Role of Quinolones in the Treatment of Bronchopulmonary Infections, Particularly Pneumococcal and Community-Acquired Pneumonia

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In view of their antimicrobial activity and pharmacological properties, fluoroquinolones should be suitable for the treatment of lower respiratory tract infections. The overall clinical success rate using enoxacin, ofloxacin, pefloxacin, and ciprofloxacin ranges from 81% to 89%. Despite relatively high MICs of the fluoroquinolones for *Streptococcus pneumoniae*, the clinical success rate of these drugs in pneumococcal infections is 91%, but the eradication rate of this pathogen is lower (73%). In addition, fluoroquinolones appeared to be as effective as standard antibiotic regimens for treatment of bronchopulmonary infections in most of the comparative trials reported. The new quinolones could be a good alternative for treatment of acute exacerbations of chronic bronchitis, especially if examination of the sputum reveals gram-negative pathogens. In community-acquired pneumonia, drugs other than quinolones seem indicated because of the limited efficacy of the new quinolones in the treatment of severe pneumococcal infections and the poor activity of these drugs against the anaerobic flora causing aspiration pneumonia. In contrast, new quinolones should be very suitable for treatment of nosocomial pulmonary infections due to gram-negative pathogens. Quinolones used with or without erythromycin and rifampicin, might be useful in the treatment of Legionnaires' disease. The role of these drugs in treatment of *Chlamydia* and *Rickettsiae* infections remains to be defined.

The new fluoroquinolones have good antibacterial activity against most of the respiratory pathogens. In vitro studies have shown enoxacin, pefloxacin, ofloxacin, and ciprofloxacin to be active against *Haemophilus* spp., *Moraxella catarrhalis*, *Staphylococcus aureus*, *Enterobacteriaceae* and *Pseudomonas aeruginosa* (1, 2); *Legionella pneumophila*, *Chlamydia trachomatis* and *Mycoplasma pneumoniae* are also susceptible to these drugs (1, 2). Least susceptible of the common respiratory pathogens is *Streptococcus pneumoniae*, especially to enoxacin and pefloxacin (1, 2). In addition, penetration of the quinolones into respiratory tissues and secretions is good. Comparing the ratio of the areas under the concentration curves in bronchial secretions and in serum, the penetration of these drugs from the blood to the bronchial lumen may approach 1.0 (3, 4). High levels of some quinolones have been found in bronchial mucosa and lung tissues (5, 6, 7).

Moreover, excellent penetration of the drugs into phagocytic cells may be important in the treatment of infections due to intracellular pathogens such as *Mycoplasma* and *Legionella* (8). Thus, in view of their antimicrobial activity and pharmacological properties, these new compounds may have an important role in the treatment of lower respiratory tract infections.

Before reviewing clinical studies on the role of quinolones in the treatment of bronchopulmonary infections, some reservations must be expressed. Many available references are summaries of large multicenter studies or short abstracts which are sometimes difficult to interpret. In many studies which include cases of both bronchitis and pneumonia, the response rates in the two groups are often not separated. Patients with various types of bronchial infections are often grouped together. It must be kept in mind that in acute exacerbations of chronic bronchitis the criteria for the efficacious use of antimicrobial therapy are poorly defined (9): it is quite likely that many patients had viral infections or trivial bacterial infections which would have cleared without antimicrobial therapy. Moreover, in
numerous studies the microbiological data are not sufficient. Screening of sputum samples by microscopic examination before culture to exclude specimens with heavy contamination by oral secretions is not regularly performed, so that the results of sputum culture could be questioned. Important bacteriologic information (e.g. the emergence of resistant strains, colonization, or superinfection) is frequently lacking. Finally, very few comparative studies are of sufficient size to detect small differences between the groups compared.

Among the quinolones, ciprofloxacin and ofloxacin have been the most extensively studied in the treatment of respiratory infections. Clinical experience with enoxacin and pefloxacin is more limited. The most informative data on the efficacy of these four compounds in the treatment of lower respiratory tract infections will be summarized, especially for pneumococcal infections. Information on other quinolones currently under preliminary clinical investigation such as lomefloxacin (G. Amaya et al., 29th Interscience Congress on Antimicrobial Agents and Chemotherapy (ICAAC), 1989, Abstract no. 549) and temafloxacin (P. Aldons, 7th Mediterranean Congress of Chemotherapy (MCC), 1990, Abstract no. 847) will not be presented.

