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ORIGINAL RESEARCH

Bioavailability and Pharmacokinetics of Once-Daily Amantadine Extended-Release Tablets in Healthy Volunteers: Results from Three Randomized, Crossover, Open-Label, Phase 1 Studies

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ABSTRACT

Introduction: In February 2018, OS320—an amantadine extended-release (ER) tablet formulation with once-daily morning administration—was approved for the treatment of Parkinson's disease and drug-induced extrapyramidal reactions in adults. The purpose of this study was to describe three phase 1 studies that assessed the pharmacokinetics (PK) and bioavailability of amantadine ER in healthy adult volunteers.

Methods: Study 1 was an open-label, four-treatment, single-dose, crossover study comparing amantadine ER 129, 193, and 258 mg tablets with an equivalent dose of immediate-release (IR) amantadine 40 mg/5 mL syrup. Study 2 was an open-label, single-dose, crossover food-effect study with amantadine ER 258 mg. Study 3 was an open-label, multiple-dose, crossover study comparing amantadine ER and amantadine IR syrup.

Results: Amantadine ER displayed a steady release of amantadine, with the peak amantadine concentration occurring at ~ 7.5 h postdose or in the middle of the day (following a morning dose) with steady-state administration. Administration of amantadine ER 258 mg with a high-fat meal did not affect amantadine bioavailability. Amantadine plasma exposure increased proportionally with increasing doses, and at steady state, amantadine exposure from an amantadine ER 258-mg tablet was bioequivalent to twice-daily 129-mg amantadine IR syrup.

Conclusion: The PK profile of amantadine ER 129-mg, 193-mg, and 258-mg tablets allows for once-daily dosing in the morning; the 24-h average amantadine plasma concentration is equivalent to that for the same daily dose of IR amantadine administered twice daily.

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Keywords: Absorption; Amantadine; Bioavailability; Bioequivalence; Pharmacokinetics

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INTRODUCTION

Amantadine is a weak, uncompetitive antagonist of the *N*-methyl-D-aspartate (NMDA) receptor [1, 2]. Amantadine hydrochloride (HCl) in an immediate-release (IR) formulation is indicated for the prophylaxis and treatment of infection caused by the influenza A virus, for the treatment of Parkinson's disease (PD), as well as for drug-induced extrapyramidal

reactions (EPRs; also referred to as extrapyramidal symptoms). Amantadine HCl IR is available as a 100-mg tablet (equivalent to 81 mg base amantadine) and 50 mg/5 mL syrup (equivalent to 40 mg/5 mL base amantadine), and is typically administered twice daily [3].

Due to Food and Drug Administration (FDA) guidelines, unless otherwise stated, all amantadine doses are reported herein as the base dose of amantadine, rather than the equivalent amantadine HCl dose. Amantadine IR plasma pharmacokinetics were studied in healthy volunteers shortly after its approval in the 1970s. Amantadine is readily absorbed orally and is primarily excreted unchanged in the urine by glomerular filtration and tubular secretion [1, 4, 5]. The antiparkinsonian effect of amantadine is observed within 48 h following dosage initiation [1]. More recent studies have focused on amantadine pharmacokinetics in specialized populations, including comatose children, PD patients, and the elderly [6–8]. Following oral administration of an 81-mg amantadine IR formulation (equivalent to 100 mg amantadine HCl) twice daily for 5 days in healthy adults, maximum blood levels were 636.2 ng/mL, with the peak concentration occurring 2.1 h postdose [9].

A once-daily extended-release (ER) formulation of amantadine, OS320 (Osmolex ER^{TM}), was approved by the FDA in February 2018 via the 505(b)(2) regulatory pathway for the treatment of PD and drug-induced EPRs in adults [10]. OS320 is available in strengths of 129-mg, 193-mg, or 258-mg amantadine (160, 240, or 320 mg amantadine HCl, respectively) [10]. The approval of OS320 was informed by the bioequivalence it exhibited when compared with amantadine IR. OS320 is not interchangeable with other amantadine IR or ER products. Here, we describe the pharmacokinetics (PK) and bioavailability of amantadine ER tablets in three phase 1 clinical studies in healthy volunteers.

The aim of these three PK studies was to provide a comprehensive assessment of OS320 bioavailability and pharmacokinetics. We hypothesized that OS320 would be absorbed slowly following a single dose, that eating a high-fat meal would not influence OS320 pharmacokinetics, and that OS320 bioavailability is equal to an equivalent daily dose of amantadine IR.

