Comparative Bioavailability Study of Single-Dose Film-Coated and Sugar-Coated Ethionamide Tablets in Healthy Volunteers

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ABSTRACT

Background: Ethionamide sugar-coated tablets have been reformulated to film-coated tablets to improve dissolution and stability.

Objective: The study objective was to compare the bioavailability of the film-coated (test) and sugar-coated (reference) formulations of ethionamide.

Methods: After providing informed consent and undergoing screening procedures, 40 healthy subjects were assigned to receive a single dose of ethionamide 250-mg film- or sugar-coated tablets, in randomized order, in the fasted state. Serial blood samples were collected before and from 0.5 to 24 hours after dosing. After a 7-day washout, procedures were repeated for the other formulation. The blood samples were processed to provide plasma samples, which were frozen until assay. Plasma ethionamide concentrations were measured using a validated LC-MS/MS method, with a lower limit of quantitation of 20 ng/mL. Pharmacokinetic parameters were determined using noncompartmental methods, with subsequent evaluation for bioequivalence.

Results: All 40 subjects (37 men, 3 women; mean age, 28 years; mean weight, 74 kg) completed the study. Seven subjects reported a total of 10 adverse events (5 with each formulation), all of which were mild and considered possibly related to drug treatment. None of the events resulted in discontinuation from the study. Mean (SD) pharmacokinetic properties observed with the film- and sugar-coated tablets, respectively, were as follows: C_{max}, 2160 (614) and 1484 (636) ng/mL; T_{max}, 1.0 (0.5) and 1.5 (0.9) hours; k_e, 0.369 (0.053) and 0.232 (0.114) h^{-1}; $t_{½}$, 1.92 (0.27) and 4.06 (2.52) hours; and AUC, 7668 (1688) and 6594 (1764) ng · h/mL.

Conclusions: Comparing AUC values, the formulations were bioequivalent. The maximum concentrations observed with the film-coated product were higher but were more consistent (%CV, 28%) compared with those of the sugar-coated formulation (%CV, 43%). (*Clin Ther*. 2014;▮:▮▮▮–▮▮▮) © 2014 Published by Elsevier HS Journals, Inc.

Key words: bioequivalence, ethionamide, tuberculosis, Trecator.

INTRODUCTION

Ethionamide was first synthesized in 1956 and is used, in combination with other agents, for the treatment of tuberculosis.[1] It is unpleasant for some patients to take, causing nausea and vomiting, and so is used as second-line treatment when other agents are not effective or not tolerated. Its mechanism of action is to inhibit the formation of mycobacterial cell walls.[2] The goal is to maintain the serum concentrations of drug above the minimum inhibitory concentration (MIC) of the mycobacteria for most or the entire dosing interval. Dosing is initially started at 250 mg/d and gradually increased over several days to 1000 mg/d, in 3 or 4 divided doses. Administration with food does not change the pharmacokinetic properties of ethionamide.[3]

Ethionamide is commercially available as 250-mg tablets, and the recommended dose is 250 mg each morning and 500 mg each evening. The original

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ethionamide formulation, a sugar-coated tablet,* was reformulated in 2005 to a film-coated tablet† to provide a more stable, convenient dosage formulation to support patient acceptability. The inactive ingredients in the film-coated formulation include croscarmellose sodium, FD&C Yellow #6, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polyvinyl alcohol, povidone, silicon dioxide, talc, and titanium dioxide.

The aim of the present study was to compare the bioavailability of the 2 oral formulations (film- and sugar-coated tablets) in healthy volunteers. The observed concentrations and pharmacokinetic properties of ethionamide were to have been summarized and evaluated using bioequivalence criteria.

SUBJECTS AND METHODS

Inclusion Criteria

Healthy adults of either sex and aged 18 years or older were recruited to participate in the study. All had to be within 20% of ideal body weight. Sexually active women of childbearing potential had to have been prepared to use a nonhormonal, barrier method of birth control for at least 2 weeks before and throughout the study and for 30 days after the completion of the study. Subjects were eligible for inclusion after successful completion of a personal interview to obtain the medical history, complete physical examination, and diagnostic testing including ECG, chest radiography, complete blood count, metabolic and hepatic testing, urinalysis, pregnancy testing (for female volunteers), and serologic testing for hepatitis B and HIV antibodies. Before inclusion, all eligible subjects provided written informed consent to participate.

Study Design and Drug Administration

The study was conducted in accordance with the principles of the Declaration of Helsinki and its amendments[4] and the International Conference on Harmonisation Guideline for Good Clinical Practice.[5] The study protocol and the informed-consent form were reviewed and approved by the Novum Independent Institutional Review Board, Pittsburgh, Pennsylvania.

*Trademark: Trecator SC (Pfizer Inc, New York, New York).
†Trademark: Trecator® (Pfizer Inc, New York, New York).

Ethionamide 250-mg film-coated tablets were the test treatment, and ethionamide 250-mg sugar-coated tablets were the reference treatment. Each volunteer received a single dose of each formulation in a randomized, crossover fashion, in the fasted state. A dosing randomization schedule was generated by the investigator before the start of the study.

Subjects arrived at the clinical study unit on the evening before dose administration. Vital signs were assessed before dosing. After a fast of $\geq$10 hours, the study drug was administered with 250 mL of room-temperature water. Standardized meals were provided at 4, 9, and 13 hours after dose administration; water was permitted as desired throughout. No caffeine, alcohol, or grapefruit juice was permitted throughout the study period. Use of tobacco was not permitted from 1 hour before dosing until 4 hours after dosing, nor within 30 minutes before the assessment of vital signs. Blood samples for the assessment of plasma ethionamide concentrations were collected before dose administration and at 0.5, 1, 1.5, 1.75, 2, 2.25, 2.5, 3, 4, 5, 6, 8, 10, 12, 16, and 24 hours after dosing. Blood samples were collected into 7-mL EDTA tubes (Vacutainer, Becton, Dickinson, and Company, Franklin Lakes, New Jersey). After collection, samples were kept chilled in an ice water bath. Within 60 minutes of collection, they were centrifuged at 4°C at 2500 rpm for 15 minutes. The resulting plasma was separated into 2 aliquots in polypropylene transfer tubes and stored at –20°C until shipment to the analytical laboratory. After the collection of the last sample and assessment of well-being, the subjects were discharged from the unit. After a washout period of at least 7 days, they were readmitted to the clinical study unit, with the alternate treatment administered and the procedures repeated.

Tolerability Assessment

Medical history and physical examination were performed during the screening visit. On check-in to the clinical unit, vital signs (temperature, respiration rate, blood pressure, and pulse) were measured. Pulse and blood pressure measurements were repeated after the collection of the 24-hour blood sample. After the alternate treatment administration during the second period, blood samples for chemistry and hematology were also collected.

Bioanalytical Methods

Bioanalytical analyses were performed at Bioassay Laboratory Inc, Houston, Texas (later acquired and