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Evaluation of Single-Dose Ciprofloxacin in the Eradication of *Neisseria meningitidis* from Nasopharyngeal Carriers

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The ability of a single oral 750-mg dose of ciprofloxacin to eradicate *Neisseria meningitidis* from persistent nasopharyngeal carriers was prospectively evaluated in a placebo-controlled, randomized, double-blinded study. Cultures of specimens taken from all 23 ciprofloxacin-dosed subjects 1 day postdose were negative; cultures from 96% of these subjects were negative at 7 and 21 days postdose, including a specimen from a subject colonized with a minocycline-resistant strain. Of 22 placebo recipients, 20 (91%) remained culture positive. Single-dose ciprofloxacin appears efficacious for meningococcal prophylaxis.

Rifampin and minocycline are currently recommended prophylactic antimicrobial agents for *Neisseria meningitidis* infections. Although both drugs are effective, their use entails multidose regimens, as well as a risk of toxicity or occasional emergence of resistance (7, 10). The carboxyquinolone ciprofloxacin has excellent in vitro activity against *N. meningitidis* (3). In previous placebo-controlled studies, multidose regimens of ciprofloxacin have been shown to be effective in eradicating *N. meningitidis* from chronic nasopharyngeal carriers up to 2 weeks after dosing (13). Furthermore, in an uncontrolled study, 11 of 12 *N. meningitidis* carriers given a single oral 750-mg dose of ciprofloxacin remained culture negative for 2 weeks after the dose (14). We report here the results of a placebo-controlled, randomized, double-blinded study of single-dose ciprofloxacin in persistent *N. meningitidis* carriers.

Written informed consent was obtained from 620 healthy young volunteers, who were then evaluated for persistent nasopharyngeal carriage of *N. meningitidis* by means of two cultures taken 1 week apart, followed by a third culture taken 9 days later. Forty-six subjects whose cultures grew *N. meningitidis* on all three occasions were identified. These subjects provided a medical history and underwent a physical examination. They were tested for pregnancy by means of a qualitative test for human β-choriogonadotropin in urine; pregnant individuals were excluded from the trial. No subjects were allergic to quinolone drugs, had used antibiotics within 2 weeks of ciprofloxacin dosing, or had a symptomatic infection.

Subjects were randomly assigned to take a single 750-mg oral dose of ciprofloxacin or a placebo tablet with an identical appearance. Nasopharyngeal cultures were taken 1, 7, and 21 days after dosing. All tablets were administered under supervision, and subjects were requested to report all adverse effects. At the time of the 7-day-postdose culture, a repeat physical examination was performed.

Nasopharyngeal swabs were streaked onto modified Thayer-Martin agar and incubated at 37°C in 10% CO_2–90% air for 48 h. Colonies that resembled *N. meningitidis* were identified by Gram stain, positive oxidase reaction, and fermentation of glucose and maltose but not sucrose and lactose. Serogroups were determined by the slide agglutination technique with the cells suspended in physiological saline. Antisera were obtained from Burroughs Wellcome Co., Research Triangle Park, N.C. Ciprofloxacin, minocycline, and rifampin MICs were determined by using an inoculum of 10^5 CFU per spot incubated onto Mueller-Hinton agar in 10% CO_2 in air at 37°C. Sulfonamide susceptibility was screened by the same method with plates containing 10 μg of sulfamethoxazole per ml (12). Susceptibility tests and serogrouping were performed on the isolates obtained from the third predose culture (immediately before dosing), as well as on any isolates obtained in postdose cultures from subjects who took ciprofloxacin.

Of the 46 subjects who entered the study, 24 received ciprofloxacin and 22 received placebo. Three ciprofloxacin recipients and two placebo recipients noted gastrointestinal symptoms of abdominal cramps, nausea, or diarrhea. One subject who received ciprofloxacin noted headache and fatigue. All symptoms were short lived (less than 24 h) and did not interfere with normal activities.

