

## In Vitro Susceptibilities of *Campylobacter jejuni* and *Campylobacter coli* to Azithromycin and Erythromycin

DIANE E. TAYLOR<sup>1,2\*</sup> AND NICHOLAS CHANG<sup>1</sup>

Department of Medical Microbiology and Infectious Diseases<sup>1</sup> and Department of Microbiology,<sup>2</sup>  
University of Alberta, Edmonton, Alberta, Canada T6G 2H7

Received 8 March 1991/Accepted 17 June 1991

**MICs of azithromycin and erythromycin for 20 *Campylobacter coli* and 20 *Campylobacter jejuni* strains were determined. The results demonstrated that, for *Campylobacter* species, all high-level erythromycin-resistant strains were also resistant to azithromycin and that azithromycin did not exhibit increased potency in comparison with that of erythromycin.**

Azithromycin (CP-62,933; Pfizer Central Research) is a new macrolide antibiotic which belongs to a recently described subclass of antibiotics known as azalides (1). The in vitro activity of azithromycin was noted against a substantial number of pathogens, and a significant improvement in its potency against gram-negative organisms was observed in comparison with that of erythromycin (9).

Erythromycin is the drug of choice for the treatment of serious gastrointestinal infections caused by *Campylobacter jejuni* and *Campylobacter coli* (6). Several studies have reported the in vitro activity of azithromycin against *Campylobacter* species (5, 8, 9). MICs of azithromycin have ranged from 0.03 to 0.12 µg/ml (5) to 0.12 to 128 µg/ml (8), whereas MICs of erythromycin were slightly higher, ranging from 0.06 to 1 µg/ml (5) to 1 to 128 µg/ml (8). These studies suggest that, in general, *C. jejuni* and *C. coli* strains are 4- to 10-fold more susceptible to azithromycin than they are to erythromycin.

To determine whether individual strains of *C. jejuni* and *C. coli* are more susceptible to azithromycin than to erythromycin, we determined the MICs of azithromycin and erythromycin for 20 *C. coli* strains and 20 *C. jejuni* strains from our collection. MICs were determined on Mueller-Hinton agar (Oxoid, Basingstoke, United Kingdom), without additional supplements, by previously published procedures (6).

The ranges of MICs of azithromycin and erythromycin are given in Table 1, and the various combinations of MIC patterns for the two antibiotics are given in Table 2. Many of the *C. coli* strains in our collection are resistant to a high concentration of erythromycin and have been collected especially for the purpose of studying the mechanism of erythromycin resistance (14). Of the 16 *C. coli* strains and 1 *C. jejuni* strain which were resistant to erythromycin (MICs, 256 to 1,024 µg/ml), all showed cross resistance to azithromycin (MICs, >1,024 µg/ml). Our results confirm that all high-level erythromycin-resistant strains are also resistant to azithromycin (8).

The results given in Table 2 demonstrate that of the 19 susceptible *C. jejuni* strains tested, 10 strains were equally susceptible to erythromycin and azithromycin (MICs, 0.12 to 0.25 µg/ml) and 5 strains were slightly more susceptible to erythromycin than to azithromycin. Of the other five strains tested, azithromycin was from two- to eightfold more effective than erythromycin, as determined by MIC testing. Of

the four susceptible *C. coli* strains tested, two strains were more susceptible to azithromycin than they were to erythromycin (two- and fourfold, respectively), for one strain, MICs of both drugs were identical, and the other strain was twofold more susceptible to erythromycin than it was to azithromycin. Therefore, although some individual strains of *C. jejuni* and *C. coli* appear to be more susceptible to azithromycin than to erythromycin, this is not true of all, or even the majority, of *C. jejuni* and *C. coli* strains.

The *Campylobacter* strains used in this study were acquired from a variety of sources and geographic locations, including Canada, the United States, the United Kingdom, Belgium, The Netherlands, Germany, and Switzerland. The *C. coli* strains, in particular, were preselected for a preponderance of erythromycin-resistant strains. One would not normally expect such a high incidence of erythromycin-resistant strains among clinical isolates from humans.

Resistance to erythromycin was reported to be less than 1% in the United Kingdom (2) and Canada (7). More recently, in the United States, 3% of *C. jejuni* strains were resistant to erythromycin, but a much greater incidence was noted among *C. coli* isolates, with 70% of isolates from hogs found to be resistant (13). Others have also noted a greater prevalence of erythromycin-resistant strains among *C. coli* than among *C. jejuni* isolates (3, 6). In a recent Centers for Disease Control survey, 2.4% of *Campylobacter* strains were found to be resistant to erythromycin (10). A higher incidence of resistance (9%) has been reported in Belgium (11) and Sweden (10%) (12).

The low incidence of resistance to erythromycin and azithromycin in the United States and Canada means that macrolide antibiotics are still the treatment of choice for serious *Campylobacter* infections. There may be certain situations in which azithromycin would be preferred over

TABLE 1. Susceptibilities of *C. jejuni* and *C. coli* strains to erythromycin and azithromycin

Organism (no. of strains)	Compound	MIC (µg/ml) <sup>a</sup>		
		Range	50%	90%
<i>C. jejuni</i> (20)	Erythromycin	0.12->1,024	0.25	4
	Azithromycin	0.12->1,024	0.25	4
<i>C. coli</i> (20)	Erythromycin	2->1,024	1,024	1,024
	Azithromycin	0.25->1,024	1,024	1,024

<sup>a</sup> 50% and 90%, MIC for 50 and 90% of isolates, respectively.

