

Delafloxacin, a New Miracle in Antibiotics Armamentarium for Bacterial Infections

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The persistent antibiotics resistant issue has emerged as an influencing factor to deteriorate community health. So, new antibiotics development is urgent for the treatment of bacterial infections. Alternatively, delafloxacin is an eminent new fluoroquinolone, and chemically distinct from older fluoroquinolones. There is lack of proton substituent that indicates the poor acidic property of the drug. It also has a good intracellular penetration capacity that increases the intensity of the bactericidal property in acidic environment. Delafloxacin is a super active drug against the skin and soft tissue infections (SSTIs) and community-acquired respiratory tract infections. Delafloxacin also exhibits better efficacy against pathogens which are resistant to other fluoroquinolones, such as methicillin-resistant *Staphylococcus aureus* (MRSA). Delafloxacin received approval from the US Food and Drug Administration (FDA) for the treatment of acute bacterial skin and skin structure infections (ABSSI). Phase III clinical trial among patients with community-acquired pneumonia (CAP) is ongoing to evaluate the effectiveness of delafloxacin. From the aforementioned arguments, delafloxacin will be a prominent candidate for the upcoming antibacterial agent. Similarly, delafloxacin can be a crucial drug to fight against ABSSI.

Key Words: Antibiotics, Delafloxacin, Fluoroquinolones, Acute bacterial skin and skin structure infections

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INTRODUCTION

Fluoroquinolones are commonly prescribed antibiotics to treat bacterial infections. Delafloxacin is a unique fluoroquinolone that is structurally different from other fluoroquinolones. It is weakly acidic in nature and effective against a large number of parasites. It is also unique in the well balanced target for inhibition of enzymes (1). Delafloxacin is a potential anionic fluoroquinolone available in intravenous (IV) as well as oral dosage form. It is used for the treatment of acute bacterial skin and skin structure infections (ABSSSI) caused by both gram-positive and gram-negative bacteria (2). Exclusive structure keeps it as a weak acid that increases efficacy in acidic environments (2). Phase III clinical trial showed that delafloxacin is superior for treatment of ABSSSI and were well tolerated antibacterial agent (2). Delafloxacin also exhibits better activity against pathogens resistant to other fluoroquinolones as well as multiresistant strains (3). Although fluoroquinolones are not traditionally the first-line choice for ABSSSI, however, delafloxacin fulfill a therapeutic role for ABSSI. Delafloxacin is

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suggested for certain bacterial infections in the acidic environment. However, it is difficult to treat infection in an acidic environment. (4). In addition, its double targeting mechanism of action may remain its potential for the emergence of resistance (5).

Mechanism of action and structure activity relationship

Inhibition of DNA gyrase and topoisomerase are the major mechanism of antimicrobial activity of fluoroquinolones. These two enzymes are essential for replication (6). DNA gyrase is the most susceptible target in gram-negative bacteria, while topoisomerase IV is the more favorable target in gram-positive bacteria (6). Delafloxacin shows 3-5 folds less minimum inhibitory concentration (MIC) than other fluoroquinolones against gram-positive pathogens because of their better affinity for DNA gyrase. DNA gyrase plays a crucial role in transcription as well as replication. Topoisomerase IV has a potent decatenating activity. Delafloxacin is superior to other fluoroquinolones due to its dual-targeting nature. It shows almost similar activity against DNA gyrase as well as topoisomerase IV (7). This unique property of delafloxacin considers it as a broad-spectrum antibiotics against both gram-negative as well as gram-positive bacteria, including methicillin-resistant *Staphylococcus aureus* (MRSA) (7).

Distinguishing structure, size, shape, and polarity of delafloxacin increase its efficacy against bacteria. At position N-1, a heteroaromatic substitution exhibited more molecular surface area. At position C-8, a chlorine addition withdraws electrons from the aromatic ring at N-1. This electron withdrawing effect keeps delafloxacin molecule more stable. At position C7, the absence of basic group keeps delafloxacin in an anionic nature at neutral pH. In contrast, other fluoroquinolones exist as zwitterions at normal physiologic pH (4). The novel anionic character of delafloxacin upgrades the activity in acidic environments. It is also mentionable that a reduction of 2-32 folds MIC of delafloxacin has been observed in acidic medium (4). Urinary tract, decubitus ulcers, abscess fluid, phagolysosomes of infected cells and epithelial lining fluid are common local acidic sites of infections. Delafloxacin exerts its greater efficacy rather than other agents like fluoroquinolones, aminoglycosides, and macrolides which lose antimicrobial activity under the acidic environment (4).

