A double-blind comparison of low-dose ofloxacin and amoxycillin/clavulanic acid in acute exacerbations of chronic bronchitis


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The efficacy and safety of ofloxacin 400 mg once daily and amoxycillin/clavulanic acid 500/125 mg three times daily were compared in a double-blind manner in patients with an acute exacerbation of chronic bronchitis. Of 102 patients enrolled, 95 (93%) could be assessed for effectiveness. Treatment success was achieved in 41 (84%) of 49 patients in the ofloxacin group compared with 41 (89%) of 46 patients in the amoxycillin/clavulanic acid group. One patient who received ofloxacin and four patients in the amoxycillin/clavulanic acid group stopped medication because of unacceptable side effects. Microbiological results were evaluable in 47% of the patients. Predominant initial pathogens were Haemophilus influenzae, Streptococcus pneumoniae, sometimes in combination, and less frequently Branhamella catarrhalis. In two patients with clinical failure, randomized to ofloxacin, the initial pneumococcal strains persisted in the sputum after treatment.

Introduction

Ofloxacin, a quinolone inhibitor of bacterial DNA gyrase, has a wide spectrum of antibacterial activity and exhibits favourable pharmacokinetic properties, including good penetration into bronchial secretions (Davies et al., 1987; Lode et al., 1987; Rademaker et al. 1989). In contrast to other quinolones it can be safely administered to patients who are on chronic theophylline therapy (Wijnands et al., 1987). Several studies have assessed the clinical efficacy and safety of ofloxacin in patients with exacerbations of chronic bronchitis (Maesen et al., 1986, 1987; Grassi, Grassi & Mangiarotti, 1987; Harazim, Wimmer & Mittermayer, 1987). Doses ranged from 100–800 mg per day given once or twice daily. Most studies were non-comparative or non-randomized. In few studies was bacteriological efficacy assessed. In the studies of Maesen et al. (1986, 1987), the bacteriological and clinical results of ofloxacin treatment were better when a single daily dose was given in comparison with twice daily administration. The number of patients evaluated however was limited. In this double-blind randomized study we compared the efficacy and safety of a low dose of ofloxacin once daily versus amoxycillin/clavulanic acid three times daily in patients with an acute exacerbation of chronic bronchitis.
Patients and methods

Patients

One hundred and two adult in- or out-patients with an acute exacerbation of chronic bronchitis were enrolled in this study. Patients were recruited at two locations: the Central Military Hospital and the University Hospital in Utrecht, The Netherlands. In this double-blind study, patients were randomized to receive either ofloxacin 400 mg once daily or amoxycillin/clavulanic acid 500/125 mg three times daily orally in a double dummy manner. Duration of treatment was ten days. Patients who were also taking an aluminium or magnesium containing antacid took the antibiotics after an interval of at least 4 h.

Patients were excluded in cases of terminal illness, detection of new pulmonary infiltrates on chest X-ray, fever above 38.5°C, pregnancy or lactation, any history of convulsive disorders, known allergy to one of the study drugs, known renal impairment with serum creatinine above 125 μmol/l, and concomitant use of antibiotics or use of antibiotics within 48 h prior to treatment. The study protocol was approved by the hospital’s Medical Ethics Committee for Human Studies. Informed consent was obtained from all patients.

Chronic bronchitis was defined according to the American Thoracic Society as a chronic or recurrent productive cough present on most days for a minimum of three months a year and for at least two successive years. An acute exacerbation was defined in terms of symptoms according to Anthonisen et al. (1987). Three levels of severity of exacerbation were recognised. Type-1 exacerbation (the most severe grade) was defined as increased dyspnoea, increased sputum volume and increased sputum purulence. Type-2 exacerbation (a lesser grade) was defined as occurring when two of these three symptoms were present and Type-3 exacerbation (the least severe grade) as occurring when one of the three symptoms was present in addition to at least one of the following findings: fever 37.5°-38.5°C, sore throat or nasal discharge within the previous five days, increased wheezing or increased cough.

Study procedures

Each patient was clinically examined before, during (days 3–5), and after (days 14–17) therapy. Before and after therapy serum biochemistry and haematology were monitored. Creatinine clearances were calculated according to Cockcroft & Gault (1976). If the body weight diverged more than 20% from the Lean Body Mass, corrections according to Devine (1974) were made. The second visit, which was scheduled during therapy, included monitoring for possible side effects of the drug. Compliance was confirmed by counting remaining tablets which were returned on the third visit (after therapy). If a patient had not fully recovered on the third visit, he was seen again one week later to assess definite outcome after 21–24 days from the start of treatment.

