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FULL-LENGTH ORIGINAL RESEARCH

Effects of lamotrigine and phenytoin on the pharmacokinetics of atorvastatin in healthy volunteers

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Summary

Purpose: Statins and antiepileptic drugs (AEDs) are frequently coprescribed to individuals with hypercholesterolemia and new-onset seizures. Statins are metabolized by the cytochrome P450 (CYP) enzyme system. Interactions between statins and agents that undergo CYP metabolism are common. In this study, the effects of two commonly prescribed AEDs, lamotrigine and phenytoin, with different routes of metabolism (CYP3A4 versus glucuronic acid conjugation) on atorvastatin pharmacokinetics were evaluated.

Methods: Healthy volunteers (n = 119) received atorvastatin 40 mg/day for 7 days followed by addition of lamotrigine (target 300 mg/day) or phenytoin (target ~4 mg/kg per day) in this open-label, single-sequence, two-cohort study. Serial pharmacokinetic sampling of atorvastatin was conducted on day 7 of atorvastatin dosing and day 70 of lamotrigine + atorvastatin dosing or day 28 of phenytoin + atorvastatin dosing. Main outcome measures were steady-state area under the curve over the 24-h dosing interval ($AUC_{(0-\tau)}$) and maximum concentration (C_{max}) of atorvastatin and its metabolites, 2OH-atorvastatin and 4OH-atorvastatin, in the presence of lamotrigine or phenytoin.

Key Findings: When atorvastatin was administered with lamotrigine compared with when atorvastatin was administered alone, atorvastatin $AUC_{(0-\tau)}$ was within bounds indicating no interaction, whereas C_{max} was slightly higher(14%); $AUC_{(0-\tau)}$ and C_{max} were 3% and 20% higher, respectively, for 2OH-atorvastatin and 25% and 21% higher, respectively, for 4OH-atorvastatin.When atorvastatin was administered with phenytoin compared with when atorvastatin was administered alone, reductions in $AUC_{(0-\tau)}$ and C_{max} were observed for atorvastatin (54% and 24%, respectively), 2OH-atorvastatin (53% and 22%, respectively), and 4OH-atorvastatin (44% and 52%, respectively).

Significance: Pharmacokinetics of atorvastatin were not significantly affected by coadministration with lamotrigine. Phenytoin significantly reduced atorvastatin bioavailability. Consistent with the published literature, these data are consonant with the possibility that atorvastatin does not require dose adjustment when coadministered with lamotrigine at doses to 300 mg/day, whereas atorvastatin coadministered with phenytoin may require atorvastatin dose adjustment to maintain atorvastatin exposure.

KEY WORDS: Lamotrigine, Epilepsy, Pharmacokinetics.

Epilepsy, which affects approximately 1% of the U.S. population (Hauser et al., 1996), can require lifelong treatment with antiepileptic drugs (AEDs). Because AEDs have the potential to interact adversely with other AEDs and/or with other classes of medication, and because polypharmacy is frequent in epilepsy, drug interactions are of particular concern (Patsalos et al., 2002; Diaz et al., 2008). In a 2009 claims analysis involving >11,000 patients ≥18 years old with epilepsy, use of concomitant medications was prevalent and increased with age: mean numbers of concomitant non-AEDs in the 18- to 24-year to ≥85-year age groups ranged from 2.41 to 7.67 in men and 4.04 to 7.05 in women (Gidal et al., 2009). Statins were the most common non-AED medications with potential for adverse drug interactions. Statins lower blood lipids by inhibiting 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, an enzyme involved in cholesterol biosynthesis, and reduce the risk of major cardiovascular events including death (Ridker et al., 2008; Spatz et al., 2009). One (1) in four older Americans is taking a statin, and an estimated 80% of middle-aged-to-elderly adults has a potential indication for statin therapy (Ridker et al., 2008; Spatz et al., 2009).

