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In vitro bactericidal activity and post-antibiotic effect of ABT-773 versus co-amoxiclav against anaerobes


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Sir,

ABT-773, a novel ketolide, has demonstrated in vitro activity against a variety of anaerobic bacteria.1–3 While several studies have investigated the susceptibility profile of ABT-773, additional data on the activity of this new ketolide against anaerobes would be useful. The purpose of this study was to compare the in vitro bactericidal activity and post-antibiotic effect (PAE) of ABT-773 and co-amoxiclav against common anaerobes.

ABT-773 (Abbott Laboratories, Abbott Park, IL, USA) and co-amoxiclav (United States Pharmacopeia, Rockville, MD, USA) powders were prepared according to NCCLS guidelines or manufacturer’s recommendations.4 The antimicrobial concentrations studied were 2 × 106 and 8 × MIC. Two clinical strains each of Peptostreptococcus anaerobius and Bacteroides fragilis were tested. Each bacterial suspension at log-phase growth was diluted in precluded Wilkins–Chalgren broth (Acumedia, Baltimore, MD, USA) to obtain a final inoculum of c. 5 × 105 cfu/mL for MIC and time–kill studies and 5 × 106 cfu/mL for PAE determinations. All procedures were performed in duplicate in a Bactron anaerobic chamber (Sheldon Manufacturing, Cornelius, OR, USA), containing an atmosphere of 5% carbon dioxide, 10% hydrogen and 85% nitrogen.

The MICs of ABT-773 and co-amoxiclav were determined by the microbroth dilution method.4 The control organism, B. fragilis ATCC 25285, was used for validation of MIC results. Time–kill assays were performed according to NCCLS guidelines.5 The inoculum was confirmed at time zero; subsequent viable counts were performed at 2, 6 and 24 h. Antibiologic carryover was prevented by saline dilutions. The rate and extent of killing were determined by plotting viable count (log10 cfu/mL) against time (h). The lower limit of detection was 1.3 log10 cfu/mL. Bactericidal activity was defined as a ≥3 log10 decrease in cfu/mL, whereas bacteriostatic activity was defined as a <3 log10 decrease in cfu/mL.

The PAEs of the agents were determined using a method of repeated washing.6 Following a 1 h exposure period, the antibiotics were removed by washing three times. Viable counts were performed at this time and every hour thereafter until the broth became cloudy. The PAE was defined as T – C, with T as the time required for the count in the test culture to increase 1 log10 above the count observed immediately after drug removal, and C as the time for the count in the untreated control to increase 1 log10 above the count observed immediately after the wash procedure.6

The ABT-773 MIC (mg/L) ranges were 0.004–0.008 and 1.0 for P. anaerobius and B. fragilis, respectively. The true MICs are probably lower, as CO2 is known to raise the MICs of macrolides and ketolides. The co-amoxiclav MIC (mg/L) ranged from 0.125/0.06 to 1.0/0.5 for the four anaerobes. The ABT-773 PAE (h) against P. anaerobius ranged from 1.50–2.66 at 8 × MIC to 1.03–2.15 at 2 × MIC. Against B. fragilis, the PAE (h) of ABT-773 ranged from 2.01–3.27 at 8 × MIC to 1.52–2.14 at 2 × MIC. These data indicate a trend towards concentration-dependent PAEs with ABT-773. In comparison, the PAEs of co-amoxiclav were <1 h for all isolates, with ranges (h) of 0.31–0.53 against P. anaerobius and 0.04–0.4 against B. fragilis.

The results of the time–kill experiments are shown in Figure 1. The killing rate of ABT-773 8 × MIC was higher against both strains of P. anaerobius. Regrowth was observed in both P. anaerobius strains with ABT-773 2 × MIC at 24 h. Bactericidal activity was observed with co-amoxiclav against three of the anaerobes. A high MBC (16/5.3 mg/L) was responsible for the lack of activity against one of the P. anaerobius (PA 3871) strains.

Limited data are available on the time–kill kinetics and PAEs of ketolides against anaerobes.7–8 Boswell et al.7 examined the bactericidal activity and PAE of telithromycin against three strains of B. fragilis. The MICs of telithromycin for the B. fragilis isolates ranged between 0.25 and 1.0 mg/L. Telithromycin 10 × MIC demonstrated bactericidal activity against all three strains when tested with a high (105 cfu/mL) inoculum, but was only bacteriostatic at the standard 106 cfu/mL inoculum. No differences were noted in the duration of the PAE of telithromycin at higher (1.2–2.9 h at 10 × MIC) versus lower (1.2–3.4 h at 1 × MIC) concentrations, suggesting no

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Figure 1. Bactericidal activity of ABT-773 versus co-amoxiclav against *P. anaerobius* (a and b) and *B. fragilis* (c and d). Control, filled diamonds; ABT-773 8×MIC, filled squares; ABT-773 2×MIC, open squares; co-amoxiclav 8×MIC, filled circles; co-amoxiclav 2×MIC, open circles; lower limit of detection, dotted line.

Credito et al. conducted time–kill studies with telithromycin against 11 Gram-negative and Gram-positive anaerobic bacteria, including one strain of *B. fragilis* and two strains of *Peptostreptococcus* sp. At 24 h, telithromycin at 8× and 2× MIC demonstrated bactericidal activity for five and three strains, respectively. Individual data were only available for one strain of *Peptostreptococcus magnus*. Time–kill curves for this strain exhibited bactericidal activity with telithromycin concentrations of 4× and 8× MIC at 24 h. Similarly, bactericidal activity was achieved with ABT-773 8×MIC against both *P. anaerobius* strains in our study.

In conclusion, ABT-773 8×MIC demonstrated bactericidal activity and moderate PAEs against clinical isolates of *P. anaerobius* and *B. fragilis*. Further studies are needed to determine the potential role of ABT-773 in anaerobic infections.

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