Short Communication

Effect of Amiodarone on the Serum Concentration/Dose Ratio of Metoprolol in Patients with Cardiac Arrhythmia

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Summary: Amiodarone has pharmacokinetic interactions with a number of therapeutic drugs, including warfarin, phenytoin, flecainide, and cyclosporine. Metoprolol is mainly metabolized by CYP2D6, and desethylamiodarone, a metabolite of amiodarone, has a markedly greater inhibitory effect on CYP2D6 than amiodarone. Therefore, the goal of this study was to evaluate the effect of amiodarone and desethylamiodarone on the serum concentration/dose ratio (C/D) of metoprolol in 120 inpatients with cardiac arrhythmias that received either metoprolol and amiodarone (MET + AMD group, n = 30) or metoprolol alone (MET group, n = 90). The ratio of administered metoprolol was compared between the MET and the MET + AMD groups. The dose of metoprolol and patient age were significantly higher in the MET group when compared with the MET + AMD group (1.00 ± 0.480 versus 0.767 ± 0.418 mg/kg/day, p < 0.050; 68.6 ± 10.6 versus 57.6 ± 14.1 years, p < 0.001, respectively), but the C/D ratio was significantly lower in the MET group than in the MET + AMD group (90.8 ± 64.0 versus 136 ± 97.8, p < 0.01). Furthermore, a significant correlation was found between the C/D ratio and desethylamiodarone concentration (n = 30, r = 0.371, p < 0.01). The results suggest that there is a significant interaction between amiodarone and metoprolol via desethylamiodarone-induced inhibition of CYP2D6. Therefore, careful monitoring of metoprolol concentrations/bioactivity of CYP2D6 is required in the context of co-administration of amiodarone and metoprolol.

Key words: amiodarone; metoprolol; interaction; CYP2D6

Introduction

Amiodarone is a class III antiarrhythmic agent1,2 that is widely used for the prevention of sustained ventricular tachycardia and fibrillation.3-5 The utility of amiodarone is supported by its rapidly growing use in the management of all types of atrial arrhythmias.6,7) Amiodarone is mainly metabolized to desethylamiodarone by CYP3A4 and CYP2C8, and desethylamiodarone is further metabolized by CYP3A4.8,9) Amiodarone interacts with a number of therapeutic drugs,10,11) including warfarin,12-14) phenytoin,15-17) flecainide18-20) and cyclosporine.21,22)

Metoprolol is a cardioselective β-adrenergic blocking agent with predominant class II effects that is used to treat hypertension, angina pectoris, and arrhythmia.1,2,23) About 70% of metoprolol metabolism is mediated by CYP2D6,24) and metoprolol interacts with a number of drugs that inhibit CYP2D6.25) Further, metoprolol is often coadministered with amiodarone for the treatment of arrhythmias in patients with chronic heart failure. Previous studies have demonstrated that amiodarone inhibits CYP2D626) and that plasma concentrations of metoprolol are increased by a loading dose of amiodarone.27) Moreover, there are reports of patients who developed hypotension and severe
atropine-resistant and isoproterenol-responsive sinus bradycardia in response to co-administration of metoprolol and amiodarone.10,28

Therefore, the goal of the present study was to investigate the interaction between amiodarone and metoprolol by comparing the plasma concentration/dose ratio (C/D) of metoprolol in patients receiving these agents for the treatment of cardiac arrhythmias.

Materials and Methods

Subjects: The study population consisted of a series of Japanese inpatients with cardiac arrhythmias that received metoprolol therapy at the National Cardiovascular Center from January 2002 to December 2003. A total of 120 inpatients (76 males and 44 females) with a mean age of 65.6 years and a mean body weight of 56.7 kg received fixed-maintenance oral metoprolol therapy (twice-daily, 0700 and 1900 h; mean dose of 56.7 mg/day) for at least 7 days at the discretion of the staff cardiologists. Thirty of the patients received concomitant amiodarone therapy (MET + AMD group), and the mean dose of amiodarone was 170 mg/day (twice-daily, 0700 and 1900 h; 100–400 mg/day) for at least 1 month. Ninety of the patients received metoprolol alone (MET group).

