Abstract

Background: Finafloxacin (FIN), a novel fluoroquinolone (FQ), in clinical development, has the unique property of being active under acidic conditions, unlike other marketed FQs. Since local acidic environments are a hallmark of bacterial infection, FIN may have an advantage over existing agents in treating these infections. This study was performed to determine the PK/PD parameter that best correlates to in vivo efficacy. Methods: Mice for FIN and other FQs were determined at pH 6 and 7. Female 5-6 wk old CD-1 mice were rendered neutropenic by ip injection of Cytoxan (150/100 mg/kg at days -4/-1 pre-infection). E. coli thigh infection was established by injection of 10^6 CFU at pH 5 and 6 and 7.5 into each of the right legs. Dose fractionation studies (100, 200 and 60 mg/kg) were performed from 0.5 to 100 mg/kg. All treatment was repeated at 48 hr post-infection and performed for 4 FQs. FIN was administered SC from 1 to 100 mg/kg to determine PK parameters at each dose. Results: FIN was more active than the other FQs tested at pH 5. The static dose for both the MSSA and Ec was 88.1. The corresponding C_max:MIC ratio for the static effect was 38.8 for the MSSA and 22.4 for the Ec. Conclusion: The efficacy of FIN in the neutropenic thigh model, for both MSSA and Ec, correlated best to the AUC/MIC and further investigation is warranted to determine the effect of pH on the rate of infections in the model of this parameter.

Methods and Materials

Finafloxacin is an novel member of the fluoroquinolone class of antibiotics with a novel pH activated profile offering therapeutic potential for severe and difficult to treat bacterial infections. Some of the characteristics of finafloxacin which set it aside from other members of the FQ class can be summarised as follows: anti-inflammatory properties of the drug, fewer side effects at therapeutic doses, excellent oral and intravenous bioavailability, drug has a clearly superior safety profile to other FQs, drug has a useful therapeutic window compared to other FQs. The current study was performed to determine the PK/PD parameter that is most predictive for the efficacy of finafloxacin.

Introduction

Finafloxacin is a novel member of the fluoroquinolone class of antibiotics with a novel pH activated profile offering therapeutic potential for severe and difficult to treat bacterial infections. It is a novel class of antibiotics which is active at lower pH than other marketed FQs. This study was performed to determine the PK/PD parameter that best correlates to in vivo efficacy of finafloxacin.

Summary and Conclusions

- Finafloxacin was 4- to 16-fold more active than the other fluoroquinolones by MIC testing at pH 5 to pH 6.
- Finafloxacin exhibited a good correlation for the pharmacokinetic parameters of AUC and C_max to dose.
- This novel FQ exhibited a good correlation between total administered dose and antibacterial effect against both E. coli and S. aureus in the murine thigh infection model.
- The PK/PD parameter which best predicted finafloxacin activity in this model was AUC/MIC, closely followed by C_max.
- The preliminary PK/PD target of an AUC/MIC of 88.1 for E. coli is in the region of those described for other fluoroquinolones to Gram negative organisms (~125).
- Finafloxacin exhibited a good correlation between total administered dose and antibacterial effect against both E. coli and S. aureus in the murine thigh infection model.
- The PK/PD parameter which best predicts finafloxacin activity in this model was AUC/MIC, closely followed by C_max.
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- The preliminary PK/PD target of an AUC/MIC of 88.1 for E. coli is in the region of those described for other fluoroquinolones to Gram negative organisms (~125).
- Further testing is warranted with a larger strain set to more accurately define the magnitude of the PK/PD parameters which describe the in vivo efficacy of finafloxacin.

References

Determination of the Effect of Age and Gender on the Pharmacokinetics (PK) and Tolerability of a Single Dose of Finafloxacin HCl (FIN) in Healthy Volunteers

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Abstract

Background

• Finafloxacin is a novel fluoroquinolone that exhibits improved antibacterial and pharmacokinetic properties under acidic conditions which other characteristic infections sites. Previous clinical studies have indicated that FIN is well tolerated with few treatment-related adverse events (AE).

Methods

The study was conducted under protocol of Clinical IRR and the FDA IND # 392342, and in accordance with GCP. This was a single-center, open-label study in 40 healthy subjects (10 young adult females, 10 young adult males, 10 elderly adult females, and 10 elderly adult males). All subjects received a single oral dose of 400 mg FIN (2 x 200 mg tablets).

Results

• The administration of a single oral dose of 400 mg finafloxacin was safe and well tolerated in the young and elderly male and female subjects in this study.

Conclusions:

• The average systemic availability (AUC0-∞) of finafloxacin was approximately 18% greater in elderly versus young subjects (not statistically significant). Mean systemic exposure was similar in males and females (16% difference) and Cmax was statistically higher in females (6190-6440 ng/mL).

