Original Article

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Pharmacokinetics of 8 mg galantamine hydrobromide prolonged-release capsules under fed and fasting conditions

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ABSTRACT

Objective: The objective of the study was to determine the pharmacokinetics of 8 mg galantamine prolonged-release capsules under fed and fasting conditions. **Materials and Methods:** A randomized, open-label, single-dose, two-treatment, two-period, two-sequence, parallel design of the administration of 8 mg galantamine hydrobromide prolonged-release capsules under fed and fasting conditions in 52 healthy Thai volunteers. Each subject was randomly assigned to receive a single oral dose of galantamine under fed or fasting conditions with a 7-day washout period. Blood samples were collected at 0.0, 1.0, 2.0, 3.0, 4.0, 4.5, 5.0, 5.5, 6.0, 6.5, 7.0, 7.5, 8.0, 9.0, 10.0, 12.0, 24.0, 36.0, and 48.0 h following drug administration. Liquid chromatography–tandem mass spectrometry was used for the quantitation of galantamine in plasma. Pharmacokinetic parameters were analyzed including C_{max}, T_{max}, $T_{1/2}$, ke, $AUC_{0\text{-}48h}$, and $AUC_{0\text{-}inf}$. **Results:** A total of 46 subjects completed the present study. The mean Cmax (range) values were 41.95 ± 10.05 (24.86–61.88) ng/mL and 25.96 ± 4.18 (18.82–33.60) ng/mL, and the mean $AUC_{0\text{-}48h}$ values were 599.45 ± 159.54 ng.h/mL and 503.47 ± 79.62 ng.h/mL under fed and fasting conditions, respectively. The mean $AUC_{0\text{-}inf}$ values under fed and fasting conditions were 620.89 ± 173.95 ng.h/mL and 527.43 ± 83.97 ng.h/mL, respectively. The mean (range) T_{max} value under fed conditions was 5.70 ± 1.36 (4–8) h and under fasting conditions was 5.61 ± 1.71 (1–8) h, which were not significantly different (P = 0.10; Mann–Whitney U-test). The C_{max} was 59% higher under fed conditions, with a treatment condition ratio of 1.5906, which was significantly different. **Conclusions:** High-fat and high-calorie foods increased the maximum concentration (C_{max}) and the extent of absorption (AUC) but did not affect the galantamine absorption rate (T_{max}).

Keywords: Absorption, food effect, galantamine, pharmacokinetic

INTRODUCTION

The use of nicotinic acetylcholine receptor (nAChR) agonists and/or allosteric potentiators has been investigated in an attempt to compensate for the loss of these receptors in Alzheimer's disease. In the cerebral cortex, presynaptic nAChRs modulate the activity of neuronal networks through inhibitory and disinhibitory mechanisms, suggesting their involvement in cognitive functioning. Direct stimulation of nAChRs is one approach to preserving cognitive function in Alzheimer's disease, providing that adequate numbers of nAChRs remain functional. Galantamine is a centrally acting, reversible, competitive inhibitor of cholinesterase (AChE), which is unique among the AChE inhibitors since it enhances

cholinergic function through two mechanisms of action: Inhibition of AChE and enhancement of acetylcholine effects at nAChRs.[1-3] In 2001, the Food and Drug Administration approved galantamine for the treatment of mild-to-moderate dementia of the Alzheimer's type.[4] Clinical studies have demonstrated broad, sustained efficacy in the management of Alzheimer's disease, including improvements in cognition, global function, behavioral symptoms, and the ability to perform activities of daily living. Galantamine hydrobromide is available as an immediate release tablet, prescribed for twice-daily dosing. To simplify dosing, enhance compliance, and further reduce subject and caregiver burden, a once-daily formulation of galantamine hydrobromide (prolonged-release capsule) has been developed.[1-4]

