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In Vitro Activities of a New Ketolide, ABT-773, Alone and in Combination with Amoxicillin, Metronidazole, or Tetracycline against Helicobacter pylori

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The in vitro activity of ABT-773, a new ketolide, was compared with those of clarithromycin, amoxicillin, metronidazole, and tetracycline against 15 strains of Helicobacter pylori. The MIC of ABT-773 at which 90% of isolates were inhibited was 0.25 μg/ml, which was 3 dilutions higher than that of the most active agent, clarithromycin. Synergy and antagonism were not seen with any combinations. Additive activity was seen with tetracycline, metronidazole, and amoxicillin in 100, 60, and 40% of the combinations, respectively.

Infections with Helicobacter pylori have been successfully treated with several different regimens. Combination therapy with a proton pump inhibitor, bismuth salt or ranitidine bismuth citrate, and two antibiotics is most commonly used, with no optimum regimen yet determined. The antimicrobial agents used in the treatment of H. pylori infections consist primarily of clarithromycin, metronidazole, amoxicillin, and tetracycline. While these antibiotics have demonstrated good in vitro activities and high cure rates, there is concern about increasing resistance and adverse effects associated with these agents. New antibiotics are needed to augment the current arsenal of agents effective against H. pylori. ABT-773 is a novel ketolide possessing a spectrum of activity similar to the macrolide class of antibiotics. The purpose of this study was to determine the in vitro activity of ABT-773 alone and in combination with the other antibiotics commonly used against H. pylori.

(This work was presented in part at the poster session of the 39th Interscience Conference on Antimicrobial Agents and Chemotherapy, San Francisco, Calif., 1999.)

Fourteen clinical isolates of H. pylori were obtained from the University of Illinois Hospital Microbiology Laboratory (Chicago, Ill.), Abbott Laboratories (Abbott Park, Ill.), and D. Y. Graham (Houston, Tex.). Most of the isolates were collected prior to 1995. One control strain, ATCC 43504, was obtained from the American Type Culture Collection (Manassas, Va.). The isolates were kept frozen at −70°C in skim milk and 17% glycerol. Prior to the susceptibility studies the organisms were thawed and subcultured once to ensure reliable growth.

ABT-773, clarithromycin (Abbott Laboratories), amoxicillin, metronidazole, and tetracycline (U.S. Pharmacopeia, Rockville, Md.) powders were prepared according to National Committee for Clinical Laboratory Standards (NCCLS) guidelines or per the manufacturer’s recommendation (7). Agar dilution procedures were used for the MIC and checkerboard assays. The agar medium used for MIC and checkerboard determinations was Mueller-Hinton (Difco, Detroit, Mich.) supplemented with 10% defibrinated horse blood (Remel, Lenexa, Kans.) at a neutral pH.

The final inoculum of the H. pylori strains was 10⁵ CFU/spot. The inocula were prepared by suspending organisms in Mueller-Hinton broth (Difco) and adjusting the turbidity to that of a 2.0 McFarland standard using a spectrophotometer at 625 nm. The organisms were inoculated onto the agar plates with a replicator device (Craft Machine Inc., Chester, Pa.) which delivered 8 μl per spot. All procedures were performed in triplicate, and all plates were incubated at 37°C in 10% CO₂ for 3 days.

The MIC was read as the lowest concentration of antimicrobial agent(s) showing no visible growth or only a faint haze. Combination activity was determined by calculating the fractional inhibitory concentration (FIC) index (3). The activity ranges used for interpretation of the FIC indices were as follows: ≤0.5, synergy; >0.5 to 1, additive; >1 to 4, indifference; >4, antagonism.

The agar dilution procedure used in this study differs from the current tentative NCCLS guidelines for H. pylori susceptibility testing (8). First, 10% defibrinated horse blood was used as the blood supplement instead of 5% aged sheep blood. Second, the plates were incubated in a 10% carbon dioxide incubator rather than under the microaerophilic conditions (5% oxygen, 10% carbon dioxide, 85% nitrogen) used for campylobacters. In order to assess any differences in results between the methods, MIC assays were performed on all antibiotics against the ATCC control strain using the different blood supplements and incubation conditions.

The MICs of ABT-773, clarithromycin, amoxicillin, metronidazole, and tetracycline for the H. pylori strains are shown in Table 1. ABT-773 demonstrated excellent in vitro activity against the H. pylori organisms, with MICs of ABT-773 being approximately 2 to 3 doubling-dilutions above those of clarithromycin. Clarithromycin was the most active of the antibi-
hydroxy clarithromycin plus amoxicillin demonstrated additive activity against 32% of the same isolates (5). Others have also reported additive effects with the combination of clarithromycin and amoxicillin (1).

The combination of ABT-773 and metronidazole demonstrated additive effects against 69% of the isolates. Breakpoint levels for metronidazole have not been established for _H. pylori_. Based on an arbitrary breakpoint of 16 μg/mL, four of the strains were resistant to metronidazole. Additive effects were seen with three of these organisms. Like clarithromycin, metronidazole is metabolized to a hydroxy metabolite that also has activity against _H. pylori_. We did not include the metabolite in the present study. However, in previous synergy testing, the addition of hydroxy metronidazole to the parent compound resulted in enhanced activity when combined with paromomycin against _H. pylori_ (6). The addition of the hydroxy metabolite could potentially increase the activity of the combination of ABT-773 and metronidazole.

The greatest in vitro activity was seen with the combination of ABT-773 and tetracycline, with 100% of isolates demonstrating additive activity. FIC indices of ≤0.75 were seen in 93% of the isolates. FIC indices between 0.5 and 0.75 have been described as partially synergetic by several investigators. These data suggest that the combination of ABT-773 and tetracycline may be superior to combinations of the ketolide with amoxicillin or metronidazole. With increasing resistance reported with metronidazole, the availability of a dual antibiotic regimen with enhanced combination activity would be most appealing.

Based on its excellent in vitro activity, ABT-773 may be a viable alternative for the treatment of infections due to _H. pylori_. The activity of ABT-773 should not be decreased and may actually be enhanced when combined with other agents commonly used to treat _H. pylori_. ABT-773 warrants further investigation as a potential therapeutic agent for the treatment of _H. pylori_ infections.

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### REFERENCES


