ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Oct. 2001, p. 2922–2924 Vol. 45, No. 10
0066-4804/01/$04.00+0 DOI: 10.1128/AAC.45.10.2922–2924.2001

NOTES

In Vitro Activity of the Ketolide ABT-773

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Received 19 March 2001/Returned for modification 5 June 2001/Accepted 3 July 2001

The in vitro activities of ABT-773, azithromycin, erythromycin, and clindamycin were compared by testing 1,223 clinical isolates selected to represent different species and phenotypes. ABT-773 was particularly potent against staphylococci (the MIC at which 90% of the strains tested were inhibited [MIC_{90}] was ≤0.06 μg/ml), including all strains that were macrolide resistant but clindamycin susceptible. *Streptococcus pneumoniae* and other streptococci were inhibited by low concentrations of ABT-773, and that included most erythromycin-resistant strains. Against *Haemophilus influenzae*, ABT-773 and azithromycin were similar in their antibacterial potency (MIC_{90}, 4.0 and 2.0 μg/ml, respectively).

The ketolide class of antimicrobial agents includes 14-membered-ring macrolides that differ from erythromycin A in that they have a 3-keto group in place of the cladinose moiety in the macrolide ring. Telithromycin was the first ketolide to be developed for clinical use. ABT-773 is another ketolide that is currently being evaluated in phase III clinical trials. Both ketolides are active against gram-positive cocci, including all erythromycin-susceptible strains and most erythromycin-resistant strains (1, 3, 4, 6, 7). Strains of *Streptococcus pneumoniae* which are macrolide resistant by virtue of *erm* or *mef* mechanisms are fully susceptible to ABT-773, because the drug concentrates within the bacterial cell, where it tightly binds to the ribosomes and subsequently inhibits protein synthesis (5).

In the present study we evaluated the in vitro activity of ABT-773 compared to those of azithromycin, erythromycin, and clindamycin. Broth microdilution tests were performed according to the procedures defined by the National Committee for Clinical Laboratory Standards (NCCLS) (8). The agar dilution method was used for testing *Neisseria gonorrhoeae* and *Neisseria meningitidis* isolates, and in that case, ABT-773 and erythromycin A were the only drugs tested. The clinical isolates in our stock culture collection were selected to represent different species and phenotypes. Table 1 describes the 1,223 isolates that were included in this evaluation. Those isolates were initially recovered from patients throughout North America, and most had been stored no longer than two years when this study was begun.

ABT-773 was very potent against macrolide-susceptible staphylococci (the MIC at which 90% of the strains tested were inhibited [MIC_{90}] was 0.06 μg/ml versus 0.5 μg/ml for erythromycin A). That in vitro activity was also seen with macrolide-resistant strains that were susceptible to clindamycin. Staphylococci that were resistant to the macrolides and to clindamycin were not inhibited by the ketolide ABT-773 (MIC, >16 μg/ml). The other ketolide, telithromycin, has also been shown to have little activity against staphylococci with the macrolide- and lincosamide-resistant phenotype (3). That phenotype is not uncommon; i.e., Auckenthaler et al. (2) found that 15% of 1,465 clinical isolates of *Staphylococcus aureus* from 23 medical centers in 18 different countries had that phenotype, as did 30% of 667 coagulase-negative *Staphylococcus* spp. Clindamycin resistance was more common among oxacillin-resistant staphylococci (3% of oxacillin-susceptible *S. aureus* but 42% of oxacillin-resistant *S. aureus*). Only clindamycin-susceptible staphylococci might be expected to be clinically responsive to the ketolides, and that would include 97% of all oxacillin-susceptible *S. aureus* isolates, of which 82% would be susceptible to the macrolides (2).

The 317 *S. pneumoniae* strains that we tested included 75 penicillin-susceptible strains, 83 strains intermediately resistant to penicillin (penicillin intermediate), and 159 penicillin-resistant strains. Half of the penicillin-resistant strains were resistant to erythromycin A, as were 29 of 83 (35%) penicillin-intermediate strains. All *S. pneumoniae* isolates were susceptible to ABT-773 including clindamycin- and erythromycin-resistant strains. The other ketolide, telithromycin, has also been shown to be active against all three phenotypes of pneumococci (4). The clindamycin-susceptible and erythromycin-resistant phenotype is probably associated with an efflux mechanism that does not affect the ketolides (9). The other species of streptococci included in the present study were inhibited by low concentrations of ABT-773, even though some were resistant to erythromycin A and to clindamycin. Although all streptococci were inhibited by ≤0.5 μg of ABT-773 per ml, MICs for erythromycin-susceptible strains were consistently lower than those for erythromycin-resistant strains.