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Generally, statins are metabolized by the cytochrome P450 (CYP) enzyme system, and clinically relevant interactions between statins and other agents that undergo CYP metabolism (e.g., cyclosporine, erythromycin, itraconazole, ketoconazole) are common (Williams & Feely, 2002; Neuvonen et al., 2006). Drugs that inhibit the CYP system and increase statin plasma concentrations (e.g., erythromycin-associated increase of atorvastatin concentrations) can heighten the risk of statin adverse effects such as elevation of liver enzymes and myopathy, whereas drugs that induce the CYP system and decrease statin plasma concentrations (e.g., rifampicin-associated decrease of fluvastatin and atorvastatin concentrations) have the potential to reduce statin efficacy (Murphy & Dominiczak, 1999; Williams & Feely, 2002; Khandwala, 2006; Neuvonen et al., 2006; Tan et al., 2007). The study reported herein was conducted to evaluate the effect of two AEDs with different routes of metabolism on the pharmacokinetics of atorvastatin, which, according to the most recent data from the National Center for Health Statistics, was the third most commonly mentioned medication (behind only aspirin and ibuprofen) in all of U.S. ambulatory medical care in 2003–2004 (Raofi & Schappert, 2006). (A ''mentioned'' drug was defined as an ordered, supplied, administered, or continued medication.) Atorvastatin is metabolized by CYP3A4 to two active metabolites, 2-hydroxy-atorvastatin (2OH-atorvastatin) and 4-hydroxy-atorvastatin (4OH-atorvastatin), which account for approximately 70% of the circulating inhibitory activity for HMG-CoA reductase (Jacobsen et al., 2000; Lipitor, 2009). CYP3A4 appears to contribute to the metabolism of atorvastatin active metabolites. In addition, in vitro data suggest that both atorvastatin and its metabolites are glucuronidated by the UDP glucuronosyltransferase isoforms UGT1A1 and UGT1A3.

The AEDs assessed in this study were phenytoin and lamotrigine. Phenytoin, a first-generation AED, is a widely prescribed AED in some countries and the one used most frequently in the 11,000+-patient cohort in the claims analysis described earlier (Gidal et al., 2009). A potent CYP3A4 inducer, phenytoin is metabolized by the CYP system (CYP2C9 and CYP2C19) (Perucca, 2005). It was hypothesized that because phenytoin could affect the metabolism of atorvastatin through CYP3A4 induction and glucuronidation, phenytoin would decrease bioavailability of atorvastatin. (Similar effects might also be expected with carbamazepine and phenobarbital, which are also CYP3A4 inducers.) Lamotrigine is a second-generation AED introduced into clinical practice in 1990 (Biton, 2006; Lamictal XR, 2009). Lamotrigine is metabolized predominantly by glucuronic acid conjugation by the UDP glucuronosyltransferase isoforms UGT1A3 and UGT1A4 to inactive metabolites, mainly a 2-*N*-glucuronide conjugate, a 5-*N*-glucuronide, and a 2-*N*-methyl metabolite (Garnett, 1997; Lamictal XR, 2009). Because lamotrigine and its metabolites are not substrates of, and do not inhibit, any of the major CYP isoenzymes, it was hypothesized that lamotrigine would not significantly affect atorvastatin bioavailability.

Methods

Participants

Women of non–childbearing potential and men were eligible if they were healthy, were 18–55 years of age, had a body mass index (BMI) from 19 to 32 kg/m^2, weighed >50 kg for men and >45 kg for women, and had a screening 12-lead electrocardiogram (ECG) that was normal or had abnormalities that the investigator considered not to be clinically significant. Exclusion criteria included creatine phosphokinase 1.5 times the upper limit of normal at baseline or before dosing with study medication; exposure to lamotrigine (in the Lamotrigine + Atorvastatin Cohort) or phenytoin (in the Phenytoin + Atorvastatin Cohort) in the 18 months before the first dose of study medication; exposure to a statin ≤1 month before the first dose of study medication or past experience of adverse events with prior exposure to a statin ≥1 month before the first dose of study medication; and receipt of any known CYP3A4 inducer or inhibitor within 14 days of the first dose of study medication. Women receiving hormone replacement therapy or oral contraceptives were also excluded. All participants provided written informed consent.

Study design and treatments

The protocol for this open-label, single-sequence, two-cohort study (GlaxoSmithKline protocol LEP108937) was approved by an institutional review board (IntegReview) for the single study site in Buffalo, NY, U.S.A. The study comprised a screening visit, a treatment period during which two mutually exclusive cohorts of participants received study medication (Lamotrigine + Atorvastatin Cohort, Phenytoin + Atorvastatin Cohort), and a taper/follow-up period. During the screening visit, volunteers' eligibility for the study was determined; physical examinations and standard clinical laboratory tests were performed; and 12-lead ECGs were obtained. Brand name formulations of lamotrigine (Lamictal XR), phenytoin (Dilantin Kapseals), and atorvastatin (Lipitor) were the investigational products used in this study. During the treatment period, enrollment in the Lamotrigine + Atorvastatin Cohort proceeded first until the target number of 75 participants (to obtain 56 evaluable participants) was enrolled. After enrollment into the Lamotrigine + Atorvastatin Cohort was completed, enrollment into the Phenytoin + Atorvastatin Cohort began and proceeded to a target of 44 participants (to obtain 36 evaluable participants). Table 1 shows the dosing schedules and the timing of treatments. The target maintenance dose of lamotrigine was 300 mg/day, and that of phenytoin was 4 mg/kg per day. Atorvastatin was administered at a dose of 40 mg/day.