Enoxacin

Five studies have evaluated the clinical efficacy of enoxacin in 150 courses of treatment in 148 assessable patients presenting with a lower respiratory tract infection (purulent bronchitis or allied disorders, 123 cases; pneumonia, 25 cases) (10-14). The daily dose was 800 mg (400 mg twice a day) for 7 to 14 days; in two of these studies (10, 11), a larger dose (600 mg twice a day) was given to 29 patients, 23 of them presenting with a Pseudomonas aeruginosa infection. Of the 150 treatment courses, 137 (91 %) were considered clinically successful. Ninety-nine (75 %) of 132 pathogens were eradicated, including all but one 41 Haemophilus influenzae strains and 27 (71 %) of 38 Streptococcus pneumoniae strains. Only 13 (42 %) of 31 Pseudomonas aeruginosa strains were eradicated. In one series, the MICs for most persisting strains of Pseudomonas aeruginosa after enoxacin therapy were two to four times higher than pretreatment values (10). Streptococcus pneumoniae persisted in the sputum of 11 patients, eight of whom were clinically cured. Treatment failed clinically and bacteriologically in three patients infected with Staphylococcus aureus; superinfection occurred in six cases (Streptococcus pneumoniae, 4; Streptococcus agalactiae, 1; Pseudomonas aeruginosa, 1) (10, 13).

The clinical efficacy of enoxacin was evaluated in 121 patients with pneumonia (16 cases) or various bronchial infections (105 cases) (data on file, Warner Lambert/Parke Davis, Ann Arbor, MI, USA). An oral dose of 400 mg was administered twice a day to most of these patients. The clinical response rate was satisfactory in 107 patients (88 %). One hundred and ten patients were infected with 131 pathogens sensitive to the study drug: 83 (63 %) of the strains were eradicated, including all 40 strains of Haemophilus influenzae, but only 13 (62 %) of 21 Streptococcus pneumoniae strains and 13 (35 %) of 37 Pseudomonas aeruginosa strains. After eradication of the primary pathogen, colonization of the sputum occurred in eight patients, Streptococcus pneumoniae being found in six patients.

The efficacy of enoxacin treatment in acute exacerbations of chronic bronchitis due to gram-negative pathogens (mostly Haemophilus influenzae and Moraxella catarrhalis) was compared with that of amoxicillin in a small series of patients: clinical and bacteriological cure rates were similar (15).

Pefloxacin

In one study, 42 patients with an acute exacerbation of chronic bronchitis were treated with pefloxacin (400 mg twice a day) for ten days (16). The causative organisms were Haemophilus influenzae (20 cases), Moraxella catarrhalis (20 cases), Streptococcus pneumoniae (13 cases), and Pseudomonas aeruginosa (6). Thirty-four patients (81 %) were either cured of the infection or their condition improved. All strains of Haemophilus influenzae and all but two strains of Moraxella catarrhalis were eradicated. In contrast, pneumococci persisted in the purulent sputum of 8 of 13 patients at the end of treatment; in the week after treatment eight more patients had purulent sputum from which Streptococcus pneumoniae was isolated. Similarly, only three of the six strains of Pseudomonas aeruginosa were suppressed. In addition, strains of Pseudomonas aeruginosa and Streptococcus pneumoniae were more resistant after treatment, the geometric mean MICs before and after treatment being 3.8 and 8.3 mg/l for Streptococcus pneumoniae and 3.0 and 16.0 mg/l for Pseudomonas aeruginosa, respectively. Benard et al. (17) treated 89 patients with an acute superinfection of various bronchial diseases, including 76 in whom previous antibiotic therapy had failed. Pefloxacin was given as a single daily dose (800 mg). Seventy-five (84 %) of the patients were cured. The bacterial eradication rate, which was assessable for 32 of 45 pathogens, was 91 %. No Streptococcus pneumoniae were observed among four persisting or superinfecting strains.