Methods

MICs were determined for FIN and LVX against H. pylori strains (n=55) that were obtained from patients gastroscoped in the Southwest of France. MICs were performed by agar dilution at 3 different pHs: 7.3, 6.3 and 5.3. An inoculum equivalent to a 6.5FU/100,000 cells suspension (Fi 3 standard) from a 48 h culture was plated on Mueller Hinton agar enriched with 10% sheep blood prepared extemporaneously and containing progressive concentrations of the FQs (0.015 - 128 mg/L). Reading was performed after 2 - 3 days of incubation at 37° in a microaerobic atmosphere.

Results and Discussion

Introduction: cyano subclass. FIN exhibits optimal efficacy at slightly acidic pH (5.0 - 6.0), strains (n= 55) that were obtained from patients gastroscoped in the Southwest of France. MICs were performed by agar dilution at 3 different pHs: 7.3, 6.3 and 5.3. An inoculum equivalent to a 6.5FU/100,000 cells suspension (Fi 3 standard) from a 48 h culture was plated on Mueller Hinton agar enriched with 10% sheep blood prepared extemporaneously and containing progressive concentrations of the FQs (0.015 - 128 mg/L). Reading was performed after 2 - 3 days of incubation at 37° in a microaerobic atmosphere.

Results and Discussion

Introducing FIN

This is a novel, broad spectrum fluoroquinolone (FQ) that belongs to a new 8-cyano subclass [1]. FIN contains a novel chiral base component which confers improved antibacterial activity at slightly acidic pH (5.0 - 6.0) which other marketed FQs exhibit significantly reduced activity [2]. FIN also exhibited superior activity to comparator FQs against sensitive bacteria in vitro [3] and in a wide range of robust infection models [4]. Additionally, FIN displayed an excellent safety profile in a wide range of preclinical tests in vivo, toxicity assays [5] and was well tolerated in healthy human volunteers [6]. These attributes suggest that FIN warrants clinical investigation for bacterial infections that are associated with low pH such as urinary tract infection and Helicobacter pylori eradication.

FQs such as levofloxacin (LVX) have shown good antibacterial activity against H. pylori and a successful eradication rate when used in triple combination therapy. The antibacterial activity of FIN was investigated against FO susceptible and resistant strains at acidic pH and against H. pylori in a novel infection that was developed to be a stringent evaluator of anti-Helicobacter therapy.

Results and Discussion

Susceptibility of H. pylori isolates to FIN and LVX under standard conditions

In total, 55 H. pylori isolates were investigated for their susceptibility to FIN and LVX. Initially, a panel of 31 strains were investigated (Table 1). These were pre-determined as FQ susceptible (n = 18) or resistant (n = 13) based on their susceptibility to LVX.

Under standard susceptibility testing conditions (pH 7.3), FIN and LVX exhibited similar activities against the tested strains (Table 1).

Effect of pH on the activity of FIN against H. pylori

Agar dilution MICs were determined at pH 7.3, 6.3 and 5.3 against 24 LVX susceptible strains. The antibacterial activity of FIN, as seen by its MIC distribution (Figure 2), increased in a step-wise manner as the pH became more acidic. This effect was more pronounced in pH 5.0 cultures compared to pH 7.3 or 6.3 cultures. Under the same conditions, other marketed FQs exhibited significantly reduced activity. This unusual property has been attributed, at least in part, to the relatively low intrinsic basic capacity (pKa) of FIN compared to that of other FQs [7]. This most probably results in an increased cellular accumulation of FIN under acidic conditions. This is illustrated in Figure 3, in which a correlation is drawn between low intrinsic basic capacity of experimental and commercially available FQs and their improved therapeutic efficacy as in vivo model of Helicobacter colonization [8].

Conclusions

• FIN exhibited improved antibacterial activity, in vitro, against a panel of both FO susceptible and resistant strains at acidic pH.

• In addition to exhibiting clearly superior efficacy in an murine model of persistent Helicobacter pylori infection, FIN (sub-therapeutic dose) did not lead to resistance in this model.

• The pH activation observed with FIN against H. pylori in vitro and its efficacy in a difficult to treat model of Helicobacter pylori infection, suggest that FIN may be a promising treatment that could improve H. pylori eradication therapy in humans.

Literature