Table 1. Treatment protocol and schedule for blood draws for pharmacokinetic analyses

Lamotrigine + Atorvastatin Cohort			
Atorvastatin maintenance	Lamotrigine escalation	Lamotrigine + Atorvastatin maintenance	Taper/Follow-up
1 week (days 1–7)	7 weeks (days 8–56)	3 weeks (days 57–77)	Up to 3 weeks (days 78–98)
• Atorvastatin once daily at 8:00 a.m. • Discontinue atorvastatin after day 7 • Samplings: Days 5 and 6: single sample just prior to 8:00 a.m. (trough) Day 7: 16 samples at trough, 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8,10, 12, 16, 20, and 24 h	• Escalate on lamotrigine[a] • Samplings: Day 56: single sample just prior to 8:00 a.m. (trough)	• Reach target dose of lamotrigine[a] • Resume atorvastatin once daily at 8:00 a.m. on day 57 • Discontinue atorvastatin after day 77 • Samplings: Days 75 and 76: single sample just prior to 8:00 a.m. (trough) Day 77: 16 samples at trough, 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8,10, 12, 16, 20, and 24 h	• Taper lamotrigine[a] and exit study

Phenytoin + Atorvastatin Cohort		
Atorvastatin maintenance	Phenytoin + Atorvastatin maintenance	Taper/Follow-up
1 week (days 1–7)	3 weeks (days 8–28)	Up to 2.5 weeks (days 29–46)
• Atorvastatin once daily at 8:00 a.m. • Samplings: Days 5 and 6: single sample just prior to 8:00 a.m. (trough) Day 7: 16 samples at trough, 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8,10, 12, 16, 20, and 24 h	• Phenytoin[b] and atorvastatin once daily at 8:00 a.m. • Atorvastatin discontinued after day 28 • Samplings: Day 15: single sample just prior to 8:00 AM (trough) Days 26 and 27: single sample just prior to 8:00 a.m. (trough) Day 28: 16 samples at trough, 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8,10, 12, 16, 20 and 24 h	• Taper phenytoin[b] and exit study

[a]Lamotrigine was dosed once daily at 25 mg on days 8–21, 50 mg on days 22–35, 100 mg on days 36–42, 200 mg on days 43–49, 300 mg on days 50–77, 200 mg on days 78–79,100 mg on days 80–81, and 50 mg on days 82–84.

[b]Phenytoin dose was based on participants' weights at screening as follows: <62.5 kg: 200 mg/day on days 8–28, 100 mg/day on days 29–30, 100 mg/day on days 31–32;≥62.5 to ≤87.5 kg: 300 mg/day on days 8–28, 200 mg/day on days 29–30, 100 mg/day on days 31–32; >87.5 kg: 400 mg/day on days 8–28, 200 mg/day on days 29–30, 100 mg/day on days 31–32.

Table 1 shows the schedule according to which blood samples were drawn in the clinic for pharmacokinetic analyses. Participants were required to fast a minimum of 10 h on the evenings prior to pharmacokinetic sampling days and to stay in the clinic for the night prior to serial pharmacokinetic sampling and for 24 h on the pharmacokinetic sampling day, when they received standardized meals. Food or beverages that might have interfered with CYP activity were prohibited for the 7 days before initiation of study medication and for the duration of the pharmacokinetic sampling period. Alcohol consumption was required to be stable and not >7 units/week during the study. Unaccustomed strenuous physical activity was prohibited from 72 h before the screening visit through the duration of the study. Medications that could have affected serum concentrations of lamotrigine, atorvastatin, and phenytoin were prohibited for the duration of the study. Ibuprofen (not exceeding 400 mg three times daily or >3 days for the same indication) was permitted to treat any intercurrent illness or adverse event.

Assessments and statistics

Pharmacokinetics

Plasma concentrations of atorvastatin, 2OH-atorvastatin, and 4OH-atorvastatin were determined by the Department of Worldwide Bioanalysis, The Frythe, Welwyn, Herts, United Kingdom using a validated analytical method based on solid-phase extraction followed by high-performance liquid chromatography/mass spectrometry/mass spectrometry (HPLC-MS/MS) with a lower limit of quantification (LLQ) of 0.1 ng/ml and a higher limit of quantification (HLQ) of 250 ng/ml. Serum concentrations of lamotrigine were determined by the Department of Worldwide Bioanalysis, GlaxoSmithKline, Research Triangle Park, NC, U.S.A., using a validated analytical method based on protein precipitation followed by HPLC-MS/MS with an LLQ of 10 ng/ml and an HLQ of 10,000 ng/ml. Total phenytoin was isolated from human plasma and free phenytoin from ultrafiltrate human plasma by liquid–liquid extraction using 5,5′-diphenyl-D_{10}-hydantoin (phenytoin-d_{10}) internal standard working solution. Extracts were analyzed by PPD, Middleton, WI, U.S.A., by HPLC-MS/MS using a TurboIonSpray interface with negative ion multiple reaction monitoring with an LLQ of 0.100 μg/ml and an HLQ of 30 μg/ml for total phenytoin and an LLQ of 0.0500 μg/ml and an HLQ of 15.0 μg/ml for free phenytoin. Plasma was filtered with Centriprep Centrifugal Filter Devices (30,000 molecular weight cutoff) to obtain the ultrafiltrate.