Of the 46 initial isolates of *N. meningitidis*, serogroups B (19 isolates) and Z (15 isolates) were encountered most frequently. There were three isolates each of serogroups X and Y, two isolates each of serogroups A and C, and two nontypeable isolates. The distribution of serogroups between the ciprofloxacin- and placebo-dosed groups did not differ significantly. The MIC of ciprofloxacin for the 46 initial isolates ranged from 0.0019 to 0.0040 μg/ml. For minocycline, one resistant isolate (MIC, 4.0 μg/ml) was encountered; the MICs for the remaining 45 isolates were ≤0.5 μg/ml. Two rifampin-resistant isolates were found (MIC, >0.25 μg/ml). For the remaining, MICs were ≤0.12 μg/ml. Eighteen sulfonamide-resistant isolates (39%) were encountered (MIC, >10 μg/ml).

Of the 24 subjects who received ciprofloxacin, 23 returned for all three postdose cultures. All 23 subjects whose specimens were cultured on day 1 postdose were negative; 22 remained negative at days 7 and 21 postdose. One subject did not return for the day 1 postdose culture, but was culture negative on days 7 and 21 postdose. One subject was culture negative on day 1 postdose, but reverted to being culture positive on days 7 and 21. The serogroup of and MIC for this postdose isolate did not differ from those associated with the predose isolate. Six ciprofloxacin-dosed subjects had sulfonamide-resistant isolates, and one had a minocycline-resistant isolate; all isolates were eradicated by ciprofloxacin.

Of the 22 subjects who received placebo, 20 (91%) persis-

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tently carried *N. meningitidis* when cultures were performed 1, 7, and 21 days later.

After the appearance of sulfonamide resistance among *N. meningitidis* strains, a number of antibiotics were studied for possible efficacy in prophylaxis of meningococcal infections (1, 2, 5, 6, 8, 10). Rifampin (5, 10) and minocycline (10) were shown to eradicate nasopharyngeal meningococcal carriage and are currently the approved agents for prophylaxis. However, multidose regimens of these antibiotics are required. In addition, minocycline has associated vestibular toxicity (11), and rifampin resistance has been noted among meningococcal strains isolated from subjects given the drug (7, 10). A case of meningitis caused by a rifampin-resistant strain in a child given rifampin prophylaxis has been reported (4).

Ciprofloxacin has excellent in vitro activity against *N. meningitidis* (3). Moreover, obtainable levels in both serum and nasopharyngeal secretions exceed the MIC for meningococci (17). In a previous study, we showed that a 5-day regimen of ciprofloxacin (500 mg every 12 h) is highly effective in eradicating *N. meningitidis* from persistent nasopharyngeal carriers for at least 2 weeks after dosing (13). A similar study from Finland indicated that administration of 250 mg perorally twice daily for 2 days eradicated meningococcal carriage in 96% of subjects when specimens were cultured 4 days after dosing (15). We noted in the former study that all carriers were culture negative after 24 h of ciprofloxacin administration, suggesting that a shorter dosing period might be adequate (13). A single-dose regimen would significantly improve patient compliance. An uncontrolled study of a single 750-mg oral dose of ciprofloxacin in 12 subjects showed meningococcal eradication in all subjects at 24 h, and this effect persisted for 2 weeks in 11 of the 12 subjects (14). Subsequently, an open study involving a single dose of 500 mg demonstrated similar results, eliminating nasopharyngeal meningococcal carriage for up to 9 weeks in 93% of subjects (9).

The present controlled, blinded study confirms the results of the open studies cited above the demonstrates that sulfonamide- or minocycline-resistant strains are also eradicated by ciprofloxacin. This antibiotic appears to be well tolerated, and its use has not been associated with the emergence of resistant strains. We believe that ciprofloxacin, 750 mg orally, given once, is effective prophylaxis for meningococcal infections in indicated populations. Because ciprofloxacin causes cartilage deterioration in juvenile laboratory animals, its use is not recommended in patients less than 17 years old or in pregnant or nursing women. Meningococcal prophylaxis during pregnancy remains a difficult problem in that tetracyclines are contraindicated and rifampin is not recommended. Ceftriaxone may prove to be a suitable alternative (16).

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