Oral Bioavailability of Rifampicin, Isoniazid, Ethambutol, and Pyrazinamide in a 4-Drug Fixed-Dose Combination Compared With the Separate Formulations in Healthy Chinese Male Volunteers

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ABSTRACT

Background: Fixed-dose combination (FDC) formulations for the treatment of tuberculosis are now being recommended by the World Health Organization and used worldwide for reducing the risk of emerging drug resistance. China also plans that the FDC coverage will be achieved 100% in 2015 in every county in the country. However, the quality of FDCs with respect to variable bioavailability is a major issue.

Objectives: This study was conducted in healthy Chinese subjects to compare the bioavailability of rifampicin, isoniazid, ethambutol, and pyrazinamide from a 4-drug FDC formulation versus that of the separate formulations.

Methods: The study was designed as randomized, single-dose, 2-treatment, 2-period crossover trial with a washout period of 1 week. Blood samples were collected at 0 (baseline), 10, 20, and 40 minutes and at 1, 1.5, 2, 3, 4, 6, 9, 12, and 24 hours postdose. Plasma concentrations of the 4 drugs were measured by using a rapid chromatography-tandem mass spectrometry method. Pharmacokinetic parameters were calculated by using noncompartmental methods. Bioequivalence was determined if the 90% CIs of the log-transformed test/reference ratios AUC_{0-24}, $AUC_{0-\infty}$, and C_{max} were within the predetermined range of 80% to 125%. Tolerability was assessed by using clinical parameters and subject reports.

Results: A total of 18 male subjects (mean [SD] age, 36.4 [10.6] years) were enrolled and completed the study. In the case of rifampicin, the 90% CIs for the log-transformed ratios of C_{max}, AUC_{0-24}, and $AUC_{0-\infty}$ were 81.8 to 100.9, 89.5 to 100.2, and 87.1 to 98.0, respectively. For ethambutol, these values were 84.7 to 105.7, 93.5 to 105.1, and 92.1 to 105.4. For pyrazinamide, these values were 83.3 to 93.9, 95.8 to 101.4, and 97.0 to 104.1. For isoniazid, the 90% CIs for the log-transformed ratios of AUC_{0-24}, and $AUC_{0\infty}$ were 83.5 to 94.6 and 83.4 to 94.4. However, the point estimates for C_{max} (62.2–86.7) were outside the limit for bioequivalence. No adverse events were observed during the study.

Conclusions: The findings from this single-dose study in healthy Chinese male volunteers suggest that the combined formulation was bioequivalent to separate formulations of rifampicin, ethambutol, and pyrazinamide at the same dose levels. However, isoniazid was not bioequivalent based on C_{max} values. Both formulations were well tolerated. Chinese Clinical Trials registration number: ChiCTR-TTRCC-12002451. (*Clin Ther*. 2013;35:161–168)

Key words: bioavailability, bioequivalence, fixed-dose combination, pharmacokinetics, tuberculosis.

INTRODUCTION

Tuberculosis (TB) remains 1 of the greatest health problems in the world. China has the second highest TB burden globally[1] as well as a serious epidemic of drug-resistant TB. It was estimated that ~120,000 new multidrug-resistant (MDR) TB cases emerge annually in China, accounting for ~24% of the global burden of MDR-TB.[2] As determined in a recent national anti-TB

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drug resistance survey, ~25% of patients had TB that was resistant to rifampicin, isoniazid, or both. MDR-TB is linked to inadequate treatment in both the public health system and the hospital system.[3]

Currently, the standard 6-month chemotherapy regimen for the treatment of TB is highly effective. However, patient adherence is poor due to the long duration of treatment coupled with the large number of tablets to be consumed. As a result, therapeutic failure may occur with such a regimen. Fixed-dose combination (FDC) therapy is a simple approach to simplify treatment by combining all the requisite drugs into 1 formulation at a fixed proportion. A recent multicenter, randomized controlled trial investigating the efficacy and safety of a 4-drug FDC for the treatment of TB found FDCs had efficacy comparable to the drugs administered separately.[4] Another multicenter trial also found FDCs to have efficacy equivalent to single-tablet regimens and to be more acceptable to patients.[5] Using FDCs does not obviate the need for separate drugs for patients who develop drug toxicity or for those with contraindications to specific drug components.[6] Although it is difficult to identify the drug within the combination that is potentially responsible for an adverse event (AE), use of FDCs is preferred because of potential advantages associated with their administration compared with separate-drug formulations.[4,6] The inherent advantages associated with FDCs are: limited risk of emergence of drug-resistant strains, simplified treatment, reduced risk of medication errors, improved patient compliance, and simplified drug supply management.[6] For these reasons, the National Plan for Prevention and Control of Tuberculosis (2011–2015) set the target that the FDC coverage will be achieved 100% in 2015 in every county of China.[7]

However, a major concern regarding use of FDCs is the quality of these dosage forms, especially the poor bioavailability of rifampicin in FDC tablets.[8–10] Use of substandard FDCs will lead to the development of drug resistance and treatment failure. Hence, we conducted the current study to investigate the bioequivalence of rifampicin, isoniazid, ethambutol, and pyrazinamide from a 4-drug FDC versus the separate equivalent formulations in healthy Chinese subjects.

SUBJECTS AND METHODS

Study Design

The clinical trial was designed as a randomized, single-dose, 2-treatment, 2-period crossover trial with a 1-week washout period between the 2 study arms. The study was approved by the institutional medical ethical committee, and written informed consent was obtained from all volunteers before initiating the study in December 2011.

Subjects

Healthy male volunteers were screened by performing a medical history, physical examination, blood pressure, hemogram, liver function tests, hepatitis B virus test, chest radiograph, ECG, and routine urine analysis. Eligible healthy subjects had to be aged between 18 and 55 years and weigh >50 kg with no history of tobacco or alcohol abuse or heart, liver, kidney, or gastrointestinal disorders. Subjects were excluded if they had a history of allergies to related drugs; a history of metabolic diseases; and if they had taken any drugs in the 2 weeks before the study.

In this study, the sample size of 18 subjects was calculated from the results of previous studies[11,12] that have reported a 16% intraindividual variation for AUC. With posterior power analysis, the sample size had >80% power to detect a 20% difference in pharmacokinetic parameters between the 2 formulations ($\alpha = 0.05$). For this reason, we chose 18 subjects and a sampling time of 24 hours.

Procedures

The separate formulations were rifampicin (4 × 150 mg; batch no. 1102041; manufacturing date, January 2011; expiration date, December 2012), isoniazid (3 × 100 mg; batch no. 1103021; manufacturing date, March 2011; expiration date, February 2014), ethambutol (4 × 250 mg; batch no. 11032921; manufacturing date, September 2011; expiration date, February 2013), and pyrazinamide (6 × 250 mg; batch no. 1103031; manufacturing date, March 2011; expiration date, February 2014). The FDC formulation (batch no. 1104022; manufacturing date, March 2011; expiration date, February 2013) used in this study was a film-coated tablet consisting of 150 mg of rifampicin, 75 mg of isoniazid, 275 mg of ethambutol, and 400 mg of pyrazinamide. Four FDC tablets were given to each volunteer according to the administration sequence. The separate formulations were obtained from Hong Qi Pharmaceutical Co, Ltd, China, and the FDC formulations were supplied by the Chinese health system.