Pharmacokinetic analyses were performed for all participants who received study medication and provided at

least one pharmacokinetic sample. Actual sampling times were used to estimate atorvastatin, 2OH-atorvastatin, and 4OH-atorvastatin area under the plasma concentration-versus-time curve during the 24-h dosing interval ($AUC_{(0-\tau)}$, calculated by a combination of linear and logarithmic trapezoidal methods), maximum plasma concentration (C_{max}), and time to C_{max} (t_{max}) in a noncompartmental analysis performed using WinNonlin Professional Edition version 5.2 software (Pharsight Corporation, Mountain View, CA, U.S.A.). The primary endpoints were steady-state $AUC_{(0-\tau)}$ and C_{max} of atorvastatin in the presence and absence of lamotrigine and phenytoin. Other endpoints of interest were $AUC_{(0-\tau)}$ and C_{max} of 2OH- and 4OH-atorvastatinin the presence and absence of lamotrigine or phenytoin.

To test for a pharmacokinetic interaction between lamotrigine and atorvastatin, an analysis of variance (ANOVA) model was adopted with regimen as a fixed-effect term and subject as a random-effect term. Logarithmically transformed values of atorvastatin, 2OH-atorvastatin, and 4OH-atorvastatin $AUC_{(0-\tau)}$ and C_{max} were used in the analyses. Point estimates and corresponding 90% confidence intervals (CIs) were constructed for the primary assessments of interest of atorvastatin + lamotrigine/atorvastatin alone using the residual variance and were back-transformed to provide point estimates and corresponding 90% CIs for the geometric mean ratios for atorvastatin + lamotrigine/atorvastatin alone. No pharmacokinetic interaction between steady-state lamotrigine and atorvastatin was to be concluded if the 90% CI for the geometric mean ratios (atorvastatin + lamotrigine/atorvastatin alone) of $AUC_{(0-\tau)}$ and C_{max} of atorvastatin were each contained within the range (0.800, 1.250). Similar analyses were conducted to estimate possible interactions between atorvastatin and phenytoin and between 2OH-atorvastatin and 4OH-atorvastatin and lamotrigine or phenytoin. Because the latter analyses used as an estimation approach to analysis, they were not subject to meeting the 0.80, 1.250 criteria.

A sample size of 56 evaluable participants in the Lamotrigine + Atorvastatin Cohort was estimated to provide >90% power to establish a lack of effect of lamotrigine on atorvastatin $AUC_{(0-\tau)}$ or C_{max} based on a within-subject coefficient of variation (CV) of 31.5% and a true ratio of the geometric means of the test and reference treatments of 1.05.

Based on a within-subject CV of 31.5% and a sample size of 36 evaluable subjects, it was estimated that the 90% CI for 4 mg/kg per day phenytoin + 40 mg atorvastatin: 40 mg atorvastatin alone would be obtained by dividing/multiplying the point estimates for a factor of approximately 1.13—that is, if the point estimate of the ratio was 1.0, then the 90% CI would have been 0.88–1.13. If the point estimate of the ratio was 0.7, then the 90% CI would have been 0.61–0.79.

To evaluate whether steady state was achieved for atorvastatin, statistical analysis of concentration levels was performed after a $\log_e$-transformation of predose (trough) concentrations (C_{trough}) on days 5, 6, and 7 for each cohort separately. A mixed-effect model was fitted for each cohort with day as a continuous covariate and subject as a random effect. The coefficient of the slope of the day effect on the log-scale for each cohort was used to determine whether steady state was achieved after 7 days of atorvastatin. Using the estimate of variance, the 90% CIs for the slopes were calculated. For steady state to be statistically confirmed, the 90% CIs for the slopes were to be contained within the limits 0.90–1.10.

Tolerability and safety

Tolerability and safety endpoints included the incidences of adverse events, serious adverse events, and premature withdrawals because of adverse events; clinically relevant changes in clinical laboratory abnormalities; and ECG findings. An adverse event was defined as any untoward medical occurrence temporally associated with the use of study medication regardless of the suspected cause. A serious adverse event was defined as any untoward experience, regardless of its suspected cause, that was fatal, life threatening, or resulted in incapacitation/disability; was a congenital anomaly/birth defect; required or prolonged inpatient hospitalization; or was otherwise considered serious by the investigator. Adverse events were recorded beginning with the first administration of study medication through the end of the taper/follow-up period. Standard clinical laboratory tests and 12-lead ECGs after 10 min at rest in the supine position were performed at screening, the end of atorvastatin monotherapy maintenance treatment, the end of combination therapy maintenance treatment, and 7 days after the last dose of study medication in both cohorts. Tolerability and safety data were summarized with descriptive statistics for all participants who received study medication.

