Additive effect of continuous low-dose ofloxacin on erythromycin therapy for sinobronchial syndrome

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It has been established that long-term low-dose erythromycin therapy (EM therapy) is very effective for sinobronchial syndrome, a common condition in Japan characterized by chronic upper and lower airway inflammation. The effect does not result from its bacteriocidal activity and the detailed mechanisms are not known. It takes 3-6 months for EM therapy to improve the symptoms. This study was designed to evaluate the additive effect of continuous low dosage or intermittent usual dosage of ofloxacin (OFLX) on EM therapy in patients with sinobronchial syndrome.

Patients with sinobronchial syndrome were randomly allocated to receive one of the following four regimens. Patients in Group A received both low-dose OFLX and EM therapy daily for 6 months. Patients in Group B received EM therapy and intermittent treatment of OFLX for 6 months. Patients in Group C underwent EM therapy for 6 months. Patients in Group D received neither OFLX nor EM therapy. All patients were given carbocystein for more than 2 months before starting each treatment and during the study period.

In patients receiving OFLX and/or EM therapy, these antimicrobial agents were well-tolerated during the treatment period. Amount of sputum in the morning was significantly less in Group C than in Group D after 3-6 months, and decreased significantly in Group A as compared with Group B after 2 weeks, Group C after 2 weeks to 2 months, and Group D after 2 weeks to 6 months. Other symptoms such as number of expectorations, difficulty of expectoration and severity of cough also improved rapidly in Group A.

These findings suggest that it is useful to add low-dose OFLX to EM therapy for sinobronchial syndrome, especially within 1-2 months from starting treatment, and it may be cost-effective as this combination therapy can shorten the treatment period of EM therapy.

Introduction

Sinobronchial syndrome (SBS) (1,2) is a common airway disease in Japan, which consists of chronic sinusitis and chronic non-specific inflammation of lower airways such as diffuse bronchoectasis (3), diffuse panbronchiolitis (4) and chronic bronchitis, which is not related to smoking. Sinobronchial syndrome was found in 55-4% of 74 patients with chronic lower respiratory infectious disease by Suzuki et al. (5). They suggested that a gene controls susceptibility to SBS, especially diffuse panbronchiolitis which was significantly associated with HLA-Bw 54; this was found specifically in Japanese and not in Caucasians. Sinobronchial syndrome has had a poor prognosis until long-term low-dose erythromycin therapy (EM therapy) was discovered to be extremely effective (6-9). Although EM therapy has been established to have an excellent effect in SBS (10), 3-6 months are required to improve the symptoms and signs. Patients with acute exacerbation of SBS are usually treated with antimicrobial agents such as cephalosporins or new quinolones.

Ofl oxacin (OFLX) is one of the new quinolones, commonly prescribed and characterized by excellent antimicrobial effects and few adverse reactions (11). This study was designed to assess the effectiveness, acceptability and toxicity of a continuous long-term regimen of low-dose OFLX (200 mg day−1) or an intermittent usual-dose OFLX (600 mg day−1) added to EM therapy in patients with SBS.
Table 1  Patient characteristics and pulmonary function before and after treatment