Many enterococci required relatively high concentrations of ABT-773 for inhibition; they were also relatively resistant to the other study drugs. More than half of the vancomycin-susceptible *Enterococcus* spp. were inhibited by low concentrations of ABT-773 (MIC, ≤0.03 μg/ml), but the MIC_{90}s were ≥4.0 μg/ml. Most vancomycin-resistant enterococci were not

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TABLE 1. Antibacterial activities of ABT-773 and three structurally related compounds

Microorganism (no. tested) and antimicrobial agent	MIC (μg/ml)		
	Range	50%	90%
Staphylococcus aureus			
Erythromycin susceptible, clindamycin susceptible (46)			
ABT-773	0.015–0.06	0.03	0.03
Erythromycin	0.12–0.5	0.25	0.5
Azithromycin	0.12–4.0	1.0	2.0
Clindamycin	0.03–0.25	0.12	0.25
Erythromycin resistant, clindamycin susceptible (14)			
ABT-773	0.03–0.06	0.03	0.06
Erythromycin	>32	>32	>32
Azithromycin	>8.0	>8.0	>8.0
Clindamycin	0.12–0.25	0.12	0.25
Erythromycin resistant, clindamycin resistant (47)			
ABT-773	>16	>16	>16
Erythromycin	>32	>32	>32
Azithromycin	8.0–>8.0	>8.0	>8.0
Clindamycin	>32	>32	>32
Staphylococcus spp., CoNS[a]			
Erythromycin susceptible, clindamycin susceptible (51)			
ABT-773	0.015–0.25	0.03	0.06
Erythromycin	0.12–0.5	0.25	0.5
Azithromycin	0.12–2.0	1.0	1.0
Clindamycin	0.06–0.25	0.12	0.25
Erythromycin resistant, clindamycin susceptible (15)			
ABT-773	≤0.008–0.25	0.03	0.06
Erythromycin	16–>32	>32	>32
Azithromycin	>8.0	>8.0	>8.0
Clindamycin	0.06–0.5	0.12	0.12
Erythromycin resistant, clindamycin resistant (10)			
ABT-773	>16	>16	>16
Erythromycin	>32	>32	>32
Azithromycin	>8.0	>8.0	>8.0
Clindamycin	>32	>32	>32
Streptococcus pneumoniae			
Erythromycin susceptible (211)			
ABT-773	≤0.008	≤0.008	≤0.008
Erythromycin	0.015–0.25	0.06	0.06
Azithromycin	0.015–0.5	0.12	0.12
Clindamycin	0.03–0.12	0.06	0.06
Erythromycin resistant (106)			
ABT-773	≤0.008–1.0	0.03	0.25
Erythromycin	2.0–>32	8.0	>32
Azithromycin	2.0–>8.0	>8.0	>8.0
Clindamycin	0.03–>32	0.06	>32
Streptococcus agalactiae (40)			
ABT-773	≤0.008–0.03	0.015	0.015
Erythromycin	0.03–>32	0.06	0.06
Azithromycin	0.03–>8.0	0.06	0.12
Clindamycin	0.06–>32	0.06	0.12
Streptococcus pyogenes			
Erythromycin susceptible (88)			
ABT-773	≤0.008–0.015	0.015	0.015
Erythromycin	0.03–0.12	0.06	0.06
Azithromycin	0.06–0.25	0.12	0.12
Clindamycin	0.03–0.12	0.06	0.06
Streptococcus pyogenes			
Erythromycin resistant (19)			
ABT-773	≤0.008–0.06	0.015	0.06
Erythromycin	1.0–16	2.0	16
Azithromycin	4.0–>8.0	8.0	>8.0
Clindamycin	0.06–>32	0.06	>32
Viridans group streptococci			
Erythromycin susceptible (12)			
ABT-773	≤0.008	≤0.008	≤0.008
Erythromycin	0.03–0.12	0.03	0.06
Azithromycin	0.03–0.06	0.03	0.06
Clindamycin	0.03–0.06	0.03	0.06
Viridans group streptococci			
Erythromycin resistant (28)			
ABT-773	≤0.008–0.5	0.015	0.12
Erythromycin	1.0–>32	4.0	>32
Azithromycin	1.0–>8.0	4.0	>8.0
Clindamycin	0.03–>32	0.06	32
Enterococcus faecalis			
Vancomycin susceptible (20)			
ABT-773	0.015–8.0	0.03	4.0
Erythromycin	0.5–>32	>32	>32
Azithromycin	2.0–>8.0	>8.0	>8.0
Clindamycin	16–>32	>32	>32
Vancomycin resistant (15)			
ABT-773	0.06–>16	>16	>16
Erythromycin	>32	>32	>32
Azithromycin	>8.0	>8.0	>8.0
Clindamycin	>32	>32	>32
Enterococcus faecium			
Vancomycin susceptible (20)			
ABT-773	≤0.008–>16	0.03	16
Erythromycin	0.06–>32	4.0	>32
Azithromycin	0.25–>8.0	>8.0	>8.0
Clindamycin	0.12–>32	16	>32
Vancomycin resistant (15)			
ABT-773	4.0–>16	>16	>16
Erythromycin	>32	>32	>32
Azithromycin	8.0–>8.0	>8.0	>8.0
Clindamycin	32–>32	>32	>32
Haemophilus influenzae			
Ampicillin susceptible (123)			
ABT-773	0.06–8.0	2.0	4.0
Erythromycin	0.12–32	4.0	8.0
Azithromycin	0.12–4.0	1.0	2.0
Clindamycin	0.12–32	8.0	16
BLNAR[b] (53)			
ABT-773	0.03–4.0	4.0	4.0
Erythromycin	4.0–16	4.0	16
Azithromycin	1.0–4.0	2.0	4.0
Clindamycin	4.0–32	8.0	32
β-Lactamase positive (139)			
ABT-773	0.5–>16	2.0	4.0
Erythromycin	0.015–>32	4.0	8.0
Azithromycin	0.015–>8.0	1.0	2.0
Clindamycin	1.0–32	8.0	16
Corynebacterium jeikeium (10)			
ABT-773	0.03–8.0	0.03	0.06
Erythromycin	8.0–>32	>32	>32
Azithromycin	>8.0	>8.0	>8.0
Clindamycin	32–>32	>32	>32
Listeria monocytogenes (20)			
ABT-773	0.03–0.06	0.06	0.06
Erythromycin	0.12–0.5	0.25	0.25
Azithromycin	0.5–2.0	1.0	2.0
Clindamycin	0.5–2.0	1.0	2.0
Moraxella catarrhalis (50)			
ABT-773	0.03–0.25	0.06	0.12
Erythromycin	0.12–0.5	0.12	0.25
Azithromycin	0.03–0.12	0.06	0.06
Clindamycin	2.0–16	4.0	8.0
Neisseria gonorrhoeae (35)			
ABT-773	≤0.008–0.12	0.03	0.06
Erythromycin	≤0.015–2.0	0.25	0.5
Neisseria meningitidis (36)			
ABT-773	≤0.008–0.25	0.015	0.12
Erythromycin	0.12–1.0	0.5	1.0

