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In Vitro Antibacterial Activity of Norfloxacin (MK-0366, AM-715) and Other Agents Against Gastrointestinal Tract Pathogens

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A comparison was made of the in vitro activities of norfloxacin and of nine other orally administered antibacterial agents against 180 clinical isolates representing the bacterial species most frequently implicated in infections of the gastrointestinal tract in humans. The 90% minimal inhibitory concentrations showed norfloxacin to be 4, 15, 4, 17, 17, 17, and 33 times more active than the next best compound tested against *Campylobacter fetus* subsp. *jejuni*, *Escherichia coli*, *Salmonella* spp., *Shigella* spp., *Vibrio cholerae*, *Vibrio parahaemolyticus*, and *Yersinia enterocolitica*, respectively, with an overall 90% minimal inhibitory concentration of ≤0.5 μg/ml. Norfloxacin was least active against *Clostridium difficile* (90% minimal inhibitory concentration, 128 μg/ml). These results should encourage further evaluation of norfloxacin as a potential chemotherapeutic agent in the treatment of enteric bacterial infections for which antibiotic therapy is indicated.

Norfloxacin (MK-0366, AM-715) is a new orally absorbed synthetic organic acid structurally related to nalidixic acid (14, 24). Its increased potency and expanded antibacterial spectrum compare with those of nalidixic acid (9, 13, 20, 22, 23), and its desirable pharmacokinetic properties (4) make it desirable to evaluate it further as a potentially promising agent for the treatment of urinary tract infections (19; Y. Nishimura, H. Kishi, O. Tsukada, T. Tominaga, and T. Niijima, Program Abstr. Intersci. Conf. Antimicrob. Agents Chemother. 20th, New Orleans, La., abstr. no. 76, 1980). The present study was undertaken to determine the in vitro activity of norfloxacin and other oral antimicrobial agents against major bacterial species causing treatable infections of the gastrointestinal tract in humans.

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MATERIALS AND METHODS

Sources of bacterial species. A total of 180 clinical bacterial isolates of human origin were tested. *Clostridium difficile* and *Vibrio parahaemolyticus* isolates were gifts from the Centers for Disease Control (Atlanta, Ga.); enterotoxigenic strains of *Escherichia coli* were obtained from the University of Maryland School of Medicine Center for Vaccine Development (Baltimore, Md.); 01 and non-01 strains of *Vibrio cholerae* were supplied by the Thomas Jefferson Medical College *Vibrio* Reference Laboratory (Philadelphia, Pa.). Isolates of the remaining bacterial species were acquired fresh from medical centers at different locations around the United States. Upon receipt, the identity of each isolate was reconfirmed, and the organisms were stored at −70°C until needed. Before testing, all cultures were regrown in appropriate media.

Antibacterial agents. Test compounds of known potency were provided as follows: norfloxacin, Merck & Co., Inc. (Rahway, N.J.); nalidixic acid, Aldrich Chemical Co. (Milwaukee, Wis.); ampicillin sodium, Ayerst Laboratories (New York, N.Y.); tetracycline hydrochloride, Lederle Laboratories (Pearl River, N.Y.); neomycin sulfate, Sigma Chemical Co. (St. Louis, Mo.); trimethoprim, Hoffmann-LaRoche Inc. (Nutley, N.J.); chloramphenicol, Parke, Davis & Co. (Detroit, Mich.); erythromycin gluceptate, penicillin G potassium, and vancomycin hydrochloride, Eli Lilly & Co. (Indianapolis, Ind.); and clindamycin hydrochloride, The Upjohn Co. (Kalamazoo, Mich.).

Susceptibility testing. Susceptibility of the various bacterial isolates to the test agents was determined with serial twofold dilutions of each compound incorporated into Mueller-Hinton agar. For *Campylobacter fetus* subsp. *jejuni* and *Clostridium difficile*, Mueller-Hinton agar plus 5% sheep blood and Wilkins-Chalgren agar plus hemin (5 μg/ml) and vitamin K_1 (0.5 μg/ml), respectively, were used. Proper testing of trimethoprim required that Mueller-Hinton agar be supplemented with thymidine phosphorylase (0.1 U/ml) or 5% lysed horse blood.

