Effects of Food Intake on the Relative Bioavailability of Amifampridine Phosphate Salt in Healthy Adults

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ABSTRACT

Purpose: Amifampridine (3,4-diaminopyridine) has been approved in the European Union for the treatment of Lambert-Eaton myasthenic syndrome. Amifampridine has a narrow therapeutic index, and supratherapeutic exposure has been associated with dose-dependent adverse events, including an increased risk for seizure. This study assessed the effect of food on the relative bioavailability of amifampridine in healthy subjects and informed on conditions that can alter exposure.

Methods: This randomized, open-labeled, 2-treatment, 2-period crossover study enrolled 47 healthy male and female subjects. Subjects were randomly assigned to receive 2 single oral doses of amifampridine phosphate salt (20 mg base equivalents per dose) under fed or fasted conditions separated by a washout period. Blood and urine samples for pharmacokinetic analyses were taken before and after dosing. Plasma concentrations of amifampridine and an inactive 3-*N*-acetyl metabolite were determined. The relative bioavailability values of amifampridine and metabolite were assessed based on the plasma PK parameters $AUC_{0-\infty}$, AUC_{0-t}, and C_{max} in the fed and fasted states using noncompartmental pharmacokinetic analysis. Parent drug and metabolite excretion were calculated from urinary concentrations. A food effect on bioavailability would be established if the 90% CI of the ratio of population geometric mean value of $AUC_{0-\infty}$, AUC_{0-t}, or C_{max} between fed and fasted administration was not within the bioequivalence range of 80% to 125%. Tolerability was assessed based on adverse-event reporting, clinical laboratory assessments, physical examination including vital sign measurements, 12-lead ECG, and concurrent medication use.

Findings: Food slowed and somewhat decreased the absorption of amifampridine. There was a decrease in exposure (C_{max}, 44%; AUC, 20%) after oral administration of amifampridine phosphate salt in the presence of food, and mean T_{max} was 2-fold longer in the fed state. The extent of exposure and plasma elimination half-life of the major metabolite was greater than those of amifampridine in the fed and fasted conditions. Mean AUCs in the fed and fasted states were slightly greater in women than men, with no difference in mean C_{max}. Orally administered amifampridine was renally eliminated (>93%) as the parent compound and metabolite within 24 hours. Single oral doses of 20 mg of amifampridine phosphate salt were considered well tolerated in both the fed and fasted conditions. High intersubject variability (%CVs, >30%) in amifampridine pharmacokinetic parameter values was observed.

Implications: At the intended dose under fasting conditions, amifampridine exposure may be increased. European Union Drug Regulating Authorities Clinical Trials identifier: 2011-000596-13. (*Clin Ther*. 2015; 37:1555–1563) © 2015 The Authors. Published by Elsevier HS Journals, Inc.

Key words: amifampridine, food effects, pharmacokinetics, 3,4-diaminopyridine, 3,4-DAP, Lambert-Eaton Myasthenic Syndrome.

INTRODUCTION

3,4-Diaminopyridine (3,4-DAP) has been used for >25 years for treating a variety of neurologic disorders of axonal or synaptic transmission, including Lambert-Eaton myasthenic syndrome (LEMS),[1,2] myasthenia gravis, congenital myasthenia, multiple sclerosis, and downbeat nystagmus.[3–5] 3,4-DAP blocks voltage-dependent potassium ion channels, thereby prolonging the action potential and presynaptic cell

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membrane depolarization, enhancing influx or transport of calcium into the nerve ending. The resulting increase in intracellular calcium concentration facilitates exocytosis of acetylcholine-containing vesicles, leading to an increased concentration of acetylcholine at the motor end plate,[6] which in turn results in improved neuromuscular transmission and augmented muscle contraction and strength.[7,8]

Over the past 25 years, a considerable amount of clinical experience with 3,4-DAP has been gained, providing a strong body of evidence supporting its efficacy and tolerability in the treatment of patients with LEMS.[1,2] 3,4-DAP is a standard of care for LEMS in the United States and has been recommended by the European Academy of Neurology (formerly, European Federation of Neurological Societies) for first-line symptomatic treatment of patients with LEMS.[9] For many years, the absence of a product approved for the treatment of this condition led physicians to prescribe ad hoc preparations of amifampridine base from compounding pharmacies or independent small-scale manufacturers. The process of producing these products was associated with considerable batch variability, lack of reliability in drug quality, safety concerns for the people manipulating the free base, and a risk for overdose due to compounding errors.[10]

A new oral phosphate salt formulation of 3,4-DAP (amifampridine) was approved by the European Medicines Agency in 2009.[11] Comparability of the base versus the phosphate salt formulation of 3,4-DAP was demonstrated in a previously conducted double-blind, single-dose, crossover, bioavailability/bioequivalence study conducted in 27 healthy male subjects.[2] The pharmacokinetic (PK) profiles of both the 3,4-DAP free base and phosphate salt forms in this study were highly variable, with up to 10-fold differences in C_{max}, AUC, and $t_{½}$ between subjects. The most probable explanation for this variability appears to be the single metabolic disposition of 3,4-DAP via the activity of *N*-acetyl transferases (NATs) to form a single major 3-*N*-acetyl metabolite, which is inactive.[12] NAT enzymes are highly polymorphic in humans and vary considerably with ethnicity. Phenotypically, a patient's NAT status can be classified, through a range of acetylation activities, from slow to rapid. Variations of polymorphic NAT corresponding with fast and slow acetylator phenotypes have been found to significantly affect the PK and tolerability profiles of amifampridine.[12]

Understanding the PK properties of amifampridine is particularly important because amifampridine has a narrow therapeutic index, and supratherapeutic exposure has been associated with an increase in the risk for seizures.[2] The purpose of this study was to evaluate the effects of food on the PK properties and relative bioavailability of amifampridine phosphate salt.

SUBJECTS AND METHODS

Subjects

This study enrolled healthy subjects, both men and women, aged 18 to 65 years and with a body mass index between 18.5 and 30 kg/m^2, inclusive. Subjects underwent screening to confirm eligibility within 28 days before the administration of the first dose of study drug. Screening included physical examination, clinical laboratory evaluations (hematology, chemistry, and urinalysis), and ECG. Women of childbearing potential must have had a negative pregnancy test at screening. Sexually active subjects of childbearing potential must have been willing to use 2 acceptable methods of contraception while participating in the study, with 1 method spermicidal.

Subjects were excluded if they could not tolerate the study-specific diet or were breast-feeding. Subjects were also excluded if they had received any prescribed systemic or topical medication; nonprescribed systemic or topical medication (including herbal remedies, but excluding vitamin/mineral supplements); any medication (including St. John's wort or other herbal remedy) known to chronically alter drug absorption or elimination processes; medication that prolongs the QT interval or QT interval corrected for heart rate; alcohol, caffeine, poppy seed, or grapefruit containing products; or amifampridine (base or phosphate salt) or fampridine (4-aminopyridine) within defined time periods before planned administration of the first dose of study drug.

Other exclusion criteria included a variety of significant diseases, disorders, or illnesses; high or low blood pressure; ECG abnormalities; a history of cardiac disease; and current or history of alcohol abuse, drug abuse, or smoking within defined time periods before planned administration of the first dose of study drug.

Study Design

This was a randomized (1:1), open-labeled, 2-treatment, 2-period crossover study to assess the tolerability and effect of food on the relative bioavailability of amifampridine phosphate salt in healthy subjects after single-dose administration. Written informed consent was obtained from each subject before