Introduction

Macrolides are frequently recommended as first-line treatment for acute community-acquired respiratory tract infections because their spectrum of activity includes not only the typical Gram-positive and Gram-negative organisms usually responsible for these infections in general practice, but also atypical organisms, such as Legionella, Mycoplasma and Chlamydia spp.

Roxithromycin was the first of the new-generation macrolides. It is an acid-stable, semisynthetic, 14-membered molecule that retains the appropriate antibacterial profile of the older macrolides, but has significantly better pharmacokinetic characteristics enabling it to be given in a single or divided dosage of 300 mg daily. Its antibacterial profile includes Staphylococcus aureus, Streptococcus pneumoniae, Streptococcus pyogenes, Moraxella catarrhalis, Mycoplasma pneumoniae, Legionella pneumophila, Chlamydia trachomatis, some anaerobes and other less common pathogens. Clarithromycin is an acid-stable analogue of erythromycin with a methoxy substitution at position C-5 of the erythromycin ring. At therapeutic dosage, the concentration of clarithromycin in blood and tissues exceeds MICs for a variety of bacteria. In general, none of the macrolide antibiotics are active against mecillinam-resistant S. aureus, Staphylococcus epidermidis or Pseudomonas spp.

Patients were randomly assigned to two parallel groups in a trial to compare the efficacy and tolerance of roxithromycin and clarithromycin in the treatment of lower respiratory tract infection (LRTI).

Materials and methods

Study design

The trial was an open, randomized, study of 60 hospital patients and outpatients suffering from exacerbation of chronic bronchitis or community-acquired pneumonia, randomly allocated to one of two parallel groups, A and B (see below). The study was approved by the Evangelismos Hospital Ethics Committee and by the Greek Drug Organization. All patients gave written informed consent and their medical history was taken before entry. Biochemical tests, chest X-rays and a sputum culture were carried out before and immediately after treatment. For patients with pneumonia, blood cultures and serological tests were taken for M. pneumoniae, L. pneumophila, and Chlamydia pneumoniae, and an additional chest X-ray made on day 2 or 3 of treatment. A follow-up assessment was carried out on day 28. Patients were excluded from the study if they had received antibiotics within 3 days before entry or were receiving antibiotics for other reasons, had a history of hypersensitivity to macrolides or were pregnant.

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or lactating females. Those suffering from hepatic or renal impairment, or significant gastrointestinal disease (including previous major surgery) were excluded.

**Patients**

Group A comprised 16 patients with chronic bronchitis and 14 with pneumonia. Group B comprised 12 patients with chronic bronchitis and 18 with pneumonia. All patients had active disease, as was evident from purulent sputum, fever, cough, chest pain, or shortness of breath. Details of the sex, age, height and weight of patients in each group are shown in Table I; there was no statistically significant difference in these demographic details between the two groups.

**Statistical analysis**

The size of the study was such that it had a very low power to detect a difference in efficacy between the two drugs. The unpaired *t*-test for continuous variables was used in statistical analysis of rates of adverse events.

**Clinical and microbiological assessment**

The clinical response was classified as: (i) ‘satisfactory’ if the infection cleared completely or improved appreciably, based on the resolution of signs and symptoms, with laboratory and radiographic evidence of improvement or cure; (ii) ‘unsatisfactory’ if infection worsened or remained the same; or (iii) ‘unevaluable’ if the assessment was not classified due to different reasons.

The bacteriological efficacy was classified as: (i) ‘satisfactory’ if the causative pathogen was eradicated from post-treatment culture, even if a new potential pathogen was present without clinical evidence of a new infection, or the patient improved to such an extent that a post-treatment culture could not be obtained; (ii) ‘unsatisfactory’ if a causative pathogen was present in post-treatment culture, or the causative pathogen was eradicated but a new pathogen cultured with clinical evidence of a new infection; or (iii) ‘unevaluable’ if no pathogenic organism was cultured either before or after treatment.

**Treatment**

Patients in group A were treated with roxithromycin 300 mg od, and those in group B with clarithromycin 500 mg bd. The mean duration of treatment was 8 days for both groups, with a range of 4–17 days in group A and 4–16 days in group B. The duration of treatment did not differ significantly between the two groups.

