Finafloxacin HCl - a novel experimental fluoroquinolone with monotherapeutic potential for Helicobacter pylori eradication

A. J. Bishop, H. Labischinski, W. Stubbings, A. D. Buss MerLion Pharmaceuticals Pte Ltd, Singapore

Abstract

Finafloxacin HCl is a novel fluoroquinolone antibiotic under early stage clinical development by MerLion Pharmaceuticals as a potential monotherapy for the eradication of Helicobacter pylori (H. pylori). Finafloxacin HCl has been shown to be equipotent to a range of marketed fluoroquinolones at pH 7.4, in vitro. However, at pH 5 it demonstrates markedly increased activity when compared with these agents.

The in vitro activity of finafloxacin HCl against H. pylori is similar to amoxicillin, clarithromycin and telithromycin - the most effective antibiotics used in combination for the eradication of H. pylori in man. Importantly, when head-to-head comparisons of finafloxacin HCl and these antibiotics were studied in vivo using a modified Helicobacter pylori H. felis mouse model, finafloxacin HCl was unique amongst the agents in being able to eliminate the organism when dosed as a monotherapy. Finafloxacin HCl is more potent in vitro than meropenem and is also effective against meropenem-resistant and clarithromycin-resistant Helicobacter strains.

Although most antimicrobials are effective against H. pylori in vitro, in vivo activity is limited by a range of factors including the low pH environment of the gastric mucosa that results in the effectiveness of these drugs. Finafloxacin HCl has a distinct pH/activity profile which may be used to overcome this barrier to efficacy.

Results and Discussion

Activity against H. pylori: The potency of growth inhibition by finafloxacin HCl was within the range demonstrated by the most effective antibiotics used for the eradication of H. pylori in man, and clindamycin (Table 1). Finafloxacin HCl was also effective against a metronidazole-resistant strain and against at least 5 of 10 clarithromycin-resistant strains. However, at pH 5 it demonstrates markedly increased activity when compared with these agents.

In vivo Activity: Infection models in experimental animals bridge the gap between in vitro testing and the clinical evaluation of an antibiotic. However, because H. pylori exhibits a limited host range, a H. felis model in mice was used to mimic the clinical aerobiosis of H. pylori in man (2). The model was adapted to mimic the pattern seen in humans whereby the stomach is invaded by pre-existing infected mice rather than from drug. With each passage H. felis becomes better adapted to the mouse stomach and more refractory to treatment until only triple therapy approaches are effective. If passed further, H. felis cannot be eradicated even with Triple Therapy.

In this model, triple therapy gave an eradication rate of 60% slightly below that seen in a clinical setting. Finafloxacin HCl at 10 and 20mg/kg b.i.d. for 10 days showed 100% eradication of H. felis (Figure 1).

Finafloxacin HCl was also more effective than monotherapy with amoxicillin, clarithromycin, ciprofloxacin, metronidazole and clarithromycin (results not shown). These comparator antibiotics showed no eradication when used as a monotherapy. Experiments with further passaged H. felis showed eradication rates of 100% using 12.5mg b.i.d. finafloxacin HCl for 14 days compared with only 30% using 14 days of triple therapy q.d. (results not shown).

The pH activity profile of finafloxacin HCl is distinct from that of all fluoroquinolones tested. This effect was confirmed across a range of bacteria (Table 2). Figure 2 shows an example of the pH activity relationship.

Methods

MIC (H. pylori): These were established using 5 x 10^4 bacterial inoculum in brain-heart infusion medium supplemented with 5% fetal calf serum (Boehringer, Mannheim). Microtitre plates were inoculated at 37°C for 48 – 72hrs in an atmosphere containing 10% CO2.

Helicobacter felis mouse model: Female Swiss Webster mice (ca. 20 g body weight) were used. Donor mice were challenged once to generate with 0.1 ml of a homogenate of infected stomach tissue (1 infected stomach homogenized in 10 ml BHI broth, 10^7 CFU/ml) and sacrificed after 1-3 months. Gastric homogenate from donor mice was examined microscopically for the presence of highly motile Helicobacter cells and assayed for urease activity to estimate the infectious load. Groups of Webster mice (ca. 20 g body weight) were then infected by a single challenge containing 10% CO2 incubated at 37ºc for 48 – 72hrs in an atmosphere containing 10% CO2.

Results and Discussion

Effect of pH on Activity: Fluoroquinolones may only diffuse through bacterial membranes to reach their molecular targets when in an uncharged state. The uncharged state of fluoroquinolones is stabilised under pH conditions below neutral. Therefore, “standard” MIC values, generated at near-neutral pH range tend to underestimate the relative efficacy of finafloxacin HCl under in vivo conditions within the acidic gastric mucosal niche of H. pylori.

Conclusions

• Finafloxacin HCl shows a pH dependent activity which is the opposite of marketed fluoroquinolones. Its activity is enhanced at lower pH.

• Finafloxacin HCl has shown equivalent in vitro activity to the commonly used antibiotics in triple therapy and shows a low cross resistance with clarithromycin.

• Finafloxacin HCl shows higher eradication rates in an adapted H. felis model than Triple Therapy.

• Overall, finafloxacin HCl appears to be a promising potential monotherapy for H. pylori eradication.

References


