Phase I Clinical Studies of S-1090: Safety and Pharmacokinetics

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S-1090, an oral cephem antibiotic, was given to healthy male volunteers in single (10 to 400 mg) and multiple (200 mg, twice a day) doses. There were no abnormalities in subjective and objective signs, or physical findings, in any subjects. The intestinal and oropharyngeal bacterial flora were not significantly affected by S-1090. These results suggest that S-1090 is a safe and well-tolerated drug. Food intake increased the absorption of S-1090, but did not affect its half-life. The plasma concentration increased with increasing doses, but at a rate less than proportional to the dose, in the single-dose studies. S-1090 was eliminated with a half-life of 2 to 3 hours after oral administration under nonfasting conditions, independent of dose. Urinary recovery rate decreased with increasing doses. The maximum plasma concentration, half-life, and area under the concentration-time curve at the dose of 100 mg in nonfasting conditions were 3.78 μg/mL, 2.77 hours, and 25.51 μg·h/mL, respectively. S-1090 may be absorbed by both unsaturable passive and saturable active transport systems. During multiple dosing, the extent of absorption decreased slightly, but steady state was achieved within several days without changes in half-life. S-1090 binds to serum protein constantly, at a very high 97%, which might cause the long half-life of this drug. The high plasma concentration and long half-life of S-1090 are favorable for clinical use.

Key words: S-1090, oral cephem antibiotic, phase I clinical studies, pharmacokinetics

INTRODUCTION

S-1090 is a nonester-type oral cephem antibiotic, with strong antibacterial activity against a wide range of both gram-positive and gram-negative bacteria.1-4 Its structure is presented in Fig. 1. After oral administration in various laboratory animals, S-1090 was well absorbed and reached a significant level in the plasma.5 The oral administration of S-1090 was effective against infections of the respiratory and urinary tract, and systemic infections, caused by representative pathogens in mice.5-8 Toxicity studies of S-1090 using various species of animals did not show any serious symptoms.

The purpose of this study was to evaluate the safety and tolerance of S-1090 and to characterize its pharmacokinetics in healthy adult volunteers after single and multiple oral administration.

SUBJECTS AND METHODS

Subjects

Thirty-six healthy Japanese male volunteers between the ages of 26 and 50 years (mean, 34.7 years), and weighing between 49 and 79 kg (mean, 65.1 kg), participated in the study. Candidate selection was based on the results of physical examinations and clinical laboratory tests (hematologic analyses, blood chemistry test, and urinalyses). Subjects were given information about the purpose and methods of this study, and the safety and efficacy of S-1090. All subjects provided informed written consent. The study was approved by a local ethics committee.

Study design

This phase I clinical trial was subdivided into 5 studies (Table 1). The initial dose was set at 10 mg, based on consideration of the nonclinical data and the proposed therapeutic dose. Study 1 was designed to evaluate only the safety and tolerance of S-1090; study 2 evaluated the effects of food; study 3 evaluated the safety, tolerance, and dose dependence of the pharmacokinetics; and study 4 determined effects of the maximum dose (100 mg). Study 5 was a multiple-dose study in which 200 mg of S-1090, or a placebo, was given to volunteers in the nonfasting condition twice a day for 8 days. This study was conducted to investigate the effects of multiple administration on the pharmacokinetics of S-1090.

The safety tests that were performed included clinical observations (subjective and objective symptoms), physical examinations (blood pressure, pulse rate, respiratory rate, body temperature, pulmonary function, and electrocardiogram), laboratory tests including hematologic analyses, blood chemistry tests (electrolytes,
Fig. 1. Chemical structure of S-1090, a new oral cephem antibiotic.

and liver and renal functions), urinalyses, and other tests (the Coombs' test and the coagulation tests). Intervals of the safety tests are listed in Table 1. The spontaneously reported information on side effects was collected in written form according to the schedule listed in Table 1.

The volunteers were not allowed to take any other drug, alcohol, or caffeine throughout the studies. These 5 studies were conducted at Sagisu Clinic (Osaka, Japan).

