In Vivo Activity of HSR-903, a New Fluoroquinolone, against Respiratory Pathogens

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The in vivo activity of HSR-903, a new fluoroquinolone, against major bacteria which cause respiratory tract infections was evaluated. HSR-903 was active against experimental respiratory tract infections in mice challenged with penicillin-susceptible and penicillin-resistant *Streptococcus pneumoniae* and *Haemophilus influenzae* strains. Treatment with HSR-903 reduced the bacterial numbers in infected murine lungs. In accord with the pulmonary clearance results, the rates of survival for mice treated with HSR-903, sparfloxacin, levofloxacin, ciprofloxacin, and benzylpenicillin were 50, 30, 10, 0, and 0%, respectively, 14 days after being infected with penicillin-resistant *S. pneumoniae*. A pharmacokinetic study with pneumonic mice showed that the levels of HSR-903 in the lungs were seven to eight times higher than those in the plasma. These results indicate that clinical studies of HSR-903 against respiratory tract infections may be warranted.

Several fluoroquinolones with broad antibacterial spectra, such as ciprofloxacin (22), lomefloxacin (3), sparfloxacin (7), and levofloxacin (17, 21), have been developed, and used in the therapy of bacterial infections. However, many clinical isolates of *Streptococcus pneumoniae*, a major respiratory pathogen, are no longer susceptible to benzylpenicillin or the currently available fluoroquinolones (1, 2).

HSR-903, (S)-(-)-5-amino-7-(7-amino-5-azaspiro[2.4]hept-5-yl)-1-cyclopropyl-6-fluoro-1,4-dihydro-8-methyl-4-oxoquinoline-3-carboxylic acid methanesulfonate, is a new quinolone synthesized by Hokuriku Seiyaku Co., Ltd., Fukui, Japan, that possesses potent antibacterial activity (13, 15). In the study described here, we used in vivo murine models to examine the activities of HSR-903 in comparison with those of ciprofloxacin, sparfloxacin, and levofloxacin, against the major respiratory pathogens *S. pneumoniae* and *Haemophilus influenzae*.

MATERIALS AND METHODS

Antimicrobial agents. The following antimicrobial agents were used in this study and were obtained from the indicated sources: HSR-903, Hokuriku Seiyaku Co., Ltd.; ciprofloxacin, Bayer Yakuhin Ltd., Osaka, Japan; sparfloxacin, Daiinippon Pharmaceutical Co., Ltd., Osaka, Japan; levofloxacin, Daiichi Pharmaceutical Co., Ltd., Tokyo, Japan; and benzylpenicillin, Meiji Seika Kaisha, Tokyo, Japan.

Bacterial strains. The bacterial strains used in this study were maintained at the Department of Microbiology, Toho University School of Medicine.

Experimental pulmonary infection caused by *S. pneumoniae*. The in vivo activities of HSR-903 and the other drugs tested against penicillin-susceptible *S. pneumoniae* (PSSP) TUH39 were evaluated in 4-week-old male ICR mice (weight, about 20 g; SLC Japan Inc., Shizuoka, Japan). The bacteria were inoculated in Todd-Hewitt broth (Difco) supplemented with 30% horse serum, and the mixture was incubated at 35°C until the culture became turbid to the naked eye. When the bacteria were in the late logarithmic phase they were harvested by centrifugation at $2,000 \times g$ for 10 min at 4°C. The organisms were suspended in 0.9% saline to the desired concentration. The mice were placed under anesthesia with ketamine and xylazine, and each mouse was challenged with 3.7×10^6 CFU by intranasal instillation of 0.05 ml of bacterial suspension. We did not determine the 50% lethal dose, but this inoculum resulted in 100% mortality among the controls. The drugs were administered orally 18 h after infection twice daily for 3 days. We calculated the 50% effective dose (ED_{50}), including 95% confidence limits, by the probit method (8) from the survival rates on day 7 after infection. The efficacy of HSR-903 against penicillin-resistant *S. pneumoniae* (PRSP) TUM741 was examined on the basis of pulmonary clearance and survival studies