References


In vitro Investigation of Finafloxacin Under Conditions Simulating Lower Respiratory Tract Infection

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Introduction
Finafloxacin (FNF) is a novel fluoroquinolone that exhibits improved antibacterial and pharmacodynamic properties at pH values below neutral which offers characteristic sites such as in chronic and lower respiratory tract infections (LTIF). The aim of this study was to investigate the activity of FNF in water at various conditions (simulating LTIF including pH, low oxygen, presence of sputum components and biofilms).

Methods
MICs against LTIF pathogens were determined in an artificial sputum media (AS) at pH 7.2, 6.2 and 5.2 under both aerobic and anaerobic conditions. Time kill curves were conducted to assess the presence of sputum from cystic fibrosis (CF) patients. Mucin biofilm eradication concentration (MBC) were determined using a modified CAMP disk.

Results
Finafloxacin exhibited MICs in AS at lower pH against P. aeruginosa (PA), K. pneumoniae (KP), and S. maltophilia (SM). In AS at pH 5.2 and 6.2 lower anaerobic and at pH 8.5, under anaerobic conditions. FNF MICs in AS at pH 7.4-7.8 lower than those of the others: FQs, ciprofloxacin (CIP), levofloxacin (LVX), levofloxacin (LVX), meropenem (ME), and tobramycin (TOB) against all organisms tested in AS at pH values below neutral or under anaerobic conditions.

Conclusions
FNF pH 7.2 had a 2-fold reduced MICs compared to FNF pH 6.2. FNF exhibited reduced activity when examined under anaerobic conditions simulating the environment and warrants further clinical investigation.

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Finafloxacin Exhibits Enhanced Activity Under Acidic And Anaerobic Conditions

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Revised Abstract

Background

Finafloxacin (FIN) is a novel fluorquinolone that exhibits improved antibacterial and pharmacokinetic properties at pH values below neutral which offers characteristic infection sites. Deep seated and chronic infections sites e.g. intradural abscesses and in optic sinus areas can also be composed of areas with low oxygen. The aim of this study was to determine the effect of pH and oxygen on the activity of FIN and comparator antibiotics.

Methods

MICs were performed aerobically and anaerobically at pH 7.2, 6.2 and 5.2 against 176 clinical isolates. Results

Comparative aerobic and anaerobic median MICs (MIC50) are shown in the table. The activity of tobramycin (TOB) decreased under anaerobic conditions whereas FIN activity was increased. pH activity was increased, pH readings confirmed this effect was not due to changes in pH during incubation. Under anaerobic conditions, FIN activity increased by a factor of 2 at pH 6.2 / 5.2 compared to at pH 7.2. Conversely, the activities of ciprofloxacin (CIP), levofloxacin (LVX), moxifloxacin (MXF) and TOB were decreased by a factor of 2-8 in the acidic media. Meropenem (MEM) and ceftazidime (CAZ) activity was not affected by pH.

Under anaerobic and low pH conditions, the activity of FIN was similar to at pH 7.2 (anaerobic); CIP, LVX, MXF and TOB all exhibited decreased activity at lower pH, compared to at pH 7.2, under anaerobic conditions.

Conclusions:

- These data highlight the impact of environmental conditions on antibacterial activity, and that pH and oxygen can influence the activity of FIN.
- FIN demonstrated enhanced activity under both anaerobic and acidic conditions, and warrants clinical investigation for infections in these conditions.

The potency of antibiotics against organisms that grow aerobically is routinely performed at pH 7.3-7.4 and in atmospheric conditions (or 5% CO2, for more fastidious organisms). However, the pH and oxygen availability at the site of infection could be quite different and thus standard susceptibility testing may under- or overestimate the capacity of an antibiotic to work in certain locations.

The enhancing effect of acidic pH on the activity of finafloxacin (and the negative effect on activity of other fluorquinolones) has been described before. The aim of this study was to investigate the activity of finafloxacin and other antibiotics against a selection of clinically relevant facultative anaerobes, using variables of pH and oxygen availability.

Results

Comparative aerobic and anaerobic median MICs (MIC50) for finafloxacin and comparator antibiotics, determined at pH 7.2, pH 6.2 and pH 5.2 with and without oxygen are shown in the table.

Conclusions

- In addition to pH activation, finafloxacin activity was enhanced under anaerobic, compared to aerobic conditions. This effect was most pronounced at pH 7.2, suggesting that there may be an overlapping mechanism for pH and anaerobic activation of finafloxacin.
- Acidic pH had a negative effect on the activity of other fluorquinolones and tobramycin.
- Tobramycin also exhibited reduced activity under anaerobic conditions (compared to aerobic) against most species tested. In general, the activities of ciprofloxacin, levofloxacin and moxifloxacin were unaffected by oxygen with several exceptions e.g. Klebsiella spp. and Enterobacter spp.
- These data suggest that finafloxacin could exhibit greater antibacterial and bactericidal activity at infection sites with low pH or oxygen availability, than would be predicted from its MIC (at pH 7.2); whereas other fluorquinolones and tobramycin could exhibit worse than expected activities.

