A Bioequivalence Comparison of Two Formulations of Rifampicin (300- vs 150-mg Capsules): An Open-Label, Randomized, Two-Treatment, Two-Way Crossover Study in Healthy Volunteers

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ABSTRACT

Background: Rifampicin is a semisynthetic antibiotic derivative of rifamycin used worldwide for the treatment of various forms of tuberculosis.

Objective: The objective of this study was to compare, under fasting conditions in healthy volunteers, the rate and extent of absorption of a generic rifampicin capsule in oral dosage form versus the proprietary equivalent formulation for the purpose of registration approval of the test formulation.

Methods: This was an open-label, randomized, 2-treatment, 2-way crossover study with an 8-week washout period between the 2 study arms. Healthy volunteers received a 300-mg capsule of the test formulation (Idaman Pharma Manufacturing Sdn. Bhd.) or two 150-mg capsules of the reference formulation. Blood samples were collected predose and at 45 minutes and 1.25, 1.5, 2, 2.25, 2.5, 3, 3.5, 4, 6, 8, 10, 12, and 24 hours postdose. Plasma concentrations of rifampicin and its metabolite, 25-desacetyl rifampicin, were analyzed using a validated HPLC method. The formulations were considered bioequivalent if the 90% CIs for Cmax and AUC0–∞ with the test formulation/reference formulation ratio for the logarithmic transformations of both Cmax and AUC0–∞ were within the bioequivalence limit of 80% to 125% (80.9–109.7 and 80.7–103.2, respectively). No adverse events were reported during the study.

Results: Fourteen healthy subjects (10 males, 4 females) with a mean age of 22.6 years (range, 20–28 years) and a mean body mass index of 22.2 kg/m² (range, 18.3–29.9 kg/m²) were enrolled in the study; all 14 completed the trial as outlined in the protocol. The mean values for Cmax, Tmax, AUC0–24, and AUC0–∞ were within the bioequivalence range (80.9–109.7 for Cmax and 80.0–104.7 for AUC0–24), respectively; for the reference formulation, the values were 7.65 µg/mL, 1.71 hours, 38.92 µg/mL · h, and 42.24 µg/mL · h. However, the 90% CI for Cmax (78.4–102.2) was outside this limit but still within the acceptance limit for Cmax when adhering to the bioequivalence range of 75% to 133%. No adverse events were reported during the study.

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Conclusions: This study found that the 300-mg test capsule and the 150-mg reference capsules of rifampicin met the regulatory criteria for assuming bioequivalence in these fasting healthy volunteers. Both formulations appeared to be well tolerated in the population studied. (Clin Ther. 2010;32:XXX–XXX) © 2010 Excerpta Medica Inc.

Key words: rifampicin, bioequivalence, pharmacokinetics, tuberculosis, HPLC.

INTRODUCTION

Rifampicin is a semisynthetic antibiotic derivative of rifamycin used worldwide for the treatment of various forms of tuberculosis.1 It is often combined with other agents, such as isoniazid or pyrazinamide, for a more effective treatment of tuberculosis and to avoid the development of drug-resistant bacteria.2 It is readily absorbed from the gastrointestinal tract, but absorption is reduced by ~36% when the drug is ingested with food.3 Rifampicin is widely distributed throughout the body. It is present in effective concentrations in many organs and body fluids, including cerebrospinal fluid. Rifampicin is ~80% protein bound.4 Its t½ varies from 1.5 to 5 hours and is increased in the presence of hepatic dysfunction.1 The mean biological t½ of rifampin has been reported to be 2.5 hours after a 600-mg oral dose.5 The absorbed dose of rifampicin undergoes acetylation in the liver. The metabolic derivative, desacetyl rifampicin, is microbiologically active and more polar than the parent compound. Rifampicin and its metabolite are excreted in the bile and urine. The most frequently reported adverse reactions to rifampicin are rash (0.8%), fever (0.5%), and nausea and vomiting (1.5%).1

Because one objective of the Ministry of Health Malaysia is to ensure the quality, efficacy, and safety of all marketed pharmaceutical products, the ministry decided in 1999 to revise the registration of generic products so that bioequivalence studies would be required for certain categories of oral immediate-release products.6 The Malaysian Guideline for the Conduct of Bioavailability and Bioequivalence Studies6 was published by the ministry to provide instruction to local researchers in conducting bioequivalence studies in accordance with established international standards, such as those published by the US Food and Drug Administration (FDA)7 and the European Medicines Agency (EMEA).8

The objective of the present study was to compare, under fasting conditions in healthy volunteers, the rate and extent of absorption of a generic rifampicin capsule in oral dosage form versus the proprietary equivalent formulation for the purpose of registration approval of the test formulation.