\* Corresponding author.

TABLE 2. MIC patterns of erythromycin and azithromycin for 40 strains of *C. jejuni* and *C. coli*

No. of strains with pattern	Hippurate hydrolysis <sup>a</sup>	MIC ( $\mu\text{g/ml}$ )	
		Erythromycin	Azithromycin
1	+	>1,024	>1,024
3	+	0.12	0.12
7	+	0.25	0.25
1	+	0.25	0.5
2	+	2	0.5
2	+	2	4
1	+	1	4
1	+	4	0.5
1	+	4	1
1	+	4	8
1	-	256	>1,024
1	-	512	>1,024
2	-	1,024	>1,024
12	-	>1,024	>1,024
1	-	2	0.25
1	-	2	0.5
1	-	2	2
1	-	2	4

<sup>a</sup> Hippurate hydrolysis: +, *C. jejuni*; -, *C. coli*.

erythromycin, since this antibiotic is active against intracellular pathogens and attains very high and persistent intracellular concentrations (1, 4). However, compared with erythromycin, azithromycin did not appear to have significantly increased potency against many of the *Campylobacter* strains examined in this study.

We thank J. Bryner, H. Endtz, H. Goosens, I. Heinzer, M. A. Karmali, P. Kibsey, G. Marien, L. Mueller, J. Prescott, D. Ribeiro, V. Stich-Groh, and R. Vanhoof for strains; B. Bablitz for technical assistance; and Pfizer Central Research for azithromycin.

This work was supported in part by an operating grant from the Natural Sciences and Engineering Research Council of Canada. D.E.T. is a Heritage Medical Scientist.

#### REFERENCES

- Bright, G. M., A. A. Nagel, J. Bordner, K. A. Desai, J. N. Dibrino, J. Nowakowska, L. Vincent, R. M. Watrous, F. C. Sciaolino, A. R. English, J. A. Retsema, M. R. Anderson, L. A. Brennan, R. J. Borovoy, C. R. Cimochoowski, J. A. Faiella, A. E. Girard, D. Girard, C. Herbert, M. Manousos, and R. Mason. 1988. Synthesis, in vitro and in vivo activity of novel 9-deoxo-9a-aza-9a-homo-erythromycin A derivatives; a new class of macrolide antibiotics, the azalides. *J. Antibiot.* **41**:1029-1047.
- Brunton, W. A. T., A. M. M. Wilson, and R. M. Macrae. 1978. Erythromycin resistant campylobacters. *Lancet* **ii**:1385. (Letter.)
- Burridge, R., C. Warren, and I. Phillips. 1986. Macrolide, lincosamide and streptogramin resistance in *Campylobacter jejuni/coli*. *J. Antimicrob. Agents Chemother.* **17**:315-321.
- Gladue, R. P., G. M. Bright, R. E. Isaacson, and M. F. Newborg. 1989. In vitro and in vivo uptake of azithromycin (CP-62,993) by phagocytic cells: possible mechanism of delivery and release at sites of infection. *Antimicrob. Agents Chemother.* **33**:277-282.
- Hardy, D. J., D. M. Hensey, J. M. Beyer, C. Vojtko, E. J. McDonald, and P. B. Fernandes. 1988. Comparative in vitro activities of new 14-, 15-, and 16-membered macrolides. *Antimicrob. Agents Chemother.* **32**:1710-1719.
- Karmali, M. A., S. DeGrandis, and P. C. Fleming. 1981. Antimicrobial susceptibility of *Campylobacter jejuni* with special reference to resistance patterns of Canadian isolates. *Antimicrob. Agents Chemother.* **19**:593-597.
- Karmali, M. A., S. A. DeGrandis, D. E. Taylor, and P. C. Fleming. 1982. On the association between erythromycin resistance and the failure to hydrolyse hippurate in *Campylobacter jejuni*, p. 218-220. In D. G. Newell (ed.), *Campylobacter—epidemiology, pathogenesis and biochemistry*. MTP Press Ltd., Lancaster, United Kingdom.
- Kitzis, M. D., F. W. Goldstein, M. Miégi and J. F. Acar. 1990. In vitro activity of azithromycin against various gram-negative bacilli and anaerobic bacteria. *J. Antimicrob. Chemother.* **25**: 15-18.
- Retsema, J., A. Girard, W. Schelkly, M. Manousos, M. Anderson, G. Bright, R. Borovoy, L. Brennan, and R. Mason. 1987. Spectrum and mode of action of azithromycin (CP-62,993), a new 15-membered-ring macrolide with improved potency against gram-negative organisms. *Antimicrob. Agents Chemother.* **31**:1939-1947.
- Tenover, F. C. (Centers for Disease Control, Atlanta). Personal communication.
- Vanhoof, R., N. P. Vanderlinden, R. Dierickx, S. Lauwers, E. Yourassowsky, and J. P. Butzler. 1978. Susceptibility of *Campylobacter fetus* subsp. *jejuni* to 29 antimicrobial agents. *Antimicrob. Agents Chemother.* **14**:553-556.
- Walder, M., and A. Forsgren. 1978. Erythromycin-resistant campylobacters. *Lancet* **ii**:1201. (Letter.)
- Wang, W.-L., L. B. Reller, and M. J. Blaser. 1984. Comparison of antimicrobial susceptibility patterns of *Campylobacter jejuni* and *Campylobacter coli*. *Antimicrob. Agents Chemother.* **26**: 351-353.
- Yan, W., and D. E. Taylor. Submitted for publication.