DRUG CORNER

Garenoxacin

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Antibiotic resistance is a rising concern and a problem yet to be answered especially for Respiratory tract infections. The rising MICs for β-lactam/β-lactamase inhibitor combinations and Macrolides against Gram positive and Atypical organisms respectively especially in Asian subcontinent have only increased our quest for a safe yet effective antibiotic against Community-acquired infections.[1,2]

Garenoxacin is a newly developed novel des-fluoro[6] quinolone in Japan that was further researched and developed by Toyoma Ltd in collaboration with Bristol Meyers Squibb, USA

Mechanism of Action

Garenoxacin acts on DNA gyrase and DNA topoisomerase IV to inhibit the transcription and replication of DNA[3] like conventional Fluoroquinolones. However, Garenoxacin demonstrates unique Structure-Activity Relationship to offer one of the lowest MICs against respiratory pathogens with low potential for resistance development. The complimentary presence of bulky side chains of Difluoromethoxy and Methylisoindolinyl groups increases the spectrum of activity while preventing 'Efflux' that is so important for prevention of resistance development.[4]

Spectrum

Garenoxacin demonstrates wide spectrum of antibacterial activity against Gm positive, Gm negative, Atypical and Anaerobic pathogens. The mean MIC90s for Garenoxacin were 0.03, 0.12, 0.25, 0.5 and 1 for MSSA, Strep. pneumoniae, Grp A streptococci, Enterococcus and MRSA respectively. Similarly the MIC90s were 0.06, 0.5, 0.06, ≤0.03, 0.03 and 1 for E.coli, Klebsiella sp., Salmonella sp. Shigella sp. H. Influenzae, B. Fragilis. Against Atypcials the MIC90s were 0.008, 0.06, 0.03, 0.06, 0.016 mcg/ml for Legionella penumophila, M. pneumoniae, M. hominis, Ureaplasma urealyticum.[5]

Garenoxacin also demonstrates low Mutation Prevention Concentrations preventing the development of resistant strains with double-point mutations. This was further confirmed by in vitro analyses of 106 clinical isolates of Strep. pneumoniae with Garenoxacin demonstrating the least potential to select mutant strains compared to Levofloxacin and Moxifloxacin – 0, 2.8% and 0.9% respectively.[6] Similarly the novel structure resulted in complete bacteriological eradication rates against Quinolone-resistant (100%), β-lactam resistant (97.7%) and Macrolide resistant (98.7%) strains of Strep. pneumoniae.[7]

Pharmacokinetics

Cmax was 7.43 mcg/mL and the AUC was 100.7 mcg h/mL with a half-life (t1/2) of 12.36 h with a single dose of 400mg Garenoxacin. Garenoxacin shows excellent penetration across the tissues with Penetration ratios (sputum/plasma concentration) after 3 h and 24 h were 0.54 and 0.51, respectively. Garenoxacin concentration in sputum was much higher than the MIC90 (≤0.06 mcg/mL) seen with most causative pathogens, even 24 h after administration. The free AUC/MIC ratio was calculated to be >50 in patients when the MIC of causative pathogens was <0.5 mcg/mL. This ratio can be expected to be associated with >90% efficacy.[7] The calculated AUC/MIC demonstrated by Garenoxacin and Moxifloxacin against resistant Gm positive organisms including MRSA was ≅101 and ≅26 respectively

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Clinical Data

Clinical efficacy of Garenoxacin has been evaluated in 20 Phase II/III/IV clinical trials involving ≈10,000 patients for various therapeutic indications including RTIs. In a large multicentric study involving 6412 patients with Respiratory tract infections with PRSP, Gm negative and Atypical organisms, Garenoxacin administered at dosages of 400 mg for 5 days showed clinical efficacy rates of 92 to 100%.[8]

In a randomized, double-blind, multicentric study, switch therapy to oral Garenoxacin was bacteriologically and clinically evaluated in 108 patients with mild to moderate severe CAP requiring hospitalization. Garenoxacin administered for 3 days following injectable therapy showed comparable clinical and radiological resolution rates to the control arm receiving continuous Injection Amp-Sulbactam with Clarithromycin.[9]

Indications

Garenoxacin is indicated for the following bacterial infections caused by susceptible microorganisms including Pharyngitis, Sinusitis Laryngitis, Tonsillitis, Otitis media, Acute bronchitis, Pneumonia and Secondary infection in chronic respiratory lesion.

Precaution and Contraindication

Garenoxacin should be administered with caution in High-risk patients who have convulsive disorders such as epilepsy, and elderly patients. Garenoxacin is contraindicated in the patients who have a history of hypersensitivity to any component of the formulation

Adverse effects

Garenoxacin is a well tolerated drug with its safety profile well differentiated due to lack of any significant concerns on Photosensitivity, Abnormal hepatic functioning, Seizures, Arthropathy and QTc prolongation. The most frequent adverse effects reported in clinical trials were diarrhea, nausea, and headache.

Dosage and Administration

The usually recommended dose for adults, 2 tablets (400 mg) to be taken once daily at the same time of the day for 5 to 14 days depending on the severity and type of infection.

Place in Therapy

Garenoxacin is a novel des-fluoro[6] quinolone with unique Pharmacokinetic profile that promises to cover a wide spectrum of organisms commonly encountered in community acquired infections including Gm positive, Gm negative, Atypical & Anaerobic organisms with negligible potential for resistance development. Garenoxacin has been associated with high clinical success rates in patients with Bronchitis, Pneumonia and Otorhinolaryngological infections when used as initial- or secondline settings

Garenoxacin with its Pharmacodynamic and Pharmacokinetic correlates promises to have the therapeutic efficacy while treating Skin and Skin Structure infections, Urinary tract infections, Intraabdominal infections and Gastrointestinal infections including Enteric fever though the clinical data is sparse

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