SUBJECTS AND METHODS

Study Design

This was an open-label, randomized, 2-way crossover study (2 treatments, 2 periods, and 2 sequences) with an 8-week washout period between the 2 study arms. The first period of the study was conducted in November 2007 and the second in January 2008. A longer washout period in this study (compared with the minimum requirement of ≥5 half-lives usually required for drug elimination6) was mainly due to unavailability of the clinical study ward and the fact that some of the volunteers were not available due to unavoidable circumstances from week 2 until week 7. Bioequivalence studies need to be conducted in a clinical study ward for proper monitoring of the subject. The same ward was also used for medical students’ examination and this caused further delays in completing the study.

Ethical approval was obtained from the medical ethics committee of the University Malaya Medical Centre (Kuala Lumpur, Malaysia). The study was conducted in compliance with the principles of the Declaration of Helsinki,9 the Malaysian Guideline for the Conduct of Bioavailability and Bioequivalence Studies,6 and the Malaysian Guidelines for Good Clinical Practice.10 Written informed consent was obtained from all volunteers after presentation of verbal and written explanations of the study and before initiation of any screening procedures.

Volunteers were randomized to receive 1 of the 2 study formulations according to a computer-generated randomization scheme developed by a statistician. Each volunteer was assigned a subject number; the treatment sequence was randomized, and all subjects received the test and reference formulations. The test formulation* comprised 1 capsule containing 300 mg of rifampicin (batch no. 27E1546; manufacturing date, May 2007; expiration date, May 2010). The reference formulation† comprised 2 commercially available capsules each

†Trademark: Rimactane® (Novartis South Africa [Pty.] Ltd., Kempton Park, South Africa).
Subjects

Healthy volunteers were recruited (through advertisements posted around the medical center) and assessed for inclusion in the study. A medical history was taken, including the recording of any illnesses; allergies; consumption of tobacco, alcohol, and drugs of abuse; and current use of other medically active substances. After a physical examination (to exclude any abnormality of the cardiovascular, respiratory, abdominal, or central nervous system), blood pressure and pulse rate were measured and a general examination (to rule out anemia, cyanosis, clubbing, jaundice, and lymphadenopathy) of the subject was conducted to exclude any illness or abnormality. Resting blood pressure was recorded using a sphygmomanometer while the subject was in a sitting position. Blood samples (10 mL) were collected for full blood count, urea and electrolytes, liver function tests, renal function tests, and random blood glucose. Serologic tests were conducted for the presence of hepatitis B surface antigen and HIV antibodies. Blood analysis for these parameters was performed by Pantai Premier Pathology (Pantai Medical Centre, Kuala Lumpur, Malaysia). The accuracy and reliability of their results were ensured through their accreditation by the International Organization for Standardization (standard no. 15189 and 9001). Urine samples were also collected for urine formed elements with microscopic examination analysis, and urinary pregnancy tests were conducted in all female subjects. Subjects were admitted to the study after review of pathology reports, medical history, and if they met all the study inclusion and exclusion criteria. Blood samples were drawn from each subject at study end for assessment of all laboratory parameters as mentioned here, except for the HIV antibodies and hepatitis B surface antigen, which were not tested again.

Inclusion and Exclusion Criteria

Eligible subjects were healthy volunteers between the ages of 18 and 55 years, who had passed all the screening parameters and had a body mass index (BMI) between 18 and 30 kg/m². They had to be able to communicate effectively with study personnel, be literate, and able to give consent. Female volunteers of childbearing potential had to be practicing an acceptable method of birth control, as (eg, condoms, foams, jellies, diaphragm, intrauterine device, abstinence) judged by the investigator, for the duration of the study. Women who were breastfeeding were ineligible.