<table>
<thead>
<tr>
<th></th>
<th>Group A*</th>
<th>Group B*</th>
<th>Group C*</th>
<th>Group D*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>13</td>
<td>10</td>
<td>11</td>
<td>10</td>
</tr>
<tr>
<td>Male:Female</td>
<td>5:8</td>
<td>10:0</td>
<td>5:6</td>
<td>5:5</td>
</tr>
<tr>
<td>Age (years)</td>
<td>59.0 ± 3.7</td>
<td>59.8 ± 4.5</td>
<td>52.1 ± 5.1</td>
<td>55.8 ± 4.2</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>156.9 ± 2.7</td>
<td>163.4 ± 2.3</td>
<td>158.0 ± 2.7</td>
<td>154.3 ± 1.7</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>51.7 ± 3.1</td>
<td>54.2 ± 3.7</td>
<td>55.0 ± 3.5</td>
<td>52.5 ± 2.8</td>
</tr>
<tr>
<td>Smoking Yes:No</td>
<td>3.10</td>
<td>5.5</td>
<td>1.10</td>
<td>2.8</td>
</tr>
<tr>
<td>Duration of illness (yr)</td>
<td>5.8 ± 1.9</td>
<td>9.8 ± 1.8</td>
<td>8.8 ± 3.4</td>
<td>4.5 ± 1.5</td>
</tr>
<tr>
<td>Pulmonary function tests</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FVC (l)</td>
<td>2.55 ± 0.34</td>
<td>2.65 ± 0.33</td>
<td>2.51 ± 0.23</td>
<td>2.59 ± 0.13</td>
</tr>
<tr>
<td>FVC (%pred)</td>
<td>88.4 ± 8.1</td>
<td>76.3 ± 8.7</td>
<td>86.2 ± 5.4</td>
<td>93.5 ± 6.7</td>
</tr>
<tr>
<td>FEV₁ (l)</td>
<td>1.86 ± 0.29</td>
<td>1.94 ± 0.29</td>
<td>1.87 ± 0.21</td>
<td>1.58 ± 0.08</td>
</tr>
<tr>
<td>FEV₁ (%pred)</td>
<td>92.2 ± 10.1</td>
<td>84.6 ± 8.9</td>
<td>97.7 ± 3.6</td>
<td>90.4 ± 7.8</td>
</tr>
<tr>
<td>FEV₁/FVC ratio (%)</td>
<td>73.2 ± 3.7</td>
<td>65.5 ± 3.7</td>
<td>79.2 ± 3.7</td>
<td>65.9 ± 2.3</td>
</tr>
<tr>
<td>Arterial blood gas analysis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PaO₂</td>
<td>66.0 ± 3.0</td>
<td>63.5 ± 1.6</td>
<td>65.4 ± 3.4</td>
<td>73.1 ± 4.9</td>
</tr>
<tr>
<td>PaCO₂</td>
<td>44.6 ± 0.5</td>
<td>46.5 ± 2.4</td>
<td>45.5 ± 1.7</td>
<td>41.5 ± 1.3</td>
</tr>
</tbody>
</table>

*Group A: EM (600 mg day⁻¹), carbocystein (1500 mg day⁻¹) and OFLX (200 mg day⁻¹) every day; Group B: EM (600 mg day⁻¹) and carbocystein (1500 mg day⁻¹) every day and OFLX (600 mg day⁻¹) for 1 week every 3 weeks; Group C: EM (600 mg day⁻¹) and carbocystein (1500 mg day⁻¹) every day; Group D: carbocystein (1500 mg day⁻¹).

Materials and Methods

SUBJECTS

A total of 51 patients (16 Group A; 10 Group B; 13 Group C; 11 Group D) were followed in this prospective randomized open trial. The number of patients in each group was not equal as some patients declined to be entered in this study. Seven patients were excluded for various reasons before the start of chemotherapy. Three patients were withdrawn because of complicating bronchorrhea, another patient had diabetes, and three patients were early defaulters. Therefore, 44 patients (13 Group A; 10 Group B; 11 Group C; 10 Group D) were given treatment regimens. Of the 44 patients (Table 1), 56% were male (25 males; 19 females), and aged 24–83 years. Although there was a mismatch of sex in Group B, significant differences in other factors including respiratory function test were not detected. Mild suppression in arterial oxygen pressure and obstruction of small airways were observed in these patients as previously reported on SBS (12).

Sinobronchial syndrome (1) was diagnosed based on the following criteria (12,13): (i) productive cough on most days for at least 3 months for 2 consecutive years; (ii) chronic sinusitis diagnosed based on symptoms (postnasal drip, nasal discharge and nasal obstruction), physical examinations and plain roentgenogram as indicated by opacities or air-fluid levels of one or more paranasal sinuses; (iii) no history suggesting to the attending physician that they had bronchial asthma; (iv) no history of wheezing syndrome (14); (v) no significant emphysema documented by chest computed tomographic scan. Patients included in this study had fulfilled the following criteria: (i) the patients were willing to accept the 6-months chemotherapy for SBS; (ii) they were older than 16 years of age; (iii) they did not have other respiratory infections; (iv) they had not taken other antimicrobial agents in the previous 2 weeks; (v) they did not have a history of allergic reactions for new quinolones; (vi) they were not suffering from other disorders such as diabetes, liver dysfunction, renal insufficiency, etc.; (vii) they were not pregnant women.

