Pharmacokinetics of an Everninomicin (SCH 27899) in Mice, Rats, Rabbits, and Cynomolgus Monkeys following Intravenous Administration

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The pharmacokinetics of SCH 27899, a novel oligosaccharide compound of the everninomicin class with excellent activity against gram-positive strains, was studied with mice, rats, rabbits, and cynomolgus monkeys following intravenous administration as SCH 27899-N-methylglucamine-hydroxypropyl β-cyclodextrin. Concentrations of SCH 27899 in mouse serum, rat plasma, and rabbit serum were determined by a high-pressure liquid chromatography method on a poly(styrene-divinyl benzene) column, and those in monkey plasma were determined by a paired-ion chromatographic method. Plasma and serum concentrations of SCH 27899 exhibited a biexponential decline in all species following intravenous administration. The half-lives at β phase were 3.0 to 7.9 h in mice, rats, and rabbits and 24 h in cynomolgus monkeys. There was a linear relationship between the area under the curve extrapolated to infinity [AUC(I)] in mice and dose. Rabbits also exhibited dose proportionality in AUC(I). However, in rats, increasing the dose from 3 to 60 mg/kg of body weight resulted in a 49-fold increase in AUC(I). When the species was changed from mouse to rat, rabbit, or cynomolgus monkey, AUC(I) increased, whereas clearance (CL) decreased. It was concluded that the pharmacokinetics of SCH 27899 in animals varied with species; CL was the highest in mice and rats, followed by rabbits and cynomolgus monkeys.

SCH 27899, 56-deacetyl-57-demethyl-45-O-de(2-methyl-1-oxopropyl)-12α-(2,3,6-trideoxy-3-C-methyl-4-oxopropyl)-12β-L-arabino-hexopyranosyl)-flambamycin 56-(2,4-dihydroxy-6-methylbenzoate), is a novel oligosaccharide compound of the everninomicin class (14, 15). It exhibits more potent antibacterial activity than clinafloxacin, teicoplanin, and vancomycin (7). SCH 27899 also shows excellent activity against fluoroquinolone-resistant strains (MIC at which 90% of the isolates are inhibited, 0.25 μg/ml) and all gram-positive strains resistant to vancomycin (MICs, ≤4 μg/ml). These in vitro data indicate that SCH 27899 could be useful against emerging gram-positive strains resistant to other contemporary antimicrobial agents.

Vancomycin has emerged as the dominant alternative therapy for serious infections caused by oxacillin-resistant staphylococci and any gram-positive infection observed in a patient with intolerance to β-lactams or macrolides. Furthermore, infections caused by enterococci that are resistant to penicillins are often treated with vancomycin (3, 5, 6, 10, 11, 13). However, this choice has been recently compromised by the rapidly increasing development of vancomycin resistance among enterococci (12). Therefore, it is important that a new compound, such as SCH 27899, be developed against these emerging gram-positive pathogens.

The objective of this study was to evaluate the pharmacokinetics of SCH 27899 in mice, rats, rabbits, and cynomolgus monkeys following intravenous administration.

MATERIALS AND METHODS

Compound. SCH 27899 (lot 23779-081-01) and SCH 9931 (internal standard) were supplied by Schering-Plough (Kenilworth, N.J.). Thiabendazole (internal standard) was obtained from Sigma Chemical Co. (St. Louis, Mo.). Acetonitrile (high-pressure liquid chromatography [HPLC] grade), ethyl acetate ammonium hydroxide (29%; American Chemical Society grade), ammonium phosphate (HPLC grade), ammonium acetate (HPLC grade), tetramethylammonium hydroxide (HPLC grade), methanol (HPLC grade), orthophosphoric acid (85%; HPLC grade), and water were obtained from Fisher Scientific Co. (Pittsburgh, Pa.).

Drug administration. Charles River male mice (weighing 18 to 20 g) received an intravenous bolus dose (15, 30, or 45 mg of SCH 27899 equivalents/kg of body weight) of SCH 27899-N-methylglucamine-hydroxypropyl β-cyclodextrin (SCH 27899·3NMG·5HPβCD). Blood samples (n = 3) were obtained predose and at 0.05, 0.08, 0.25, 0.5, 0.75, 1, 2, 4, 6, 8, and 24 h after drug administration by jugular incision immediately following euthanasia by cervical dislocation; blood samples were allowed to coagulate at room temperature. Serum samples were obtained following centrifugation at 4°C and stored at −20°C.

Charles River male rats (weighing 182 to 201 g) received an intravenous bolus dose (60 mg of SCH 27899 equivalents/kg) of SCH 27899·3NMG·5HPβCD. Blood samples (n = 3) were collected predose and at 0.08, 0.25, 0.5, 0.75, 1, 2, 3, 4, 6, and 24 h postdose into heparinized tubes by cardiac puncture following anesthesia with ketamine. Plasma samples were obtained following centrifugation at 4°C and stored at −20°C.

New Zealand White male rabbits (weighing about 3 kg) received an intravenous bolus dose (3 or 15 mg/kg) of SCH 27899·3NMG·5HPβCD. Blood samples (n = 4) were obtained predose and at 0.08, 0.5, 1, 2, 4, 6, 8, 24, and 48 h postdose from the carotid artery by means of a catheter and were allowed to clot. Serum samples were obtained following centrifugation at 4°C and stored at −20°C.

Male cynomolgus monkeys received an intravenous bolus dose (60 mg/kg) of SCH 27899·3NMG·5HPβCD via the femoral vein. Blood samples (n = 6) were collected from the leg contralateral to the injection site leg predose and at 0.08, 0.5, 1, 2, 3, 4, 6, 8, 24, 48, 72, and 96 h postdose into heparinized tubes at 4°C and were stored at −20°C.

