Phase I Study of Single-Dose BMY-28100, a New Oral Cephalosporin

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The objective of this Phase I study was to evaluate the safety, tolerance, and pharmacokinetics of BMY-28100 in 250, 500, and 1,000 mg doses respectively, and the area under the curve increased in a dose-proportional manner. The elimination half-life and renal clearance averages were 1.2 h and 200 ml/min, respectively. The values for renal clearance suggest that BMY-28100 is excreted by glomerular filtration and tubular secretion. Mean concentrations of the drug in urine were highest during the first 4 h after the doses and ranged from 175 to 658 µg/ml following the 250- and 1,000-mg doses, respectively. The mean urinary recovery ranged from 57 to 70% of the dose. The results from this Phase I study indicate that BMY-28100 is well tolerated and exhibits linear pharmacokinetics.

BMY-28100, (6R,7R)-7-[(R)-2-amino-2-(p-hydroxyphenyl)acetamido]-8-oxo-3-[(Z)-1-propenyl]-5-thia-1-azabicyclo(4.2.0)-oct-2-ene-2-carboxylic acid, is a recently developed semisynthetic cephalosporin antibiotic. It is structurally related to cefadroxil, cephalexin, and cefaclor. It has a p-hydroxyphenylglycyl substituent at position 7 and a propanyl side chain at position 3. Its antimicrobial spectrum includes important gram-positive and gram-negative organisms usually associated with infections of the urinary and respiratory tracts (1, 3, 6, 11). The antimicrobial spectrum of BMY-28100 is superior to those of cephalexin and cefadroxil and similar to that of cefaclor (1, 3). Animal studies suggest that BMY-28100 may have some pharmacokinetic advantage over cefaclor (6).

The purpose of this Phase I study was to evaluate the safety, tolerance, and pharmacokinetics of BMY-28100 following the administration of single 250-, 500-, and 1,000-mg oral doses to healthy volunteers.

MATERIALS AND METHODS

Antibiotic. BMY-28100 was prepared and packaged by the Pharmaceutical Product Development Department, Bristol-Myers Co., Marne la Vallee, France. Each dose of the antibiotic was derived from powder prepared from milled bulk drug. Single doses of 250, 500, and 1,000 mg were prepared and individually packaged in standard 250-ml bottles. The drug was dissolved in 200 ml of distilled water and administered as an aqueous solution.

Subjects. A total of 36 healthy male subjects, 12 per dose, participated in the study after signing a consent form. The subjects had a mean (± standard deviation) age of 27.2 ± 5.9 years, a mean body weight of 69.9 ± 6.8 kg, and a mean height of 177 ± 7 cm. Subjects with a history of drug allergies or idiosyncrasies, drug abuse (as confirmed by urine screening), or alcohol abuse were excluded. Subjects who used medications of any kind within 1 week of the start of the study were also excluded. Subjects were screened approximately 1 week prior to the start of the study and were admitted to the clinical site 12 h prior to drug administration. The subjects were released 24 h after receiving the dose if their physical conditions were unchanged since entry and if there were no clinically significant modifications in electrocardiogram and clinical laboratory values.

Drug administration. The subjects fasted from 10 p.m. of the day before dosing until 4 h after dosing. Upon rising on the study day, each subject emptied his bladder. Approximately 1 h prior to drug administration, the subjects drank approximately 400 ml of water. In order to ensure an adequate urine flow, the subjects drank 100 ml of water per h for the first 3 h after dosing and as desired thereafter. Twelve subjects were assigned to each of the three dose groups (250, 500, and 1,000 mg). Dose administration proceeded sequentially, with increasing doses given only after the safety and tolerance of the previous dose were determined. Each dosing solution was prepared by adding 200 ml of distilled water to each 250-ml bottle containing a single dose. The subjects drank the dosing solution from the bottle immediately after preparation. The bottle was then rinsed with 100 ml of distilled water, which the subject immediately drank.

Sample collection and processing. Blood samples (approximately 10 ml) were drawn into heparinized VACUTAINER tubes 5 to 10 min prior to drug administration (predose) and at 15, 30, and 45 min and 1, 2, 3, 4, 5, 7, 9, and 12 h after dosing. Immediately after collection, each blood sample was gently inverted a few times to mix it completely with the anticoagulant and then was placed in chipped ice. Within 1 h of collection, each blood sample was centrifuged for 15 min at 1,000 × g at 5°C to prepare plasma. At least 3.0 ml of

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plasma was transferred to a screw-cap polypropylene tube (101 by 16.5 mm) and stored at −70°C. Plasma quality control samples for BMY-28100 were prepared at concentrations of 2.0 and 20.0 μg/ml in drug-free human plasma on each dosing day. These quality control samples were stored and assayed with the study samples. Urine samples were collected from each subject for the following time intervals: just before dosing and 0 to 2, 2 to 4, 4 to 6, 6 to 8, 8 to 12, and 12 to 24 h after dosing. At the end of each urine collection period, the volumes (to the nearest milliliter) and pHs of the urine samples were recorded on the case report forms. A portion (5.0 ml) of each urine sample was transferred to a 15-ml screw-cap polypropylene tube containing 5.0 ml of 0.01 M sodium acetate (pH 3.5), mixed, and stored at −70°C. Urine quality control samples containing 50 and 1,000 μg of BMY-28100 per ml were prepared in drug-free human urine on each dosing day. The quality controls were diluted in acetate buffer exactly as described for the study samples and were stored and assayed with the study samples.