Subjects were excluded if they had a history of allergic responses to rifampicin or other related drugs; a history of drug dependence or a recent (ie, within 1 month) history of alcoholism or moderate (ie, ≤2 drinks/d) alcohol use; significant diseases or clinically significant abnormal findings during screening, medical history, physical examination, laboratory evaluations, ECG, and radiographic assessments; any disease or condition that might compromise the hematopoietic, gastrointestinal, renal, hepatic, cardiovascular, respiratory, central nervous, or other body system; diabetes mellitus or psychosis; a history or presence of asthma (including aspirin-induced asthma) or nasal polyp; a positive screening for hepatitis; a positive test result for HIV antibody or syphilis (rapid plasma reagin/venereal disease research laboratory tests); or a history of difficulty with donating blood (based on subject’s experience in any prior procedures) or difficulty with accessibility of veins. Also excluded were smokers who smoked ≥10 cigarettes per day or those who could not refrain from smoking during the study period. Also excluded were the following: anyone who was receiving an investigational product or who had participated in a drug research study within 90 days before the first dose of study medication administration (elimination t₁/₂ of the study drug should be considered for inclusion of subject in the trial, if blood loss was ≤200 mL); subjects who had donated a minimum of 350 mL of blood within 90 days before receiving the first dose of study medication (if blood loss was ≤200 mL, subject could be enrolled in the trial if 60 days had passed since blood donation); or anyone adhering to an unusual diet (eg, low sodium), for whatever reason, for 4 weeks before receiving the study medication and throughout the subject’s participation in the study.

Admission and Procedures

The subjects were admitted to the Clinical Examination Ward of the University of Malaya Medical Centre between 7:30 and 8:30 pm the day before study drug administration. No other medications or outside foods were permitted. The nature and the risks of the study were again explained by study personnel, and subjects then signed informed-consent forms for participation in the study. Blood pressure and pulse rate were measured after subjects had rested for 10 minutes; this was
followed by a physical examination conducted by a medical physician (R.C.B.). Subjects ate a standardized meal between 8:30 and 10:00 PM. A standardized meal consisted of typical Malaysian food (boiled rice ±400 kcal) with a meat dish ±300 kcal and a vegetable dish ±40 kcal). No foods were allowed after 10:00 PM.

Starting from 7:00 AM of the dosing day (day 1), a 20-gauge cannula was inserted into a large antecubital vein of each subject, and 5 mL of blood was drawn into EDTA tubes for baseline sampling. The tubes were then centrifuged at 5000 rpm for 10 minutes. The plasma was carefully pipetted into cryogenic vials in duplicate and stored at –80°C. Resting blood pressure, radial pulse, and oral temperature were measured for tolerability assessments. Starting from 8:00 AM, subjects (in a seated position) received the study drug according to their randomization schedule, taken with 240 mL of water at ambient temperature. Drug administration was followed by a mouth check to assess compliance with dosing. After drug administration, subjects were allowed to engage in nonstrenuous activities such as watching television or reading but had to maintain an upright position for ≥2 hours. Subsequent blood samples were collected at 45 minutes and 1.25, 1.5, 2, 2.25, 2.5, 3, 3.5, 4, 6, 8, 10, 12, and 24 hours postdose. This sampling protocol was determined based on T_max after oral administration of rifampicin, which ranges from 1.5 to 2.5 hours, and a t1/2 of 1.5 to 5 hours. Blood pressure and radial pulse were checked 2, 6, and 12 hours postdose. Standardized meals (lunch, tea break, and dinner) were served 4, 8, and 11 hours after dosing.

A medical physician who was blinded to the study treatment was present at all times throughout the study to monitor the subjects and watch for possible adverse effects of the medication. Subjects were questioned at the time of blood pressure examination regarding their overall well-being and any feelings of discomfort. All events reported by the subjects (serious or mild) were recorded on adverse-event forms. Blood samples were again drawn and analyzed (full blood count and clinical chemistry) at the end of the study to monitor any changes.

**Analysis of Plasma Samples**

All the plasma samples obtained from this study were analyzed and stored at Info Kinetics Laboratory (Penang, Malaysia). Using courier services, the samples were transferred packed with dry ice to maintain the integrity of the frozen plasma. The plasma samples were stored at –80°C until further analysis.