Microbiological procedures

Sputum cultures were performed before and after therapy. Micro-organisms were isolated and identified according to standard bacteriological methods. Antimicrobial susceptibility to the study drugs was determined by minimal inhibitory concentrations using an agar dilution method with Iso-Sensitest agar (Oxoid, UK). From each sputum
a Gram stain was examined to determine the number of leucocytes. A sputum was considered to be reliable for culture if it contained less than ten epithelial cells per microscopic field (× 1000). On the first and the third visit blood samples were obtained for serological examination. Antibodies against respiratory pathogens such as influenza virus type A and B, parainfluenza virus, respiratory syncytial virus, adenovirus, Chlamydia psittaci, Mycoplasma pneumoniae, Ch. pneumoniae and Coxiella burnetii were determined. Infection was diagnosed if there was at least a four-fold rise in antibody titres.

**Evaluation of therapy**

Clinical response to therapy was classified as follows. Treatment success was defined as cure or major improvement of symptoms; failure was defined as persistence or deterioration of symptoms of infection or if side effects of the study drug led to discontinuation of therapy. The patient had to take the study medication for a minimum of five full days, unless there was clear evidence of therapeutic failure or presence of side effects, to be eligible for evaluation. Bacteriological response was graded as follows: eradication of causative micro-organism when the second culture became negative; persistence when the second culture remained positive yielding the same organism; reinfection when the second culture showed growth of a new pathogen; indeterminate when the pre-study culture was negative.

**Statistical analysis**

The two treatment groups were compared for efficacy by the chi square test. For comparison of means ± S.D. of patient’s demographic and medical characteristics before study entry, the Student’s t-test was used.

**Results**

**Clinical evaluation**

Of 102 patients enrolled 95 (93%) were evaluable for clinical efficacy. Seven patients were withdrawn for reasons other than the occurrence of side effects. In one case another diagnosis was made; in six cases the patients did not take their study medication or did not attend for the third visit. Table I shows the patient characteristics. The two treatment groups were comparable with respect to age, creatinine

<table>
<thead>
<tr>
<th>Table I. Patient characteristics</th>
<th>Ofloxacin</th>
<th>Amoxycillin/ clavulanic acid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>49</td>
<td>46</td>
</tr>
<tr>
<td>Mean age (± S.D.)</td>
<td>56 (17)</td>
<td>56 (17)</td>
</tr>
<tr>
<td>Creatinine clearance (± S.D.)</td>
<td>85 (31)</td>
<td>86 (27)</td>
</tr>
<tr>
<td>Type-1 exacerbation</td>
<td>37</td>
<td>36</td>
</tr>
<tr>
<td>Type-2 exacerbation</td>
<td>10</td>
<td>7</td>
</tr>
<tr>
<td>Type-3 exacerbation</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

*ml/min.
clearance and the majority of patients suffered a Type-1 exacerbation. Clinical response is presented in Table II. Treatment was successful in 41 (84%) patients receiving ofloxacin compared with 41 (89%) patients in the amoxycillin/clavulanic acid group. Treatment failures occurred in 8 (16%) patients in the ofloxacin group versus 5 (11%) in the amoxycillin/clavulanic acid group (n.s.).

**Microbiological evaluation**

Nearly half (47%) of the patients were evaluable for microbiological response and data are presented in Table III. The predominant initial pathogens were *Haemophilus influenzae, Streptococcus pneumoniae*, sometimes in combination, and, less frequently, *Branhamella catarrhalis*. Eradication or reduction to clinically insignificant numbers occurred in 38% in the ofloxacin group versus 33% in the amoxycillin/clavulanic acid group. Persistence of the causative organism or subsequent isolation of another pathogen was seen in 10% in the ofloxacin group versus 12% in the amoxycillin/clavulanic acid group. Table IV shows the pathogens isolated from sputum before and after therapy. Fifteen patients in the ofloxacin group had initial cultures of *H. influenzae* compared with 13 patients in the amoxycillin/clavulanic acid group. These pathogens were all eradicated in the patients treated with ofloxacin while *H. influenzae* strains persisted in the sputum of three patients treated with amoxycillin/clavulanic acid. *S. pneumoniae* was isolated before therapy in five patients in the ofloxacin group and six in the amoxycillin/clavulanic acid group. After treatment three pneumococcal strains persisted in the ofloxacin group compared with one in the group treated with amoxycillin/clavulanic acid. Two of these patients in the ofloxacin group suffered a clinical failure and needed to be treated with other antibiotics. *B. catarrhalis*
Table IV. Pathogens isolated from sputum before and after therapy

