Safety and Tolerability of Galantamine in Possible Alzheimer's Disease with or without Cerebrovascular Disease and Vascular Dementia in Thai Patients

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The purpose of this study was to explore factors that influence the clinical safety and tolerability associated with galantamine administration in Thai Alzheimer's disease patients with or without cerebrovascular disease and vascular dementia. This was an analysis of previous study. Tolerability and safety profile were analyzed according to sex, age, body weight, Thai mental state examination (TMSE) score, Alzheimer's disease assessment scale-cognitive subscale (ADAS-cog) score, and Alzheimer's disease cooperative study/activities of daily living (ADCS/ADL) score.

The most common adverse events were nausea, dizziness, and weight loss which more often occurred during the dose-escalation phase. Mean body weight lost at week 24 was 0.9 kg. Sex, age, body weight, and ADAS-cog score did not influence the incidence of any adverse events. Dizziness was more likely to occur in patients with low TMSE and high ADCS/ADL score ($p = 0.02$ and $p = 0.050$, respectively). Patients with TMSE score equal or higher than 23 more often experienced muscle cramps and fatigue than who had TMSE lower 23 ($p < 0.05$). However, flexible dose escalation of galantamine with a 4-week schedule was safe and well tolerated in Thai AD patients.

Keywords: *Alzheimer disease, Dementia, Vascular, Drug tolerance, Galantamine, Safety*

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Galantamine, a novel treatment for Alzheimer's disease (AD), has a dual mechanism of action, providing both a reversible competitive inhibition of acetyl cholinesterase and an allosteric modulation of nicotinic acetylcholine receptors. Several randomized, placebo-controlled studies have demonstrated the effectiveness of galantamine in improvement of cognition, global change, and behavioral symptoms in patients with AD with or without cerebrovascular (CVD) disease. Some trials showed effects in patients with vascular dementia (VaD).

In an efficacy study of 6-month, multi-centre, open-label trial of galantamine in Thai patients with AD with or without CVD and VaD was found that a flexible dose of galantamine (16 mg/day) was effective in the treatment of cognition and behavior symptoms in Thai AD patients[1]. In addition, galantamine was shown to improve global functioning, activities of daily

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living, and sleep quality. The adverse events associated with galantamine were well tolerated.

Because of these potential benefits and low risks of galantamine, it is important to identify factors that enable physicians able to predict which patients may have greater risk for adverse events. Some animal studies suggested that gender may modify treatment response and adverse events to cholinesterase inhibitors[2]. Human clinical studies are limited. Thus, the purpose of this analysis was to explore factors that influence the clinical tolerability and safety profile with galantamine administration in Thai AD patients with or without CVD and VaD patients.

Material and Method

Study design

This was the report of an analysis of results from a 6-month, multi-centre, open-label, uncontrolled trial of galantamine in Thai patients with AD with or without CVD and VaD[1].

The study was an open-label trial collecting data over 6 months. Patients received a 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 change in ADAS-cog score less than 4 points at the evaluation of week 8, the dose was increased to 12 mg twice daily. The inclusion and exclusion criteria and details of the study were published previously. All patients were prescribed an antiemetic drug, domperidone, during the escalation phase and were allowed to take it for relieving nausea and vomiting symptoms. Frequency of taking domperidone was recorded by their caregivers.

Withdrawal criteria included patients who withdrew their consent form, or developed a serious adverse event, or who safety withdrew reasons as was judged by the investigators.

Assessments

Tolerability and safety assessments throughout the study were evaluated on the basis of spontaneous reporting for all adverse events by the patients and their caregivers. Physical examination, vital signs, and body weight were performed at every visit (week 0, 4, 8, 12, and 24). In addition, a resting 12-lead electrocardiogram (ECG) and clinical laboratory test were taken at week 0, 12 and 24. Laboratory analysis included BUN, creatinine, electrolytes, AST, ALT, total bilirubin, direct bilirubin, CPK, and CBC with differential, urinalysis.