**Results**

Of the 60 enrolled patients, only 50 (25 from each group) completed the study and were clinically evaluable. Ten patients were withdrawn from the study and not clinically assessed (Table II). All 50 patients were treated for 3 days or more. Three patients on clarithromycin withdrew after the second day of treatment, two because of melaena and one because of epigastric pain. The melaena was not known to be drug-related. It was documented macroscopically, and one patient underwent gastroscopy that revealed gastritis. Chronic renal insufficiency in a patient on roxithromycin was not considered drug-related.

**Clinical efficacy**

Clinical outcome was satisfactory in 22 (88%) of 25 patients on roxithromycin and 20 (80%) of 25 patients on clarithromycin. Patients had to receive a minimum of 3 days’ treatment to be evaluable for efficacy.

**Table I. Patient demographic details**

<table>
<thead>
<tr>
<th></th>
<th>Roxithromycin (n = 30)</th>
<th>Clarithromycin (n = 30)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex (n, %)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>male</td>
<td>17 (56.6)</td>
<td>17 (56.6)</td>
<td>34 (56.6)</td>
</tr>
<tr>
<td>female</td>
<td>13 (43.3)</td>
<td>13 (43.3)</td>
<td>26 (43.3)</td>
</tr>
<tr>
<td><strong>Age (years)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>range</td>
<td>18–83</td>
<td>20–83</td>
<td>18–83</td>
</tr>
<tr>
<td>mean ± s.d.</td>
<td>58 ± 19</td>
<td>60 ± 17</td>
<td>59 ± 18</td>
</tr>
<tr>
<td><strong>Height (cm)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>range</td>
<td>145–184</td>
<td>142–175</td>
<td>142–184</td>
</tr>
<tr>
<td>mean ± s.d.</td>
<td>165 ± 9</td>
<td>165 ± 8</td>
<td>165 ± 9</td>
</tr>
<tr>
<td><strong>Weight (kg)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>range</td>
<td>42–97</td>
<td>54–87</td>
<td>42–97</td>
</tr>
<tr>
<td>mean ± s.d.</td>
<td>68 ± 15</td>
<td>69 ± 9</td>
<td>68 ± 13</td>
</tr>
</tbody>
</table>
Resolution of fever occurred after 1–13 days' treatment, while symptoms (cough and sputum) disappeared after 2–8 days' treatment. There was no statistically significant difference between the groups. The radiological response at the end of treatment was satisfactory (chest radiograph normal) in 20/25 patients (80%) in each groups and unsatisfactory (unsuccessful) in two patients (8%) in each group. Three patients from each group were not evaluable radiologically. No change in clinical or radiological condition was recorded at follow-up (day 28). For both groups, the chest radiograph on day 2 or 3 of treatment in patients with pneumonia showed an improvement.

**Bacteriological efficacy**

Sputum culture was performed before and after treatment in all evaluable patients. Bacteriological assessment after treatment was not performed in the ten patients withdrawn from the trial. Of the 60 patients enrolled, ten had a single pathogen isolated at the beginning of the study and one had two pathogens isolated; the remaining 49 patients had normal flora. The pathogens isolated from sputum before treatment were resistant to both macrolides in four of the 11 patients, three of whom were in the roxithromycin group and one in the clarithromycin group. These patients were excluded from the final evaluation. Resistant pathogens in group A were *Klebsiella pneumoniae* (n = 1) and *Pseudomonas aeruginosa* (n = 2). *Proteus mirabilis* and *Enterobacter* spp. were isolated from one patient in group B. A further patient from group B was lost to follow-up before the final bacteriological evaluation could be performed.

Of the 11 patients from whom bacteria had been isolated or diagnosed serologically before treatment, six (three from each group) were evaluable for bacteriological efficacy. Details of these pathogens are given in Table III.

