Single-Dose, Randomized, Open-Label, 2-Way Crossover Study of the Pharmacokinetics of Amitriptyline Hydrochloride 10- and 25-mg Tablet in Healthy Male Korean Volunteers

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ABSTRACT

Purpose: Amitriptyline is the most widely used tricyclic antidepressant (TCA). Although amitriptyline hydrochloride 10 and 25 mg has been marketed in Korea, no data on the dose proportionality of amitriptyline in Korean subjects are available. This clinical trial was designed to evaluate and compare the relative bioavailability with regard to dose proportionality between the two marketed strengths of amitriptyline hydrochloride tablets after a single-dose, oral administration under fasting conditions in healthy, male, Korean volunteers.

Methods: This single-dose, randomized, open-label, 2-way crossover study was conducted in healthy male Korean subjects. Subjects were randomly assigned to 1 of 2 dose groups and received a single dose of 10 or 25 mg amitriptyline hydrochloride under fasting conditions, followed by the alternate dose in the subsequent study period. High performance liquid chromatography (HPLC)- mass spectrometry (MS)/MS detection was applied to determine plasma concentrations. Pharmacokinetic parameters were calculated, C_{max}, AUC_{last}, $AUC_{0-\infty}$, $t_{½}$, and T_{max}. Statistical analysis was performed for the assessment of dose proportionality. Tolerability was assessed for up to 96 hours after administration.

Findings: Twelve healthy Korean subjects completed this trial (mean [SD] age, 21.7 [1.9] years; height, 174.5 [5.0] cm; and weight, 66.7 [9.4] kg). Although 4 subjects experienced a total 5 adverse events (AEs), no serious AEs were reported during the study. The mean values of C_{max} and AUC were proportional to the doses of 10 and 25 mg. The C_{max}, AUC_{last}, and $AUC_{0-\infty}$ of amitriptyline hydrochloride 10 mg were 5.96 ng/mL, 91.35 ng · h/mL and 109.74 ng · h/mL, respectively. The C_{max}, AUC_{last}, and $AUC_{0-\infty}$ of amitriptyline hydrochloride 25 mg were 17.69 ng/mL, 260.68 ng · h/mL, and 296.87 ng · h/mL, respectively.

Implications: Our results suggest that the 2 strengths of amitriptyline hydrochloride (10 and 25 mg) exhibited linear (dose-dependent) pharmacokinetics in these healthy, male, Korean subjects. Based on these results, a predictable and linear increase in systemic exposure can be expected.ClinicalTrials.gov identifier: NCT01367080. (*Clin Ther.* 2014;▮:▮▮▮–▮▮▮)

Keywords: amitriptyline hydrochloride, antidepressant, Etravil, pharmacokinetic, proportionality.

INTRODUCTION

Amitriptyline was developed by Merck & Co, Inc, and was approved by the US Food and Drug Administration on April 7, 1961, for the treatment of major depression.[1] Amitriptyline is the most widely used

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tricyclic antidepressant (TCA). In Korea, amitriptyline hydrochloride 10 and 25 mg are commercially available.[*†]

Although TCAs have largely been replaced in recent decades by new classes of antidepressants such as serotonin–norepinephrine reuptake inhibitors and selective serotonin reuptake inhibitors, amitriptyline is still frequently used.[2] Amitriptyline has a wide range of pharmacologic actions. In addition to increasing receptor-site concentrations of norepinephrine and serotonin,3,4 amitriptyline has an affinity for the muscarinic, histaminergic, cholinergic, and adrenergic systems.[5,6] Amitriptyline has been suggested to interact with the σ-1 receptor,[7] tropomyosin receptor kinase receptor,[8] *N*-methyl-D-aspartate receptor, and phencyclidine receptor.[9] Amitriptyline is also a sodium, calcium, and potassium channel blocker.[10,11]

Amitriptyline offers variability in dosing, often ranging between 25 and 150 mg. The drug has been associated with a number of adverse events (AEs) such as blurred vision, constipation, urination problems, dry mouth, delirium, vertigo, and sedation.[2] Although many studies have been conducted with regard to treating amitriptyline overdose and acute poisoning,[12,13] few data on the dose proportionality of amitriptyline in Korean subjects are available. Thus, this study was designed to evaluate and compare relative bioavailability in terms of dose proportionality between the 2 marketed strengths (10 and 25 mg) of amitriptyline hydrochloride tablets after single-dose, oral administration in fasting, healthy, male, Korean volunteers.

SUBJECTS AND METHODS

Study Design

In this single-dose, single-center, randomized, open-label, 2-way crossover study, a single oral dose of amitriptyline hydrochloride 10 or 25 mg was administered under fasting conditions in each study period. To ensure that no carryover effect was observed, a washout period of 14 calendar days was instituted between drug administrations, corresponding to >10-fold the expected half-life of the moiety to be measured. The randomization code was not made available to the personnel in charge of the determination of plasma drug concentrations until the results were audited by the quality-assurance department. The protocol and informed-consent forms were approved by the institutional review board of the Chung-ang University College of Medicine (Seoul, Korea). All subjects voluntarily agreed to participate in this study and provided informed consent before the initiation of the study procedures. This study was conducted in accordance with the Declaration of Helsinki and International Conference on Harmonisation Guideline for Good Clinical Practice.[14,15]

Study Population

Healthy, male, Korean volunteers between 19 and 50 years of age were enrolled in this trial. Volunteer-screening procedures included informed consent; inclusion/exclusion criteria assessment; collection of demographic data, medical history, medication history, and physical-examination data; and ECG and laboratory test results (routine blood chemistry, blood cell count with white blood cell differential, urinalyses, and coagulation tests). Eligible participants' weights were >50 kg and within 20% of the ideal body weight for height.[16]

Subjects were excluded if they had congenital or chronic disease, a history of clinically significant diseases or drug hypersensitivity, use of prescription medication within 14 days or over-the-counter medications within 7 days before dosing, low or high blood pressure (systolic blood pressure, ≤100 or ≥150 mm Hg, diastolic blood pressure, ≤65 or ≥95 mm Hg), blood donation <60 days before dosing, excessive alcohol or caffeine consumption, and/or smoking habit.

All participating subjects were considered eligible for the study after the assessment of the inclusion and exclusion criteria. Participants were immediately removed from the study if safety issues arose as determined by the investigator. They could also be withdrawn because of protocol violations, administrative problems, and difficulties in blood collection, emesis during the time interval described in the protocol, and/or other reasons described in the protocol. Furthermore, subjects were allowed to discontinue their participation in the study at any time.

Treatment Schedule

Subjects received the amitriptyline hydrochloride tablet 10 or 25 mg in the first study period under

[*]Marketed as Endep® (Roche), Etravil® (DDSA), Laroxyl® (Roche), Lentizol® (Parke-Davis), Sarotex® (H. Lundbeck), and Tryptizol® (Merck Sharp & Dohme).

[†]Trademark: Etravil® (Dong-Hwa Pharmaceutical Corporation, Seoul, Korea).