Results

Participants

The number of participants enrolled in the study was 119 (75 in the Lamotrigine + Atorvastatin Cohort and 44 in the Phenytoin + Atorvastatin Cohort) (Table 2). Pharmacokinetic analyses included 73 participants in the Lamotrigine + Atorvastatin Cohort and 44 in the Phenytoin + Atorvastatin Cohort who received study medication and provided at least one pharmacokinetic sample. Adverse event summaries included 75 participants in the Lamotrigine + Atorvastatin Cohort and 44 in the Phenytoin + Atorvastatin Cohort who received study medication. The number of participants who prematurely withdrew from the study was 10 in the Lamotrigine + Atorvastatin Cohort and 7 in the Phenytoin + Atorvastatin Cohort. The most common reason for premature withdrawal in both cohorts was adverse events (Table 2). In each cohort, the majority of participants were white men (Table 2).

Table 2. Participants' demographic characteristics

	Lamotrigine + Atorvastatin Cohort	Phenytoin + Atorvastatin Cohort
Number enrolled	75	44
Number included in adverse event summaries	75	44
Number included in pharmacokinetic analyses	73	44
Completed the study, n (%)	65 (87)	37 (84)
Withdrew from the study, n (%)	10 (13)	7 (16)
Lost to follow-up	1 (1)	1 (2)
Adverse events	3 (4)	5 (11)
Protocol violation	2 (3)	0
Investigator discretion	2 (3)	1 (2)
Withdrew consent	2 (3)	0
Demographics		
Mean age, years (range)	36.2 (18–55)	31.8 (18–55)
Female, n (%)	12 (16)	2 (5)
Mean BMI, kg/m^2 (range)	26.3 (20–32)	26.7 (21–32)
Mean height, cm (range)	175.5 (152–191)	176.5 (160–193)
Mean weight, kg (range)	81 (58–109)	83.2 (64–99)
Race, n (%)		
White	49 (65)	25 (57)
Black	23 (31)	17 (39)
Asian	2 (3)	2 (5)
Mixed	1 (1)	0

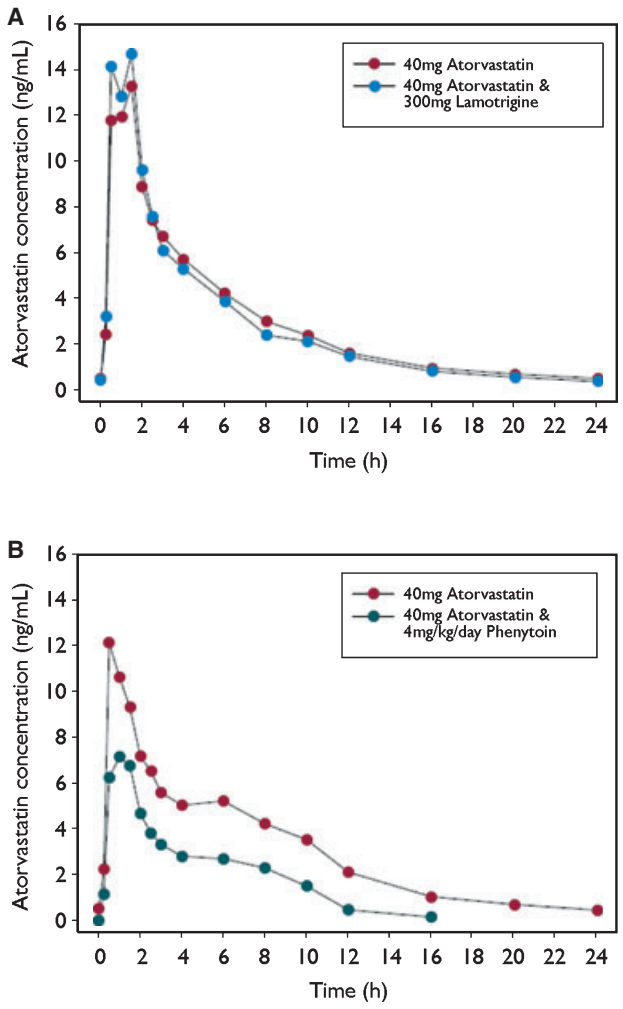

Figure 1.
(**A**) Atorvastatin concentrations as a function of time after dosing for the Lamotrigine + Atorvastatin Cohort when atorvastatin was administered with or without lamotrigine. (**B**) Atorvastatin concentrations as a function of time after dosing for the Lamotrigine + Phenytoin Cohort when atorvastatin was administered with or without phenytoin.