References

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**Abstract**

Introduction  
Finafloxacin (FIN) is a novel fluoroquinolone (FQ) that exhibits improved antibacterial and pharmacokinetic properties at pH values below neutral which often characterize infection sites. The aim of this study was to determine the propensity of FIN and other FQs to select for resistance in the opportunistic pathogen Pa and to determine the effects of defined target and efflux resistance mechanisms on activity.

Methods  
Mutation prevention concentrations (MPC) for FIN, ciprofloxacin (CIP), and levofloxacin (LVX) were determined for Pa ATCC27853 from an inoculum of 10^6 CFUs at pH 7.2, 6.2 and 5.2. Susceptibility testing was also performed at these pHs (CLSI method).

Results  
MICs for FIN were 0.25, 1, and 4 mg/L at pH 7.2, 6.2 and 5.2 respectively, for CIP (0.5, 8, and 64) and for LVX (8, 32 and 64). MPC/MIC ratios were in the range 4-16, resistance frequencies were in the range 10^-8 - 10^-11, and mutant MICs were 4-fold greater than that of the parent. The susceptibility of genomic sets of its harboring defined mutations in efflux regulators, target mutations and combinations thereof are shown in Table 2.

Conclusions  
• Finafloxacin is a novel pH activated, broad spectrum fluoroquinolone in development for infection indications in the hospital and critical care setting [1].
• Finafloxacin exhibits enhanced activity at low pH and under other environmental conditions associated with infection [1, 2].
• Finafloxacin exhibits bactericidal activity against forms of quiescent growth, thought to be relevant in vivo e.g. non-growing cells, biofilms and persister [3].
• Other fluoroquinolones lose activity under such conditions. Consequently, finafloxacin exhibited superior activity in a series of infection models [4,5].
• The activity of finafloxacin under infection relevant conditions and against infection relevant growth forms in combination with the high dosing potential predicted from its safety profile [6, 7, 8], suggest finafloxacin will offer improved properties over currently marketed fluoroquinolones.

**Background and aim**

Introduction  
*P. aeruginosa* is an important hospital pathogen which is becoming increasingly difficult to treat due to the emergence and selection of resistant strains. Resistance to fluoroquinolones is usually mediated through combinations of target mutations in gyrA and mutations giving rise to increased activity of efflux pumps.

The aims of this study were to investigate the propensities of finafloxacin and other marketed fluoroquinolones to select for resistance in *P. aeruginosa* and to measure their activities against strains harboring combinations of mutations within target and regulatory genes affecting drug efflux.

**Methods**

Background  
• Finafloxacin is a novel pH activated, broad spectrum fluoroquinolone in development for infection indications in the hospital and critical care setting [1].
• Finafloxacin exhibits enhanced activity at low pH and under other environmental conditions associated with infection [1, 2].
• Finafloxacin exhibits bactericidal activity against forms of quiescent growth, thought to be relevant in vivo e.g. non-growing cells, biofilms and persister [3].
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• The activity of finafloxacin under infection relevant conditions and against infection relevant growth forms in combination with the high dosing potential predicted from its safety profile [6, 7, 8], suggest finafloxacin will offer improved properties over currently marketed fluoroquinolones.

References  

**Results**

**Table 1: Mutation prevention concentrations and mutation frequencies of fluoroquinolone, ciprofloxacin and levofloxacin, determined at pH 5.2, 6.2 and 7.2 determined with Pa ATCC27853.**

<table>
<thead>
<tr>
<th>pH 5.2</th>
<th>pH 6.2</th>
<th>pH 7.2</th>
</tr>
</thead>
<tbody>
<tr>
<td>FIN MPC (mg/L)</td>
<td>CIP MPC (mg/L)</td>
<td>LVX MPC (mg/L)</td>
</tr>
<tr>
<td>FIN</td>
<td>0.25</td>
<td>1</td>
</tr>
<tr>
<td>CIP</td>
<td>0.06</td>
<td>0.25</td>
</tr>
<tr>
<td>LVX</td>
<td>0.06</td>
<td>0.25</td>
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</tbody>
</table>

**Table 2: MICs of isogenic strains harboring MDR mutations, in the presence and absence of efflux pump inhibitor (EPI).**

**Table 3: MICs of isogenic strains harboring MDR mutations, in the presence and absence of efflux pump inhibitor (EPI).**

**Conclusions**

• Finafloxacin activity against *P. aeruginosa* was reduced by the presence of mutations in the target gene (gyrA) and MDE backgrounds nfxB, nfxC and nfxD, to a similar degree to other fluoroquinolones. Despite this, the pH activation exhibited by finafloxacin resulted in an overall greater potency than ciprofloxacin and levofloxacin against fluoroquinolone resistant *P. aeruginosa* under acidic conditions (Table 2).

• The pH activation also translated into finafloxacin exhibiting a lower resistance than ciprofloxacin or levofloxacin to select for resistance under acidic conditions (Table 1).

• Based on these findings, finafloxacin could exhibit improved antibacterial properties over other fluoroquinolones, against *P. aeruginosa* in infection sites acidified by inflammation and other physiological processes relating to infection.