Concentrations of rifampicin and its metabolite, 25-desacetyl rifampicin, were measured in plasma using an HPLC method previously validated to demonstrate adequate sensitivity, specificity, linearity, accuracy, and precision. All the validation parameters tested were to fulfill the criteria as outlined in the FDA’s guidelines for bioanalytical analysis. A Zorbax Eclipse XDB-C_8 column (internal diameter, 150 × 4.6 mm; particle size, 5 µm) from Agilent Technologies (Santa Clara, California) was used, with the column compartment set at 30°C. Rifampicin, 25-desacetyl rifampicin, and sulindac (internal standard) were identified by comparing the peaks given at λ = 333 nm in human plasma with the standard solution at a similar retention time. The mobile phase used was 40% acetonitrile and 60% triethylamine, and the pH was adjusted to 3.0 with orthophosphoric acid. Plasma extraction was achieved using liquid–liquid extraction.

During routine analysis, the mean retention times for rifampicin and 25-desacetyl rifampicin were 5.60 and 3.1 minutes, respectively; the mean retention time for sulindac was 4.8 minutes. Mean recovery percentages of rifampicin and 25-desacetyl rifampicin were 98.5% and 89.9%; the mean recovery percentage for sulindac was 91.9%. Calibration curves in spiked plasma were linear (R^2 >0.999) from 100 to 10,000 ng/mL. The quality-control concentrations used during validation were 300, 4000, and 7000 ng/mL for low, medium, and high concentrations, respectively. Intraday %CVs for quality-control concentrations of rifampicin were 4.4%, 6.5%, 2.9%, and 3.1%, respectively, and interday values were 6.0%, 3.5%, 1.8%, and 1.2% for limit of quantitation (LOQ) and low, medium, and high concentrations. Intraday %CVs for quality-control concentrations of 25-desacetyl rifampicin were 2.0%, 5.3%, 3.0%, and 3.1%; interday %CVs were 10.0%, 4.9%, 1.4%, and 2.7%, for LOQ and low, medium, and high concentrations. The mean percent inaccuracy values of rifampicin for LOQ and low, medium, and high concentrations were 5.0%, 5.2%, 2.0%, and 2.8% for intraday values and 4.4%, 3.0%, 1.4%, and 1.0% for interday values. The mean percent inaccuracy values of 25-desacetyl rifampicin for LOQ and low, medium, and high concentrations were 2.7%, 4.2%, 3.7%, and 3.6% for intraday values and 8.1%, 3.2%, 3.2%, and 2.5% for interday values.

During the samples assay, the low, medium, and high quality-control samples were injected along with the
sample run. In each batch run, 3 samples were analyzed. All the quality-control results were <15% inaccurate compared with the nominal concentrations. The LOQ was 100 ng/mL, which was also the lowest concentration of rifampicin and 25-desacetyl rifampicin that can be quantitated with an intraday variability of 6.3% for rifampicin and 2.5% for 25-desacetyl rifampicin. Furthermore, the inaccuracy and imprecision at this level were <20%. The peak at this concentration is >5 times higher than the noise at the retention time of rifampicin and 25-desacetyl rifampicin. The peak at this concentration is 3 times higher than the noise at the retention time of rifampicin and 25-desacetyl rifampicin. The response of interfering peaks at the retention time of rifampicin, 25-desacetyl rifampicin, and sulindac were 0%, 0%, and 3.3%, respectively.

Rifampicin and 25-desacetyl rifampicin were found to be stable for at least 9 hours in the autosampler. The sample was stable for 3 freeze-thaw cycles. For long-term stability, the frozen sample (at less than −70°C) was stable for at least 2 weeks, with a maximum inaccuracy of −1.8% and −1.9% for rifampicin and −5.0% and 3.5% for 25-desacetyl rifampicin, respectively, for low and high concentrations. Short-term stability was conducted for up to 4 hours and the %CVs for rifampicin at low and high concentrations were 4.8% and 1.5%, respectively, and the %CVs for 25-desacetyl rifampicin at low and high concentrations were 4.9% and 1.3%, which indicates that the short-term stability for rifampicin and 25-desacetyl rifampicin was 4 hours.