METHODS

Study Design

Study 1 was a randomized, open-label, laboratory-blinded, four-treatment, four-period, four-sequence, single-dose, crossover study in healthy adult volunteers. Single oral doses of the following four treatments were administered under fasting conditions: (A) amantadine ER tablet, 129 mg; (B) amantadine ER tablet, 193 mg; (C) amantadine ER tablet, 258 mg; and (D) amantadine IR syrup, 40 mg/5 mL (reference treatment). Eligible subjects were randomized to receive the treatments with approximately 240 mL water in one of four treatment sequences (ABCD, BCDA, CDAB, DABC) after an overnight fast. Each treatment period was separated by a washout period of 7 days. See the summary of the study design shown in Table 1.

Study 2 was a randomized, open-label, laboratory-blinded, two-treatment, two-period, two-sequence, single-dose, crossover study in healthy adult volunteers. Single oral doses of amantadine ER 258-mg tablets were administered under fasting (reference) and fed (test) conditions. Both treatments were administered after an overnight fast with approximately 240 mL water. Eligible subjects were randomized to receive the treatments in one of two treatment sequences. The treatment periods were separated by a washout period of 7 days (Table 1).

Study 3 was a randomized, open-label, laboratory-blinded, two-treatment, two-period, two-sequence, multiple-dose, crossover study in healthy volunteers. The two treatment groups were amantadine 258-mg ER tablet (258-mg dose once daily for seven consecutive days; Treatment A, test) and amantadine 40 mg/5 mL IR syrup (129-mg dose twice daily for seven consecutive days; Treatment B, reference). Eligible volunteers were randomized to receive the treatments in one of two treatment sequences (AB, BA). Following a 2-day titration period,

Table 1 Summary of study design for the three phase 1 trials

	Study 1	Study 2	Study 3
Primary objective	To determine the relative bioavailability of amantadine 129-mg ER tablets compared with the plasma profiles and pharmacokinetic parameters of a reference formulation of amantadine IR syrup (129 mg) after single-dose administration under fasting conditions	To determine the bioavailability of amantadine 258-mg ER tablets after single-dose administration under fasting and fed conditions	To determine the steady-state relative bioavailability after multiple-dose administration of amantadine 258-mg ER tablets compared with an equivalent daily dose (258 mg) of amantadine IR syrup under fasting conditions
Study design	Randomized, open-label, laboratory-blinded, four-treatment, four-period, four-sequence, single-dose, crossover design	Randomized, open-label, laboratory-blinded, two-treatment, two-period, two-sequence, single-dose, crossover design	Randomized, laboratory-blinded, two-treatment, two-period, two-sequence, multiple-dose, crossover design
Population	Healthy volunteers	Healthy volunteers	Healthy volunteers
Dosing regimen	Single dose	Single dose	Multiple dose (2 days of titration followed by 7 days of administration for each treatment)
Treatments	A. Amantadine ER tablet, 129 mg B. Amantadine ER tablet, 193 mg C. Amantadine ER tablet, 258 mg D. Amantadine IR syrup, 40 mg/5 mL (129 mg)	A. Amantadine ER tablet, 258 mg (fasting) B. Amantadine ER tablet, 258 mg (with food)	A. Amantadine ER tablet, 258 mg once daily for 7 days B. Amantadine IR syrup, 40 mg/5 mL (129-mg dose twice daily for 7 days)

ER extended-release, *IR* immediate-release

treatments were administered on days 3 through 9 (treatment period 1) and days 18 through 24 (treatment period 2). Each treatment period was separated by a washout period of 7 days (Table 1).

These studies have not been registered per FDA guidelines that state registration of phase 1 studies is not required.

Compliance with Ethical Standards

All studies were conducted in accordance with Good Clinical Practice as defined by the International Conference on Harmonisation, the Declaration of Helsinki, and in accordance with the ethical principles underlying European Union Directive 2001/20/EC and the United States Code of Federal Regulations, Title 21, Part 50 (21CFR50). Studies 1 and 3 received ethics committee approval from IRB Services (Aurora, Ontario, Canada). Study 2 received approval from the Optimum Ethics Review Board (Oshawa, Ontario, Canada). All participants provided written informed consent before study participation.

Materials

Amantadine ER tablets, 129 mg (study 1: Osmotica Pharmaceutical Corp., batch number

1408001A); amantadine ER tablets, 193 mg (study 1: Osmotica Pharmaceutical Corp., batch number 1408002A); amantadine ER tablets, 258 mg (all studies: Osmotica Pharmaceutical Corp., batch number 1408003A); and amantadine IR syrup, 40 mg/5 mL (studies 1 and 3: Morton Grove Pharmaceuticals, Inc., batch number UQ1262).