[a] CoNS, coagulase negative.
[b] β-Lactamase negative, ampicillin resistant.

inhibited by any of the study drugs at the highest concentrations tested. Telithromycin has also been shown to have similarly elevated MICs against vancomycin-resistant *Enterococcus faecalis* and *Enterococcus faecium* (1, 3).

Against *Haemophilus influenzae* strains, the MIC_{90} of ABT-773 was 4.0 μg/ml, and its in vitro activity was not affected by ampicillin resistance or susceptibility. The proper interpretation of these MICs must await clinical response data. The other ketolide, telithromycin, has been found to have nearly identical MICs against *H. influenzae* (1, 3).The MICs of both ketolides are only two times greater than those of azithromycin and one-half those of erythromycin A.

For the other gram-positive strains that were studied, the MICs of ABT-773 were lower than those of azithromycin or erythromycin A. The three species of gram-negative cocci that we tested were inhibited by low concentrations ($\leq$0.25 μg/ml) of ABT-773; erythromycin A was less potent, but all MICs were $\leq$1.0 μg/ml.

The potency of ABT-773 against susceptible staphylococci and pneumococci is particularly noteworthy, as is its activity against erythromycin- and azithromycin-resistant pneumococci. Provided that reasonable pharmacokinetic properties can be demonstrated and that there are no unexpected toxicity problems, ABT-773 should be a helpful addition to the list of antimicrobial agents that are available for treating community-acquired infections of the respiratory tract or skin and soft tissue, especially in communities where strains that are resistant to the macrolides are endemic.

This study was made possible by a grant from Abbott Laboratories, North Chicago, Ill.

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