with an established mouse model (9, 16, 18). To evaluate the effects of HSR-903 and other drugs on the number of bacteria in the lungs, CBA/J mice (Charles River Japan, Shizuoka, Japan), which are susceptible to intranasal infection caused by PRSP, were used. The bacterial suspension was prepared as mentioned above. Four-week-old CBA/J mice (weight, 15 to 22 g) were placed under ketamine-xylazine anesthesia, and each animal was challenged with 1.4×10^6 CFU, which resulted in 100% mortality among the controls. A quinolone was administered orally or benzylpenicillin was administered subcutaneously at 36 h after infection to groups of four or five animals each three times a day for 3 days. The animals were killed 18 h after the last administration of the drugs. The lungs and trachea were removed and were homogenized in 0.9% saline, and 0.1-ml aliquots of serial 10-fold dilutions of the homogenate were spread onto blood agar for the determination of viable counts. The results are presented as the mean $\pm$ standard deviation (SD) log CFU per set of lower respiratory tract organs. Statistical analysis was done by the Bonferroni-Dunn multiple comparison method. To compare the effects of HSR-903 and the reference drugs on survival, groups of 10 mice each were infected with strain TUM741, and 50 mg of each drug per kg of body weight was administered as described above. Survival rates were recorded daily for 14 days after infection.

Experimental respiratory tract infection caused by *H. influenzae*. The effects of HSR-903 on a pulmonary infection caused by *H. influenzae* were examined in a mouse model constructed by Miyazaki et al. (10). Four-week-old male ICR mice (weight, about 20 g) were used. For airway impairment, 40 μ l of 1% formalin was instilled intranasally into mice while they were under ketamine-xylazine anesthesia. An overnight culture of *H. influenzae* TMS8 was inoculated into brain heart infusion broth (Difco) supplemented with hemin and NAD at a final concentration of 5%, and the culture was incubated at 35°C for 3 h. The organisms in the culture were harvested by centrifugation and were suspended in Eagle's minimal essential medium to make a volume similar to that of the original culture. This bacterial suspension was added to MFL cell monolayers, and the monolayers were incubated at 35°C for 1 h with gentle shaking. Free-floating bacteria were removed and washed three times with saline. Then, cell-bound organisms were removed from the flask and suspended in Eagle's minimal essential medium. Three days after treatment of the mice with formalin as described above, 50 μ l of a cell-bound organism suspension (1.0×10^4 CFU/

TABLE 1. Protective effects of HSR-903 and other drugs against pulmonary infection caused by *S. pneumoniae* TUH39^a

Drug	MIC (μ g/ml)	ED_{50} (mg/kg)	95% Confidence limits
HSR-903	0.063	9.94	5.79–17.62
Ciprofloxacin	1	>50	
Sparfloxacin	0.25	16.32	9.78–32.27
Levofloxacin	1	>50	

^a ICR mice were infected intranasally with *S. pneumoniae* TUH39. The challenge dose was 3.7×10^6 CFU/mouse. The results were calculated as the ED_{50} with 95% confidence limits by the probit method from the survival rates on day 7 after challenge.

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FIG. 1. Therapeutic effects of HSR-903 and other drugs in terms of pulmonary clearance of *S. pneumoniae* TUM741. CBA/J mice ($n = 4$ or 5) were infected intranasally with PRSP. A drug (50 mg/kg) was administered three times a day for 3 days, beginning 36 h after infection. The numbers of bacteria in the lungs were determined 18 h after the last administration. The results are presented as the mean $\pm$ SD log CFU (see text). The MICs of HSR-903, ciprofloxacin, sparfloroxacin, levofloxacin, and benzylpenicillin were 0.063 , 1 , 0.25 , 1 , and 1 μ g/ml, respectively. *, $P < 0.01$ versus results for control, ciprofloxacin, or benzylpenicillin treatment and $P < 0.05$ versus results for levofloxacin treatment; †, $P < 0.01$ versus results for control or benzylpenicillin treatment and $P < 0.05$ versus results for ciprofloxacin treatment; ‡, $P < 0.05$ versus results for control treatment.