Study Population

In all studies, healthy volunteers—as determined by medical history, physical examinations, vital signs, 12-lead electrocardiograms, and clinical laboratory tests—were eligible to enroll if they were between 18 and 55 years of age, with a body mass index of 18–32 kg/m^2 in study 1 and study 3 and of 18.5–29.9 kg/m^2 in study 2. Exclusion criteria included lactating female subjects; history of hypersensitivity to amantadine or related drugs; history or evidence of psychiatric, cardiac, pulmonary, gastrointestinal, endocrine, musculoskeletal, neurological, hematological, immunological, hepatic, or renal disease, or malignancies; and positive screening of alcohol and/or drugs of abuse.

Sample Collection and Bioanalytical Methods

In study 1, 28 blood samples were collected serially up to 72 h postdose from each subject in each treatment period to determine the amantadine plasma concentration and for PK analysis. The plasma samples were assayed for amantadine using a validated high-performance liquid chromatography method with tandem mass spectrometry detection (LC/MS/MS) (Algorithme Pharma, Quebec, Canada). The lower and upper limits of quantitation were 2 ng/mL and 2000 ng/mL, respectively.

In study 2, 22 blood samples were collected serially up to 72 h postdose from each subject in each treatment period. The plasma samples were assayed for amantadine using a validated LC/MS/MS method for amantadine (Lambda Therapeutic Research Inc., Toronto, Canada). The lower and upper limits of quantitation were 2 ng/mL and 1501 ng/mL, respectively.

In study 3, 31 blood samples were collected serially from each subject in each treatment period up to 72 h following the last morning dose. The plasma samples were assayed for amantadine using the same validated LC/MS/MS as for study 1.

Pharmacokinetic Assessments

Noncompartmental PK parameters were calculated for amantadine and included the maximum plasma concentration (C_{max}), time to maximum plasma concentration (T_{max}), area under the plasma concentration versus time curve (AUC) from time 0 to infinity (AUC_{inf}), apparent elimination half-life ($t_{1/2}$), and apparent elimination rate constant (λ_Z). In studies 1 and 3, the PK analyses were generated using Phoenix® WinNonlin® version 6.3 and Phoenix® Connect™ version 1.3.1. In study 2, the PK analyses were generated using Phoenix® WinNonlin® version 5.3.

Planned Sample Size and Statistical Analysis

PK parameter data were summarized using descriptive summary statistics. The 90% confidence interval (CI) for the exponential of the difference in least squares (LS) means between the test and reference products was calculated for the natural-log-transformed parameters. In all studies, PK parameters were statistically analyzed using an analysis of variance model that included subject as a random effect and treatment, period, and sequence as fixed effects. In studies 1 and 3, the statistical analyses were generated using SAS® version 9.4 (mixed procedure). In study 2, the statistical analyses were generated using SAS® version 9.3. In study 1, C_{max} and AUC were taken to be bioequivalent if the slope of a power model was within 0.80–1.25. In addition, the geometric LS mean ratio and the corresponding 90% CIs of the dose-normalized, natural-log-transformed AUC_{inf} values were evaluated.

The sample size chosen was sufficient to allow characterization of the relative bioavailability for amantadine ER tablets. No formal statistical sample size calculations were conducted, as the sample sizes were based on our estimate of the number of subjects needed to achieve the study objectives.

RESULTS

Demographics and Baseline Clinical Characteristics

In study 1, 22 of 24 enrolled subjects completed the study [two subjects discontinued due to adverse events (AEs): one subject for a urinary tract infection and one subject for decreased appetite, nausea, dizziness, headache, and vomiting]. In study 2, 24 subjects completed the study. In study 3, 23 of 24 enrolled subjects completed the study (one subject discontinued due to AEs: scotomata in both eyes and muffled hearing in both ears). A summary of the demographics of all subjects who received amantadine and completed at least one study period in the three studies is presented in Table 2.