Pharmacokinetic Analysis

All pharmacokinetic parameters were determined using noncompartmental analysis. Pharmacokinetic analysis was performed for the concentration of rifampicin and its metabolite, 25-desacetyl rifampicin, in plasma before and up to 24 hours after dosing. All the parameters were determined from the actual plasma concentration of rifampicin and 25-desacetyl rifampicin. C\textsubscript{max} and T\textsubscript{max} were obtained directly from the individual plasma concentration–time data. AUC\textsubscript{0–24} was determined using the linear trapezoidal rule. AUC\textsubscript{t–∞} was calculated as the sum of AUC\textsubscript{0–24} and AUC\textsubscript{t–∞}, and AUC\textsubscript{t–∞} values were obtained by extrapolating the last measurable plasma concentration to the time axis using the following equation:

\[ AUC_{t–∞} = \frac{C_1}{k_e} \]

where \( k_e \) is the elimination rate constant that was obtained as the slope of linear regression of ln-transformed plasma concentration–time curve in the elimination phase. The elimination t\textsubscript{1/2} was calculated using the following equation:

\[ t_{1/2} = \frac{\ln 2}{k_e} \]

Statistical Analysis

The sample size for this study was estimated using a power calculation conducted on the basis of data obtained from earlier bioequivalence studies. The significance of the bioavailability parameters C\textsubscript{max} and AUC\textsubscript{0–∞} obtained after administration of the test and reference formulations was analyzed, with and without logarithmic (log\textsubscript{10}) transformation, using ANOVA for crossover studies that accounted for variations due to subjects, formulations, and periods. Analyses were conducted using WinNonlin version 5.0.1 (Pharsight Corporation, Mountain View, California).

Bioequivalence testing was based on the 90% CI for the ratio of the population means (test formulation/reference formulation) for C\textsubscript{max} and AUC\textsubscript{0–∞}. The formulations were considered bioequivalent if the 90% CIs for AUC and C\textsubscript{max} were within the predetermined bioequivalence range of 80% to 125%. The European Commission and the EMEA (EC-EMEA) and the National Pharmaceutical Control Bureau of Malaysia also set bioequivalence limits (75%–133%) for C\textsubscript{max}. Using CIs rather than hypothesis testing is in accordance with internationally accepted guidelines for the assessment of bioequivalence. This method is considered equivalent to the corresponding Schuirmann’s two 1-sided t tests, with the null hypothesis of bioinequivalence set at the 5% significance level.

Assessment of the difference in T\textsubscript{max} values between the test and reference formulations was performed using the nonparametric Wilcoxon signed rank test. Statistical analysis was conducted using SAS version 9.1.3 (SAS Institute Inc., Cary, North Carolina).
RESULTS

Demographic Characteristics

Fourteen healthy subjects (10 males, 4 females), with a mean age of 22.6 years (range, 20–28 years) and a mean BMI of 22.2 kg/m\(^2\) (range, 18.3–29.9 kg/m\(^2\)), were enrolled in this study (Table I). All 14 subjects completed the trial as outlined in the protocol.

Pharmacokinetic Analysis

Rifampicin was measurable in plasma at the first sampling time (45 minutes) in all 14 subjects after administration of the test and reference formulations. The mean plasma rifampicin and 25-desacetyl rifampicin concentrations versus time for the 2 formulations are depicted in Figures 1 and 2. Tables II and III display the pharmacokinetic parameters obtained for the reference and test formulations for rifampicin and 25-desacetyl rifampicin, respectively. The mean values for \(C_{\text{max}}, T_{\text{max}}, \text{AUC}_{0-24}, \text{and AUC}_{0-\infty}\) with the test formulation of rifampicin were 7.20 µg/mL, 1.32 hours, 37.12 µg/mL · h, and 39.69 µg/mL · h, respectively; for the reference formulation, the values were 7.65 µg/mL, 1.71 hours, 38.92 µg/mL · h, and 42.24 µg/mL · h. For 25-desacetyl rifampicin, the mean values for \(C_{\text{max}}, T_{\text{max}}, \text{AUC}_{0-24}, \text{and AUC}_{0-\infty}\) with the test formulation were 0.63 µg/mL, 3.45 hours, 4.92 µg/mL · h, and 6.27 µg/mL · h, respectively.