<table>
<thead>
<tr>
<th>Organism</th>
<th>Number of patients</th>
<th>ofloxacin before</th>
<th>ofloxacin after</th>
<th>amoxycillin/ clavulanic acid before</th>
<th>amoxycillin/ clavulanic acid after</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>H. influenzae</em></td>
<td>15</td>
<td>0</td>
<td>13</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td><em>S. pneumoniae</em></td>
<td>5</td>
<td>3*</td>
<td>6</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td><em>B. catarrhalis</em></td>
<td>1</td>
<td>0</td>
<td>4</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

*Two patients with clinical failure.

was eradicated in all patients. The MICs of ofloxacin for *H. influenzae* and *B. catarrhalis* were 0.06 and 0.12 mg/l respectively and did not alter after therapy. The MIC of ofloxacin for initial isolates of *S. pneumoniae* was in the range of 1–4 mg/l and did not change after treatment in patients with persistence of the strains. Viral serology was performed in fifty patients. Six (12%) of them showed a significant rise in antibody titres. In four of these six patients no pathogenic bacteria were cultured from the sputum at admission; one patient had *H. influenzae* and another a combination of *H. influenzae* and *S. pneumoniae*. All six patients with a rise in viral antibody titres were cured after therapy.

Side effects

One patient in the ofloxacin group and four patients in the amoxycillin/clavulanic acid group stopped treatment because of unacceptable side effects. These included gastrointestinal symptoms such as nausea, vomiting and diarrhoea. One patient in the amoxycillin/clavulanic acid group discontinued treatment because of a rash. In addition one patient in each group had nausea, but the study drug did not have to be discontinued.

Discussion

Most physicians include an antibiotic in their treatment regimen for acute exacerbations of chronic bronchitis. However, the question of the need for antibiotics in the management of such patients is still unanswered (Leading article, 1987). Anthonisen et al. (1987) reported a large community-based study in which exacerbations were followed in 173 patients with chronic bronchitis over a 3-5 year period. Treatment consisted of antibiotic or placebo administered in a randomized double-blind crossover fashion. They defined three levels of severity of exacerbation (we recognized the same types in our study) and demonstrated that there was a significant benefit associated with antibiotic treatment in the most severe exacerbation, classified as Type-1 at onset and comprising worsening dyspnoea with increased sputum volume and purulence. However in order to assess the value of antibiotics it is necessary to know how often the exacerbation has a bacterial cause rather than a viral cause. Contrary to other studies (Lamy, Pouthier-Simon & Debacker-Willame 1974; Gump et al., 1976); only 12% of exacerbations in this study could be related to viral infections.
The clinical outcome of ofloxacin 400 mg administered once daily was satisfactory when compared with amoxycillin/clavulanic acid 500/125 mg three times daily. After treating 95 patients no statistical difference was found between the two study drugs. Our study showed a minor relationship between the clinical and the microbiological response of the study drugs. In three patients with clinical failures, randomized to ofloxacin, there was a correlation with the results of the sputum cultures: in two patients the initial pneumococcal strains persisted and in one patient the pre-study sputum was negative but the second sputum yielded pneumococci. One patient in the amoxycillin/clavulanic acid group who did not respond to therapy was cleared of H. influenzae but became colonized with Citrobacter freundii after therapy. In the other clinical failures no pathogens were cultured after therapy (four patients) or medication was discontinued because of side effects (five patients). Several times pathogens were cultured from the second sputum (which was taken four to seven days after end of therapy) without any symptoms of infection. This may be due to colonization of the respiratory tract with these organisms, a well known phenomenon in patients with chronic bronchitis.

The dose of ofloxacin used in this study was low compared with that used in other studies. Pharmacokinetic studies have shown that a 400 mg dose of ofloxacin results in a maximum serum concentration of 3.5–5.3 mg/l (Lode et al., 1987) and in a maximum sputum concentration of 2.7 mg/l (Davies et al., 1987). Although the corresponding concentrations at the sites of infections in chronic bronchitis may be higher (Couraud et al., 1987) it seems advisable to treat pneumococcal infections (MIC of ofloxacin was 1–4 mg/l for pneumococci) with 600 or 800 mg ofloxacin rather than with a low dose of 400 mg once daily.

In conclusion, in this study involving 95 patients, we could not demonstrate differences in clinical response in the treatment of exacerbations of chronic bronchitis between ofloxacin 400 mg once daily and amoxycillin/clavulanic acid 500/125 mg three times daily. Ofloxacin seems a useful antibiotic in the treatment of Gram-negative infections in chronic bronchitis. If the sputum smear reveals the presence of Gram-positive diplococci, some reservation has to be expressed about the use of ofloxacin in such a low dose.

Acknowledgement

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References