Inocula of each test strain, except for *Campylobacter fetus* and *Clostridium difficile*, were prepared from overnight cultures grown in Trypticase soy broth (BBL Microbiology Systems, Cockeysville, Md.). For

Campylobacter fetus, inocula were prepared in Mueller-Hinton broth from scrapings of 48-h cultures previously grown on GC agar slants supplemented with 1% hemoglobin and 1% IsoVitaleX (BBL Microbiology Systems). Anaerobic bacteria (*Clostridium difficile*) were handled in an anaerobic chamber (Forma Scientific, Marietta, Ohio) and processed by established methods (35). A multipoint inoculator capable of delivering 1-μl quantities of appropriately diluted bacterial suspensions (equivalent to 0.5 McFarland standard) was used throughout. The final inoculum size was approximately 10^5 colony-forming units per spot in each case. All test plates were incubated at 37°C for 18 to 24 h except those of *Clostridium difficile* and *Campylobacter fetus*, which were incubated for 48 h at 37 and 42°C, respectively. The microaerophilic environment (7% CO_2) for optimum growth of *Campylobacter fetus* was achieved through the use of GasPak jars with Campy Pak II envelopes (BBL Microbiology Systems). The minimal inhibitory concentration (MIC) was defined as the lowest concentration of the test agent which inhibited the formation of visible colonies.

RESULTS

The comparative in vitro activities of norfloxacin and nine other antimicrobial agents against enteric pathogens, expressed as 50 and 90% MICs (MIC_{50}, MIC_{90}), are presented in Table 1. The anaerobic bacterium *Clostridium difficile* was less susceptible to norfloxacin (MIC_{90}, 128 μg/ml) and to nalidixic acid (MIC_{90}, >128 μg/ml) than to other agents and was most susceptible to vancomycin (MIC_{90}, 0.5 μg/ml). The MIC_{90}s of norfloxacin against all the aerobic isolates tested were less than 1 μg/ml, ranging from 0.008 μg/ml for *E. coli* to 0.5 μg/ml for *Campylobacter fetus* subsp. *jejuni*. With MIC_{90}s of >128 μg/ml against *Salmonella* spp., *Shigella* spp., *V. parahaemolyticus*, and *Yersinia enterocolitica*, ampicillin was the least active compound in this study. No significant difference was noted between 01 and non-01 strains of *V. cholerae* in the spectra of their antimicrobial susceptibility. *Salmonella* spp. isolates were very susceptible to norfloxacin; the two strains of *Salmonella typhi* included in this study had MICs of 0.016 and 0.03 μg/ml.

DISCUSSION

Acute diarrheal disease, usually marked by a relatively low mortality rate and high morbidity rate, remains a serious public health problem worldwide, especially in developing countries, where the problem is further complicated by malnutrition and inadequate sanitation. The proper role of antimicrobial therapy in gastrointestinal infections has remained a controversial subject, partly because of the self-limiting nature of the illnesses and the rapid emergence of resistant strains. Nevertheless, depending on (i) the severity of the disease, (ii) the likelihood of secondary transmission, (iii) the antimicrobial agent susceptibility profile of the isolate, and (iv) the safety and appropriateness of available drugs, guidelines have been formulated for the use of antimicrobial agents in specific infections involving the gastrointestinal tract or related sites (25, 26, 33). Antibiotic therapy is, therefore, indicated in the following situations: severe shigellosis, systemic salmonellosis, enteric fever, severe *Campylobacter* spp. infection, cholera, yersiniosis, and pseudomembranous colitis due to *Clostridium difficile*. More recently, the use of antimicrobial agents as chemoprophylactic agents for traveler's diarrhea owing to enterotoxigenic *E. coli* has been suggested (3).