Statistical analysis

All patients who received at least one dose of the study medication and had at least one post-baseline data study were included in the data analysis (ITT). Adverse events were revealed in terms of frequency and percent. The results for changes in physical examination and EEG were summarized by the number and percent of abnormalities at each scheduled time point. Changes in vital signs, body weight, or other laboratory values from baseline were assessed by using a two-tailed, student paired t-test. Unpaired student t-test was used to evaluate gender difference of the occurrence of adverse events (intention-to-treat analysis). Unpaired student t-test was used to analyze the difference in adverse events between those with TMSE < 23 and those with TMSE score $\geq$ (intention-to-treat analysis). Difference in the occurrence of adverse events between those with probable AD and AD with vascular risk factors (Hachinski ischemic score ≥ 5) was assessed by usinf Pearson Chi-Square. Difference in the occurrence of adverse events between our study and the international galantamine trial was assessed by utilizing a two-tailed, student paired t-test. All adverse events were analyzed as an outcome to evaluate if gender, age, body weight, Thai mental state examination (TMSE) score, Alzheimer's disease assessment scale-cognitive subscale (ADAS-cog) score, and Alzheimer's cooperative study activities of daily living inventory (ADCS/ADL) score were the risk factors of these outcomes. All statistical tests were performed at the 5% significance level.

Results

There were 75 patients enrolled in this study and 59 patients (79%) completed the study. Thirty-two (42.3%) were men and 43 (57.7%) were women. The mean age of our cohort was 74.5 (0.9) years. The mean body weight was 53.6(9.9) kilograms. Means ADAS-cog and TMSE was 21.78 (1.1) and 19.7 (4.2)

Table 1. Causes of premature withdrawal from the study

Causes	Number of patients (%)
Loss follow-up	3 (4)
Nausea and vomiting	8 (10.6)
Weight loss (>15% from baseline)	1 (1.3)
Dizziness	3 (4)
Rash	1 (1.3)
Abnormal ECG	1 (1.3)

accordingly. Thirty-seven (50%) had probale AD, 32 (42.1%) had possible AD with cerebrovascular disease, and 6 (7.9%) had vascular dementia[1]. Seventeen patients were discontinued early from the study. Causes of withdrawal are summarized in Table 1.

There were 28 patients (47%) and 31 patients (53%) who maintained galantamine at the dose of 16 mg/day and 24 mg/day at week 24, respectively. No serious adverse events were reported. There was no significant difference in the incidences of any adverse events among these 2 groups (p = 0.568, Chi-square test: continuity correction). The most common adverse events found in this study were nausea, vomiting, abdominal pain, diarrhea, muscle cramp, fatigue, headache, dizziness, anorexia, and weight loss (Table 2). The majority of adverse events were mild, tolerable and predictable. Only two patients needed to take domperidone during the dose-escalation phase to alleviate symptoms of nausea and vomiting.

Considering differences in their demographic data, dizziness was statistically found to be of significance in patients who had lower TMSE score and higher ADCS/ADL score (more disable) when compared to patients did not developed dizziness (p = 0.02, and p = 0.050, respectively; Table 3). Fig. 1 revealed that gender did not have an effect on the risk

Table 2. Number of patients with adverse events during the dose-escalation and maintenance phase

Adverse events	Number of patients			
	Dose-escalation phase		Maintenance phase	
	Week 4	Week 8	Week 12	Week 24
Nausea	12	5	6	1
Vomiting	5	2	3	1
Abdominal pain	3	3	3	1
Diarrhea	2	1	2	2
Muscle cramps	2	2	1	0
Fatigue	2	4	3	0
Headache	2	3	3	1
Dizziness	7	13	11	4
Weight loss (< 15% from baseline)	11	11	3	2
Anorexia	3	7	1	3