Pharmacokinetics

No formal analysis of steady-state drug levels was performed for either lamotrigine or phenytoin concentrations; however, in the Lamotrigine + Atorvastatin Cohort, examination of trough serum lamotrigine levels on days 56 and 57 and days 75 and 76 suggests that lamotrigine concentrations were at steady state. In the Phenytoin + Atorvastatin Cohort, examination of trough plasma levels of phenytoin on days 26 and 27 suggests that phenytoin concentrations were at steady state.

Effect of lamotrigine on pharmacokinetics of atorvastatin and its metabolites

The 90% CI of the ratio for atorvastatin + lamotrigine relative to atorvastatin alone fell within the limits considered to reflect no pharmacokinetic interaction between atorvastatin and lamotrigine for atorvastatin $AUC_{(0-\tau)}$ (Fig. 1A; Table 3). The 90% CI of the ratio for atorvastatin + lamotrigine relative to atorvastatin alone fell slightly outside the limits considered to reflect no interaction for atorvastatin C_{max} (Table 3). Atorvastatin C_{max} was 14% higher, on average, when atorvastatin was administered with lamotrigine compared with when atorvastatin was administered alone. When atorvastatin was administered with lamotrigine compared with when atorvastatin was administered alone, 2OH-atorvastatin $AUC_{(0-\tau)}$ was 3% higher and 2OH-atorvastatin C_{max} was 20% higher, whereas 4OH-atorvastatin $AUC_{(0-\tau)}$ was 25% higher and 4-OHatorvastatin C_{max} was 21% higher, on average (Table 3).

Effect of phenytoin on pharmacokinetics of atorvastatin and its metabolites

When atorvastatin was administered with phenytoin compared with when atorvastatin was administered alone, atorvastatin $AUC_{(0-\tau)}$ was 54% lower and atorvastatin C_{max} was 24% lower, on average (Fig. 1B, Table 3). When atorvastatin was administered with phenytoin compared with when atorvastatin was administered alone, 2OH-atorvastatin $AUC_{(0-\tau)}$ was 53% lower and 2OH-atorvastatin C_{max} was 22% lower, whereas 4OH-atorvastatin $AUC_{(0-\tau)}$was 44%

Table 3. Pharmacokinetic parameters for atorvastatin, 2OH-atorvastatin, and 4OH-atorvastatin after administration of atorvastatin alone, lamotrigine with atorvastatin, and phenytoin with atorvastatin[a] and statistical results of bioavailability comparisons[b]

Pharmacokinetic parameters[a]		
Lamotrigine + Atorvastatin Cohort		
	Atorvastatin	Lamotrigine + Atorvastatin
Atorvastatin		
$AUC_{(0-\tau)}$ (ng · h/ml)	62.0 (55.6, 69.2)	61.0 (54.6, 68.2)
C_{max} (ng/ml)	14.3 (12.4, 16.4)	16.2 (13.8, 19.1)
t_{max} (h)	1.0 (1–6)	1.0 (1–3)
2OH-Atorvastatin		
$AUC_{(0-\tau)}$ (ng · h/ml)	75.0 (67.3, 83.6)	77.0 (69.7, 85.0)
C_{max} (ng/ml)	10.3 (9.1, 11.7)	12.3 (10.8, 14.1)
t_{max} (h)	1.5 (1–10)	1.5 (1–6)
4OH-Atorvastatin		
$AUC_{(0-\tau)}$ (ng · h/ml)	14.2 (12.3, 16.4)	17.8 (15.5, 20.5)
C_{max} (ng/ml)	1.2 (1.0, 1.4)	1.4 (1.2, 1.7)
t_{max} (h)	1.5 (1–20)	2.0 (1–20)
Phenytoin + Atorvastatin Cohort		
	Atorvastatin	Phenytoin
Atorvastatin		
$AUC_{(0-\tau)}$ (ng · h/ml)	63.4 (54.3, 74.0)	29.2 (24.4, 35.0)
C_{max} (ng/ml)	12.1 (10.1, 14.6)	9.2 (7.7, 10.9)
t_{max} (h)	1.0 (1–10)	1.0 (1–8)
2OH-Atorvastatin		
$AUC_{(0-\tau)}$ (ng · h/ml)	85.2 (75.0, 96.9)	40.4 (35.3, 46.2)
C_{max} (ng/ml)	10.5 (9.0, 12.2)	8.2 (6.8, 9.8)
t_{max} (h)	1.5 (1–10)	1.5 (1–8)
4OH-Atorvastatin		
$AUC_{(0-\tau)}$ (ng · h/ml)	20.5 (17.6, 24.0)	11.6 (10.1, 13.3)
C_{max} (ng/ml)	1.6 (1.3, 1.9)	0.8 (0.7, 0.9)
t_{max} (h)	8.0 (2–20)	2.0 (1–10)
Bioavailability comparisons[b]		
Lamotrigine + Atorvastatin Cohort (for lamotrigine 300 mg/day)		
	$AUC_{(0-\tau)}$, ng h/ml	C_{max} (ng/ml)
Atorvastatin	0.990 (0.899, 1.091)	1.140 (0.988, 1.316)
2OH-Atorvastatin	1.028 (0.948, 1.116)	1.196 (1.063, 1.347)
4OH-Atorvastatin	1.251 (1.113, 1.406)	1.207 (1.046, 1.392)
Phenytoin + Atorvastatin Cohort (for phenytoin 4 mg/kg/day)		
Atorvastatin	0.463 (0.385, 0.556)	0.757 (0.647, 0.885)
2OH-Atorvastatin	0.473 (0.410, 0.545)	0.778 (0.674, 0.897)
4OH-Atorvastatin	0.565 (0.477, 0.670)	0.484 (0.394, 0.595)