Two patients on roxithromycin developed super-infection during treatment (the initial culture was negative). No pathogen was cultured before treatment, but after 5 days' treatment, sputum culture revealed two pathogens resistant to both macrolides: *K. oxytoca* in one patient and *P. mirabilis* in the other. Sputum culture from one patient on clarithromycin revealed *Enterobacter* spp. resistant to both macrolides during treatment. In a second patient on clarithromycin who had a pre-treatment *Enterobacter* spp. sensitive to both macrolides, sputum culture revealed *Enterobacter* spp. and *K. pneumoniae* resistant to both macrolides on day 5. Of those patients who were evaluable before and during treatment a satisfactory response was found in 60% given roxithromycin and 50% given clarithromycin. The response was both bacteriological and clinical.

**Safety**

All 60 patients were evaluated for tolerance as they had all received at least one dose of the study drug. Only one (3.3%) of the patients on roxithromycin reported an adverse event, a slight epigastric pain which did not require treatment. However, seven (23.3%) of the 30 patients on clarithromycin reported adverse events (Table IV). In three of these patients the study medication was withdrawn after the third day of treatment and so these patients were not clinically evaluated (Table II). In three other patients the study medication was withdrawn after the third day of treatment and so these patients were clinically evaluated. In one patient with epigastric pain, no action was taken. The incidence of adverse events noted for the two drugs was statistically significant (*P* < 0.05).

**Discussion**

Macrolides have been shown to be safe antibiotics with good activity against common respiratory pathogens such as *Streptococcus* spp., *Legionella* spp. and, in some cases,
Haemophilus spp. The newer macrolides have better pharmacokinetic profiles than erythromycin, with peak serum concentrations generally occurring between 1 and 4 h after oral administration. Roxithromycin achieves higher peak serum concentrations than erythromycin; peak concentrations of clarithromycin are lower than those of erythromycin. Single doses of roxithromycin produced serum concentrations as measured by microbiological assay and HPLC, respectively, of 2.4 and 2.6 mg/L 12 h after a dose of 150 mg, and 2.3 and 2.8 mg/L 24 h after a dose of 300 mg. After repeated dosing schedules, serum concentrations of roxithromycin far exceed the minimum concentration required for antibacterial activity, with a dosage regimen of either 150 mg bd or 300 mg od. Concentrations of roxithromycin similar to that in the serum (4–6 mg/L, 2–8 h post-dose) have been demonstrated in respiratory tissue (i.e. lungs and bronchial secretions) and synovial fluid.

In the present study clarithromycin, administered at the higher dose of 500 mg bd, produced a clinically satisfactory effect in 20 (80%) of 25 patients compared with 22 (88%) of 25 patients given roxithromycin 300 mg od. These efficacy rates are similar to those reported in previous studies of roxithromycin and clarithromycin. For instance, in a multicentre trial of the efficacy and tolerance of roxithromycin in LRTI (14,385 patients), there was a clinical resolution or improvement of exacerbation of chronic bronchitis or pneumonia in 94% and 95% of patients, respectively. In another study comparing clarithromycin 250 mg po bd with roxithromycin 150 mg po bd for pneumonia, the clinical efficacy of clarithromycin and roxithromycin was 76% and 84%, respectively. Resolution or improvement of the appearance of a chest radiograph was observed after treatment in 76% of patients given clarithromycin and in 87% given roxithromycin.

The bacteriological efficacy rate in bacteriologically evaluable patients in the present study was 60% for roxithromycin and 50% for clarithromycin. Higher rates have been reported for both macrolides in previous studies: 57–96% for clarithromycin and 83% for roxithromycin, probably because the causative pathogen was unknown in a high and variable proportion of pneumonias.

Tolerance data in the study described here gave a 23.3% rate of adverse events (gastrointestinal) for clarithromycin and only 3.3% for roxithromycin. Previous studies have found a similar low rate of adverse events, 3.1–4%, at the same dose. The incidence of adverse events observed with clarithromycin (23.3%) is higher than that reported in previous studies (10.5–12.5%) and may be due to the high dose. No previous study has shown clarithromycin to be a cause of melaena.

Although the number of patients recruited in this study was small and the study had very low power to detect any difference in efficacy between the two drugs, roxithromycin was tolerated significantly better than clarithromycin and proved effective given as a once-daily dose, thus promoting compliance.

**Acknowledgement**

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References