One of the most common adverse effects of cholinesterase inhibitors, including galantamine, is gastrointestinal issues such as nausea, vomiting, mild anorexia, and diarrhea.[5,6] To increase adherence to this medication and minimize gastrointestinal effects, the administration of galantamine through the oral route is recommenced simultaneously with food, for instance breakfast and/or dinner.[7]

It has been previously reported that the coadministration of food has an effect on the absorption of galantamine. After the film-coated galantamine tablet (immediate release) has been coadministered with food, the rate of absorption is delayed but not the extent.[2,8] In contrast, it has been reported that the rate of absorption of extended-release tablet formulations after multiple dosing tends to increase following coadministration with high-fat food.[9] Thus, the present study determined the pharmacokinetics of 8 mg galantamine prolonged-release capsules when given under fed and fasting conditions, the former being a high-fat and high-calorie diet.

MATERIALS AND METHODS

Study Design

A randomized, open-label, single-dose, two-treatment, two-period, two-sequence, parallel design was used for drug administration under fed and fasting conditions.

Clinical Study

The clinical study complied with the International Conference on Harmonization's Good Clinical Practice Guideline and was conducted at the Clinical Trial Unit, Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand. The study protocol and informed consent were approved by the Research Ethics Committee, Faculty of Medicine, Chiang Mai University, Thailand, on July 18, 2014, approval number 260/2014.

A total of 52 healthy Thai subjects, consisting of an equal number of males and females, were enrolled in the present study. The inclusion criteria were as follows: 18–45 years old; body mass index (BMI) of 18.5–25.0 kg/m^2; body weight no <45 kg; healthy status based on medical history and physical examination; normal or clinically insignificant abnormal laboratory results; negative hepatitis B; no clinically significant findings with respect to vital signs or electrocardiogram; non-smokers or those who had stopped smoking for at least 6 months; non-pregnant females and those unable to have children or those of childbearing potential who committed to using an acceptable non-hormonal contraceptive method of birth control for at least 2 weeks before and during the study as judged by the clinical investigators, and not currently breastfeeding. Subjects with the following conditions were excluded: Allergic history to galantamine or drugs of related structure or the components of the medication; current or a history of alcoholism or substance abuse; current or a history of severe asthma, lung disease, seizures, stomach bleeding or ulcers, heart rhythm problems, hepatic, renal, endocrine, or cardiovascular diseases, or any other conditions that may affect the bioavailability of the medication or safety of the subjects; any medication use, especially enzyme-modifying drugs, within 14 days before the study; unable to refrain from the consumption of orange, pomelo, or grapefruit for 7 days before and during the study; unable to refrain from caffeine-containing beverages and foods for 3 days before and during the study; a history of blood donation >300 mL, significant blood loss, or participation in other clinical trials within 90 days before the initiation of the study; vulnerable to hypotension or volume depletion as considered by the clinical investigators, a systolic blood pressure <90 mmHg, a diastolic blood pressure <60 mmHg, and a pulse rate <50 beats/min or more than 100 beats/min; and female subjects with a history of hypermenorrhea. Volunteers who met the above criteria were eligible for participation in the present study after voluntarily providing written informed consent.

Drug Administration

The galantamine formulation used in the present study comprised galantamine hydrobromide prolonged-release capsules (8 mg REMINYL®) manufactured by Janssen-Cilag SpA., Italy.

All volunteers were confined to the medical ward of the Clinical Trial Unit. After overnight fasting for at least 10 h, each volunteer was randomly assigned to receive a single oral dose of 8 mg galantamine hydrobromide prolonged-release capsules with 240 mL water following a standard high-fat breakfast, consisted of approximately 800 kcal and 50% total caloric content from fat (fed condition) or without breakfast (fasting condition).