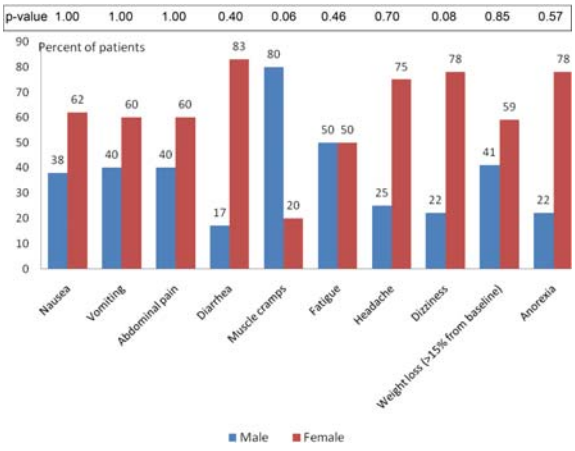

Fig. 1 Percent of patients who developed any adverse events according by gender (intention-to-treat analysis by using unpaired student t-test)

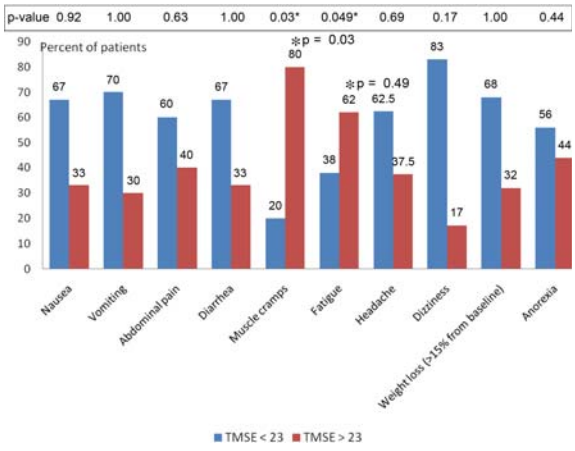

Fig. 2 Percent of patients who developed any adverse events according by TMSE score (< 23, ≥ 23) (intention-to-treat analysis by using unpaired student t-test, * = p < 0.05)

Table 3. Mean age, body weight, TMSE score, ADAS-cog score, and ADCS/ADL score correlated with the presence of adverse events (using student unpaired t-test)

