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Finafloxacin: A Novel Fluoroquinolone Introduced in Clinical Trials

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Quinolones were introduced into clinical practice in 1962, in form of nalidix acid and oxolinic acid and both were effective against most Enterobacteriaceae. Several changes on basic quinolone ring yielded fluoroquinolones that have increased antibacterial potency and broadened spectrum. Substituents on the basic chemical structure that improve pharmacokinetic properties are namely, fluorine atomin position 6; cyclopropyl or difluorophenyl in position 1; halogen, methoxy or fused third ring in position 8; and piperazine in position 7 [1,2].

The most frequently applied fluoroquinolones in clinical use are ciprofloxacin, ofloxacin, levofloxacin, and moxifloxacin. Ciprofloxacin and ofloxacin are mostly used in treatment of urinary tract, intestinal infections caused by Gram-negative bacteria. Levofloxacin is an active isomer of ofloxacin and it possesses a broader-antibacterial spectrum, that includes Gram-negative as well as Gram-positive bacteria. Levofloxacin is mostly used in treatment of respiratory tract infections. Moxifloxacin's spectrum includes Gram-positive aerob and anaerob bacteria [3-5]. Fluoroquinolone mechanism of action is inhibition of bacterial DNA synthesis as these agents target bacterial DNA gyrase and topoisomerase IV enzymes [6-9]. Fluoroquinolone antibiotics have a concentration dependent antibacterial activity. Peak serum concentration is reached rapidly after administration, keeping its effect as long as the concentration exceeds the minimum inhibitory concentration (MIC) value [10].

Finafloxacin belongs to the class of fluoroquinolones with chemical structure including a 8-cyano-substituent and 7-pyrrolo-oxazinyl moiety. It has a zwitterion chemical structure with a 6.7pH isoelectric value. During *in vitro* studies finafloxacin showed extended spectrum activity against several human bacterial pathogens namely, methicillin-susceptible *Staphylococcus aureus* and methicillin-resistant *Staphylococcus aureus*, *Streptococcus pneumoniae Legionella pneumophila, Listeria monocytogenes, Helicobacter pylori*, uropathogenic bacteria including *Escherichia coli*, *Pseudomonas aeruginosa, Klebsiella pneumoniae, Proteus mirabilis* [11,12]. Finafloxacin can be administered in otic drop formulation for treating acute otitis externa infection and can be treatment option of both complicated and uncomplicated urinary tract infections. Its optimal bactericidal effect was noticed in acidic environment and Phase II studies have shown remarkable results about the oral administration of finafloxacin in combination with amoxicillin or omeprazol against *H. pylori* gastritis [9,13-15].

The antibacterial effect of finafloxacin was investigated in infectious mouse models namely, in *Burkholderia pseudomallei* infection of BALB/c mice. Orally administrated finafloxacin (37.5 mg/kg) achieved the maximum concentration (7.24 mg/l) within 2 hours and resulted in eradication of the bacterium from lung, liver and spleen [16].

In vivo study demonstrated that 1 mg/kg/day dosage of oral finafloxacin lead to teratogenesis (neural tube and skeletal defects: spina bifida, missing lumbar vertebra and arch, sternebra fusion etc.) in rabbits [17].

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Finafloxacin is absorbed rapidly following oral administration and can be used both intravenously and locally. After 300-600-800 mg oral adminsitration of finafloxacin peak serum concentration (Cmax: 4.15 mg/l; 6.76 mg/l; 8.95 mg/l) was attained within 1 hour. Bioavability of oral formations possess 62-100 %, half life of about 10 h and prolonged post antibiotic effect was observed. Approximately 30% of a dose of finafloxacin is eliminated unchanged in the urine. Renal clearance was increased at dose of 100 and 200 mg in contrast with higher dosage (400 and 800 mg) due to saturable transport mechanism [18,19].

One study found that elimination rate was significantly lower in healthy eldery individuals, than healthy young volunteers. Urinary bactericidal concentration of finafloxacin was 69.3 mg/ml (given 200 mg single oral dose) and 150 mg/l (given 800 mg single oral dose). In addition it was also observed that bactericidal effect of finafloxacin was enhanced against uropathogens such as *E. coli, K. pneumoniae, P. mirabilis, P. aeruginosa* and *Enterococcus faecalis* [19].

Finafloxacin exhibits higher activity in acidic urine, than in alkaline or neutral environment due to pH dependent function. It exhibits optimal activity at pH 5-6 in contrast with other fluoroquinolones that can't achieve antibiotic effect in acidic conditions. Finafloxacin achieves a 4 to 32-fold lower MIC against *S.aureus* and *E. faecalis* at pH 5.8 compared to ciprofloxacin MIC [11].

Furthermore, advanced activity was observed under anaerobic condition mainly at neutral pH value, that was verified by MIC values of finafloxacin against Gram-negative anaerob patogens including Bacteroides fragilis. It shows antibacterial effect with 0.5/4 µg/ml of MIC_{50}/MIC_{90} at pH 7.2 whilst these values were decreased (0.25/4 µg/ml) under acidic conditions [9,20].

Finafloxacin can pass into the cytoplasm of phagocytes thus it is adapted to kill the intracellular pathogens. Finafloxacin showed remarkable antibacterial effect against both *L. monoytogenes* and *L. pneumophila*. In comparison with ciprofloxacin the MIC values of finafloxacin (MIC of *L. pneumophila* = 0,01 mg/l; MIC of *L. monocytogenes* = 1 mg/l) for intracellular bacteria were similar than the other quinolones [14].

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Altogether seven clinical trials have been performed to analyse antibacterial efficacy and toxicity of finafloxacin. A double-blind, placebo controlled, radomized dose escalation study examined toxicity and urinary antibacterial activity of dose of 200 mg and 800 mg finafloxacin in 6 healthy individuals. Drug proved to be safe and tolerable and did't cause serious side effects during the treatment period and urinary recovery was 32.1±12.2% and 33.4±7%, respectively [19].

In a double-blind, placebo controlled, randomized study 95 healthy volunteers were given orally placebo and finafloxacin once daily (25, 50, 100, 200, 400 and 800 mg dose) or for 7 days (150, 300, 600, 800 mg dose). Headache, diarrhea, loose stool, nause, flatulance, nasopharingitis and rhinitis were the most frequently adverse effects in addition ECG was normal and prolonged QT interval was not found [18].

Pharmacokinetic properties of finafloxacin were evaluated and during adminsitration of once daily dose (25, 50, 100, 200, 400 and 800 mg) the C_{max} values ranged between 0.24 - 11.1 mg/L and t_{max} was between 0.5-1 hour, while half life time was 1,28-10 hours [18].

In two studies four drops from 0,3% finafloxacin was administrated twice daily for 1 week to patients with acut otitis externa caused by S. aureus or P. aeruginosa. Clinical cure rates were 71 % and finafloxacin demonstrated high microbiology eradication rate (89%) against two observed patogens. In two phase III clinical trials studies 618 patients with otitis externa received 0.3% finafloxacin in otic formulation. Ear pruritus and nause were the most common adverse effect that was present in 1% of patients [17].

Based on the studies so far, it can be assumed, that finafloxacin is a potential antibacterial agent against major Gram-positive and Gram-negative human pathogens. Moreover, finafloxacin can inhibit biofilm formation of *E.* coli [13], that can be benefitial in therapy of catheter associated infections. Finafloxacin can achieve potency against bacterial pathogens in acidic environment thus, it enables finafloxacin for therapy of *H. pylori* infections.

Competing Interests

The authors declare that they have no competing interests.

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