Pharmacokinetic interaction between oral cyclosporin and mibefradil in stabilized post-renal-transplant patients

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Abstract

Background. The potential for interaction between oral cyclosporin (Sandimmun®) and the new calcium antagonist mibefradil was assessed as part of the clinical development of the new compound.

Methods. Six stable renal transplant patients on long-term, oral, twice-daily (Q 12 H) cyclosporin (CsA) therapy received 25 mg mibefradil on Day 1, followed by 50 mg once daily for 5 or 6 days. At baseline, as well as on the last day of mibefradil dosing, complete steady-state CsA blood concentration-time profiles were characterized over a dosing interval.

Results. Mibefradil led to mean increases in minimum and maximum CsA blood concentrations and area under the curve of CsA by 2.7-, 2.1-, and 2.3-fold, respectively (all significantly different from CsA alone, P < 0.02). Mibefradil is therefore associated with a clinically relevant increase in CsA blood concentrations. The mechanism of elevation of CsA blood concentrations is probably mibefradil and/or metabolite inhibition of the cytochrome P-450 isoenzyme 3A4. CsA had no clinically significant effect on mibefradil plasma concentrations.

Conclusions. These results confirm previous findings of cytochrome P-450 3A4 inhibition by mibefradil and suggest that, for patients receiving CsA, its dose must be adjusted and its plasma concentration must be monitored when adding or stopping mibefradil.

Key words: cyclosporin, drug interaction, mibefradil, pharmacokinetics, transplant

Introduction

Cyclosporin (CsA) is a powerful immunosuppressant widely used in organ-transplant patients to prevent rejection. As many as 80% of patients receiving long-term CsA therapy have elevated blood pressure [1], and calcium antagonists (CAs) are often used as antihypertensives in this patient population. However, the routine concomitant use of CAs in patients undergoing kidney transplantation is controversial [2]. CA–CsA combination therapy may have certain advantages, including prevention of ischaemic injury following transplant surgery, reduction of CsA-induced renal dysfunction, and potentiation of CsA's immunosuppressive effect [3–11]. Additionally, some CAs inhibit CsA metabolism and elevate blood concentrations, thereby leading to decreased CsA dosage requirements and costs [12,13].

Mibefradil is a tetralol derivative that belongs to a new class of CAs. It binds to a unique receptor site and, unlike other CAs, selectively blocks T-type calcium channels [14]. Like verapamil and diltiazem, mibefradil is a coronary and peripheral artery dilator, but unlike these agents at equipotent doses, mibefradil neither depresses myocardial contractility nor is associated with a reflex increase in neurohormones [15–17]. Mibefradil has also been shown to be an effective and well-tolerated antihypertensive compound at the recommended once-per-day oral doses of 50 and 100 mg 18. It effectively reduces blood pressure in patients with chronic renal failure, with no adjustment in dosage necessary [19].

Mibefradil is virtually completely metabolized, with less than 3% appearing intact in urine. [20] Systemic clearance is 95–125 ml/min, and oral terminal exponential volume of distribution is about 180 litres. More than 99.5% is plasma protein bound, predominantly to alpha 1-acid glycoprotein. Following multiple oral doses, its terminal exponential half-life is approximately 17–25 h. Food has no impact on its absorption, and pharmacokinetic parameters are not affected by hypertension or renal impairment.

CsA has an oral absolute bioavailability in the range of 27–77% [21,22]. It is virtually completely metabolized and has a mean oral clearance of about 59 l/h and has a steady-state volume of distribution of about 130–190 litres. [22]. Disposition half-life is approximately 5.6 h [22]. In whole blood, 50–60% of cyclosporin accumulates in erythrocytes. Leukocytes also avidly accumulate about 10–20% of the total amount of drug in the circulation with the remainder of the drug in
the circulation associated with plasma lipoproteins [23]. Consequently, blood concentrations are clinically more relevant than plasma concentrations.

Mibefradil is both a substrate for and an inhibitor of cytochrome P-450 (CYP) 3A4, which is the enzyme primarily responsible for CsA metabolism [21,24,25]. CsA intestinal metabolism (predominantly gut wall) by CYP3A4 is about twice that of hepatic first-pass metabolism [21]. Inhibitors of CYP3A4 generally inhibit both sites of enzymatic activity during the absorption/hepatic first-pass process. This is especially relevant for CsA, since it is virtually completely metabolized, with less than 1% of a dose recovered intact in urine [23]. Ketoconazole, another inhibitor of CYP3A4, increases CsA oral bioavailability approximately 2.5-fold and reduces systemic clearance to an average of 56% of its original value [26]. Recently, it has been shown that intestinal P-glycoprotein, a protein able to transport cyclosporin, plays a significant role in the first-pass elimination of cyclosporin. Drug interactions with cyclosporin previously ascribed to intestinal CYP3A4 may instead be mediated by interactions with intestinal P-glycoprotein. [27]

The present study was undertaken to assess the safety and tolerability of concomitant administration of mibefradil and CsA in postrenal-transplant patients and to assess any potential drug interaction.