Sample Collection and Processing

Blood samples of 8 mL were collected at 0.0, 1.0, 2.0, 3.0, 4.0, 4.5, 5.0, 5.5, 6.0, 6.5, 7.0, 7.5, 8.0, 9.0, 10.0, 12.0, 24.0, 36.0, and 48.0 h following drug administration, transferred to pre-labeled 10 mL K_2EDTA-coated tubes, and transported under a controlled temperature of 0 ± 5°C to the analytical facility, Pharmacy Service Centre, Faculty of Pharmacy, Chiang Mai University, where the plasma samples were promptly separated and stored at −30 ± 5°C until analysis.

Analysis of Plasma Galantamine Concentrations

A simple, sensitive, and specific liquid chromatography–tandem mass spectrometry method was developed and validated for the quantitation of galantamine in plasma, using carbamazepine as internal standard. Structure of galantamine hydrobromide and carbamazepine is shown in Figure 1.

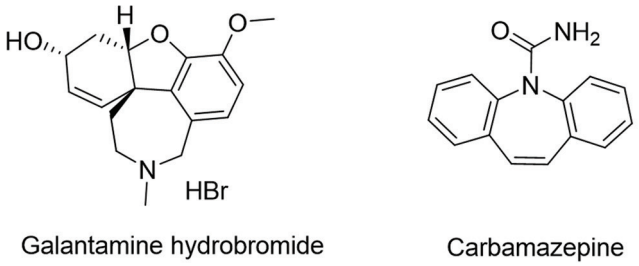

Figure 1: Galantamine hydrobromide and carbamazepine chemical structure

An HPLC Agilent 1260 system coupling with AB Sciex API 3200 electron electrospray ionization mass spectrometer (AB Sciex, Singapore) were used for quantification of galantamine. An analyst software (Version 1.6.2) was used for data processing. Galantamine was separated under C4 column (Hypersil, 150 mm ×4.6 mm i.d., 5.0 μm) which was coupled with 10 mm guard column with the same i.d. and particle size. About 10% of 10 mM ammonium formate in acetonitrile was used as isocratic mobile phase with a flow rate of 0.8 mL/min, an injection volume of 10 μL, and at temperature of 35°C. The mass spectrometer was operated in the multiple reaction monitoring mode. Quantification was achieved with MS/MS detection in

Table 1: Demographic data

Demographic data	Fed conditions, *n*=23	Fasting conditions, *n*=23	Total, *n*=46
Gender, *n*			
Female	11	11	22
Male	12	12	24
Age (years)			
Mean±SD	23.1±2.6	24.7±5.0	23.9±4.0
Range	20–29	20–38	20–38
Height (cm)			
Mean±SD	167.0±8.3	165.4±8.4	166.2±8.3
Range	155–189	150–180	150–189
Weight (kg)			
Mean±SD	60.7±8.0	58.7±9.1	59.7±8.6
Range	48.8–87.4	46.1–74.2	46. 1–87.4
Body mass index (kg/m^2)			
Mean±SD	21.7±1.5	21.3±1.8	21.5±1.6
Range	19.34–24.74	18.65–24.23	18.65–24.74
Liver function test			
Total bilirubin (mg/dl)			
Mean±SD	0.70±0.29	0.66±0.49	0.68±0.40
Range	0.31–1.48	0.17–2.70	0.17–2.70
Aspartate transaminase (U/L)			
Mean±SD	16.70±7.15	16.52±3.85	16.61±5.68
Range	7.00–39.00	11.00–27.00	7.00–39.00
Alanine aminotransferase (U/L)			
Mean±SD			
Range	33.26±9.05	33.17±9.57	33.22±9.21
Alkaline phosphatase (U/L)	22.00–57.00	25.00–62.00	22.00–62.00
Mean±SD	88.52±18.33	86.00±16.30	87.26±17.20
Range	59.00–120.00	47.00–120.00	47–120
Renal function test			
Blood urea nitrogen (mg/dl)			
Mean±SD	11.96±3.04	11.96±2.50	11.96±2.75
Range	7.00–19.00	7.00–17.00	7.00–19.00
Serum creatinine (mg/dl)			
Mean±SD	0.90±0.17	0.99±0.18	0.95±0.18
Range	0.63–1.22	0.75–1.28	0.63–1.28