Adverse events	Mean ± SD				
	Age (yr)	Body weight (kg)	TMSE score	ADAS-cog score	ADCS/ADL score
Nausea (n = 21)					
Yes	75.8 ± 9.8	53.3 ± 9.9	20.2 ± 3.8	62.5 ± 19.3	21.6 ± 7.4
No	73.9 ± 7.3	54.0 ± 9.8	19.7 ± 4.1	61.3 ± 17.2	22.9 ± 9.3
	p = 0.38	p = 0.78	p = 0.63	p = 0.80	p = 0.57
Vomiting (n = 10)					
Yes	74.5 ± 11.8	54.3 ± 10.7	20.6 ± 3.4	60.3 ± 19.7	20.2 ± 7.5
No	74.4 ± 7.4	53.9 ± 9.7	19.7 ± 4.1	61.9 ± 17.5	22.9 ± 8.9
	p = 0.98	p = 0.86	p = 0.55	p = 0.79	p = 0.38
Abdominal pain (n = 5)					
Yes	76.4 ± 5.0	55.1 ± 13.5	21.4 ± 2.9	66.6 ± 12.9	22.6 ± 11.5
No	74.3 ± 8.3	53.8 ± 9.6	19.8 ± 4.1	61.3 ± 18.0	22.5 ± 8.6
	p = 0.58	p = 0.77	p = 0.39	p = 0.53	p = 0.98
Diarrhea (n = 6)					
Yes	75.7 ± 9.9	49.9 ± 8.5	17.8 ± 5.9	57.7 ± 15.8	21.0 ± 8.6
No	74.3 ± 7.9	54.2 ± 9.8	20.1 ± 3.8	62.1 ± 17.9	22.6 ± 8.8
	p = 0.70	p = 0.31	p = 0.41	p = 0.56	p = 0.66
Muscle cramp (n = 5)					
Yes	74.0 ± 8.2	60.4 ± 12.0	21.6 ± 4.3	64.2 ± 20.1	19.5 ± 5.9
No	74.5 ± 8.1	53.4 ± 9.5	19.8 ± 4.0	61.5 ± 17.7	22.7 ± 8.9
	p = 0.90	p = 0.12	p = 0.33	p = 0.75	p = 0.43
Fatigue (n = 8)					
Yes	79.1 ± 10.1	55.2 ± 10.8	20.5 ± 5.4	58.1 ± 17.6	21.4 ± 9.0
No	73.9 ± 7.7	53.7 ± 9.7	19.8 ± 3.9	62.1 ± 17.8	22.6 ± 8.8
	p = 0.08	p = 0.68	p = 0.65	p = 0.55	p = 0.71
Headache (n = 8)					
Yes	76.9 ± 6.4	53.3 ± 11.9	20.9 ± 3.1	64.9 ± 16.8	22.2 ± 9.3
No	74.1 ± 8.3	53.9 ± 9.6	19.8 ± 4.1	61.3 ± 17.9	22.5 ± 8.8
	p = 0.37	p = 0.88	p = 0.46	p = 0.59	p = 0.91
Dizziness (n = 23)					
Yes	73.0 ± 9.5	52.9 ± 8.9	18.1 ± 4.6	61.7 ± 18.9	26.1 ± 11.2
No	75.1 ± 7.3	54.3 ± 10.2	20.1 ± 3.4	61.6 ± 17.3	20.8 ± 6.9
	p = 0.32	p = 0.56	p = 0.02	p = 0.99	p = 0.050
Weight loss > 15% from baseline (n = 22)					
Yes	76.4 ± 7.3	56.4 ± 10.1	20.4 ± 3.2	57.5 ± 17.2	19.5 ± 6.9
No	73.6 ± 8.4	52.7 ± 9.5	19.6 ± 4.3	63.5 ± 17.8	23.8 ± 9.22
	p = 0.18	p = 0.14	p = 0.46	p = 0.19	p = 0.053
Anorexia (n = 9)					
Yes	78.3 ± 7.6	54.6 ± 8.8	19.6 ± 4.3	58.4 ± 21.4	20.5 ± 5.9
No	73.9 ± 8.1	53.7 ± 9.9	19.9 ± 4.1	62.1 ± 17.3	22.7 ± 9.1
	p = 0.12	p = 0.79	p = 0.80	p = 0.56	p = 0.47

for any adverse events. Muscle cramps and fatigue were significantly found in patients with TMSE score ≥ 23 as compared to patients with TMSE < 23 (Fig. 2). In addition, patients with lower TMSE score (10-19) significantly experience dizziness more than patients with higher TMSE score (20-22; p = 0.009, using unpaired student t-test). The average body weight lost was approximately 0.9 kg at week 24 (Fig. 3).

Concerning changes in vital signs, laboratory tests, and ECG, there were no clinically relevant differences from baseline in all patients. Moreover, there was no significance difference in the incidence

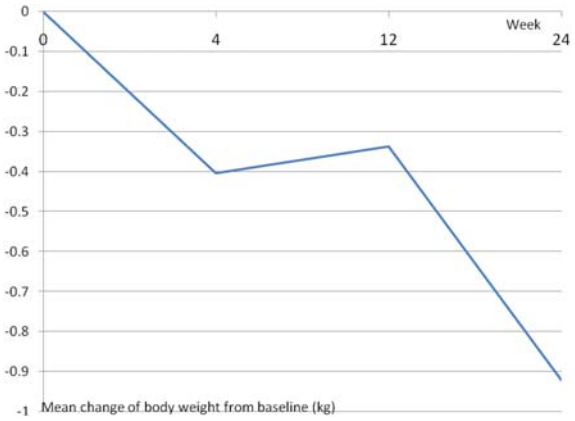

Fig. 3 Mean change of body weight compared with baseline

of adverse events (nausea, vomiting, diarrhea, fatigue, weight loss, any adverse events) between those with probable or possible AD (n = 61) and those with AD with cerebrovascular risk factors (n = 12, modified Hachinski ischemic score $\geq$ 5)[3,4].