The study protocol was approved by the Ethics Committee in our hospital and each subject gave informed consent.
Additive effect of ofloxacin on erythromycin therapy

**Fig. 1** Time course of amount of sputum in the morning (ml h⁻¹, mean ± SEM) in each treatment group. Amount of sputum in the morning was shown as the average in 1 week. Group A (n=13, solid bar), continuous low-dose ofloxacin (OFLX) (200 mg day⁻¹) added to the continuous low-dose erythromycin (EM) (200 mg three times a day) therapy; Group B (n=10, striped bar), intermittent usual dose OFLX (200 mg three times a day for 1 week every 3 weeks) added to the EM therapy; Group C (n=11, stippled bar), EM therapy; Group D (n=10, open bar), placebo. Carbocystein (500 mg three times a day) was given in all patients for 8 weeks or more prior to and during the test period. W, week; M, month.

**TREATMENT REGIMENS**

Prior to the start of the study, all patients were randomly allocated to four treatment regimens: (13, 10, 11 and 10 patients in Groups A, B, C and D, respectively). The A regimen consisted of EM therapy (200 mg three times a day) and daily low-dose OFLX (200 mg day⁻¹) for 6 months. The B regimen consisted of EM therapy and intermittent administration of usual-dose OFLX (200 mg three times a day as commonly given in Japan for 1 week every 3 weeks) for 6 months. The C regimen consisted of EM therapy for 6 months. Patients in the D regimen did not receive any antimicrobial agents. All patients were given carbocystein (500 mg three times a day) for 2 weeks before starting each tested treatment and during the test period to confirm the diagnosis and to act as placebo.

No patients were allowed to take other antimicrobial agents, corticosteroids or antiphlogistic agents during the test period.

**PRE-TREATMENT INVESTIGATIONS**

Prior to the commencement of treatment, all patients were subjected to the following tests: (i) amount of morning sputum (ml h⁻¹); (ii) number of expectorations; (iii) difficulty in expectoration; (iv) severity of cough; (v) postero-anterior chest radiograph; (vi) haemoglobin, total and differential white blood cell count; (vii) serum transaminases, lactic dehydrogenase, alkaline phosphatase, γ-glutamyltranspeptidase, leucine aminopeptidase and total bilirubin; (vii) blood urea, serum creatinine and serum uric acid; (ix) urinalysis; (x) C-reactive protein and erythrocyte sedimentation rate; (xi) arterial blood gas analysis; (xii) respiratory function test; (xiii) sputum culture for pathologic organisms and their drug sensitivity.

**INVESTIGATIONS DURING TREATMENT AND FOLLOW-UP**

The clinical symptoms mentioned above were recorded on a diary card every day during the test period. The effectiveness of treatment on number of expectorations and severity of cough was classified into: (i) ineffective, scored 0; (ii) slightly effective, scored 1; (iii) effective, scored 2; and (iv) excellent, scored 3. The effectiveness of treatment on difficulty of expectoration was classified into: (i) easy, scored 0; (ii) difficult, scored 1 and (iii) more difficult, scored 2; over 6 months of treatment. Blood, urine and sputum were examined at 2 weeks and then once every
month. Further specimens were collected if indicated clinically. Pulmonary function tests were performed at 1, 3 and 6 months.

**DATA ANALYSIS**

Values are presented as mean ± SEM. Differences among four groups were analysed by non-parametric ANOVA, and those between any pair of groups were determined using Mann–Whitney U-test. These analyses were performed using the software StatView II (Abacus Concepts, Berkeley, CA, U.S.A.). A P value of less than 0.05 was considered statistically significant.

**Results**

**CLINICAL SYMPTOMS**

Time courses of sputum amount during 1 h in the morning in the four groups are shown in Fig. 1. The sputum amount was significantly less at 2 weeks to 6 months in Group A, at 2–6 months in Group B and at 3–6 months in Group C as compared with Group D. The sputum amount decreased significantly more rapidly in Group A as compared with Group B at 2 weeks, Group C at 2 weeks and 1 and 2 months, and Group D at 2 weeks and 1–6 months. Number of expectorations is shown in Fig. 2. Significant decrease was seen at 1–6 months in Group A when compared with Group D. Time course of difficulty of expectoration are shown in Fig. 3. There was significant improvement at 2 weeks to 6 months in Group A, and at 2–6 months in Group C as compared with Group D. Time courses of severity of cough are shown in Fig. 4. There was a significant improvement at 1–6 months in Group A and at 6 months in Group C compared with Group D. In Group A, severity of cough was significantly more mild at 3, 5 and 6 months than that in Group B, and at 3 months than that in Group C, respectively.