a positive ion mode. Galantamine and carbamazepine (IS) were monitored at transition m/z 288.094→212.970 and 236.857→193.920, respectively. The ion spray voltage was set at 4500 V. The source parameters, i.e., the nebulizer gas (GS1), auxiliary gas, curtain gas, and collision gas were set at 50, 50, 35, and 8 psi, respectively. The compound parameters, i.e., the declustering potential, entrance potential, collision cell entrance, potential, collision energy, and collision cell exit potential were 46, 4, 14, 25, and 4 V for galantamine and 91, 12, 12, 21, and 4 V for carbamazepine.

Sample preparations were as the following: An aliquot of 90 μL of the IS working solution (3 μg/mL) was added into 100 μL of the plasma sample. After that, 2 mL dichloromethane was added, and the mixture was shaken at 1500 rpm for 2 min at room temperature and then centrifuged at 4000 rpm for 2 min. One milliliter of the organic phase was separated and dried under pressure. Reconstitution was done with 50 μL of 90% methanol and 10 μL of sample was injected into the analytical column.

The method was validated for selectivity, specificity, accurate, precision, robust, and stability.

Selectivity was proved using six blank plasma samples from six subjects. There is no interference peak found at the area of galantamine and IS peak. The retention time of galantamine was found approximately 6 min and of IS was found approximately 2.8 min. Lipimic and hemolysis showed no effect for analytical method and also no matrix effect was found. Calibration curve was achieved at the range of 0.39–62.50 ng/mL. Galantamine at the concentration of 0.39 ng/mL was proved as lower limit of quantitation with signal-to-noise ratio of 17.46, with accuracy as 88.44% and precision (%CV) as 2.60. The r^2 of calibration curve was found more than 0.99 and accuracy within 85–115%. Accuracy and precision were proved using four-level quality control samples (LOQ, MQC1, MQC2, and HQC samples at the concentration of 1.18, 5.87, 23.40, and 47.00 ng/mL, respectively). The accuracy and precision result of between run and within run showed % accuracy result as within 85–115% and precision result as within ±15%. Robustness determines by analysis different analytical column and different of organic phase (±2% acetonitrile) showed the validity of analytical method. Galantamine and IS stock solution were proved to be stabled at least for 6 h at 25 ± 5°C and at least 14 days at 5 ± 5°C. Galantamine in plasma was stable at least 50 days after kept in the condition of 30 ± 5°C and at least 5 h at 25 ± 5°C. Autosampler stability was proved for 48 h at 25 ± 5°C and freeze-thaw stability was studied for five cycles. Percentage deviation of the concentration at all condition was <10%.

Pharmacokinetics Parameters and Statistical Analysis

Pharmacokinetics parameters, including the C_{max}, T_{max}, $T_{1/2}$, $AUC_{0\text{-}48h}$, $AUC_{0\text{-}inf}$, and k_e, were analyzed. The C_{max} and T_{max} were obtained from the raw data; the $AUC_{0\text{-}48h}$ was calculated by the linear trapezoidal rule; the 90% confidence intervals for C_{max} and $AUC_{0\text{-}48h}$ were calculated based on the $\log_{10}$-transformed data; the pharmacokinetic parameters and 90% confidence intervals were determined using the Phoenix™ Winnonlin® 6.3 computer software.

The mean demographic data of the fasting and fed groups were tested for similarity using an independent samples *t*-test. Non-parametric analysis for the comparison of the T_{max} between the fasting and fed groups was performed by the Wilcoxon signed-rank test, evaluated at 5% significance level. Ratios and 90% confidence intervals of the AUC and C_{max} were calculated.