Pharmacology

The half-life ($t_{1/2}$) of delafloxacin is around 8 hours at the normal dose. Delafloxacin exhibits a good distribution in compartments of the body. The volume of distribution (V_d) of delafloxacin is 35 L at steady state, where the normal range of V_d is 30.21 to 38.46 L. Excretion of delafloxacin is 65% via urine, mostly as an unmetabolized form and 28% excretion through feces. Clearance decreased in patients with severe kidney disease (3).

Delafloxacin shows more potent antibacterial activity (less MIC_{90}) than other quinolones against gram-positive bacteria including MRSA. In comparing with other recognized fluoroquinolones, delafloxacin exhibits 10-folds more accumulation at acidic pH in both bacteria and cells (3).

Clinical efficacy

As an evaluating factor, phase II clinical trial of delafloxacin practiced among patients with ABSSSI was randomized, multi-center, double-blind, dose-ranging study (8). Two intravenous doses of delafloxacin (300 mg or 450 mg twice a day) were compared with tigecycline 100 mg IV once followed by 50 mg IV twice daily in phase II clinical study. Clinical response and effectiveness were evaluated at 14 to 21 days after the last dose (8). *S. aureus* comprised almost 90% of gram-positive bacteria, where MRSA was detected in 71% (1). The clinical cure and bacteriological eradication rates were more than 90% in all treatment groups (1). Intravenous 300 mg twice a day was the best-tolerated delafloxacin regimen. In case of *S. aureus*

group MIC₉₀ was observed at 0.06 µg/ml for delafloxacin, whereas 0.12, 4 and 8 µg/ml for tigecycline, levofloxacin and ciprofloxacin, respectively (8).

The phase II clinical trial was performed for evaluating the efficacy of delafloxacin in patients (n=256) with skin and soft tissue infections (SSTIs) compared with linezolid and vancomycin. Finally, 70.4% cure rates were reported in the delafloxacin group and 64.9% and 54.1% in the linezolid and vancomycin, respectively (9).

Safety and tolerability

Adverse reactions were observed in 50% or more of the patients who took 800 mg or more delafloxacin (10). Doses ranging from 50 to 1,600 mg of delafloxacin were well tolerated. Gastrointestinal diarrhea and nausea were observed at 800 mg or higher doses both in oral and intravenous dosage form (3).

In case of the treatment of SSTIs, 74.4% rate of adverse effects were observed in delafloxacin, whereas 72% and 64.6% for linezolid and vancomycin, respectively. The digestive disorder is the most frequent adverse effect (3, 9).

In a phase III clinical trial of delafloxacin detected GI related diarrhea and nausea as adverse effects (1). Tendinopathies are unfamiliar adverse effects with fluoroquinolones (11). The structural difference at C7 may play a role in tendon lesions (11). Three patients were reported tendonitis in phase III clinical study (1).

Adverse effects of the central nervous system, including headaches, dizziness, acute psychosis to seizures are the second most adverse effects in treatment associated with fluoroquinolones (12). In phase III studies, it was observed that only 3% of patients were having a headache, while other CNS adverse effects were rare (1). No patient was reported in a phase III clinical study with delafloxacin who had experienced convulsions or seizures (1).

In phase III studies, delafloxacin-induced arrhythmias were not reported (1).

CLOSING REMARKS

Targeting ABSSSI indication of new antibiotics development is very important; omadacycline is one of them for the treatment of ABSSSI (13). Recently delafloxacin received FDA approval for the treatment of ABSSSI for its effectiveness against pathogens with well-tolerable antibiotics (1, 14). Moreover, it has notable beneficial points, including oral and IV dosage form, low interaction with other drugs, and a less adverse effect for the treatment of ABSSSI.

Delafloxacin has exclusive structural and chemical properties which make it a unique addition in antibiotics armamentarium. It is very effective against *S. aureus* in case of biofilm-associated infections (15, 16). Antibiotics which are effective in eradicating intracellular non-replicating persisters bacteria in bone, deep-seated abscesses, and prosthetic device-associated infections are very essential for medical treatment (1). Treatment of bacterial infections is difficult in acidic condition. Penetration capacity of delafloxacin, particularly in acidic condition added values in the therapeutic niche (4). Antibacterial activities and excellent pulmonary penetration of delafloxacin play an important role against pneumonia. Delafloxacin is also effective in case of public health-threatening diseases like gonorrhea (1, 17). Resistance to other fluoroquinolones usually participates stepwise chromosomal mutations in the quinolone resistance determining regions (QRDR) of DNA gyrase and/or topoisomerase IV (6, 18). On the other hand, overexpression of efflux pumps also plays a crucial role in chromosomal resistance (6, 18). Delafloxacin has a better ability to overcome this quinolone-resistant phenotype due to single and double mutations in the QRDR and efflux pump expression (1). So, delafloxacin can fight against pathogens which are resistant to other fluoroquinolones. In conclusion, we can say that delafloxacin is a prominent new antibacterial agent for the treatment of infections.

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