**Assays in biological fluids.** High-performance liquid chromatography was employed for the determination of BMY-28100 levels in plasma and urine. Plasma proteins were separated by ultracentrifugation, and 100 μl of the ultrafiltrate was analyzed on a C18 Nucleosil (5 μm; 250 by 4.6 mm) reversed-phase column with 0.01 M phosphoric acid and acetonitrile (92:8, vol/vol) as the mobile phase and UV detection at 280 nm. Cephalexin was used as an internal standard. The ratios of the peak area of BMY-28100 to that of cephalexin were calculated. The least-squares regression of peak area ratio on concentration of each analytical standard of BMY-28100 was determined. The plasma assay was linear in the range of 0.25 to 50 μg/ml. The quality control samples, prepared at the start of the study, were assayed during each analytical run. The accuracy and precision of the determinations of the plasma quality control samples were generally within 8% during the course of the analysis of the study samples. The coefficient of variation values for the plasma quality control samples (2.0 and 20.0 μg of BMY-28100 per ml) were 4.4 and 1.78%, respectively. Urine samples were diluted with 0.01 M acetate buffer, pH 3.5. The samples were chromatographed on a C18 LiChrosorb (5 μm; 125 by 4.6 mm) reversed-phase column with 0.01 M phosphoric acid and acetonitrile (90:10, vol/vol) as the mobile phase and UV detection at 280 nm. Cephalexin was used as an internal standard. The ratio of the peak area of BMY-28100 to that of cephalexin was linear in the range of 10 to 1,000 μg/ml. The urine quality control samples, prepared at the start of the study, were analyzed during each analytical run. The accuracy and precision of the determinations of the urine quality control samples were within 7% during the course of the analysis of the study samples. The coefficient of variation values for the urine quality control samples (50 and 1,000 μg of BMY-28100 per ml) were 4.0 and 2.6%, respectively.

**Pharmacokinetic analysis.** The following noncompartmental pharmacokinetic parameters were calculated by standard methods (4): maximum concentration in plasma (C_{max}), time to C_{max} (T_{max}), area under the drug concentration curve (AUC_{0-∞}), elimination half-life (t_{1/2}), renal clearance (CLR), and percentage of dose excreted in the urine (X_{u}). The AUC from time zero to time m, the portion prior to the log-linear phase, was calculated by using the linear trapezoidal rule, and the AUC from time m to the last measurable time point, n, was calculated by using the log trapezoidal rule as suggested by Riegelman and Collier (10) and was extrapolated to infinity.

**Statistical analysis.** A weighted linear regression analysis was used to determine if the AUC_{0-∞} and C_{max} were linear over the 250- to 1,000-mg dose range. Weights equivalent to the reciprocal of the variance at each dose level were applied to account for heterogeneous variance. The adequacy of each linear fit was evaluated by computing a lack-of-fit statistic (8). As a second diagnostic test for the adequacy of the linear fit, the AUC_{0-∞} and C_{max} were normalized to a 1-mg dose, and analysis of variance by the Tukey multiple comparison procedure (2) were utilized to determine if there were differences in the mean dose-normalized values among the dose levels. Analysis of variance by the Tukey multiple comparison procedure was also used to compare t_{1/2}, CLR, and X_{u} among dose levels. All hypotheses were tested at the 5% significance level.

**RESULTS**

**Safety and tolerance.** There were 17 adverse clinical experiences reported in the 36 subjects. Gastrointestinal distress and experiences related to the central nervous system were the only types of events reported. Of the adverse clinical experiences, five were classified by the investigator as not related to the study drug. The remaining 12 events included headache in three subjects and dizziness in one with the 250-mg dose, nausea in five subjects with the 500-mg dose, and dyspepsia in two subjects and headache in one with the 1,000-mg dose. The frequency of the adverse clinical experiences was not related to the dose level.

