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A system of equations to approximate the pharmacokinetic parameters of lacosamide at steady state from one plasma sample

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Summary
Purpose: Frequent plasma sampling to monitor pharmacokinetic (PK) profile of antiepileptic drugs (AEDs), is invasive, costly and time consuming. For drugs with a well-defined PK profile, such as AED lacosamide, equations can accurately approximate PK parameters from one steady-state plasma sample.
Methods: Equations were derived to approximate steady-state peak and trough lacosamide plasma concentrations ($C_{peak,ss}$ and $C_{trough,ss}$, respectively) and area under concentration—time curve during dosing interval ($AUC_{\tau,ss}$) from one plasma sample. Lacosamide (k_a: $\sim 2\,h^{-1}$; k_e: $\sim 0.05\,h^{-1}$, corresponding to half-life of 13 h) was calculated to reach $C_{peak,ss}$ after $\sim$1 h ($t_{max,ss}$). Equations were validated by comparing approximations to reference PK parameters obtained from single plasma samples drawn 3—12 h following lacosamide administration, using data from double-blind, placebo-controlled, parallel-group PK study. Values of relative bias (accuracy) between −15% and +15%, and root mean square error (RMSE) values $\leq$15% (precision) were considered acceptable for validation.
Results: Thirty-five healthy subjects (12 young males; 11 elderly males, 12 elderly females) received lacosamide 100 mg/day for 4.5 days. Equation-derived PK values were compared to reference mean $C_{peak,ss}$, $C_{trough,ss}$ and $AUC_{\tau,ss}$ values. Equation-derived PK data had a precision of 6.2% and accuracy of −8.0%, 2.9%, and −0.11%, respectively. Equation-derived versus reference PK values for individual samples obtained 3—12 h after lacosamide administration showed correlation (R^2) range of 0.88—0.97 for $AUC_{\tau,ss}$. Correlation range for $C_{peak,ss}$ and $C_{trough,ss}$ was 0.65—0.87. Error analyses for individual sample comparisons were independent of time.

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Conclusion: Derived equations approximated lacosamide $C_{peak,ss}$, $C_{trough,ss}$ and $AUC_{\tau,ss}$ using one steady-state plasma sample within validation range. Approximated PK parameters were within accepted validation criteria when compared to reference PK values.

Introduction

Frequent plasma sampling is often used to characterize the pharmacokinetic (PK) profile of antiepileptic drugs (AEDs). In practice, the procedure is invasive and considerable logistical support is required to collect and process blood samples, which is costly and time consuming. Alternatively, for an AED that has a well-established PK profile with low inter-individual variability, equations can be derived that accurately predict PK parameters under steady-state conditions from a minimal number of plasma samples. This method could be integrated into a daily medical routine to characterize the PK profile using just one plasma sample. This in turn can facilitate the therapeutic drug monitoring (TDM) especially of drugs whose concentrations are not clearly related to their effects. Generally, TDM involves the measurement of concentrations in plasma and other body fluids to assist with individualizing dosage (Ghiculescu, 2008). Patients with epilepsy often require multiple AEDs, some of which have a high potential for mutual interaction due to cytochrome P450 (CYP) induction or inhibition. By taking one plasma sample it may be easier for a medical professional to characterize the PK profile of the AED. This scenario can not only be seen with antiepileptic therapy but in many other therapeutic regimes, too. Taking one blood sample at any time (but later than 1 h after administration) could be sufficient to quantify the whole range of concentrations within a dosing interval.

Approximation of AED PK parameters using a limited sampling strategy has been reported in current literature. Single plasma sample models used to estimate area under the concentration–time curve (AUC) and peak plasma concentration (C_{max}) of carbamazepine and vigabatrin have shown excellent correlation to reference values from healthy subjects (Mahmood and Chamberlin, 1998; Tammara et al., 1997). In a pooled Phase III analysis of patients with refractory epilepsy taking levetiracetam, Perucca et al. (2003) found that plasma concentrations and AUC estimated from a plasma sample drawn between 0 and 12 h were similar to those observed from multiple sampling in healthy volunteers, as well as in smaller trials of patients with epilepsy (Perucca et al., 2003). Arif et al. (2011) reported the estimation of total body clearance (CL/F) of lamotrigine using trough plasma concentration (C_{trough}) values from one serum sample; however, this method resulted in an overestimation of CL/F and yielded a lower approximation of drug plasma concentration, and thus should be used with caution (Arif et al., 2011).

Lacosamide (up to 400 mg/day) is approved as adjunctive treatment for adults with partial-onset seizures (UCB Pharma). Lacosamide has a well-established PK profile and exhibits rapid and complete absorption after oral administration and an absolute bioavailability of approximately 100% (Cawello et al., 2012a, 2012b). Plasma concentrations of lacosamide are proportional to dosage within the therapeutic range (an oral daily dose of up to 800 mg; intravenous daily dose of up to 300 mg) after a single dose or multiple doses (Bialer et al., 2004; Horstmann et al., 2002). The elimination half-life of lacosamide is approximately 13 h following a single dose or twice-daily dosing, and elimination follows first-order kinetics described by a one-compartment model. In addition, the PK parameters of lacosamide show low intra- and inter-individual variability (Cawello et al., 2008; Nickel et al., 2008; Schiltmeyer et al., 2005). Lacosamide is minimally bound to plasma proteins (Cawello et al., 2013; Fountain et al., 2012) and does not inhibit or induce cytochrome P450 isoenzymes at clinically relevant dosages (Beyreuther et al., 2007; Thomas et al., 2007). As a result, lacosamide does not exhibit clinically relevant drug–drug interactions with the common AEDs carbamazepine (Cawello et al., 2010) and valproic acid (Cawello and Bonn, 2012), oral contraceptives (Bialer et al., 2007), and other drugs susceptible to drug–drug interactions, including warfarin (Stockis et al., 2013), digoxin, omeprazole, metformin and midazolam (UCB Pharma).

This article presents a system of equations derived to calculate lacosamide PK parameters at steady state based on one blood sample drawn during a course of therapy. For validation purposes, we provide a comparison of the calculated approximations to actual PK data obtained from healthy volunteers participating in a double-blind, placebo-controlled, multiple-dose, parallel-group study of lacosamide (Sponsor Identifier: SP620; data from placebo group not used).

Methods

Approximation of lacosamide pharmacokinetic parameters at steady state from one plasma sample

The main parameters to characterize drug PK at steady state are described by the area under the concentration–time curve during a dosing interval ($AUC_{\tau,ss}$), peak and trough steady-state plasma concentrations ($C_{peak,ss}$ and $C_{trough,ss}$, respectively), as well as CL/F and terminal half-life ($t_{1/2}$) (Cawello, 1999; Gibaldi and Perrier, 1975). A hypothetical plasma concentration–time profile at steady state is depicted in Fig. 1. The plasma concentration of a blood sample drawn at time t [$C(t)_{ss}$] provides actual drug concentration between doses under steady-state conditions.

Equations derived only describe PK parameters approximated with a single-dose, orally administered of a drug in a one-compartment model over time, and were used to approximate lacosamide $C_{peak,ss}$, $C_{trough,ss}$, and $AUC_{\tau,ss}$. To calculate these steady-state PK parameters based on a single plasma concentration measurement at time t after drug administration, both the rate constant of elimination (k_e) and time to maximum concentration at steady state ($t_{max,ss}$)