**RESULTS OF LABORATORY FINDINGS**

Results of respiratory function test and arterial oxygen pressure are shown in Table 1. Although it is not statistically significant in this study, improvements as previously reported on EM therapy (12) were observed in the present study.
ADVERSE REACTIONS

Possible adverse reactions were reported in two (4.5\%) of the 44 patients during the study. Mild liver dysfunction and peripheral blood eosinophilia were found in one patient of Group B and mild liver dysfunction was seen in one patient of Group C. Their treatment was discontinued at 2 months and these adverse effects rapidly disappeared. Other adverse drug reactions including gastrointestinal symptoms (nausea and vomiting) and eruptions were not detected in the present study.

RESULTS OF SPUTUM SMEAR AND BACTERIOLOGICAL RELAPSE

Results of sputum smear are shown in Table 2. Although acute exacerbation during the test period was not reported, the bacteriological relapse after treatment was reported in one patient of Group C; from normal flora to Pseudomonas maltophilia. Bacteriological findings indicate that other patients responded to each treatment regimen because incidence of normal flora in their sputum smear increased and pyogenic sputum culture did not increase.

Discussion

Sinobronchial syndrome (1,2) is a common chronic airway disease in Japan, which consists of chronic sinusitis and chronic non-specific inflammation of lower airways, such as diffuse bronchioectasis (3), diffuse panbronchiolitis (4) and chronic bronchitis. In the criteria of the American Thoracic Society (15), chronic bronchitis is the smoking-related bronchial disease. Many patients in Japan presenting with chronic productive cough who visit the chest clinic for diagnosis and treatment, are non-smokers and are diagnosed to have SBS, while chronic bronchitis is diagnosed in the small number of patients who smoke cigarettes (16). The severe obstructive form of SBS is known as diffuse panbronchiolitis (4). Generally, chronic sinusitis precedes symptoms of lower respiratory tract inflammation. It is a special feature that the symptoms are successfully treated with long-term low-dose EM therapy (6-9).
Erythromycin has proven to be an excellent orally active agent in patients with SBS (8) and of course with diffuse panbronchiolitis (6), a subtype of SBS (4). It has been reported that the maximal serum and sputum levels of EM are below the minimal inhibitory concentrations (MICs) of clinically pathogenic bacterial agents, so EM is considered to respond for the patients with chronic lower respiratory infections by mechanisms other than its antimicrobial activity (6). This hypothesis is also supported by the presence of continuous infection and acute exacerbation in EM-effective patients (6). Although the exact mechanisms of EM therapy are still unclear, some suggesting studies have been reported. Kadota et al. (7) suggested that EM impairs the capacity for pulmonary inflammation by reducing the intrapulmonary chemotactic gradient or the ability of the neutrophils to respond to chemotactic factors, ultimately reducing the migration of neutrophils to inflammatory sites. Recent investigators have reported that EM influences the functions of immunocompetent cells (10), the inhibition of superoxide generation by neutrophils (17-19), and the reduction of the respiratory glycoconjugate secretion (20).

Patients in acute exacerbation are briefly administered other antimicrobial agents, such as cephalosporins and new quinolones, in addition to EM because Haemophilus influenzae and Streptococcus pneumoniae frequently induce the exacerbation (21,22), and patients with chronic lower respiratory tract infections often show rapid advances with long-lasting acute exacerbation, ending in a fatal outcome. Tanimoto et al. (23) have reported that treatment with EM or new quinolones showed a definite improvement of survival rate in diffuse panbronchiolitis. This prospective study was conducted with OFLX added to EM therapy for SBS, and the clinical efficacy of continuous low dosage and intermittent usual dosage of OFLX was evaluated.