Table 2 Summary of demographics of healthy volunteers in three pharmacokinetic studies of amantadine ER tablets

Parameter	Study 1 (*N* = 24)	Study 2 (*N* = 24)	Study 3 (*N* = 23)
Age (years)	36 (8)	41 (8)	31 (8)
Female, *n* (%)	7 (29.2)	12 (50.0)	3 (13.0)
Race, *n* (%)			
White	20 (83.3)	13 (54.1)	19 (82.6)
Black	2 (8.3)	4 (17.4)	2 (8.7)
Other	2 (8.3)	7 (29.2)	2 (8.7)
Weight (kg)	76.7 (12.6)	76.3 (13.4)	77.5 (11.3)
Height (cm)	172.8 (9.4)	168.2 (9.7)	174.0 (7.3)
Body mass index (kg/m^2)	25.6 (3.0)	26.8 (2.3)	25.6 (3.0)

Data are presented as mean (SD) unless otherwise specified
ER extended-release, *SD* standard deviation

Pharmacokinetic Results

In study 1, following a single oral dose of an amantadine ER 129-mg, 193-mg, or 258-mg tablet, amantadine plasma concentrations increased slowly (C_{max} values of 328.21, 459.56, and 629.52 ng/mL, respectively), with a median T_{max} value of 9–9.5 h and a decline thereafter with a half-life of 13.2–13.8 h. By comparison, following a single oral 129-mg dose of amantadine IR syrup, amantadine plasma concentrations increased rapidly with a mean C_{max}

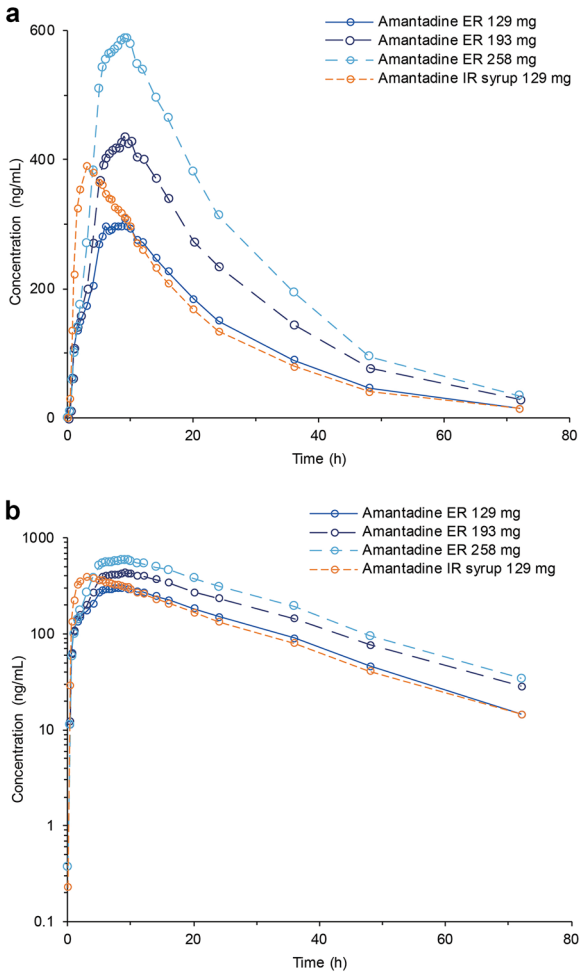

Fig. 1 Mean amantadine plasma concentration–time profile following oral administration of one 129-mg, 193-mg, or 258-mg amantadine ER tablet or 129 mg of amantadine syrup to fasted healthy volunteers in study 1: **a** linear scale, **b** semilogarithmic scale. *ER* extended-release, *IR* immediate-release

Table 3 Summary of mean pharmacokinetic parameters of amantadine following oral administration of one 129-mg, 193-mg, or 258-mg amantadine ER tablet or 129 mg of amantadine IR syrup to fasted healthy volunteers in study 1: results

Parameter	Amantadine ER tablet 129 mg (N = 23)	Amantadine ER tablet 193 mg (N = 23)	Amantadine ER tablet 258 mg (N = 23)	Amantadine IR syrup 129 mg (N = 23)
C_{max} (ng/mL)	328.21 (18.2)	459.56 (19.0)	629.52 (20.9)	403.54 (16.2)
T_{max} (h)[a]	9.00 (5.5–10.0)	9.00 (6.0–12.0)	9.50 (5.0–12.0)	3.00 (1.5–8.5)
AUC_{inf} (ng·h/mL)	8580.45 (19.0)	13,123.64 (20.4)	17,705.51 (21.3)	9007.72 (17.8)
λ_Z (h^{-1})	0.0524 (19.8)	0.0501 (28.1)	0.0515 (20.5)	0.0533 (22.2)
$t_{1/2}$ (h)[b]	13.2	13.8	13.5	13.0

Data are presented as mean (%CV) unless otherwise specified

λ_Z apparent elimination rate constant, AUC_{inf} area under the plasma concentration–time curve extrapolated to infinity, C_{max} maximum observed plasma concentration, CV coefficient of variation, ER extended-release, IR immediate-release, $t_{1/2}$ terminal elimination half-life, T_{max} time of maximum observed plasma concentration

[a] Median (range)

[b] Harmonic mean $t_{1/2}$ = 0.693/mean λ_Z

value of 403.54 ng/mL, a median T_{max} value of 3 h and a half-life of 13 h (Fig. 1 and Table 3).

