 6.8% reported worsened.

Safety analyses

The adverse events were mild to moderate intensity and transients. These included nausea, vomiting, abdominal pain, weight loss, and dizziness.

Table 1. Baseline characteristics

Characteristics	Results (n = 75)
Demography	
Male (%)	32 (42.3)
Female (%)	43 (57.7)
Age (mean $\pm$ SD, year)	74.50 $\pm$ 0.9
Bodyweight (mean $\pm$ SD, kg)	53.60 $\pm$ 9.9
Diagnosis (%)	
Possible AD	37 (50)
Vascular dementia	6 (7.9)
AD with cerebrovascular disease	32 (42.1)
Severity (%)	
Mild	52 (69)
Moderate	23 (31)
Cognitive function	
ADAS-cog (mean $\pm$ SD)	21.78 $\pm$ 1.1
TMSE (mean $\pm$ SD)	19.70 $\pm$ 4.2

Table 2. Global Pittsburgh Sleep Quality Index (PSQI) and component scores

	Mean ± SD (n = 58)			
	Week 0	Week 8	Week 12	Week 24
Global PSQI scores	5.10 ± 3.08	4.37 ± 2.48	4.65 ± 2.71	3.70 ± 2.12
Component scores				
Sleep quality	1.13 ± 0.82	1.03 ± 0.83**	1.06 ± 0.85**	0.81 ± 0.54**
Sleep latency	0.93 ± 0.98	0.86 ± 0.94**	0.93 ± 0.98**	0.82 ± 0.84**
Sleep duration	0.75 ± 0.99	0.60 ± 0.87**	0.72 ± 0.93**	0.53 ± 0.79**
Sleep efficiency	0.10 ± 0.48	0.06 ± 0.41	0.08 ± 0.33**	0.01 ± 0.13**
Sleep disturbances	1.18 ± 0.43	1.03 ± 0.37**	0.98 ± 0.43*	0.94 ± 0.43
Sleep medications	0.43 ± 1.01	0.34 ± 0.88**	0.27 ± 0.74**	0.22 ± 0.72**
Daytime dysfunction	0.55 ± 0.79	0.43 ± 0.67**	0.58 ± 0.79**	0.34 ± 0.57**

**, $p < 0.01$
*, $p < 0.05$

Table 3. Global Pittsburgh Sleep Quality Index (PSQI) and component scores between men and women in baseline study

PSQI component	Mean ± SD	
	Men	Women
Global scores (n = 22,33)	5.4 ± 2.64	4.39 ± 2.57
Component scores		
Sleep quality (n = 27,48)	1.22 ± 0.89	1.10 ± 0.8
Sleep latency (n = 26,47)	0.65 ± 0.74	0.89 ± 1.04
Sleep duration (n = 27,47)	0.88 ± 1.15	0.65 ± 0.98
Sleep efficiency (n = 26,46)	0	0.13 ± 0.54
Sleep disturbances (n = 23,34)	1.21 ± 0.51	1.14 ± 0.5
Sleep medications (n = 27,47)	0.74 ± 1.25	0.31 ± 0.88
Daytime dysfunction (n = 27,47)	0.48 ± 0.8	0.46 ± 0.68

Table 4. Global PSQI scores between mild and moderate stages in Thai AD patients

	Global PSQI mild stage (n = 43)	Global PSQI moderate stage (n = 15)
Week 0	4.58 ± 2.42	6.60 ± 4.23
Week 8	4.39 ± 2.42	4.33 ± 2.74
Week 12	4.58 ± 2.71	4.86 ± 2.82
Week 24	3.55 ± 2.22	4.13 ± 1.80

Discussion

This open-label,uncontrolled study suggests that Thai patients with mild to moderate severe AD with or without cerebrovascular disease and VaD receiving galantamine, experienced benefits in sleep quality after 24-weeks treatment.

The sleep quality was assessed by PSQI with self-analysis questionnaires. In spite of the global PSQI scores changes between week 0 and week 24 were not statistically significant but the global scores showed some trend of improvement. The relevance of these findings were emphasized by the significant differences after week 8 of most of each component score component scores except sleep efficiency (Table 2). From the present findings, the authors might conclude that galantamine treatments could maintain sleep quality and probably might be able to improve some components of sleep quality but not all since there were some statistically significant changes in the subscale scores but not the global score.

The present results were quite similar with the previous 3-months, placebo-controlled trial by Rockwood and Kershaw. The mean PSQI scores were 3.7 and 3.9 in patients treated with Galantamine and placebo respectively (mean decrease from baseline were 0.2 points in each group). The mean PSQI difference between the two groups was not statistically significant (Rockwood and Kershaw, 2000[16]). Moreover in one randomized, doubled-blind, placebo-controlled galantamine trial(Stahl et al, 2004[20]), the incidence of insomnia / sleep problems in placebo, glutamine 16 mg/day, and glutamine 24 mg/day groups were 2,2%, 1.1% 2.6% respectively. Rates of use for all concomitant medications in placebo, galantamine 16 mg/day, and

