Introduction

Macrolides are potentially useful for treating lower respiratory tract infections in transplant recipients, who may also receive immunosuppressive therapy with cyclosporin A. Cyclosporin A is metabolized primarily in the liver by the microsomal enzymatic system CYP3A4. Interactions between erythromycin and cyclosporin A have been reported, because macrolides bind to oxidized (Fe^{3+}) CYP3A4, and the resulting complex is completely inactivated, thus increasing levels of cyclosporin A. Troleandomycin has the same effect as erythromycin. Roxithromycin and clarithromycin form complexes only in vitro, while complexes have not been observed in the case of josamycin, miocamycin and spiramycin. Therefore, clarithromycin would not be expected to have a significant incidence of drug interaction.

Here we document clinical interaction between clarithromycin and cyclosporin A in six patients.

Materials and methods

Clarithromycin (Klacid, Abbott Laboratories, Madrid, Spain) was prescribed in four liver transplant and two heart transplant recipients at the University Clinic of Navarre between 1990 and 1996; the dosage was dependent on infection severity. All the patients received triple-drug immunosuppression with cyclosporin A, azathioprine and corticosteroids. Cyclosporin A was administered by mouth twice daily. Cyclosporin A concentrations in whole blood were determined before the morning administration by fluorescence polarization immunoassay (FPIA) with a specific monoclonal antibody (TDx analyser, Abbott Científica, Madrid, Spain). The dosage was adjusted in order to maintain trough concentrations between 150 and 300 μg/L.

Wilcoxon’s test was used for intra-individual comparisons between concentrations and dosage of cyclosporin A before and during the macrolide treatment. Spearman’s correlation coefficient was also calculated.

Results

The Table shows cyclosporin A concentrations during the study period and details of clarithromycin therapy. In all patients cyclosporin A had to be reduced by a mean of 33% per day depending on the macrolide dose. Normalization of the dosage parameters began on the fourth day after stopping clarithromycin treatment. Co-administration of cyclosporin A and clarithromycin may lead to increases in whole blood cyclosporin levels, and appropriate dose reductions should be considered.
B. Sádaba et al.

Statistically significant differences were observed between the values corresponding to the dosages and cyclosporin A concentrations before and during clarithromycin treatment. The cyclosporin A dosage was 1.31 \( \pm 0.66 \) mg/kg/day lower during clarithromycin treatment \( (P = 0.027) \), and the trough blood levels were a mean of 205 \( \pm 41 \) ng/mL higher than before macrolide treatment \( (mean \pm S.D.) \).

Discussion

Transplant patients may suffer from infections which could be treated with macrolides. Some of these antibiotics interact with cyclosporin A by inhibiting the cytochrome P450, CYP3A4 isozyme, which metabolizes cyclosporin A. Clarithromycin is structurally similar to erythromycin, with 14 carbon atoms, but is thought unlikely to interact with cyclosporin A because it does not form a nitrosoalkane complex with cytochrome P450. However, increases in cyclosporin A concentrations have been observed during clarithromycin treatment, as well as increases in tacrolimus, theophylline, and carbamazepine concentrations.

We believe that clarithromycin has a clinically important capacity to interact with cyclosporin A. The extent of the interaction seems to depend on the cyclosporin A dosage, as observed in our study with other macrolides. The highest cyclosporin A concentrations observed were in patients whose cyclosporin A levels were monitored daily, whose cyclosporin A dosage was increased by the trough blood level, and whose cyclosporin A levels were monitored daily. One patient had their cyclosporin A levels normalized on the fifth day. In another patient, the cyclosporin A dosage was increased by the trough blood level, but the cyclosporin A levels were not normalized. In patient 6, there were two other factors which may have complicated the situation: (i) previous erythromycin administration, and (ii) renal dysfunction.

These observations show the importance of the clinical monitoring of cyclosporin A concentrations during clarithromycin treatment. The impact of the interaction may be significant, especially in patients with impaired renal function.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Transplant type</th>
<th>Time after transplant</th>
<th>Clarithromycin treatment dosage (mg/kg/day)</th>
<th>Time after transplant (days)</th>
<th>Cyclosporin A concentration (ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>liver</td>
<td>1 month</td>
<td>1500</td>
<td>10</td>
<td>4.23</td>
</tr>
<tr>
<td>2</td>
<td>liver</td>
<td>45 days</td>
<td>500</td>
<td>13</td>
<td>7.93</td>
</tr>
<tr>
<td>3</td>
<td>liver</td>
<td>1 month</td>
<td>500</td>
<td>9</td>
<td>12.67</td>
</tr>
<tr>
<td>4</td>
<td>heart</td>
<td>2 month</td>
<td>500</td>
<td>24</td>
<td>8.75</td>
</tr>
<tr>
<td>5</td>
<td>heart</td>
<td>3 years</td>
<td>1000</td>
<td>11</td>
<td>4.1</td>
</tr>
<tr>
<td>6</td>
<td>heart</td>
<td>2 month</td>
<td>1000</td>
<td>17</td>
<td>4.28 (8)</td>
</tr>
</tbody>
</table>

\*Before erythromycin treatment.

\*During erythromycin treatment.

\*The highest cyclosporin A concentration found during the interaction is given in brackets.

Table. Parameters observed before, during and after clarithromycin treatment
Concurrent clarithromycin and cyclosporin A, probably at the level at which it is metabolized by CYP3A4. Cyclosporin A dosage should be reduced during the administration of clarithromycin from the second day of the macrolide treatment, and adjusted according to the cyclosporin A concentration.

References


Received 25 November 1997; returned 13 January 1998; revised 17 February 1998; accepted 16 March 1998