**Pharmacokinetics.** Concentrations of BMY-28100 in plasma increased rapidly, with maximum levels occurring about 1 h after drug administration. The profiles of mean concentration in plasma versus time after oral administration of 250-, 500-, and 1,000-mg oral doses of BMY-28100 are shown in Fig. 1. The pharmacokinetic parameters for BMY-28100 at each dose are summarized in Table 1. The mean C_{max} ranged from 6.2 μg/ml for the 250-mg dose to 17.7 μg/ml for the 1,000-mg dose. A significant linear trend was observed in the analysis of C_{max} versus dose, but the lack-of-fit statistic approached significance (P = 0.07), indicating a possible curvature of the

<table>
<thead>
<tr>
<th>Dose (mg)</th>
<th>C_{max} (μg/ml)</th>
<th>T_{max} (h)</th>
<th>t_{1/2} (h)</th>
<th>AUC_{0-∞} (μg · h/ml)</th>
<th>CLR (ml/min)</th>
<th>X_{u} (%)</th>
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<tbody>
<tr>
<td>250</td>
<td>6.2 ± 0.6</td>
<td>0.9 ± 0.1</td>
<td>1.1 ± 0.2</td>
<td>14.2 ± 1.6</td>
<td>207 ± 27</td>
<td>70.1 ± 8.6</td>
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<tr>
<td>500</td>
<td>9.3 ± 1.1</td>
<td>1.2 ± 0.4</td>
<td>1.2 ± 0.1</td>
<td>25.7 ± 2.9</td>
<td>212 ± 44</td>
<td>64.7 ± 12.2</td>
</tr>
<tr>
<td>1,000</td>
<td>17.7 ± 2.2</td>
<td>1.1 ± 0.3</td>
<td>1.4 ± 0.1</td>
<td>52.1 ± 6.1</td>
<td>183 ± 33</td>
<td>56.7 ± 9.9</td>
</tr>
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</table>

* Values are means ± standard deviations.
regression line. Dose-normalized $C_{\text{max}}$ values suggested a deviation from linearity for BMY-28100, with a mean value for the 250-mg dose significantly greater than those for the 500- and 1,000-mg doses ($P = 0.05$). Mean $T_{\max}$ values ranged from 0.9 h for the 250-mg dose to 1.2 h for the 1,000-mg dose. The mean $\text{AUC}_{0-\infty}$ values increased in a dose-proportional manner over the 250- to 1,000-mg range. The results of the weighted regression analysis are shown in Fig. 2. Analyses of the dose-normalized $\text{AUC}_{0-\infty}$ values indicated no significant differences among the dose levels, providing further evidence for dose proportionality.

The $t_{1/2}$ of BMY-28100 was approximately 1.2 h, and no significant differences were observed among dose levels. Cumulative urinary excretion results are plotted in Fig. 3. The mean percentage of urinary recovery for BMY-28100 slightly decreased with each dose level. The urinary recovery of the drug ranged from 70 to 57% for the 250- and 1,000-mg doses, respectively. The mean $X_{\text{e}}$ for the 250 mg-dose was significantly greater than that for the 1,000-mg dose. The $\text{CLR}$ averaged between 183 ml/min for the 1,000-mg dose and 212 ml/min for the 500-mg dose; no significant differences in mean $\text{CLR}$ values among dose levels were observed.

**DISCUSSION**

BMY-28100 was well tolerated after single oral doses up to 1,000 mg. No clinically significant side effects or adverse changes were detected in any variable examined. This is consistent with data reported for cefaclor, cephalaxin, and cefadroxil.

The data for concentration in plasma and urinary excretion suggest that BMY-28100 is well adsorbed after oral administration and is primarily excreted by the kidneys. The estimates for the pharmacokinetic parameters $t_{1/2}$, $\text{CLR}$, and dose-normalized $\text{AUC}_{0-\infty}$ were similar at each dose level. On the basis of these data, the pharmacokinetics of BMY-28100...
appear to be linear. The CLR values indicate that like cefadroxil and cephalaxin (7, 9), BMY-28100 is excreted by glomerular filtration and tubular secretion. In this respect, the pharmacokinetics of BMY-28100 are typical of other oral cephalosporins (5, 7, 9).

The in vitro antimicrobial activity of BMY-28100 is superior to those of cefadroxil and cephalaxin and similar to that of cefaclor (1, 3). Profiles of BMY-28100 levels in plasma show somewhat lower peak levels than those reported for cefaclor (5, 7). The Cmax and Tmax data indicate that the absorption of BMY-28100 is slower than that of cefaclor. Although BMY-28100 Cmax values are lower than those of cefaclor, BMY-28100 disappears from plasma at a lower rate than cefaclor. The t1/2 of BMY-28100 (1.3 h) is significantly longer than that reported for cefaclor (0.6 h). As a result, levels of BMY-28100 in plasma and urine are expected to remain above the MIC for susceptible organisms for a longer period than the cefaclor levels. In this respect, BMY-28100 offers an advantage over cefaclor.

In conclusion, BMY-28100 is well tolerated at doses up to 1,000 mg. It is well absorbed after oral administration and exhibits linear pharmacokinetics. BMY-28100 is a promising new oral cephalosporin, on the basis of its balanced pharmacokinetics and antimicrobial spectrum.

LITERATURE CITED