The current drugs of choice for managing the above-mentioned enteric infections are identified in Table 1: erythromycin for *Campylobacter fetus*, vancomycin for *Clostridium difficile*, chloramphenicol for *S. typhi*, ampicillin for other salmonellae, co-trimoxazole for shigellae and enterotoxigenic *E. coli*, and tetracycline for *V. cholerae*, *V. parahaemolyticus*, and *Y. enterocolitica* (3, 21, 25, 27). Alternative drugs are also shown (Table 1). Although all the isolates tested in this study were susceptible to the present drug of choice in each case, except for *Salmonella enteritidis* against ampicillin (MIC_{90}, >128 μg/ml), various degrees of bacterial resistance have been reported for virtually all of the marketed compounds tested (3, 11, 15, 16, 18, 29). Resistance of these various enteric pathogens is defined in vitro by MIC breakpoints of ≥32 μg/ml for norfloxacin (submitted for publication), nalidixic acid, ampicillin, co-trimoxazole, and vancomycin; ≥16 μg/ml for tetracycline and chloramphenicol; ≥8 μg/ml for erythromycin and clindamycin; and ≥4 μg/ml for trimethoprim (8, 30). Except for its apparent lack of intrinsic activity against *Clostridium difficile*, norfloxacin was substantially more active and possessed a broader spectrum than any of the antimicrobial agents of first choice against enteric pathogens for which these agents are specifically indicated.

The effective use of co-trimoxazole in treating shigellosis and in preventing and managing traveler's diarrhea has been documented (2, 3, 31). We regret the inadvertent omission of this compound in the present study. It should be pointed out, however, that in several recent reports (8, 13, 15), no significant difference was noted between the antimicrobial activities of trimethoprim and co-trimoxazole. The data presented here show norfloxacin to be approximately 15 and 17 times more active than trimethoprim against enterotoxigenic *E. coli* (MIC_{90}, 0.008 versus 0.125 μg/ml) and *Shigella* spp. (MIC_{90}, 0.03 versus 0.5 μg/ml), respectively.

In previous investigations, the quinoline drugs oxolinic and nalidixic acids, to which norfloxa-

TABLE 1. Comparative antibacterial activities of norfloxacin and selected agents against gastrointestinal tract pathogens

Organism	No. of isolates	Antibacterial agent	MIC (μg/ml)		
			Range	50%	90%
Campylobacter fetus subsp. *jejuni*	28	Norfloxacin	0.06–1	0.25	0.5
		Nalidixic acid	4–32	8	16
		Ampicillin	2–>128	32	64
		Tetracycline[a,b]	0.125–>128	4	32
		Neomycin	<0.25–2	0.5	2
		Trimethoprim	2–>128	4	>128
		Chloramphenicol[a,b]	0.25–4	0.5	2
		Erythromycin[c,d]	0.125–4	0.5	2
Clostridium difficile	11	Norfloxacin	1–128	64	128
		Nalidixic acid	>128	>128	>128
		Chloramphenicol	<0.03–2	1	1
		Tetracycline	<0.03–32	0.06	32
		Clindamycin	0.25–>128	2	8
		Vancomycin[c,e]	<0.03–32	0.25	0.5
E. coli[f]	28	Norfloxacin	≤0.002–0.016	0.004	0.008
		Nalidixic acid	0.125–2	1	2
		Ampicillin	0.5–32	1	16
		Tetracycline[a,b]	0.125–>128	0.5	>128
		Neomycin	0.125–>128	1	4
		Trimethoprim[c,g]	≤0.008–0.125	0.06	0.125
		Chloramphenicol	0.25–>128	2	>128
Salmonella spp.[h]	27	Norfloxacin	0.016–1	0.06	0.125
		Nalidixic acid	4–16	4	8
		Ampicillin[a,c,e]	1–>128	4	>128
		Tetracycline	1–>128	2	4
		Neomycin	1–8	2	4
		Trimethoprim[a,g]	0.03–8	0.25	0.5
		Chloramphenicol[a,b,c]	4–>128	8	8
Shigella spp.[i]	25	Norfloxacin	0.016–0.03	0.016	0.03
		Nalidixic acid	1–2	2	2
		Ampicillin[a,e]	2–>128	>128	>128
		Tetracycline[a,b]	1–>128	2	4
		Neomycin	1–>128	4	4
		Trimethoprim[c,g]	0.016–>128	0.06	0.5
		Chloramphenicol[a,b]	0.5–128	4	8
V. cholerae[j]	26	Norfloxacin	0.008–0.125	0.008	0.015
		Nalidixic acid	0.125–1	0.25	0.5
		Ampicillin	1–8	4	8
		Tetracycline[b,c]	0.125–0.5	0.25	0.5
		Neomycin	1–8	2	4
		Trimethoprim[a,g]	0.125–0.25	0.125	0.25
		Chloramphenicol	0.25–2	0.5	1
V. parahaemolyticus	10	Norfloxacin	0.06–0.125	0.06	0.06
		Nalidixic acid	1–2	1	1
		Ampicillin	32–>128	>128	>128
		Tetracycline[b,c]	0.5–1	1	1
		Neomycin	4–8	4	8
		Trimethoprim	1–4	2	4
		Chloramphenicol	0.5–1	1	1
Y. enterocolitica	25	Norfloxacin	<0.008–0.03	0.016	0.03
		Nalidixic acid	0.25–1	0.5	1
		Ampicillin	32–>128	128	>128
		Tetracycline[b,c]	0.5–2	2	2
		Neomycin	0.25–2	1	2