<table>
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<th>BMI, kg/m(^2)</th>
<th>Age, y</th>
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<td>153.0</td>
<td>50.0</td>
<td>18.3</td>
<td>20.0</td>
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Table I. Subject demographic characteristics.

BMI = body mass index; F = female; M = male.

Figure 1. Mean (SD) plasma rifampicin concentrations versus time after a single (double) oral dose of 300-mg rifampicin. Arrows indicate the meals given at 4, 8, 11, and 24 hours postdose. Test = 1 Siticox capsule (300 mg) manufactured by Idaman Pharma Manufacturing Sdn. Bhd., Sungai Petani Kedah, Malaysia; reference = 2 Rimactane® capsules (150 mg each) manufactured by Novartis South Africa (Pty.) Ltd., Kempton Park, South Africa.
mL · h; for the reference formulation, the values were 0.70 µg/mL, 3.27 hours, 5.23 µg/mL · h, and 6.84 µg/mL · h.

Table IV shows the 90% CIs and the mean ratios of the test-to-reference formulations for log10 $C_{\text{max}}$, AUC0–24, and AUC0–\infty. For rifampicin, the 90% CI for the test formulation/reference formulation ratio for both log10 $C_{\text{max}}$ and log10 AUC0–\infty were within the bioequivalence limit of 80% to 125% (90% CI, 80.9–109.7 and 80.7–103.2, respectively). The differences in $T_{\text{max}}$ values for the test and reference formulations did not reach the level of statistical significance. Therefore, the test

Table II. Mean (SD) pharmacokinetic parameters for rifampicin after administration of the 2 formulations to 14 subjects in the present study compared with data from an earlier study.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Present Study</th>
<th>Agrawal et al\textsuperscript{20}</th>
</tr>
</thead>
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<tr>
<td></td>
<td>Test* Formulation</td>
<td>Reference\textsuperscript{†} Formulation</td>
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<tr>
<td>$C_{\text{max}}$, µg/mL</td>
<td>7.20 (2.19)</td>
<td>7.65 (2.51)</td>
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<td>$T_{\text{max}}$, h</td>
<td>1.32 (0.40)</td>
<td>1.71 (0.61)</td>
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<td>AUC0–24, µg/mL · h</td>
<td>37.12 (15.52)</td>
<td>38.92 (13.50)</td>
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<td>AUC0–\infty, µg/mL · h</td>
<td>39.69 (15.81)</td>
<td>42.24 (13.89)</td>
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<td>$k_e$, h\textsuperscript{-1}</td>
<td>0.22 (0.04)</td>
<td>0.22 (0.04)</td>
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<tr>
<td>$t_{1/2}$, h</td>
<td>3.24 (0.59)</td>
<td>3.28 (0.59)</td>
</tr>
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</table>

$k_e$ = elimination rate constant.

*Siticox capsule (300 mg) manufactured by Idaman Pharma Manufacturing Sdn. Bhd., Sungai Petani Kedah, Malaysia.

\textsuperscript{†}Trademark: Rimactane\textsuperscript{®} capsules (150 mg each) manufactured by Novartis South Africa (Pty.) Ltd., Kempton Park, South Africa.
The differences in Tmax values for the test and reference formulations did not reach the level of statistical significance. Therefore, applying the criteria used in both the guidelines as noted here, the test and reference formulations met the regulatory definitions of bioequivalence for 25-desacetyl rifampicin.

Based on analysis using the Wilcoxon signed rank test, there were no statistically significant differences in Tmax for the reference and test formulations.

Table III. Mean (SD) pharmacokinetic parameters for 25-desacetyl rifampicin after administration of the 2 formulations to 14 subjects in the present study compared with data from an earlier study.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Present Study</th>
<th>Agrawal et al²⁰</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Test* Formulation</td>
<td>Reference† Formulation</td>
</tr>
<tr>
<td>Cₘₐₓ, µg/mL</td>
<td>0.63 (0.27)</td>
<td>0.70 (0.25)</td>
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<tr>
<td>Tₘₐₓ, h</td>
<td>3.45 (1.26)</td>
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<td>AUC₀–₂₄, µg/mL · h</td>
<td>4.92 (2.16)</td>
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<td>AUC₀–∞, µg/mL · h</td>
<td>6.27 (2.85)</td>
<td>6.84 (2.74)</td>
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<tr>
<td>kₑ, h⁻¹</td>
<td>0.18 (0.05)</td>
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<td>t₁/₂, h</td>
<td>4.28 (1.31)</td>
<td>4.23 (1.89)</td>
</tr>
</tbody>
</table>

kₑ = elimination rate constant.