Longer T_{max} and decreased C_{max} values following a single oral dose confirmed that there was a slower rate of amantadine absorption from the 129-mg amantadine ER tablet. T_{max} occurred much later (9 h postdose) for the amantadine ER tablet than for the amantadine IR syrup (3 h postdose); C_{max} for the 129-mg amantadine ER tablet was 81.05% (90% CI 77.34–84.93%) of that following the administration of amantadine IR syrup. The extent of amantadine absorption from the amantadine ER 129-mg tablet was equivalent to that from the amantadine IR 129-mg syrup. The geometric LS mean ratio of the natural-log-transformed AUC_{inf} was 95.27%, and the 90% CI of 90.24–100.57% was within the 80.00–125.00% bioequivalence limits (Table 4).

Following a single oral dose of an amantadine ER tablet (129, 193, or 258 mg), amantadine bioavailability (as reflected in the C_{max} and AUC_{inf} values) increased proportionally with increasing dose. Amantadine exposure increased in proportion with dose, as indicated by power model slope values of 0.92845 and 1.03767 for lnC_{max} and lnAUC_{inf}, respectively. When comparing doses, the geometric LS mean ratio of the dose-normalized, natural-log-transformed AUC_{inf} values ranged from 97.59–99.04% with corresponding 90% CIs between 92.03% and 105.01%. These results confirm the dose proportionality across the three amantadine ER tablet doses.

In study 2, the mean plasma concentration–time profiles of amantadine ER tablets administered under fed and fasted conditions were comparable (Fig. 2, Table 5). The geometric LS means of C_{max} and AUC_{inf} values following single oral dose administration of 258 mg amantadine ER tablets with and without food were equivalent (Table 6). The geometric LS mean fed/fasted ratios and 90% CIs of the natural-log-transformed C_{max} and AUC_{inf} values were within the predefined 80.00–125.00% limits, indicating that no significant food effect was observed (Table 6).

In study 3, following multiple-dose oral administration of the 129-mg amantadine IR syrup twice daily, plasma concentrations increased rapidly with a median T_{max} value of 2–3 h postdose ($T_{max0–12}$ and $T_{max12–24}$ were 3 and 14 h, respectively), declining thereafter with a mean half-life of 13.7 h. Following

Table 4 Summary of mean pharmacokinetic parameters of amantadine following oral administration of one 129-mg, 193-mg, or 258-mg amantadine ER tablet or 129 mg of amantadine IR syrup to fasted healthy volunteers in study 1: statistical analysis

Parameter	Amantadine ER tablet 129 mg[a] (*N* = 23)	Amantadine IR syrup 129 mg[a] (*N* = 23)	Test/reference ratio (90% CI)
C_{max} (ng/mL)	321.92	397.21	81.05 (77.34–84.93)
AUC_{inf} (ng·h/mL)	8453.50	8873.45	95.27 (90.24–100.57)

AUC_{inf} area under the plasma concentration–time curve extrapolated to infinity, *CI* confidence interval, *C_{max}* maximum observed plasma concentration, *ER* extended-release, *IR* immediate-release

[a] Geometric least-squares mean

multiple-dose oral administration of one 258-mg amantadine ER tablet once daily, the plasma concentration of amantadine increased slowly with a median $T_{max0–24}$ value of 7.5 h, declining thereafter with a mean half-life of 13.3 h. As shown in Fig. 3, amantadine ER concentration peaks in the middle of the day (following a morning dose) and is lower than amantadine IR syrup overnight. The average concentration ($C_{avg0–24}$) value for 258-mg amantadine ER tablet was 947.40 ng/mL, and was comparable to the value for 129-mg amantadine IR syrup, which was 965.13 ng/mL (Table 7). C_{max} and AUC values for twice-daily amantadine IR 129-mg syrup were equivalent to those for once-daily administration of amantadine ER 258-mg tablets (Tables 7, 8). At steady state, the 258-mg amantadine ER tablet was bioequivalent to 258-mg/day amantadine IR syrup; the 90% CI for C_{max} and AUC were within the 80.00–125.00% bioequivalence limits (Table 8).