[a]Geometric means (95% CI) except t_{max}, which is expressed as median (range).
[b]Geometric mean ratios and 90% CIs from ANOVA method.

lower and 4OH-atorvastatin C_{max} was 52% lower, on average (Table 3).

Atorvastatin steady state

In the Lamotrigine + Atorvastatin Cohort, the point estimate for the slope of atorvastatin C_{trough} for days 5, 6, and 7 after 7 days of repeated dosing of atorvastatin was 0.90 (90% CI 0.87, 0.95). The lower limit of this CI fell slightly outside the bounds of 0.90–1.10 for statistical confirmation of steady state. In the Phenytoin + Atorvastatin Cohort, the corresponding point estimate was 0.87 (90% CI 0.81, 0.93). Both the lower end of the CI and the point estimate fell outside the bounds for statistical confirmation of steady state. The slope of the steady-state analysis was <1, a finding that suggests decreases in atorvastatin concentrations. Only slight decreases in atorvastatin concentrations were detected in each cohort.

Tolerability and safety

No serious adverse events were reported. The most common adverse event in both cohorts was headache (Table 4). The number of participants prematurely withdrawn from the study because of an adverse event was three in the Lamotrigine + Atorvastatin Cohort and five in the Phenytoin + Atorvastatin Cohort. The premature withdrawals in the Lamotrigine + Atorvastatin Cohort were because of lower lip swelling (not considered drug related) in one participant, moderate pruritus (not considered drug related) and mild rash (considered drug related) in one participant, and angioedema (not considered drug related) in one participant. The premature withdrawals in the Phenytoin + Atorvastatin Cohort were because of mild rash or mild rash and pruritus (considered drug related) in four participants and viral infection (not considered drug related) in one participant. No changes in ECG parameters were considered clinically important and reported as adverse events. The only clinical laboratory changes reported as adverse events were a transient elevation of alanine aminotransferase (ALT) in one participant in the Lamotrigine + Atorvastatin Cohort and transient elevations of ALT and aspartate aminotransferase (AST) in one participant in the Phenytoin + Atorvastatin Cohort.

Discussion

Statins are instrumental in reducing cardiovascular morbidity and mortality (Kapur & Musunuru, 2008). In the middle-aged and elderly population in the United States, one in four individuals is currently being treated with a statin, and nearly four in five have an established or probable indication for a statin (Spatz et al., 2009). The current study is, to the authors' knowledge, the first to investigate prospectively the effects of the AEDs lamotrigine or phenytoin on the pharmacokinetics of a statin. Phenytoin is commonly used to treat new-onset seizures in middle-aged and elderly individuals, as they are likely to present to an emergency room for initial evaluation and treatment. After coadministration of lamotrigine and atorvastatin, systemic exposure to atorvastatin as indexed by $AUC_{(0-\tau)}$ was similar to that after administration of atorvastatin alone; atorvastatin C_{max} and $AUC_{(0-\tau)}$ and C_{max} for both atorvastatin metabolites increased slightly. These changes in the presence of lamotrigine were modest—minimal compared with the increases

Table 4. Number (%) of participants with adverse events

	Lamotrigine							
	Atorvastatin n = 75	25 mg n = 72	50 mg n = 71	100 mg n = 72	200 mg n = 70	300 mg n = 70	Lamotrigine 300 mg + Atorvastatin n = 69	Total n = 75
Lamotrigine + Atorvastatin Cohort								
Any adverse event	10 (13)	17 (24)	14 (20)	6 (8)	9 (13)	9 (13)	18 (26)	42 (56)
Headache	7 (9)	5 (7)	8 (11)	2 (3)	4 (6)	7 (10)	9 (13)	23 (31)
Nasopharyngitis	0	2 (3)	2 (3)	1 (1)	2 (3)	0	0	7 (9)
Back pain	0	3 (4)	0	1 (1)	0	1 (1)	1 (1)	6 (8)
Nausea	0	3 (4)	1 (1)	0	1 (1)	0	0	4 (5)