We compared the incidence of common adverse events namely nausea and vomiting in our study to those reported in the original galantamine trial in AD with cerebrovascular diseases from the Lancet 2002. We did not find the difference between the 2 studies in term of these adverse events (Table 4.).

Discussion

This analysis aimed to explore the safety and tolerability profile of galantamine in Thai patients with possible AD with or without CVD and VaD using a slow-titration regimen. The result suggested that galantamine is effective in the treatment of dementia due to AD, with or without CVD or VaD, with tolerable adverse effects[5] .

Seventeen patients were withdrawn from the study. Most of them were not able to tolerate the nausea and vomiting, despite being prescribed domperidone for relieving these symptoms. One patient revealed mild abnormality on ECG and was withdrawn due to safety reasons from the investigation.

The adverse events associated with galantamine in this study were generally pharmacologic explanation from cholinergic system activation. They were of mild to moderate severity as previously reported[6]. The most common adverse events were during the dose-escalation phase. Gastrointestinal adverse events, including abdominal pain, and diarrhea, were reported less frequently than the previous studies of galantamine in Caucasian populations. This tolerability may be improved by using a 4-week dose-escalation scheme. Though, the occurrence of the nausea and vomiting symptoms in this study was similar to those being reported in the original study[6]. This could be from that in our study we prescribed an anti-emetic drug routinely during the dose escalation phase. Previous trials in patients with AD and AD with CVD showed enhanced tolerability with the use of such schedule[2]. In contrast, the previous study that used more rapid titrated schedule, 2-week interval, experienced more these events as well as a higher drop out rate. Concerning concomitant taking of antiemetic medication, only 2 patients reported having domperidone during the dose-escalation phase. Moreover, taking galantamine with food enhances minimization at the gastrointestinal adverse events.

Nausea or vomiting was more likely to occur in female subjects and in those with lower mean body weight. However, this study revealed similar distribution between both sex and body weight. Using an anti-emetic drug during the dose escalation phase in our study can help to reduce gastrointestinal side effects. Dizziness was more frequently reported in patients with low TMSE and high ADCS/ADL. In contrast, patients with higher TMSE ($\geq$ 23) experienced more muscle cramps and fatigue. Patients with higher TMSE scores might have lesser deficits in acetylcholine levels in the cholinergic synapses than those with lower scores. So, they are more prone to have a side

Table 4. Comparison of the occurrence of nausea and vommitting from the previous study to our study

Common adverse events	Number of cases	T Erkinjuntti et al Lancet 2002; 350: 1283-90. (n = 396)	Number of cases	This study (n = 73)	p-value
Nausea	93	23.5%	21	29%	0.41
Vomitting	51	12.9%	10	14%	0.99

effect from excess acetylcholine in the cholinergic system. Patients with high ADCS/ADL scores indicate that they are more dependent and less mobile. They, then, are prone to suffer from dizziness because of lack of physical fitness. Age, body weight, and ADAS-cog score did not affect the incidence of any adverse events.

It was noticeable that the mean body weight of patients was 53.6 $\pm$ 9.9 kg which was lower than in previous studies (6-8). Four patients lost body weight more than 3% from baseline. The average body weight lost was approximately 0.9 kg which is less than the previously reported from galantamine use, which was 1.3-2.5 kg.