Table 1. Design of phase I clinical studies to evaluate the safety and tolerance of S-1090 and to characterize its pharmacokinetics in healthy adult volunteers.

<table>
<thead>
<tr>
<th>Study no.</th>
<th>Purpose: To evaluate</th>
<th>Dosage (mg)</th>
<th>No. of groups: Group size (condition)</th>
<th>Blood sampling interval*</th>
<th>Urine sampling interval*</th>
<th>Intervals* of clinical observations (A), physical examinations (B), blood chemistry tests (C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Safety and tolerance</td>
<td>10, 25, 50, 100, or 200; single dose</td>
<td>5:2 (fasting)</td>
<td>0.5, 3, 5, 12; after 1, 3, 7 days</td>
<td></td>
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</tr>
<tr>
<td>2</td>
<td>Effect of food (Crossover design with a 1-week interval)</td>
<td>100 single dose</td>
<td>2:3 (fasting/ nonfasting)</td>
<td>1-6, 8, 12, 16; after 1, 3, 7 days</td>
<td>0, 2, 4, 6, 8, 10, 12; after 1, 3, 7 days</td>
<td>A: before dosing; 1-4, 6, 8; after 1, 3, 7 days</td>
</tr>
<tr>
<td>3</td>
<td>Safety, tolerance, and dose-dependence of the pharmacokinetics (Latin square design with a 1-week interval)</td>
<td>50, 75, 100, and 200; single dose</td>
<td>4:3 (nonfasting)</td>
<td>0.5, 1-6, 8, 12; after 1, 3, 7 days</td>
<td></td>
<td>B: before dosing; after 1, 3, 7 days</td>
</tr>
<tr>
<td>4</td>
<td>Maximum dose</td>
<td>400; single dose</td>
<td>1:6 (nonfasting)</td>
<td></td>
<td></td>
<td>C: after 1, 3, 7 days</td>
</tr>
<tr>
<td>5</td>
<td>Effect of multiple dosing</td>
<td>200 or placebo; 2 x/day for 8 days</td>
<td>2:6, S-1090, 2, placebo (nonfasting)</td>
<td>0.5, 1-6, 8, 12; after 1, 3, 7, 14 days</td>
<td>0, 2, 4, 6, 8, 10, 12; after 1, 3, 7, 14 days</td>
<td>A: before dosing; 1-8 days; after 1, 3, 7, 14 days</td>
</tr>
</tbody>
</table>

*given as hours after dosing unless otherwise stated; blood and urine were sampled before the first dose in all studies; listed times are for the first and the last doses; blood was also sampled at 0, 4, and 8 hours after the fifth and ninth doses; block urine samples were collected at 2-hour intervals from 0 to 12 hours, and at 12-hour intervals from 12 to 24 hours (studies 1 through 4; first and 15th doses of study 5). During drug administration, block urine samples were collected at 12-hour intervals. Some physical examinations such as electrocardiogram were performed less frequently than this schedule.

Sample procedures

The sampling intervals for blood and urine are given in Table 1. For blood sampling, 4-mL samples were collected from each subject, and immediately centrifuged with cooling to obtain the plasma. The plasma was immediately frozen and stored at below −70°C until assay. Blood samples were also collected at 4 and 8 hours after the first and last dose in the multiple-dose study for determination of protein binding. The serum samples obtained from the blood by centrifugation were cooled with ice water and subjected to protein binding determination within 24 hours. For urine sampling, 4-mL aliquots were drawn from each well-mixed sample after volume measurement. Aliquots were stored frozen at below −70°C until assay.

Feces and pharyngeal secretions in study 5 were sampled as follows. Feces: before the first dose; third and fifth days; 1, 7, and 14 days after the last dose. Pharyngeal secretions: first, third, fifth, and seventh days; 1, and 7 days after the last dose.

Table 1. Design of phase I clinical studies to evaluate the safety and tolerance of S-1090 and to characterize its pharmacokinetics in healthy adult volunteers.