The number of subjects was calculated based on the intrasubject pharmacokinetics variations as described by Zhang *et al*.,[10] which is approximately 21%. μ^T/μ^X is usually applied at 1.05, and power should be at least 80%. The calculated number was 20; an additional six subjects were added for possible dropout. Thus, the total number of subjects was 26 in each group.

RESULTS

Demographic Data

A total of 52 healthy Thai volunteers were included in the present study. Six volunteers withdrew due to personal reasons without having any adverse events (AEs), and 46 volunteers, 24 males and 22 females, completed the study. There were no significant differences between the demographic data of subjects in the fasting and fed groups. The mean age ± SD of the subjects was 23.9 ± 4.0 years old (range; 20–38); the mean weight ± SD of the subjects was 59.7 ± 8.6 kg (range; 46.1–87.4); the mean height ± SD of the subjects was 166.2 ± 8.3 cm (range; 150–189 cm); and the mean BMI ± SD of the subjects was 21.5 ± 1.6 kg/m^2 (range; 18.65–24.74) as shown in Table 1.

Table 2: Average plasma galantamine concentrations under fed and fasting conditions at various sampling times in all subjects (n=23 each) following a single oral dose of galantamine hydrobromide prolonged-release capsules

Time (h)	Plasma galantamine concentration (ng/mL)	
	Fed condition	Fasting condition
0.00	0.00±0.00	0.00±0.00
1.00	3.59±4.86	17.25±4.85
2.00	10.73±7.50	19.08±3.40
3.00	20.59±9.93	20.89±3.90
4.00	30.85±8.23	22.52±4.01
4.50	37.13±9.39	24.50±4.48
5.00	38.16±10.71	23.50±4.12
5.50	37.74±9.75	23.05±3.28
6.00	37.99±9.95	23.77±3.69
6.50	36.29±9.11	23.67±4.00
7.00	35.94±8.66	24.40±4.28
7.50	35.83±8.02	24.21±3.88
8.00	35.97±8.53	24.00±4.44
9.00	32.32±8.57	21.59±4.40
10.00	29.50±7.46	20.61±4.13
12.00	25.54±6.70	18.33±3.49
24.00	8.95±3.44	8.92±2.04
36.00	3.66±0.99	3.60±1.05
48.00	1.63±0.53	1.59±0.58

Safety

AEs were monitored based on subject interview and physical examination. Safety of the subjects, AEs, and concomitant drug assessment were performed throughout the study. Vital signs were monitored during the entire study period. No abnormalities were observed in terms of blood pressure, heart rate, respiratory rate, or body temperature. A total of 15 post-dosing AEs were found in 9 of the 52 volunteers. The reported AEs were dizziness, cervical lymph node enlargement, herpes labialis, hypotension, mild phlebitis, and orbital pain. The most commonly reported AE was dizziness (6 events under the fed conditions and 0 events under the fasting conditions). Most of the AEs were assessed as mild in intensity and some were possibly related to the study drug.

Pharmacokinetic Characteristics

The average plasma galantamine concentrations at each time point under the fasting and fed conditions are illustrated in Table 2 and Figure 2, and the pharmacokinetic parameters are listed in Table 3. The mean C_{max} (range) values were 41.95 ± 10.05 (24.86–61.88) ng/mL and 25.96 ± 4.18 (18.82–33.60) ng/mL, and the mean $AUC_{0\text{-}48h}$ values were 599.45 ± 159.54 ng.h/mL and 503.47 ± 79.62 ng.h/mL under the fed and fasting conditions, respectively. The mean $AUC_{0\text{-}inf}$ values under the fed and fasting conditions were 620.89 ± 173.95 ng.h/mL and 527.43 ± 83.97 ng.h/mL, respectively. The mean (range) T_{max} value under the fed conditions was 5.70 ± 1.36 (4–8) h and under the fasting conditions was 5.61 ± 1.71 (1–8) h, which was not a significant difference (P = 0.10; Mann–Whitney U-test). The 90% confidence intervals for the ratios of C_{max},

