Investigation of Clinical Pharmacokinetic Variability of an Opioid Antagonist Through Physiologically Based Absorption Modeling

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ABSTRACT: Identifying the source of inter- and/or intrasubject variability in pharmacokinetics (PK) provides fundamental information in understanding the pharmacokinetics–pharmacodynamics relationship of a drug and project its efficacy and safety in clinical populations. This identification process can be challenging given that a large number of potential causes could lead to PK variability. Here we present an integrated approach of physiologically based absorption modeling to investigate the root cause of unexpectedly high PK variability of a Phase I clinical trial drug. LY2196044 exhibited high intersubject variability in the absorption phase of plasma concentration–time profiles in humans. This could not be explained by *in vitro* measurements of drug properties and excellent bioavailability with low variability observed in preclinical species. GastroPlus™ modeling suggested that the compound's optimal solubility and permeability characteristics would enable rapid and complete absorption in preclinical species and in humans. However, simulations of human plasma concentration–time profiles indicated that despite sufficient solubility and rapid dissolution of LY2196044 in humans, permeability and/or transit in the gastrointestinal (GI) tract may have been negatively affected. It was concluded that clinical PK variability was potentially due to the drug's antagonism on opioid receptors that affected its transit and absorption in the GI tract. © 2013 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci 102:2859–2874, 2013

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INTRODUCTION

The availability of a therapeutic agent into systemic circulation at the desired time and concentration is a prerequisite for an oral therapeutic agent to exert its pharmacological effects via engagement of the target at the right time and concentration. Low variability in systemic drug exposure or an understanding of the source of inter- and intrasubject variability is important to evaluate the relationship of pharmacokinetics (PK) and pharmacodynamics (PD) of the drug and to predict its efficacious dose and safety range for clinical applications.[1] Given that the overall PK is determined by drug absorption, distribution, metabolism, and excretion, the sources of variability may be identified from these distinctive processes. Metabolism-related variability can find classic examples in the case of genetic polymorphism of metabolizing enzymes[2] and drug–drug interactions that inhibit or induce the relevant enzymes.[3–5] Plasma binding and lipophilicity of a drug can contribute to the variability of its distribution in the body.[6] Drug excretion is subject to physiological variation of involved organs.[7] Poor absorption is often acknowledged as a potential source of high variability[8–10] and requires a closer examination of potential sources that contribute to variability in absorption. For high-solubility and high-permeability drugs that belong to Biopharmaceutical Classification System (BCS) Class I, complete and rapid absorption is expected in conventional immediate-release dosage forms.[11] However, for BCS Class II, III, and IV drugs, whose absorption are limited by solubility, permeability or both, their absorption can become more dependent on the individual gastrointestinal (GI) conditions. The solubility of weak bases with poor intrinsic solubility can be highly dependent on the GI pH.[12,13] At acidic pH in the stomach, these compounds may dissolve

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quickly due to their high degree of ionization and thus higher solubility.[14] However, upon entry in the small intestine with higher pH, the dissolved drugs may precipitate due to reduced solubility and their *in vivo* performances may be adversely affected.[15,16] Hence, elevated pH in stomach can have profound negative impact on the dissolution and subsequently the absorption of such drugs.[17–19] A lipophilic compound often has low aqueous solubility but can be effectively solubilized by bile salts through micelle formation.[20,21] However, the regulation of bile secretion is highly complex, leading to considerable variability in the output of bile salts.[22] Absorption of such a compound can thus become highly variable due to the physiological and/or pathophysiological effect on bile secretion.[23–25] GI motility variation can have a profound effect on drug absorption by means of altering the GI transit time.[26] Prolonged GI transit may be favorable for a slowly permeating molecule to achieve high absorption,[27] whereas increased GI motility can have negative impact on absorption.[28] Identification of the root causes of absorption-related variability can be particularly useful to design clinical studies and formulate strategies for improving the drug absorption. For example, one approach may be to reduce the drug's particle size, a commonly used method to improve dissolution-limited absorption and thus minimize variability.[29,30] Wetting agents and/or solubilizers can also be added to formulations to improve effective solubility and dissolution of poorly soluble drugs.[31] Lipid-based drug delivery, solid dispersion, and nanotechnology have emerged as promising approaches to overcome solubility limit for BCS II compounds.[32] Absorption enhancers have been extensively studied to overcome permeability limit on drug absorption.[33] Prodrugs are also designed for slowly permeable compounds or drugs that are susceptible to degradation or metabolism in the GI tract.[34]

LY2196044 (Fig. 1), an opioid antagonist, demonstrated acceptable preclinical bioavailability with low variability in PK profiles. However, it unexpectedly exhibited high intersubject PK variability in a Phase I trial in healthy humans. The initial examination of the PK profiles indicated that the variability was more manifest in the absorption phase, whereas the distribution and elimination of LY2196044 seemed to be relatively consistent among subjects. Investigation was thus initiated to evaluate the contribution of drug absorption to the variability and identify proper solutions, if possible. In this study, we employed an integrated approach to investigate such a complex issue. We extracted relevant information from a careful analysis of existing *in vitro* and *in vivo* data of the compound, and subsequently incorporated the knowledge into computational simulations to shed light on possible mechanisms.

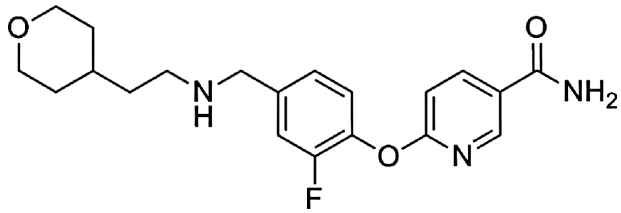

Figure 1. Chemical structure of LY2196044 (Molecular Weight = 373.43).

EXPERIMENTAL

Materials

LY2196044 was synthesized as a hydrochloride for clinical development by Eli Lilly (Indianapolis, IN). All other chemicals were purchased from commercial vendors and were of analytical grade. Human carcinoma of colon (Caco-2) cell line was purchased from the American Type Culture Collection (Rockville, MD).

Solubility Measurement

Aqueous solubility of LY2196044·HCl in a crystalline form was measured in water, 0.1 N HCl, USP buffers, phosphate buffers at pH 2–8 at 25°C, and simulated GI fluids at 37°C. The phosphate buffer solutions were prepared from mono- and di-basic phosphate to achieve the final concentration of 50–100 mM. The pH of phosphate buffer solutions was adjusted with slight additions of concentrated HCl if necessary. Fasted-state simulated gastric fluid (FaSSGF) and fasted- or fed-state simulated intestinal fluids (FaSSIF and FeSSIF) were prepared as described previously.[35]

Small quantities of the compound were placed in glass vials, and media were added to achieve a target concentration of 5 mg/mL. The vials were rotated for 6 h at room temperature. Samples were then filtered, and the drug concentrations in solutions were determined by reversed-phase high performance liquid chromatography (RP-HPLC). The solution pH values were also measured. The HPLC system was composed of a Waters 2695 (Alliance) model with a PDA detector. A Chromolith® C18 column (4.6 × 100 mm, 5 μm) was used to analyze these samples. The injection volume was 10 μL. The mobile phase consisted of a mixture of acetonitrile/0.1% trifluoroacetic acid and deionized water. The flow rate was 1 mL/min. The detector wavelength was set at 235 nm.

Permeability Assay

Apparent permeability across the Caco-2 cell monolayers was determined following the current industrial practice.[36] In summary, the assay was conducted after 21 days of cell growth on polycarbonate filters in six-well plates. Atenolol, propranolol, and sulfasalazine were included in the study as references