The weight issue is the important factor that normally occurs in patients who receive cholinesterase inhibitors (ChEIs). The changes may be a consequence of the gastrointestinal adverse effects and, more importantly, from cholinergic stimulation. In addition, it is known that galantamine can modulate norepinephrine and serotonin release from the brain through the allosteric potentiate nicotinic receptor. Both neurotransmitters are playing an important role in body weight regulation, by both reducing appetite and increasing the thermogenesis[9-11].

In conclusion, these data suggested that galantamine was well tolerated and safe in Thai AD patients with or without CVD or VaD. The maintenance dose should be 16 mg/day with a 4-week titrated schedule, while 24 mg/day should be used in cases that do not respond to the recommended dose.

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ความปลอดภัยและความทนต่อยากาลานตามีนในผู้ป่วยไทยโรคอัลไซเมอร์ที่มีหรือไม่มีโรคหลอดเลือดสมองร่วม และผู้ป่วยสมองเสื่อมจากโรคหลอดเลือดสมอง

วรพรรณ เสนาณรงค์, นิพนธ์ พวงวรินทร์, กัมมันต์ พันธ์ธุมจินดา, นันทิกา ทวิชาชาติ, ศิวาพร จันทร์กระจ่าง, รุ่งนิรันทร์ ประดิษฐ์สุวรรณ, สามารถ นิธินันทร์

วัตถุประสงค์ของการศึกษาครั้งนี้คือหาปัจจัยที่มีผลต่อความปลอดภัย และความสามารถในการทนยากาลานตามีน ที่ให้ในผู้ป่วยโรคอัลไซเมอร์ที่มีหรือไม่มีโรคหลอดเลือดสมองร่วม และในผู้ป่วยสมองเสื่อมจากโรคหลอดเลือดสมอง ผู้วิจัยวิเตราะห์จากข้อมูลการศึกษาที่ทำการศึกษาไว้ก่อนแล้ว ปัจจัยที่นำมาวิเคราะห์ว่าสามารถส่งผลถึงความปลอดภัย และความสามารถในการทนยาได้แก่ เพศ อายุ น้ำหนักตัว ผลประเมินสมรรถภาพสมองไทย ผลประเมินสัญญานพิสัยอัลไซเมอร์ และผลประเมินกิจวัตรประจำวันของกลุ่มคณะศึกษาโรคอัลไซเมอร์

ผลข้างเคียงที่พบบ่อยที่สุดได้แก่ อาการคลื่นไส้และน้ำหนักลด ซึ้งเกิดขึ้นบ่อยในห้วงปรับขนาดยา เมื่อสัปดาห์ที่ 24 ผู้ป่วยมีน้ำหนักตัวลดลงเฉลี่ย 0.9 กิโลกรัม เพศ อายุ น้ำหนักตัว และคะแนนการประเมินสัญญานพิสัยอัลไซเมอร์ ไม่ส่งผลต่อการเกิดผลข้างเคียงของยา ผู้ป่วยที่มีคะแนนสมรรถภาพสมองไทยต่ำ มีคะแนนประเมินกิจวัตรประจำวัน ของกลุ่มขณะศึกษาโรคอัลไซเมอร์สูงมักพบว่ามีอาการวิงเวียนอย่างมีนัยสำคัญ ($p = 0.02$ และ $p = 0.005$ ตามลำดับ) ผู้ป่วยที่ได้คะแนนสมรรถภาพสมองไทยเมื่อแรกเข้าโครงการเท่ากับ 23 หรือมากกว่ามักจะเกิดอาการกล้ามเนื้อเป็นตะคริว และเมื่อยล้ามากกว่าผู้ที่ได้คะแนนน้อยกว่า 23 ($p < 0.05$) อย่างไรก็ตามการปรับขนาดยา กาลานตามีน เพิ่มขึ้นในผู้ป่วยลอัลไซเมอร์หลังรับประทานยาแล้ว 4 สัปดาห์ ส่งผลให้เกิดความปลอดภัย และความสามารถทนยาได้ดี