DISCUSSION

The results of study 1 confirmed that amantadine is slowly absorbed following oral administration of amantadine ER. Amantadine plasma exposure (C_{max}, AUC_{inf}) increased dose-proportionally following oral administration of single doses of 129-mg, 193-mg, and 258-mg amantadine ER tablets. The extent of amantadine absorption from the 129-mg amantadine ER tablet is equivalent to that from 129-mg amantadine IR syrup (40 mg/5 mL).

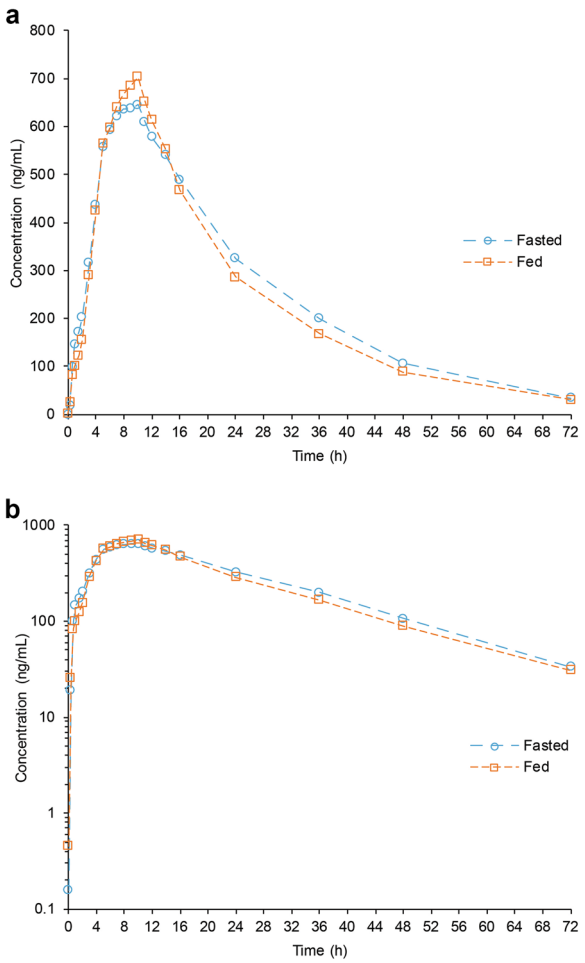

Fig. 2 Amantadine plasma concentration–time profile following oral administration of one 258-mg amantadine ER tablet under fasted (reference) or fed (test) conditions in study 2: **a** linear scale, **b** semilogarithmic scale. *ER* extended-release

Table 5 Summary of amantadine relative bioavailability following single-dose, oral administration of 258-mg amantadine ER tablets under fed and fasting conditions to healthy volunteers in study 2: results

Parameter	Fed (test) (N = 24)	Fasted (reference) (N = 24)
C_{max} (ng/mL)	726.500 (23.2)	667.406 (18.7)
T_{max} (h)[a]	9.009 (5.0–10.1)	9.000 (5.0–10.0)
AUC_{inf} (ng·h/mL)	17,379.367 (26.7)	18,481.399 (27.1)
λ_Z (h^{-1})	0.053 (21.2)	0.053 (20.6)
$t_{½}$ (h)	13.564 (22.0)	13.577 (22.5)

Data are presented as mean (%CV) unless otherwise specified

λ_Z apparent elimination rate constant, AUC_{inf} area under the plasma concentration–time curve extrapolated to infinity, C_{max} maximum observed plasma concentration, *CV* coefficient of variation, *ER* extended release, $t_{1/2}$ terminal elimination half-life, T_{max} time of maximum observed plasma concentration

[a] Median (range)

Table 6 Summary of amantadine relative bioavailability following single-dose, oral administration of 258-mg amantadine ER tablets under fed and fasting conditions to healthy volunteers in study 2: statistical analysis

Parameter	Fed (test)[a] (N = 24)	Fasted (reference)[a] (N = 24)	Test/reference ratio (90% CI)
C_{max} (ng/mL)	708.2	655.6	108.0 (102.5–113.9)
AUC_{inf} (ng·h/mL)	16,793.8	17,797.2	94.4 (88.8–100.2)

AUC_{inf} area under the plasma concentration–time curve extrapolated to infinity, *CI* confidence interval, C_{max} maximum observed plasma concentration

[a] Geometric least-squares mean

Study 2 confirmed that a high-fat meal does not affect the bioavailability of amantadine ER tablets, indicating that amantadine ER tablets may be administered irrespective of meals.