Ofloxacin was selected from the new quinolones due to its excellent antimicrobial effect against Haemophilus influenzae and Streptococcus pneumoniae and few adverse reactions in its long-term administration (24). This antimicrobial agent has proven to be excellent due to its good penetration of respiratory tissues (11), low cytotoxicity and strong inhibitory action against DNA gyrase (18) (the enzyme plays an important role in DNA replication, DNA repair and recombination).
Table 2  Bacterial findings in sputum before and after treatment

<table>
<thead>
<tr>
<th>Bacterial culture</th>
<th>Group A before</th>
<th>Group B after</th>
<th>Group C before</th>
<th>Group C after</th>
<th>Group D before</th>
<th>Group D after</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Pseudomonas aeruginosa</em></td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td><em>Klebsiella pneumoniae</em></td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td><em>Haemophilus influenzae</em></td>
<td>7</td>
<td>2</td>
<td>4</td>
<td>1</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em></td>
<td>0</td>
<td>0</td>
<td>1</td>
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<td>0</td>
<td>0</td>
</tr>
<tr>
<td><em>Streptococcus pneumoniae</em></td>
<td>2</td>
<td>1</td>
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<td>0</td>
<td>1</td>
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<td>Others</td>
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<td>0</td>
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<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Normal flora</td>
<td>6</td>
<td>9</td>
<td>1</td>
<td>5</td>
<td>3</td>
<td>8</td>
</tr>
</tbody>
</table>

*Group A: EM (600 mg day^{-1}), carbocystein (1500 mg day^{-1}) and OFLX (200 mg day^{-1}) every day; Group B: EM (600 mg day^{-1}) and carbocystein (1500 mg day^{-1}) every day and OFLX (600 mg day^{-1}) for 1 week every 3 weeks; Group C: EM (600 mg day^{-1}) and carbocystein (1500 mg day^{-1}) every day; Group D: carbocystein (1500 mg day^{-1}). EM, erythromycin; OFLX, ofloxacin.

The present study has shown the clinical efficacy of long-term administration of low-dose OFLX added to EM therapy in patients with SBS but some problems remained. The first problem is that less improvement in severity of cough and number of expectorations in patients of Group B (intermittent usual dose of OFLX) was indicated compared with the patients of group C (EM therapy) in its late treatment period (4-6 months). Although the exact cause is unknown, the authors speculate regarding the possibility of rebound phenomenon induced by repetition of intermittent chemotherapy. The second problem is that low-dose OFLX added to EM therapy was significantly more effective in its initial 2 months, but not at 3-6 months, as compared with EM therapy alone. The antimicrobial effect of OFLX is thought to be one of the mechanisms for the rapid improvement with added OFLX. Since EM and OFLX have clinical efficacy due to different mechanisms as mentioned above, additive antimicrobial effect of OFLX on the anti-inflammatory effects of EM may be responsible for the excellent effect. Thus it is thought to be useful to add continuous low-dose OFLX to EM therapy for SBS, especially in its early treatment period (1-2 months), but combination therapy should be discontinued after 3 months because clinical improvement did not differ between combination therapy and EM therapy alone from 3-6 months in this study. These findings also suggest the cost-effectiveness for the treatment of SBS, because combination therapy may shorten the treatment period of EM therapy.

Adverse reactions caused by OFLX have been reported in 5-5% of patients: gastrointestinal complaints (such as nausea, vomiting or heart burn; 4-5%), hypersensitivity reactions (0-5%) and central nervous system disorders (2-3%) (11). It has been reported that adverse reactions of EM therapy are eruption, hepatic dysfunction and gastrointestinal symptoms (6). Since EM has potent stimulating effects of gastrointestinal motor activity (25) and is a motilin receptor agonist (26), gastrointestinal symptoms after its oral administration are well-known adverse reactions. Nagai et al. (6) reported that gastrointestinal symptoms were not revealed in low-dose administration of EM. Fortunately, no adverse reactions related to gastrointestinal complaints, such as nausea, vomiting, heart burn, abdominal pain or diarrhoea, were found in this study by adding OFLX to low-dose EM therapy.

From the limited review of literature and the results of this study, it appears that it is useful to add long-term low-dose OFLX to EM therapy for SBS, especially in the early treatment period, due to its rapid efficacy, few adverse reactions and excellent acceptability. Moreover it may be cost-effective if this combination therapy can reduce the treatment period of EM therapy by its beneficial points as mentioned above. Furthermore, large population studies will be needed to confirm the efficacy of adding OFLX or other new quinolones to the long-term low-dose EM therapy for SBS especially in its early treatment period.

Acknowledgement

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References