animal) was instilled intranasally into anesthetized mice. We did not determine the minimum lethal dose for this challenge. At 48 h after infection the drugs were administered to each group ($n = 5$) orally twice daily for 3 days. The viable counts of the organisms in the lungs and trachea were determined by the same method used for the PRSP TUM741 model, except that the tissue homogenates were spread onto chocolate agar. The data are presented as the average $\pm$ SD log CFU per set of lower respiratory tract organs, and the significance of inter-group differences was calculated as described above.

Pharmacokinetics in pneumonic mice. Four-week-old male ICR mice (weight, about 20 g) were used for the analysis of pharmacokinetics. Pneumonia caused by PSSP TUM741 was induced by the method described above. At 18 h after infection the pneumonic mice were orally given 0.2 ml of HSR-903 or another quinolone at a dose of 50 mg/kg. The animals were killed and the blood was collected at 0.083, 0.25, 0.5, 1, 2, 4, and 6 h after administration of the drugs. The lungs were removed, weighed, and stored at -80°C until they were required for analysis. The blood samples were centrifuged to separate the plasma. The plasma and tissue samples were analyzed by paper disk methods, with *Escherichia coli* kp used as an indicator organism (11, 12). Extraction of HSR-903 from tissues was performed as follows. The tissue samples containing HSR-903 were homoge-

FIG. 2. Therapeutic effects of HSR-903, ciprofloxacin, sparfloroxacin, levofloxacin, and benzylpenicillin in terms of survival following infection of CBA/J mice with PRSP TUM741. A drug (50 mg/kg) was administered three times a day for 3 days, beginning 36 h after infection.

FIG. 3. Time course of numbers of viable bacteria in the respiratory tract during the therapeutic period. ICR mice were infected intranasally with *H. influenzae* TMS8 (five mice in each group). Drugs were administered orally at a dosage of 0.625 mg/kg twice a day for 3 days, starting 18 h after infection. The numbers of bacteria in the lungs were determined 18 h after the last administration of the drugs. The data are presented as the mean $\pm$ SD log CFU (see text). The MICs of HSR-903, ciprofloxacin, sparfloroxacin, and levofloxacin were ≤ 0.001 , 0.008 , 0.002 , and 0.016 μ g/ml, respectively. *, $P < 0.05$ versus results for control treatment; †, $P < 0.01$ versus results for control treatment and $P < 0.05$ versus results for ciprofloxacin or levofloxacin treatment; ‡, $P < 0.01$ versus results for control, ciprofloxacin, or levofloxacin treatment; §, $P < 0.01$ versus results for control or ciprofloxacin treatment.

nized in a Polytron (Kinematica, Littau/Lucerne, Switzerland) in 4 volumes of 1/15 M phosphate buffer (pH 6.5). The homogenates were heated at 80°C for 10 min and mixed with an equal volume of 0.2 N HCl. After vigorous vortex mixing, the sample solutions were collected by centrifugation at $2,000 \times g$ for 20 min at room temperature. Each sample solution was adjusted to neutral pH by adding 0.1 N NaOH, and the sample solutions were applied to paper disks.