Finally, study 3 confirmed that at steady state, once-daily administration of 258-mg amantadine ER tablets is bioequivalent to twice-daily administration of 129-mg amantadine IR syrup (40 mg/5 mL); equivalent $C_{avg0–24}$ values following equivalent daily doses of amantadine ER tablets and amantadine IR syrup (947.40 ng/mL ER and 965.13 ng/mL IR syrup) confirm that the amantadine daily exposure is equivalent for ER and IR formulations. OS320 is not interchangeable with other amantadine IR or ER products.

These studies provide a comprehensive analysis of OS320 bioavailability, including the food effect, single-dose and steady-state pharmacokinetics. The purpose of this study was to report on the plasma PK and relative bioavailability of OS320. This study does not take into consideration gender differences which may exist with amantadine PK. Many early pharmacokinetic studies relied on a solely male population, and previous work has indicated that there are gender-specific differences in amantadine IR excretion when dosed in combination with quinidine or quinine [4, 11]. However, another study in a population of PD patients indicates that there are no gender-specific differences in efficacy [12].

Study limitations should be considered when interpreting these results. This analysis also does not include patients with renal impairment. As amantadine is primarily excreted by glomerular filtration and tubular secretion [1, 4, 5], patients with renal impairment should

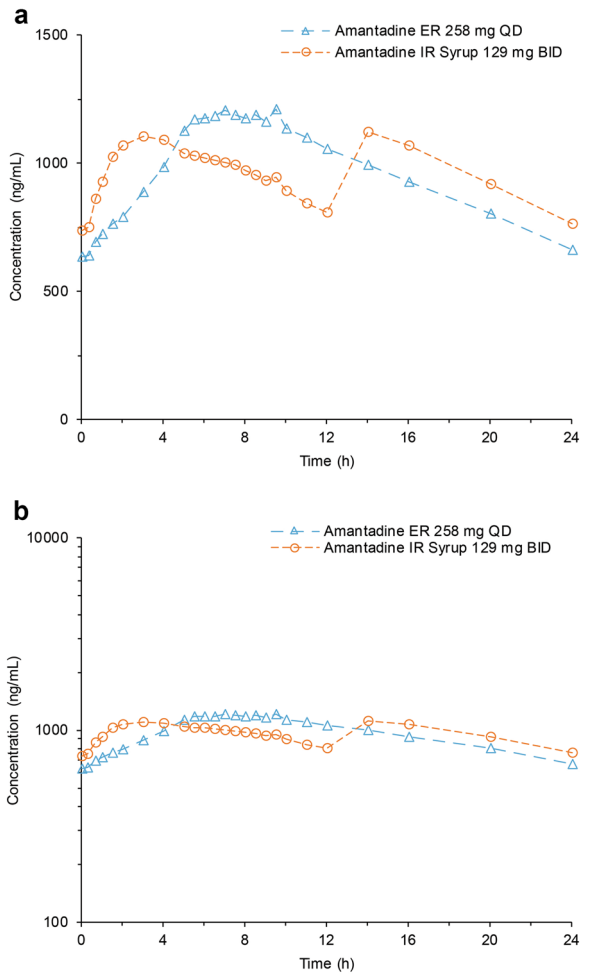

Fig. 3 Amantadine plasma concentration–time profile mean following oral administration of one 258-mg amantadine ER tablet daily or 129-mg amantadine IR syrup twice daily for 7 days to fasted healthy volunteers in study 3: **a** linear scale, **b** semilogarithmic scale. *BID* twice daily, *ER* extended-release, *IR* immediate-release, *QD* once daily

be supervised closely by their physicians. The once-daily, 258-mg dose should be used with caution in elderly patients and in patients with renal impairment. Additional research is needed to determine the effect of renal impairment on OS320 pharmacokinetics.

Amantadine has been shown to have a longer half-life in brain tissue than in plasma, raising questions regarding the utility of plasma PK in predicting amantadine efficacy [13]. However, work using a different formulation of ER amantadine (ADS-5102) concluded that plasma amantadine concentration is correlated with efficacy as measured by reduction in dyskinesia in nonhuman primates [14].

Parkinson's disease patients or patients with drug-induced EPRs whose response is not optimal with a 129-mg amantadine ER tablet once daily may benefit from an increase to an amantadine ER 193-mg tablet once daily, taken in the morning.

