Antibacterial activity of AM-1155 against penicillin-resistant
Streptococcus pneumoniae

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AM-1155, a novel fluoroquinolone, exhibited potent activity against Streptococcus pneumoniae, including penicillin-resistant strains; the MIC\textsubscript{90} for 48 clinical isolates was 0.25 mg/L. The antibacterial activity of AM-1155 against S. pneumoniae was higher than that of levofloxacin (MIC\textsubscript{90} 1 mg/L) and comparable with that of sparfloxacin. The MIC\textsubscript{90}s of penicillin G and erythromycin were 2 and > 4 mg/L, respectively. AM-1155 showed no cross-resistance to penicillin or erythromycin. For experimental murine pneumonia with S. pneumoniae intermediately resistant to penicillin, oral administration of AM-1155 showed efficacy higher than that of levofloxacin and equal to that of sparfloxacin. The efficacy of AM-1155 was also equal to that of subcutaneous penicillin G administration at the same dosage.

Introduction

Penicillin-resistant Streptococcus pneumoniae has caused serious therapeutic problems.\textsuperscript{1,2} The frequency of penicillin resistance in S. pneumoniae, a significant cause of human bacterial pneumonia, has increased in virtually every part of the world. In Japan, about 40% of S. pneumoniae are reported to be penicillin-resistant.\textsuperscript{3} Increasingly, these pathogens are also becoming resistant to macrolides.

Recent years have seen great interest in the use of quinolones for the treatment of respiratory tract infections. Potential advantages of this class of agents include good absorption following oral administration, good penetration into various tissues, and a broad spectrum of antibacterial activity. Among commercially available quinolones, sparfl oxacin and levofloxacin have demonstrated better activity against S. pneumoniae than have ofloxacin or ciprofloxacin. AM-1155 has a broad spectrum of activity and shows greater activity than ofloxacin or ciprofloxacin against Gram-positive bacteria, including S. pneumoniae.\textsuperscript{4,5}

In this study, the in-vitro activity of AM-1155 against clinical isolates of S. pneumoniae was compared with that of levofloxacin, sparfl oxacin, erythromycin, and penicillin G. The efficacy of AM-1155 against experimental murine pneumonia with penicillin-resistant pathogens was also evaluated, using survival rate and clearance of bacteria from the lungs as criteria.

Materials and methods

Antibacterial agents

Quinolones were obtained as follows: AM-1155 from Kyorin Pharmaceutical Co. Ltd (Tochigi, Japan), levofloxacin from Daiichi Pharmaceutical Co. Ltd (Tokyo, Japan), and sparfl oxacin from Dainippon Pharmaceutical Co. Ltd (Osaka, Japan). Penicillin G and erythromycin were purchased from commercial sources.

Bacteria

Forty-eight clinical isolates of S. pneumoniae (including the S. pneumoniae strain intermediately resistant to penicillin, TUM 741, used for the study of in-vivo efficacy) were obtained from the Toho University School of Medicine.

Determination of MICs

MICs of the test drugs were determined by the standard microdilution method\textsuperscript{6} using cation-adjusted Mueller-
Hinton broth (MHB, Difco, Detroit, MI, USA) supplemented with 5% lysed horse blood. MICs were defined as the lowest drug concentrations that inhibited visible growth of bacteria.

In-vivo efficacy

CBA/J male mice (5 weeks old, Charles River Japan, Kanagawa, Japan) were anaesthetized by intramuscular injection of a mixture of 6 mg/kg of ketamine (Sankyo, Tokyo, Japan) and 1 mg/kg of xylazine (Bayer Japan, Tokyo, Japan). Anaesthetized mice were infected intranasally with a bacterial suspension of S. pneumoniae TUM741 according to the method of Tateda and colleagues.7

Drugs were administered three times at 4 h intervals, beginning 36 h after infection. Quinolones were administered orally. Each dose was 60 mg/kg. Penicillin G was administered subcutaneously at the same dose. Viable bacterial cells in the lungs were counted 18 h after the final dosage. The significance of differences in bacterial counts was tested by Tukey’s method. In another experiment, mice were treated on the same schedule using doses of 100 mg/kg and the number of surviving mice was recorded for 10 days.