Materials: Metoprolol, amiodarone and amitriptyline were purchased from Wako Pure Chemical Industries, Ltd (Osaka, Japan). Desethylamiodarone and bisoprolol were supplied by Sanofi-Synthelabo Co. Ltd. (Tokyo, Japan) and Tanabe Pharmaceutical Co. Ltd. (Osaka, Japan), respectively. Reagent grade acetonitrile (Osaka, Japan) and methanol were used for high-performance liquid chromatography (HPLC). Reagent grade diethyl ether was supplied by Sano-Synthelabo Co. Ltd. (Tokyo, Japan), and crystallized by evaporation. The residue was reconstituted with methanol and injected into an HPLC system equipped with a reversed-phase column (STR ODS-II, Shinwa Chemical Industries, Ltd.) and an ultraviolet absorbance detector. A wavelength of 242 nm was used. The mobile phase consisted of a mixture of methanol, water, and 28% ammonia water (91:8.8:0.2 v/v/v), and a flow rate of 1.3 mL/min was used. The retention times of the IS, desethylamiodarone and methanol and metoprolol were 7.1, 11.7, and 19.2 minutes, respectively. The minimum measurable concentration was 5 ng/mL in 0.25 mL of serum. Inter- and intra-day variations were less than 5.0%.

Serum amiodarone and desethylamiodarone concentrations were determined by HPLC using amitriptyline as an internal standard.31 In brief, amiodarone and desethylamiodarone were extracted with diethyl ether and crystallized by evaporation. The residue was reconstituted with methanol and injected into an HPLC system equipped with a reversed-phase column (STR ODS-II, Shinwa Chemical Industries, Ltd.) and an ultraviolet absorbance detector. A wavelength of 242 nm was used. The mobile phase consisted of a mixture of methanol, water, and 28% ammonia water (91:8.8:0.2 v/v/v), and a flow rate of 1.3 mL/min was used. The retention times of the IS, desethylamiodarone, and amiodarone were 6.6, 11.7, and 19.2 minutes, respectively. The minimum measurable concentration was 100 ng/mL in 0.5 mL of serum. Inter- and intra-day variations were less than 5.0%.

Pharmacokinetic analysis: All patients in this study received a fixed-maintenance dose of metoprolol for at least 7 days; thus, it was assumed that their serum metoprolol concentration had reached steady-state. Blood samples were obtained from all patients at a uniform time (0700 h). Therefore, the C/D ratio of metoprolol was used instead of the oral clearance to compare pharmacokinetic parameters between the two groups.

Data are presented as mean values ± standard deviation (SD). Statistical analysis was performed using the unpaired Students t-test. The criterion of significance was p < 0.05.

Results

Comparison of patient characteristics and the C/D ratio between the MET group and the MET + AMD group as well as the amiodarone and desethylamiodarone concentrations found in the MET + AMD group are summarized in Table 1. The C/D ratio was significantly lower in the MET group than in the MET + AMD group (90.8 ± 64.0 versus 136 ± 97.9, p < 0.01). By contrast, the dose of metoprolol and mean patient age were significantly higher in the MET group than in the MET + AMD group (1.00 ± 0.480 versus 0.767 ± 0.418 mg/kg/day, p < 0.05; 68.6 ± 10.6 versus 57.6 ± 14.1 years, p < 0.001, respectively).

The relationship between the C/D ratio and serum desethylamiodarone concentration in the MET + AMD group is shown in Fig. 1. There was a significant correlation between the C/D ratio and desethylamiodarone concentration (n = 30, r = 0.371, p < 0.01).
Interaction between Amiodarone and Metoprolol

Table 1. Comparison of patient characteristics and the concentration/dose ratio of administered metoprolol between the MET group and the MET + AMD group