The results of these healthy volunteer studies are consistent with the previous data reported for amantadine. These studies demonstrated that following a single oral dose of OS320, plasma concentration increases in a dose-proportional manner. At steady state, once-daily administration of 258-mg amantadine ER tablets is bioequivalent to twice-daily administration of 129-mg amantadine IR syrup (40 mg/5 mL), and absorption of OS320 relative to amantadine IR syrup is slower, leading to more stable steady-state plasma levels throughout the day when given in the morning.

CONCLUSIONS

These results support the hypotheses of these three PK studies. Study 1 confirmed that amantadine is slowly absorbed following amantadine ER oral administration in healthy adults. Study 2 confirmed that food does not have a clinically significant effect on amantadine bioavailability. Study 3 confirmed that amantadine plasma exposure increases dose-proportionally with an increasing dose, and at steady state, the 24-h average amantadine plasma concentration is equivalent to that for the same daily dose of IR amantadine administered twice daily. In a clinical setting, OS320 is bioequivalent to IR amantadine and can be used in a similar manner. OS320 is not interchangeable with other amantadine IR or ER products. Prescribers should consider these factors and monitor patients when initiating therapy with OS320.

Table 7 Mean pharmacokinetic parameters of amantadine following oral administration of one 258-mg amantadine ER tablet daily or 129-mg amantadine syrup twice daily for 7 days to fasted healthy volunteers in study 3: results

Parameter	Amantadine ER tablet, 258 mg once daily (test) (N = 23)	Amantadine IR syrup 129 mg twice daily (reference) (N = 23)
$C_{max0-24}$ (ng/mL)	1275.01 (21.6)	1165.90 (18.9)
$T_{max0-24}$ (h)[a]	7.50 (5.0–12.0)	14.00[b]
AUC_{0-24} (ng·h/mL)	22,737.52 (24.7)	23,163.15 (22.0)
$C_{avg0-24}$ (ng/mL)	947.40 (24.7)	965.13 (22.0)
λ_Z (h^{-1})	0.0521 (27.6)	0.0505 (27.3)
$t_{1/2}$ (h)[c]	13.3	13.7

Data are presented as mean (%CV) unless otherwise specified

λ_Z apparent elimination rate constant, AUC_{0-24} cumulative area under the plasma concentration–time curve from 0 to 24 h, $C_{avg0-24}$ AUC_{0-24}/24 h, $C_{max0-24}$ maximum observed plasma concentration over 24 h after the last morning dose of each period, *CV* coefficient of variation, *ER* extended-release, *IR* immediate-release, $t_{1/2}$ terminal elimination half-life, $T_{max0-24}$ time of maximum observed plasma concentration over 24 h after the last morning dose of each period

[a] Median (range)

[b] T_{max} value for the 0–12 and 12–24 h interval was 3 and 2 h postdose, respectively

[c] Harmonic mean $t_{1/2}$ = 0.693/mean λ_Z

Table 8 Mean pharmacokinetic parameters of amantadine following oral administration of one 258-mg amantadine ER tablet daily or 129-mg amantadine syrup twice daily for 7 days to fasted healthy volunteers in study 3: statistical analysis

Parameter	Amantadine ER tablet 258 mg[a] (N = 23)	Amantadine IR syrup 258 mg[a] (N = 23)	Ratio (90% CI)
C_{max} (ng/mL)	1242.62	1143.30	108.69 (103.66–113.96)
AUC_{0-24} (ng·h/mL)	22,006.46	22,576.18	97.48 (93.20–101.95)

AUC_{0-24} cumulative area under the plasma concentration–time curve from 0 to 24 h, *CI* confidence interval, C_{max} maximum observed plasma concentration over 24 h after the last morning dose of each period, *ER* extended-release, *IR* immediate-release

[a] Geometric least-squares mean

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Compliance with Ethical Standards. All studies were conducted in accordance with Good Clinical Practice as defined by the International Conference on Harmonisation, the Declaration of Helsinki, and in accordance with the ethical principles underlying European Union Directive 2001/20/EC and the United States Code of Federal Regulations, Title 21, Part 50 (21CFR50). Studies 1 and 3 received ethics committee approval from IRB Services (Aurora, Ontario, Canada). Study 2 received approval from the Optimum Ethics Review Board (Oshawa, Ontario, Canada). All participants provided written informed consent before participation.

Data Availability. The datasets generated and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

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