RESULTS AND DISCUSSION

Efficacy against experimental pneumonia caused by *S. pneumoniae* in mice. The protective effects of HSR-903 and the other quinolones tested against experimental pneumonia caused by PSSP TUM741 are summarized in Table 1. HSR-903 was highly effective, with an ED_{50} of 9.94 mg/kg, and it also had the highest in vitro activity against this strain. The therapeutic effects of HSR-903 and the reference drugs in terms of the pulmonary clearance of PRSP TUM741 are presented in Fig. 1. The mean viable count of the organisms recovered from the lungs of *S. pneumoniae*-infected mice was 8.09 ± 1.40 log CFU per lung. Treatment with HSR-903 at a dose of 50 mg/kg led to a significant reduction in the numbers of viable cells in the lungs compared with those in the lungs of untreated ($P < 0.01$), benzylpenicillin-treated ($P < 0.01$), ciprofloxacin-treated ($P < 0.01$), or levofloxacin-treated ($P < 0.05$) mice. Treatment with sparfloroxacin also led to a significant reduction in the viable counts in the lungs compared with those in the lungs of untreated ($P < 0.01$), benzylpenicillin-treated ($P < 0.01$), or ciprofloxacin-treated ($P < 0.05$) mice. Treatment with levofloxacin afforded a significant reduction in the viable counts in the lungs compared with those in the lungs of untreated mice ($P < 0.05$), but a significant reduction was not found for ciprofloxacin-treated mice compared with that for untreated mice. The therapeutic effects of HSR-903, ciprofloxacin, sparfloroxacin, levofloxacin, and benzylpenicillin in terms of survival are presented in Fig. 2. All control mice died by 6 days after infection. All ciprofloxacin- and benzylpenicillin-treated mice died between 7 and 11 days after infection, while the survival rates for mice treated with HSR-903, sparfloroxacin, and levofloxacin were 50, 30, and 10%, respectively, at 14 days after infection.

FIG. 4. Pharmacokinetics of HSR-903, sparfloxacin, and levofloxacin in the plasma (a) and lungs (b) of infected mice. The drugs were administered orally at a single dose of 50 mg/kg, 18 h after infection. The results are presented as the mean $\pm$ SD. ●, HSR-903; △, sparfloxacin; □, levofloxacin.

Efficacy against experimental respiratory tract infection in mice caused by *H. influenzae*. The time course of the numbers of viable bacteria in the lower respiratory tract organs during the therapeutic period is presented in Fig. 3. The in vivo activity of HSR-903 in this murine model was comparable to that of sparfloxacin and was superior to those of ciprofloxacin and levofloxacin. The level of recovery of viable cells from the lower respiratory tract organs of mice treated with HSR-903 and sparfloxacin was significantly less than that from the controls at all time points after drug administration. Levofloxacin showed a weak therapeutic effect (not significant) compared with the effect of no treatment (control) after therapy for 3 days, while ciprofloxacin was ineffective.

Pharmacokinetics in pneumonic mice. Figure 4 presents the pharmacokinetic profiles of HSR-903, sparfloxacin, and levofloxacin in the plasma and lungs of mice infected with *S. pneumoniae* TUH39. The pharmacokinetic parameters of HSR-903 and the other drugs are presented in Table 2. The peak concentration of HSR-903 in the lungs (10.12 $\mu\text{g}/\text{ml}$) was roughly two to three times greater than those of sparfloxacin and levofloxacin. The area under the curve (AUC) for HSR-903 in the lungs (53.82 $\mu\text{g} \cdot \text{h}/\text{ml}$) was two to four times greater than those for sparfloxacin and levofloxacin. The half-life ($t_{1/2}$) of HSR-903 in the lungs (3.41 h) was longer than that of levofloxacin but was shorter than that of sparfloxacin. The best values of all parameters were for sparfloxacin in plasma. The ratios of the

maximum concentration (C_{max}) and AUC for HSR-903 in the lungs to the values of those parameters for HSR-903 in plasma were 7 and 8, respectively, whereas the ratios for sparfloxacin and levofloxacin were close to 1.