<table>
<thead>
<tr>
<th></th>
<th>MET Group (N = 90)</th>
<th>MET + AMD Group (N = 30)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (year)</td>
<td>68.6 ± 10.6</td>
<td>57.6 ± 14.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BW (kg)</td>
<td>57.3 ± 11.4</td>
<td>55.1 ± 12.4</td>
<td>NS</td>
</tr>
<tr>
<td>Dose (mg/kg/day)</td>
<td>1.00 ± 0.480</td>
<td>0.767 ± 0.418</td>
<td>0.020</td>
</tr>
<tr>
<td>C/D ratio</td>
<td>90.8 ± 64.0</td>
<td>136.0 ± 97.8</td>
<td>0.004</td>
</tr>
<tr>
<td>Duration (day)</td>
<td>—</td>
<td>742 ± 614</td>
<td>—</td>
</tr>
<tr>
<td>Dose of AMD (mg/day)</td>
<td>—</td>
<td>170 ± 70.2</td>
<td>—</td>
</tr>
<tr>
<td>AMD concentration (µg/mL)</td>
<td>—</td>
<td>0.832 ± 0.470</td>
<td>—</td>
</tr>
<tr>
<td>DEA concentration (µg/mL)</td>
<td>—</td>
<td>0.510 ± 0.277</td>
<td>—</td>
</tr>
</tbody>
</table>

MET, metoprolol; AMD, amiodarone; DEA, desethylamiodarone; BW, body weight; Dose, dose of administered metoprolol; C/D, the serum metoprolol concentration/dose ratio. Duration, duration of the therapy in days to the last data employ in each patient, and duration was fixed 1500 days in patient who received amiodarone therapy for more than 1500 days.

The MET group consisted of subjects who received metoprolol therapy. The MET + AMD group consisted of subjects who received both metoprolol and miodarone therapy. Data are shown as mean values ± standard deviation.

Fig. 1. Relationship between the serum metoprolol concentration/dose ratio of administered metoprolol and desethylamiodarone concentration in patients receiving both metoprolol and amiodarone therapy (MET + AMD group). The regression equation determined by the least-squares method is \( y = 131x + 69.1 \), \( n = 30 \), \( r = 0.371 \), \( p < 0.01 \), as shown by the solid line.

Discussion

The present study demonstrated that the C/D ratio was significantly lower in the MET group than in the MET + AMD group, despite the fact that patients in the MET group were significantly older than those in the MET + AMD group and the fact that drug clearance typically decreases with advancing age.\(^{32-35}\) This finding is consistent with data reported by Werner et al.\(^{27}\) that the mean metoprolol plasma concentration doubled following a loading dose of amiodarone.\(^{28}\) Therefore, these findings suggest that amiodarone modulates serum metoprolol concentrations, presumably by inhibiting the metabolism of metoprolol via its effects on CYP2D6.\(^{36,27}\)

Metoprolol is metabolized via \( \alpha \)-hydroxylation, O-demethylation, oxidation into metoprolol acid, and deamination to form four different metabolites.\(^{36-38}\) In humans, these pathways are mainly mediated by CYP2D6 (inhibition constant (Ki) of paroxetine of approximately \( 1 \mu M \)).\(^{34,42,43}\) amiodarone also interact with metoprolol. Amiodarone weakly inhibits CYP-mediated activities, with Ki values ranging from 45.1 to 271 \( \mu M \), while desethylamiodarone strongly inhibits the catalytic activities of CYP2C9 (Ki = 2.3 \( \mu M \)), CYP2D6 (Ki = 4.5 \( \mu M \)), CYP3A4 (Ki = 12.1 \( \mu M \)), CYP2C19 (Ki = 15.7 \( \mu M \)) and CYP1A2 (Ki = 18.8 \( \mu M \)).\(^{8,9,44-45}\) Thus, desethylamiodarone has a markedly greater inhibitory effect on CYP2D6. The present study demonstrated that there was a correlation between the C/D ratio of metoprolol and the serum concentration of desethylamiodarone (Fig. 1). This finding suggests that the interaction between amiodarone and metoprolol is secondary to desethylamiodarone-mediated modulation of CYP2D6 activity.

Approximately 0.5% of the population have abnormally low CYP2D6 activity, but the frequency of intermediate CYP2D6 activity is relatively high in the Japanese population.\(^{46}\) This large interindividual variation in CYP2D6 activity suggests that careful monitoring of metoprolol concentrations/bioactivity of CYP2D6 is required in the context of co-administration of amiodarone and metoprolol in Japanese patients.

In addition, different \( \beta \)-blockers enantiomers may possess different \( \beta \)-adrenergic blockade activity.\(^{47-49}\) Thus, further studies to characterize the stereoselective effects of amiodarone on pharmacokinetic racemic metoprolol would be of benefit.

References

3) Gill, J., Heel, R. C. and Fitton, A.: Amiodarone. An overview of its pharmacological properties, and review


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