Table 3: Mean pharmacokinetics parameters of galantamine following administration under fed and fasting conditions

Pharmacokinetics parameters	Fed conditions	Fasting conditions
	Mean±SD (range)	Mean±SD (range)
$AUC_{0\text{-}48h}$ (ng·h/mL)	599.45±159.54	503.47±79.62
	(367.48–1040.59)	(381.1–639.1)
$AUC_{0\text{-}inf}$ (ng·h/mL)	620.89±173.95	527.43±83.97
	(378.43–1125.59)	(394.01–659.6)
C_{max} (ng/mL)	41.95±10.05	25.96±4.18
	(24.86–61.88)	(18.82–33.60)
T_{max} (h)	5.70±1.36	5.61±1.71
	(4–8)	(1–8)
$T_{1/2}$ (h)	8.66±1.26	9.89±1.48
	(6.91–11.73)	(7.59–12.9)
k_e (h^{-1})	0.0816±0.0110	0.0715±0.0104
	(0.0591–0.1004)	(0.0536–0.0913)

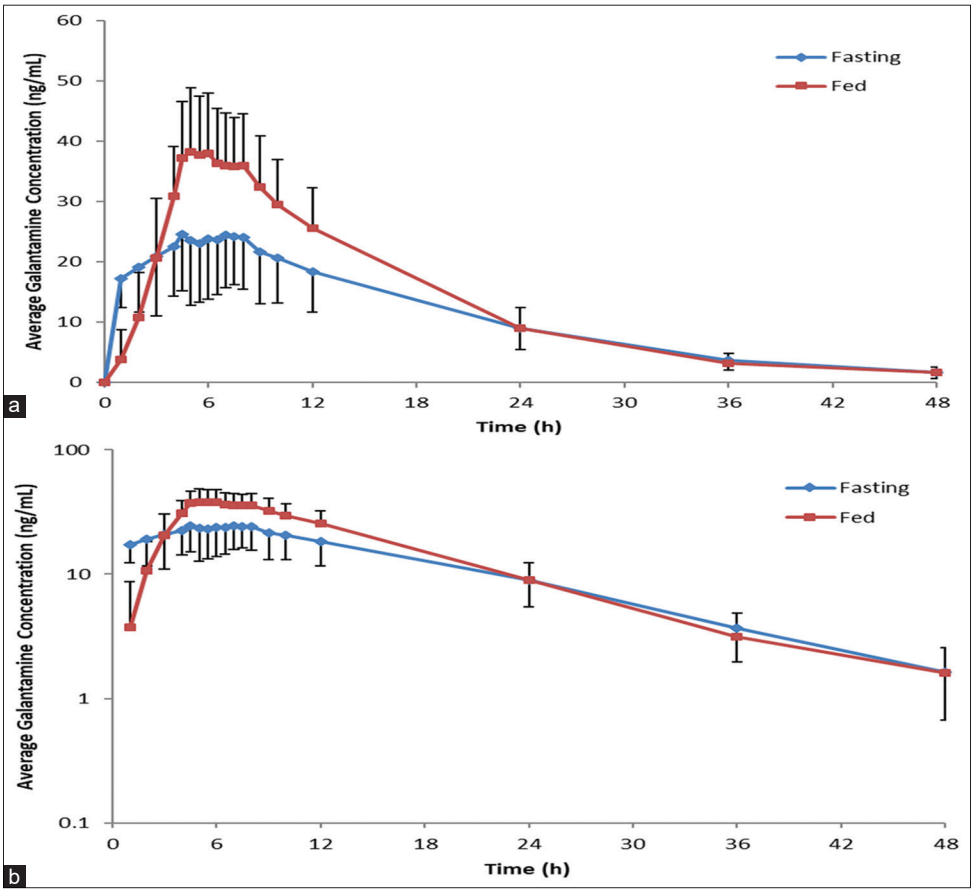

Figure 2: Average plasma galantamine concentrations under the fed (■) and fasting (♦) conditions at various sampling times in all subjects (n = 23 each) following a single oral dose of galantamine hydrobromide prolonged-release capsules; (a) = normal scale (b) = semi-log scale