	Atorvastatin n = 44	Phenytoin 4 mg/kg per day + Atorvastatin n = 44	Total n = 44
Phenytoin + Atorvastatin Cohort			
Any adverse event	7 (16)	22 (50)	25 (57)
Headache	4 (9)	11 (25)	13 (30)
Rash	1 (2)	4 (9)	5 (11)
Dizziness	0	3 (7)	3 (7)
Pruritus	1 (2)	2 (5)	3 (7)
Nasopharyngitis	0	2 (5)	2 (5)
Pyrexia	0	2 (5)	2 (5)
Vomiting	1 (2)	1 (2)	2 (5)

Adverse events reported in ≥5% of participants in a cohort are listed.

observed in clinically relevant interactions of atorvastatin with CYP3A4 inhibitors such as clarithromycin and itraconazole (Kantola et al., 1998; Amsden et al., 2002)—and unlikely to be clinically relevant. These results suggest that atorvastatin does not require dose adjustment when used in combination at lamotrigine doses of up to 300 mg/day (the range usually used in clinical practice). The potential impact of lamotrigine doses higher than 300 mg/day, which might be used in clinical practice, on atorvastatin pharmacokinetics was not assessed in the current study.

Unlike lamotrigine, phenytoin administered at a dose typical of that used in clinical practice markedly reduced atorvastatin bioavailability. Although the clinical relevance of the reduction in atorvastatin bioavailability by phenytoin was not assessed in the current study, phenytoin-associated reduction of lipid-lowering efficacy of statins has been previously documented after coadministration of phenytoin and statins including simvastatin and atorvastatin (Murphy & Dominiczak, 1999; Williams & Feely, 2002; Khandwala, 2006; Tan et al., 2007). The pharmacokinetic data from the current study considered in the context of reports of phenytoin-associated reduction of statin efficacy suggest that adjustments of atorvastatin dosing may be necessary, if supported by plasma lipid measurements, when atorvastatin and phenytoin are coadministered. Although CYP3A4 inducing AEDs other than phenytoin were not evaluated in this study, the findings with phenytoin appear to generalize to the CYP3A4 inducer carbamazepine. In a randomized, two-phase crossover study, 12 healthy volunteers took carbamazepine for 14 days (600 mg daily except 200 mg daily for the first 2 days) or no drug followed by simvastatin 80 mg on day 15 (Ucar et al., 2004). Carbamazepine decreased the mean total area under the serum concentration-time curve of simvastatin and simvastatin acid by 75% and 82%, respectively. The mean peak concentrations of both simvastatin and simvastatin acid were reduced by 68%, and half-life of simvastatin acid was shortened from 5.9 to 3.7 ± 0.5 h by carbamazepine.

Atorvastatin concentrations were not at steady state after 7 days of dosing in either cohort. However, at atorvastatin steady state, any additional increase in atorvastatin concentrations from those observed in our study was likely to have been extremely small. The statistical failure to achieve steady state is not expected to have significantly impacted the outcome of the comparisons between atorvastatin administered alone and atorvastatin administered with lamotrigine or phenytoin.

Although no formal analysis of steady state drug levels was performed for either lamotrigine or phenytoin, in the Lamotrigine + Atorvastatin Cohort, examination of trough serum lamotrigine levels on days 56 and 57 and days 75 and 76 suggests that lamotrigine concentrations were at steady state. In addition, in the Phenytoin + Atorvastatin Cohort, examination of trough plasma levels of phenytoin on days 26 and 27 suggests that phenytoin concentrations were at steady state.

Study medication was generally well tolerated in both cohorts. No pattern of adverse events or changes in clinical laboratory results, ECGs, or vital signs attributed to coadministration of atorvastatin with either lamotrigine or phenytoin was apparent.

In conclusion, the results of this study demonstrate that coadministration of lamotrigine did not significantly affect the pharmacokinetics and tolerability of atorvastatin,

whereas coadministration of the CYP3A4 inducer phenytoin significantly reduced the atorvastatin bioavailability. Consistent with the published literature, these data are consonant with the possibility that atorvastatin does not require dose adjustment when coadministered with lamotrigine at doses of up to 300 mg/day, whereas atorvastatin coadministered with phenytoin may require dose adjustment of atorvastatin to maintain atorvastatin exposure.

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Disclosure

All authors were employed by GlaxoSmithKline at the time the study was conducted and may have owned stock in GlaxoSmithKline. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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