New oral fluoroquinolones and oral and injectable expanded-spectrum cepheims have played a key role in the clinical treatment of respiratory tract infections in the last decade. However, the emergence of resistant organisms is causing clinical problems throughout the world; various mutant strains with extended-spectrum β -lactamases have appeared (4, 14). In addition, the currently available fluoroquinolones have insufficient activity against *S. pneumoniae*. HSR-903 is a new fluoroquinolone with potent antibacterial activity (13, 15). The MIC of HSR-903 at which 90% of isolates are inhibited (MIC_{90}), determined by the broth microdilution method (5, 6) for recent clinical isolates of *S. pneumoniae*, including PRSP (48 strains) collected from Toho University Hospital between 1993 and 1995, was 0.063 $\mu\text{g}/\text{ml}$, and HSR-903 was 4 to 32 times more active than ciprofloxacin, sparfloxacin, and levofloxacin (MIC_{90} s, 2.0, 0.25, and 1.0 $\mu\text{g}/\text{ml}$, respectively). Against *H. influenzae* (44 strains), the MIC_{90} of HSR-903 was 0.004 $\mu\text{g}/\text{ml}$, and its activity was two to four times greater than those of the other quinolones tested.

In an in vivo mouse model, HSR-903 showed good efficacy against both *S. pneumoniae* and *H. influenzae*, which are major causes of respiratory tract infections in humans. The frequency

TABLE 2. Values of pharmacokinetic parameters for HSR-903, sparfloxacin, and levofloxacin in *S. pneumoniae*-infected mice^a

Drug	MIC ($\mu\text{g}/\text{ml}$)	Compartment	$t_{1/2}$ (h)	C_{max} ($\mu\text{g}/\text{ml}$ or $\mu\text{g}/\text{g}$)	$\text{AUC}_{0-\infty}$ ($\mu\text{g} \cdot \text{h}/\text{ml}$ or $\mu\text{g} \cdot \text{h}/\text{g}$) ^b
HSR-903	0.063	Plasma	2.83	1.42	6.67
		Lung	3.41	10.12	53.82
Sparfloxacin	0.25	Plasma	5.18	4.38	27.69
		Lung	4.83	3.99	25.12
Levofloxacin	1.0	Plasma	1.62	4.15	9.45
		Lung	1.93	5.01	12.99

^a ICR mice were infected intranasally with *S. pneumoniae* TUH39, and a drug was administered orally 18 h after infection. Mean values ($n = 3$) were calculated from the drug concentrations in plasma and homogenates of lung tissue taken at 0.083, 0.25, 0.5, 1, 2, 4, and 6 h after drug administration.

^b $\text{AUC}_{0-\infty}$, AUC from time zero to infinity.

of occurrence of PRSP infections has increased in recent years (19). In patients infected with PRSP, most β -lactams are ineffective. In the present study, the efficacy of HSR-903 was evaluated with the nonimmunocompromised CBA/J mouse model of pneumococcal pneumonia since the histopathology in this animal model closely resembles that in humans with infection (18). The results indicate that this drug may be effective against pneumococcal pneumonia in humans. In addition, HSR-903 was effective against murine pulmonary infection due to *H. influenzae*, which mimics bronchitis in humans. These in vivo results are consistent with the potent in vitro activity of HSR-903. The AUC and $C_{\max}$ of HSR-903 in murine lungs were much higher than would be expected from the values in murine plasma. This feature may be important for the efficacy of HSR-903, although many host factors may also influence the in vivo activity of HSR-903. HSR-903 showed a long elimination $t_{1/2}$ (18 h) in a pharmacokinetic study with human volunteers given a single dose of 200 mg (20). This is far longer than the $t_{1/2}$ in mice, so the drug may prove to be particularly effective against clinical respiratory tract infections in humans.

In conclusion, HSR-903, a new fluoroquinolone, showed excellent activity in in vivo experimental models. The present data, in conjunction with the potent in vitro activity and the long $t_{1/2}$ in humans, indicate that HSR-903 has potential clinical utility against respiratory tract infections.

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