TABLE 1—*Continued*

Organism	No. of isolates	Antibacterial agent	MIC (μg/ml)		
			Range	50%	90%
		Trimethoprim[a,g]	0.25–2	0.5	1
		Chloramphenicol	1–16	4	8

[a] Alternative drug.
[b] Resistant MIC breakpoint ≥ 16 μg/ml.
[c] Current antimicrobial drug of choice for the enteric pathogen indicated.
[d] Resistant MIC breakpoint ≥ 8 μg/ml.
[e] Resistant MIC breakpoint ≥ 32 μg/ml.
[f] All strains used were enterotoxigenic.
[g] Resistant MIC breakpoint ≥ 4 μg/ml.
[h] Includes 2 *S. typhi* and 25 *S. enteritidis* strains.
[i] Includes 1 *Shigella dysenteriae*, 2 *Shigella boydii*, 10 *Shigella flexneri*, and 12 *Shigella sonnei* strains.
[j] Includes 15 01 and 11 non-01 strains.

cin is structurally related, were found to be active both in vitro (6, 16) and in vivo (10, 17) against antibiotic-resistant shigellae. Furthermore, the efficacy of oxolinic acid in treating chronic *Shigella* carriers has been reported (32). It should be interesting to determine whether norfloxacin is capable of suppressing the carrier state (fecal or urinary) in shigellosis and in enteric fever caused by *S. typhi* or *Salmonella paratyphi*.

Although the development of resistance to nalidixic and oxolinic acids during treatment of urinary tract infections has been shown (1, 7), it is believed that the quinolines still have a significant advantage over other commonly used agents in that resistance appears not to be mediated by R factors (1, 5), a property which in theory should greatly limit the spread of resistant strains. In a recent study, spontaneous mutation rates of representative bacteria commonly found in the gastrointestinal tract of humans were in each case lower for norfloxacin (ca. 10^{-12}) than for oxolinic acid (ca. 10^{-6} to 10^{-10}) (12).

Selective decontamination of the gastrointestinal tract in granulocytopenic patients involving elimination of potentially pathogenic aerobic bacteria and yeasts without disturbing the anaerobic flora has been advocated as an effective means of preventing infections in patients of this kind (34). Studies in experimental animals (36) and in humans (34) have shown several antibacterial agents, including nalidixic acid and cotrimoxazole, to be suitable for this application. Successful antibiotics appear to be those agents which, like norfloxacin, lack activity against the usual anaerobic bacteria found in the fecal flora (28, 34, 36). Since the information currently at hand suggests that resistance development among enteric gram-negative bacteria, a major disadvantage of the prophylactic use of antimicrobial agents, is much less likely to occur with norfloxacin than with nalidixic acid, it would appear that evaluation of this new agent in selective suppression of bowel flora in properly selected patients is justifiable.

We believe that the data presented in this report and the accompanying comments should stimulate an interest in further evaluation of norfloxacin as a potential drug for treatable bacterial infections of the gastrointestinal tract.

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