Table 4: Summary of the pharmacokinetics parameters and bioavailability of galantamine following administration under fed and fasting conditions

Pharmacokinetics parameters	Geometric means (least square means)		Treatment condition ratio (%) (fed/fasting)	90% confidence interval
	Fed conditions	Fasting conditions		
$AUC_{0\text{-}48h}$ (ng·h/mL)	580.83	497.40	116.78	105.12–129.72
$AUC_{0\text{-}inf}$ (ng·h/mL)	600.01	520.94	115.18	103.36–128.34
C_{max} (ng/mL)	40.78	25.64	159.06	143.44–176.38
T_{max} (h)	5.55	5.25	-	-*

*No significant difference between the two conditions (P=0.10; Wilcoxon signed-rank test)

$AUC_{0\text{-}48h}$, and $AUC_{0\text{-}inf}$ between the fed and fasting conditions were 143.44–176.38%, 105.12–129.72%, and 103.36–128.34%, respectively. The C_{max} was 59% higher under the fed conditions, with a treatment ratio of 1.5906 [Table 4].

DISCUSSION

The pharmacokinetics parameters of galantamine in the present study were within the same range of those previously reported.[2,8-11]

In terms of the absorption rate (T_{max}), food showed delaying absorption rate of galantamine. Food as well as high-fat and high-calorie food were reported to delay the absorption rate.[8,9] These food effect also showed in both the immediate release formulation and the prolonged-release formulation. However, the present study also showed delaying of absorption of galantamine in fed group but was not statistic significant. Fat in food delay the gastric emptying time resulting in rate of absorption is delayed.[12-14]

For the extent of absorption represented by AUC and C_{max} of galantamine, data are relatively different. A study by Jones *et al*.,[8] of the drug in immediate release form, showed that under fed conditions, the C_{max} was approximately 25% lower than that under fasting conditions. On the other hand, Zhao *et al*.[9] found that the C_{max} under fed conditions tended to be higher than that under fasting conditions. In the present study, it was found that the C_{max} was 59% higher under fed conditions, which was significant. The drug formulation used in our study and that of Zhao *et al*. was prolonged release. For the immediate release formulation, subjects were fed a standard breakfast instead of a high-fat and high-calorie breakfast. In studies of prolonged-release formulations using a standardized high-fat and high-calorie breakfast under fed conditions, of which fat was approximately 50% of the total calorie content (approximately 800–1000 calories),[15] the AUC and C_{max} were higher following intake of a high-fat and high-calorie diet. Galantamine is an alkaline and slightly lipophilic drug, which is easily soluble in fat. Fat-containing foods stimulate the release of bile acid, in turn increasing solubility through micelle formation and increasing the absorption of fat and fat-soluble drugs.[12,16]

A total of 13 post-dosing AEs were found, which were mild in intensity, transient, and resolved without intervention. These drug-related AEs were reported before.[6,7] Dizziness was not found under fasting conditions, but six events were found under fed conditions. The higher number of post-dosing AEs found under fed conditions (high-fat meal) may relate to the higher C_{max}. Certain side effects are related to drug dose or drug plasma level, in this case, dizziness. Nausea and vomiting have also been reported as a frequent AE following intake of galantamine; thus, there are recommendations to take galantamine after a meal to reduce this GI side effect.[7] Therefore, to minimize GI side effects and dizziness (or systematic adverse effects), galantamine should be taken following a low-fat and low-calorie meal.

CONCLUSIONS

The present study shows that high-fat and high-calorie foods increased the extent of absorption (AUC) and peak of concentration (C_{max}) but did not affect the galantamine absorption rate (T_{max}).

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DECLARATION OF CONFLICTING INTEREST

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