* Siticox capsule (300 mg) manufactured by Idaman Pharma Manufacturing Sdn. Bhd., Sungai Petani Kedah, Malaysia.
† Trademark: Rimactane® capsules (150 mg each) manufactured by Novartis South Africa (Pty.) Ltd., Kempton Park, South Africa.

Table IV. 90% CIs for the mean ratio of the test* to reference † formulations for Cₘₐₓ, AUC₀–₂₄, and AUC₀–∞ for rifampicin and 25-desacetyl rifampicin.

<table>
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<th>Parameter</th>
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<tr>
<td>Log₁₀ Cₘₐₓ</td>
<td>80.9–109.7</td>
<td>94.2</td>
</tr>
<tr>
<td>Log₁₀ AUC₀–₂₄</td>
<td>85.1–105.6</td>
<td>95.4</td>
</tr>
<tr>
<td>Log₁₀ AUC₀–∞</td>
<td>80.7–103.2</td>
<td>91.2</td>
</tr>
</tbody>
</table>

Log₁₀ = logarithmic transformation.

* Siticox capsule (300 mg) manufactured by Idaman Pharma Manufacturing Sdn. Bhd., Sungai Petani Kedah, Malaysia.
† Trademark: Rimactane® capsules (150 mg each) manufactured by Novartis South Africa (Pty.) Ltd., Kempton Park, South Africa.
Tolerability

No adverse events were reported during the study. All results of laboratory blood tests for all subjects, as assessed at the end of the study, were within clinically acceptable ranges. In addition, mean systolic/diastolic blood pressure was 116/72 mm Hg, and all other vital signs recorded during the study for all volunteers were within the normal range for healthy subjects.

DISCUSSION

All 14 volunteers enrolled completed the study; the number of subjects had sufficient statistical power for ANOVA for both log10 AUC\(_{0\rightarrow\infty}\) and log10 C\(_{\text{max}}\). In this bioequivalence study, the single 300-mg capsule of rifampicin was assessed to compare its bioavailability with the two 150-mg capsules of the reference formulation. All the pharmacokinetic parameters (T\(_{\text{max}}\), t\(_{1/2}\), and k\(_{e}\)) obtained from this study are in agreement with results obtained by Agrawal et al,\(^{20}\) except for C\(_{\text{max}}\) and AUC, which are summarized in Tables II and III. Agrawal et al conducted a bioequivalence study of 4 drugs (rifampicin, isoniazide, pyrazinamide, and ethambutol), comparing the fixed-dose combination and separate formulations at the same dose levels. According to their findings, both formulations appeared to be bioequivalent. Although the dose given was slightly higher in the study by Agrawal et al compared with the dose in the present study, C\(_{\text{max}}\) and AUC values were lower for rifampicin and higher for 25-desacetyl rifampicin in that study than in our study. These differences are probably due to the different metabolism rate in the 2 populations studied. Also, the higher absorption rate of capsules (present study) compared with tablets (Agrawal et al) and the variability in the absorption properties between the different populations studied might contribute to these differences.

Both formulations appeared to be well tolerated in this healthy, fasting volunteers, as no adverse events were recorded.

The present study had certain limitations that should be considered. This was an open-label study, and it may therefore not fully address the tolerability profiles of the formulations. Other limitations included a small sample size and the fact that it was conducted in healthy subjects. These limit the conclusions that can be drawn regarding the pharmacokinetic behavior of rifampicin. Further studies in a larger number of subjects or a patient population might be useful to show those differences observed in the rate and extent of absorption, including metabolism of rifampicin.

CONCLUSIONS

This bioequivalence study found that the 300-mg test capsule and the 150-mg reference capsules of rifampicin met the regulatory criteria for assuming bioequivalence in these fasting healthy volunteers. Both formulations appeared to be well tolerated in the population studied.

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REFERENCES


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