Table 5. Component scores between mild and moderate stages in Thai AD patients

Component scores	Mild (n = 43)				Moderate (n = 15)			
	Week 0	Week 8	Week 12	Week 24	Week 0	Week 8	Week 12	Week 24
Sleep quality	1.09±0.86	1.04±0.92	1.06±0.91	0.76±0.57	1.26±0.70	1.00±0.53	1.06±0.70	0.93±0.45
Sleep latency	0.93±0.93	0.86±0.91	0.90±0.97	0.81±0.85	0.93±1.16	0.86±1.06	1.00±1.06	0.86±0.83
Sleep duration	0.65±0.92	0.60±0.90	0.65±0.89	0.44±0.73	1.06±1.16	0.60±0.82	0.93±1.03	0.80±0.94
Sleep efficiency	0.04±0.30	0.02±0.15	0.09±0.36	0.02±0.15	0.26±0.79	0.20±0.77	0.06±0.25	0
Sleep disturbances	1.16±0.43	1.06±0.40	0.95±0.43	0.95±0.43	1.26±0.45	0.93±0.25	1.06±0.45	0.93±0.45
Sleep medications	0.25±0.81	0.37±0.92	0.27±0.73	0.23±0.78	0.93±1.33	0.26±0.79	0.26±0.79	0.20±0.56
Daytime dysfunction	0.44±0.62	0.41±0.69	0.62±0.81	0.32±0.56	0.86±1.12	0.46±0.63	0.46±0.74	0.40±0.63

24 mg/day were 4.6,2.9,5.4%, respectively. There were no significant differences in rates of use for all concomitant medications and the incidence of insomnia/ sleep problems between the placebo and galantamine treatment group. Acetylcholinesterase inhibitor drugs may have some benefits in minimizing or eliminating sleep disturbances problem in AD patients. However, donepezil showed some adverse effects in sleep problems, sleep disturbances, insomnia and abnormal dreams in AD (Burns et al, 1999[3], Rogers et al, 1998[17]). However, no evidence of such adverse effects in rivastigmine trial (Rosler et al, 1999[18], Corey-Bloom et al, 1998[4], Raskind et al, 2000[13]) nor in a galantamine trial (Rockwood et al, 2001[16], Wilcock et al, 2000[22], Markowitz et al, 2003[10]).

The prevalence of sleep problems and disruptive effects of sleep problems are greater in AD and their caregivers (McCurry et al, 1999[11]) than in the normal population. Maintenance and preservation of sleep quality is essential in AD treatment. The present study supports previous findings and suggests that Galantamine can maintain good sleep quality in Thai AD patients (Stahl et al, 2004[20]).

Conclusion

The result of the present study may be consistent with Galantamine being safe. It showed a trend of sleep quality improvement and can maintain good sleep quality for mild to moderate Thai AD patients with or without VaD. Galantamine doses of 16-24 mg/day were well tolerated.

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ผลของยา galantamine ต่อคุณภาพการนอนหลับของผู้ป่วยโรคอัลไซเมอร์ชาวไทย

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วัตถุประสงค์: *เพื่อศึกษาผลของยา galantamine ต่อคุณภาพการนอนหลับของผู้ป่วยโรคอัลไซเมอร์ชาวไทยที่มี หรือไม่มีภาวะโรคหลอดเลือดสมองร่วมด้วย*

วิธีการศึกษา: *การศึกษานี้เป็นการศึกษาแบบเปิด พหุสถาบัน ในผู้ป่วยโรคอัลไซเมอร์ที่มีระดับอาการเล็กน้อยถึงปานกลางที่มี หรือ ไม่มีภาวะโรคหลอดเลือดสมองร่วมด้วยจำนวน 75 ราย (สัดส่วนเพศหญิงต่อเพศชาย = 32:43 ช่วงอายุเฉลี่ย = 74.5 ± 0.9 ปี) โดยมีผู้ป่วยจำนวน 58 รายที่เข้าร่วมในโครงการจนจบการศึกษา (คิดเป็น 79%) ผู้ป่วยที่เข้าร่วมการศึกษาจะได้รับยา galantamine ในขนาด 16 หรือ 24 มิลลิกรัมต่อวันเป็นเวลา 24 สัปดาห์ โดยใช้แบบสอบถาม Global Pittsburgh Sleep Quality Index (PSQI) ในการประเมินคุณภาพการนอนหลับของผู้ป่วย และการวิเคราะห์ข้อมูลแบบ intent-to-treat*

ผลการศึกษา: *ผู้ป่วยที่ใช้ยา Galatamine ที่เข้าร่วมการศึกษาทั้งหมดมีค่า Global PSQI Scores ที่ดีขึ้นระหว่างสัปดาห์ที่ 0-24 (สัปดาห์ 0 = 5.10 ± 3.08, สัปดาห์ 4 = 4.37 ± 2.48, สัปดาห์ 8 = 4.65 ± 2.71 สัปดาห์ 24 = 3.70 ± 2.12) แต่ก็ไม่มีนัยสำคัญทางสถิติ แตกต่างจากค่า Component Scores* **which** *ส่วนใหญ่began to have มีความเปลี่ยนแปลงอย่างมีนัยสำคัญทางสถิติในสัปดาห์ที่ 8 นอกจากนี้พบว่าค่า Global PSQI Scores และ Component Scores ไม่มีความแตกต่างอย่างมีนัยสำคัญทางสถิติระหว่างกลุ่มผู้ป่วยโรคอัลไซเมอร์ที่มีระดับอาการเล็กน้อยและระดับปานกลาง และในระหว่างผู้ป่วยเพศชายและเพศหญิงก็ไม่พบว่ามีความแตกต่างเช่นกัน*

สรุป: *จากผลการศึกษานี้สรุปได้ว่ายา galantamine สามารถคงคุณภาพการนอนหลับที่ดีได้และไม่เป็นสาเหตุของปัญหาการนอนหลับในผู้ป่วยโรคอัลไซเมอร์ชาวไทย*