Results and discussion

Figure 1 shows the susceptibility of clinical isolates of S. pneumoniae to various drugs. MICs of penicillin G ranged from ≤ 0.008 to 4 mg/L. Twenty-seven (56%) isolates had an MIC of > 0.1 mg/L and were thus classified as penicillin resistant. Erythromycin inhibited 50% and 90% of the isolates tested at concentrations of 2 and > 4 mg/L, respectively. Thus, more than 50% of these clinical isolates were erythromycin-resistant.

A M-1155 showed potent activity against S. pneumoniae, including penicillin-resistant isolates, with an MIC of 0.25 mg/L. The MIC90 of sparfloxacin and levofloxacin were 0.25 and 1 mg/L, respectively. Thus, the in-vitro activity of A M-1155 was comparable with that of sparfloxacin and four times higher than that of levofloxacin. A M-1155 also demonstrated potent activity against penicillin-resistant and erythromycin-resistant isolates, which showed no cross-resistance to A M-1155. Our results are consistent with those of Wakabayashi & Mitsuhashi5 and of Hosaka and colleagues,4 who reported that A M-1155 shows activity comparable with that of sparfloxacin against S. pneumoniae.

Even more significantly, susceptibility to A M-1155 did not differ among isolates susceptible to penicillin (MICs

![Figure 1. Scattergrams comparing the MICs of A M-1155 with those of levofloxacin (a), sparfloxacin (b), penicillin G (c), and erythromycin (d).](image-url)
with regard to other quinolones such as and Tateda and colleagues reported that sparfloxacin is more effective compared to other drugs. Viable cell counts in untreated mice were 5.7 ± 0.6 (mean ± s.d.) log cfu/lungs. Three oral doses of 60 mg/kg of AM-1155 reduced the bacterial counts to about 1% (3.7 ± 0.8 log cfu/lungs) of those in untreated mice.

The number of viable bacteria in the lungs of mice treated with levofloxacin, sparfloxacin, and penicillin G were 4.3 ± 0.7, 3.4 ± 1.0, and 3.8 ± 0.4 log cfu/lungs, respectively. The efficacy of AM-1155 was almost equal to that of sparfloxacin and was superior to that of levofloxacin. None of the differences in efficacy among these three quinolones was statistically significant. However, A zoulay-D upuis and colleagues reported that sparfloxacin is more effective than ciprofloxacin against pneumonia caused by either penicillin-susceptible or penicillin-resistant isolates of S. pneumoniae. These data indicate that the in vitro activities of the new quinolones are reflected in their in vivo efficacies. Furthermore, oral administration of AM-1155 showed the same efficacy as subcutaneous administration of the same dose of penicillin G.

Miyazaki and colleagues and Tateda and colleagues have reported that penicillin G is not efficacious against strain TUM 741 at doses of 2.5 mg/kg, but that at doses of 10 mg/kg or more it decreases the number of viable bacteria in the lungs of animals in a dose-dependent manner. Penicillin G doses of 40 mg/kg are required to achieve efficacy comparable with that against a penicillin-susceptible strain. Furthermore A zoulay-D upuis and colleagues compared sparfloxacin with the penicillin-class antibiotic amoxicillin at equivalent subcutaneous doses: sparfloxacin offered similar efficacy against penicillin-resistant strains.

The efficacy of three 100 mg/kg doses of the test drugs was also examined, as measured by 10-day survival rates. Untreated mice all died by day 10, as did those treated with levofloxacin. Day-10 survival rates in mice treated with sparfloxacin were 20%, while 30% of the mice treated with A M-1155 or penicillin G survived.

These data suggest that A M-1155 might be a useful tool in the treatment of infection by S. pneumoniae, including penicillin-resistant strains.

References


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