Determination of SCH 27899 in plasma and serum. Concentrations of SCH 27899 in mouse serum, rat plasma, and rabbit serum were determined by an HPLC method (8). To a 0.2-ml aliquot of rat plasma were added 0.05 ml of internal standard (containing 2 μg of thiabendazole per ml), 0.05 ml of 50% acetonitrile (in water), and 1 ml of acetonitrile. The mixture was vortexed for 20 min and then centrifuged for 10 min. The organic layer was transferred to another tube and evaporated to dryness at 50°C. The residue was reconstituted...
Total body clearance (CL) was calculated with the formula 

$$\text{CL} = \frac{dose}{AUC(t_f)}$$

where CL is clearance, dose is the administered dose, and AUC(t_f) is the area under the concentration-time curve from time zero to infinity. For intravenous data, the area under the concentration-time curve from time zero to the final quantifiable concentration-time point (AUC(t_f)) was calculated using the linear trapezoidal rule. The predicted concentration was used as the concentration at time zero. The value of AUC(t_f) extrapolated to AUC(I) was calculated with the formula 

$$\text{AUC}(I) = \text{AUC}(t_f) + \text{Ct/f}t, \text{ where Ct/f is the estimated concentration determined from linear regression at time t.}$$

RESULTS

Serum concentrations of SCH 27899 in mice following intravenous doses of 15, 30, and 45 mg/kg and in rabbits following intravenous doses of 3 and 15 mg/kg are shown in Fig. 1 and 2, respectively. Plasma concentrations of SCH 27899 in rats and cynomolgus monkeys following intravenous doses of 60 mg/kg are shown in Fig. 3 and 4, respectively. The concentration-time data in all species studied exhibited a biexponential decline at all doses.

Pharmacokinetic parameters of SCH 27899 are summarized in Table 1. The half-lives at beta phase in mice, rats, and
rabbits were similar, ranging from 3 to 8 h, whereas that in monkeys was much longer, with a mean of 23.9 h. After intravenous administration, the half-life at α phase was short in all species: 0.1 to 0.5 h in mice, rats, and rabbits and 1.0 h in monkeys. In mice, there was a linear relationship ($r^2$, 0.9992) between AUC and dose. In rabbits, there was also dose proportionality in AUC.

CL in both mice and rabbits appeared to be dose independent. There was a good linear relationship between CL and log(W), with an allometric coefficient of 47.5 (Fig. 5). The allometric exponent of 0.586 was slightly lower than the value (0.69) for the creatine CL body weight relationship.

**DISCUSSION**

Concentrations of SCH 27899 in monkey plasma were determined by ion-pair chromatography, whereas concentrations of SCH 27899 in mouse serum, rat plasma, and rabbit serum were determined by an HPLC method with a polymeric HPLC column having a unique pH stability ranging from pH 1 to pH 13. Both methods have sufficient sensitivity, with LOQ of 1 μg/ml for ion-pair chromatography and 0.5 μg/ml for the HPLC method with a polymeric column.

The β-phase half-life determination for mice, rats, and rabbits may not be accurate due to the absence of concentration data beyond 8 h or between 8 and 24 h. Furthermore, the concentrations at different times were obtained from different libraries.

**TABLE 1. Pharmacokinetic parameters of SCH 27899 in mice, rats, rabbits, and cynomolgus monkeys following intravenous administration**

<table>
<thead>
<tr>
<th>Species</th>
<th>Dose (mg/kg)</th>
<th>$t_{1/2a}$ (h)</th>
<th>$t_{1/2b}$ (h)</th>
<th>AUC(0→∞) (μg h/ml)</th>
<th>CL (ml/h/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mice</td>
<td>15</td>
<td>0.23</td>
<td>3.31</td>
<td>89.9</td>
<td>167</td>
</tr>
<tr>
<td></td>
<td>30</td>
<td>0.20</td>
<td>6.49</td>
<td>164</td>
<td>183</td>
</tr>
<tr>
<td></td>
<td>45</td>
<td>0.16</td>
<td>4.38</td>
<td>234</td>
<td>192</td>
</tr>
<tr>
<td>Rats</td>
<td>60</td>
<td>0.11</td>
<td>6.16</td>
<td>570</td>
<td>105</td>
</tr>
<tr>
<td>Rabbits</td>
<td>3</td>
<td>0.43</td>
<td>3.04</td>
<td>69.6</td>
<td>43.1</td>
</tr>
<tr>
<td></td>
<td>15</td>
<td>0.50</td>
<td>7.88</td>
<td>347</td>
<td>43.3</td>
</tr>
<tr>
<td>Cynomolgus monkeys</td>
<td>60</td>
<td>1.03 (11)</td>
<td>23.9 (12)</td>
<td>3,737 (19)</td>
<td>16.7 (23)</td>
</tr>
</tbody>
</table>

* Numbers in parentheses are the percent CV of the pharmacokinetic parameters for six monkeys. In mice, rats, and rabbits, pharmacokinetic parameters were calculated from pooled concentration-time data; thus, no percent CV was calculated. $t_{1/2a}$ and $t_{1/2b}$, half-lives at α and β phases, respectively.
animals. Nevertheless, the results of the present study indicate a β-phase half-life of 3.0 to 7.9 h for SCH 27899 in mice, rats, and rabbits. On the other hand, plasma samples from cynomolgus monkeys were obtained by serial bleeding, and there were several plasma collections well beyond 24 h (every 24 h up to 96 h after intravenous administration), yielding a reliable estimation of the β-phase half-life. It is apparent that the β-phase half-life in monkeys (24 h) was longer than that in mice, rats, and rabbits (3.0 to 7.9 h).

REFERENCES