ABSTRACT

Though S-(−)-nadifloxacin has a superior in vitro potency against staphylococci compared to (RS)-(±)-nadifloxacin, it is also efficacious in systemic mouse infection model as has not been reported. We therefore, evaluated S-(−)-nadifloxacin by oral route in mouse model of sepsis induced by Staphylococcus aureus in comparison with spariloxacin. The EDso values for S-(−)-nadifloxacin and spariloxacin were 2.1 ± 0.4–3.4 and 0.5 ± 0.4–1.4 mg/kg respectively. The bioavailability of orally administered (30 mg/kg) S-(−)-nadifloxacin, (RS)-(±)-nadifloxacin and spariloxacin was monitored from 0 minutes to 4 hours in mice. S-(−)-nadifloxacin was found to be twice that of (RS)-(±)-nadifloxacin and even superior to that of spariloxacin. Average AUC of three repeated studies

MATERIALS AND METHODS

Bacterial Strain and Antibiotics

•Except Staphylococcus aureus ATCC 29213, all strains were clinical isolates identified by routine bacteriological methods. The strains were grown on Tryptic Soy agar plates (HiMedia) and were maintained at −70°C. Other microorganisms included were Staphylococcus aureus ATCC 25923 and MRSA 032.

•S-(-)-nadifloxacin and racemic- (+)-nadifloxacin as well as spariloxacin with levels of 0.4 and 0.35 µg/ml

INTRODUCTION

Staphylococci have a peculiar propensity to acquire drug resistance resulting in development of MDR strains such as MRSA and particularly in clinical setting. Moreover, the majority of methicillin resistant strains of staphylococci are also resistant to quinolone antibiotics. Efflux pumps, a topological feature is reported to play a role in the development of multidrug resistant staphylococci which are also resistant to other quinolones. Nadifloxacin has two optically active isomers, namely, S-(-)-nadifloxacin and R·(±)-nadifloxacin. The former is reported to possess superior antibacterial activity compared to the latter. Interestingly, even staphylococcal resistant to rifampicin, a potent bactericidal antistaphylococcal agent, is susceptible to low concentrations of S-(-)-nadifloxacin. The options to effectively treat infections due to multidrug resistant and quinolone resistant staphylococci are highly limited. Currently only two drugs namely vancomycin and teicoplanin are available to treat such infections. Both these antibacterial glycopeptides are parenterally administered. Particularly vancomycin needs to be administered only by IV route with intense risk of nephrotoxicity. The widespread emergence of glycopeptide resistant enterococci and the recent reports about glycopeptidase mediated efflux resistance in staphylococci have not introduced any new therapeutic potential of glycopeptides antibiotics. Therefore, developing newer antistaphylococcal agents which could be effective in the treatment of MDR staphylococci infections is an objective pursued by several investigators. In view of high antimicrobial potential of nadifloxacin, we evaluated the oral bioavailability and efficacy of S-(-)-nadifloxacin as compared with (RS)-(±)-nadifloxacin and spariloxacin and Staphylococcus aureus ATCC 25923 and MRSA 032.

DISCUSSION

In Vivo Efficacy of S-(-)-NADIFLOXACIN

•S-(-)-nadifloxacin was two to 8 fold superior antibacterial activity compared to spariloxacin. It retains high potency against resistant staphylococcal MRSA strains.

•S-(-)-nadifloxacin is rapidly bactericidal to even sparfloxacin resistant MRSA strains, which is seen in MIC levels that are 3 fold higher than that of sparfloxacin.

•S-(-)-nadifloxacin is orally well absorbed in mice resulting in serum levels above staphylococcal MIC levels of 32 µg/ml.

•Both S-(-)-nadifloxacin and spariloxacin are highly effective against S. aureus ATCC 29213. The emergence of resistant MRSA infection makes S-(-)-nadifloxacin significantly more efficacious compared to sparfloxacin.

•Oral effectiveness of S-(-)-nadifloxacin shows superior efficacy by DC path compared to oral route.

•Conclusion: S-(-)-nadifloxacin offers a promising therapeutic potential for the treatment of infection due to quinolone resistant MRSA.