Subjects and methods

Three white men and three white women without childbearing potential, mean age 61 years (range 42–68), with stable renal allograft transplants and mild-to-moderate hypertension, receiving stable doses of CsA, entered the study. Four patients completed 7 days of treatment and the follow-up on Day 8, but because of concern for patient safety, two patients received 6 days of treatment and had the follow-up on Day 7. Patients’ renal transplantation had occurred more than 6 months before the start of the study, transplant function had been stable 2 months before the start of the study, and CsA doses and blood concentrations had been stable for at least 1 month before the start of the study. Patients were excluded if they (a) were receiving concomitant medications that could affect CsA plasma concentrations; (b) had had immunologically related loss of a previous transplant within 12 months of transplantation; (c) had had vascular rejection of a transplant within 6 months; and (d) had malignant hypertension, major systemic disease, or histories of alcohol or drug abuse. The study, conducted in Switzerland, was approved by the local ethics committees and conducted in accordance with the principles of the Declaration of Helsinki as amended in Tokyo, Venice, and Hong Kong. All patients enrolled in the study gave written informed consent.

The overall design of this open-label study is summarized in Figure 1. Two days before enrollment, patients receiving twice-daily CsA (Sandimmun® Sandoz) and under treatment for hypertension had one of their antihypertensive drugs stopped. Blood samples (EDTA anticoagulated) were assayed for CsA concentration and plasma mibefradil. CsA blood concentrations were measured by fluorescence polarization immunoassay using a commercially available kit (TDx®; Immunosuppressant Drug Assay—CsA Monoclonal in Whole Blood, Abbott Laboratories, Abbott Park, Illinois, USA) having a lower limit of quantitation of 25 ng/ml in accordance with patients’ individualized dosage schedules.

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Mibefradil tablets were equivalent to the commercial formulation. CsA was taken as commercially available Sandimmun® capsules (25 and/or 100 mg) or solution (100 mg/ml) in accordance with patients’ individualized dosage schedules.

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Results

In addition to CsA, some patients also received other immunosuppressive therapy. One received prednisone, another azathioprine, and a third prednisone and...
azathioprine. Morning and evening doses of CsA remained constant from Day 1 to Day 6 for all patients. Individual doses varied from 50 mg morning and evening to 175 mg in the morning and 150 mg in the evening. Five patients had essential hypertension and one had secondary hypertension. At study entry, three patients were taking no antihypertensive medications, whereas the other three were taking from one to three antihypertensive drugs, none of which was known to affect CsA plasma concentrations.

Individual and mean pharmacokinetic parameter values for CsA with and without mibefradil coadministration are summarized in Table 1. The blood CsA concentration-time profile of a single subject is illustrated in Figure 2. On the last day of the study, $C_{\text{min}}$ increased an average of 2.7-fold in the presence of mibefradil; mean $C_{\text{max}}$ increased 2.1-fold, and $AUC_{0-11\text{h}}$ increased 2.3-fold. These increases were statistically significant ($P < 0.02$). Mean $T_{\text{max}}$ values with and without mibefradil remained essentially the same (2.2 vs 2.3 h, respectively, $P = 0.77$). Mean mibefradil plasma concentration–time profile on the last study day is illustrated in Figure 3.

The most frequent adverse event was pedal oedema, reported by three patients, one of whom was treated with 40 mg oral frusemide for 2 days. Other adverse events judged related to treatment were frequent urination, muscle cramps, increased appetite, constipation, flushing, facial oedema, and dizziness. There were no serious adverse events.

No marked laboratory abnormalities occurred during the study. However, one patient experienced an increase from baseline with coadministration of mibefradil in both serum creatinine (132 vs 166 µmol/l) and blood urea nitrogen (11.7 vs 16.5 mmol/l) at follow-up on Day 8. Steady-state trough and peak CsA blood concentrations increased approximately two- and threefold following mibefradil addition for this patient. The investigators judged this deterioration of kidney function to be caused by a mibefradil-induced enhancement of CsA blood concentrations to toxic levels.

Before mibefradil treatment, median heart rate was 70.5 beats per min (b.p.m.) (range 52–86 b.p.m.). At the end of mibefradil treatment, median heart rate was 64.5 b.p.m. (range 54–75 b.p.m.). Before mibefradil treatment, median sitting diastolic blood pressure (BP) was 84 mmHg (range 75–88 mmHg) and median sitting systolic BP was 144.5 mmHg (range 137–169 mmHg). At the end of mibefradil treatment, median sitting diastolic BP was 79.5 mmHg (range 68–84 mmHg) and median sitting systolic BP was 135.5 mmHg (range 129–141 mmHg). No clinically relevant electrocardiographic changes were seen in this study, and the mean PQ and QT intervals were unchanged.

As noted previously, four of the six patients completed the full 7-day mibefradil treatment. No CsA toxicity was observed in the two patients who ended the study early as judged by stable serum creatinine concentrations.

### Discussion

This was the first investigation of the interaction between mibefradil and CsA. After 6 or 7 days of treatment with the lower recommended antihypertens-

### Table 1. Cyclosporin pharmacokinetic parameters with and without mibefradil co-administration

<table>
<thead>
<tr>
<th>Patient number</th>
<th>Cyclosporin (mg/day)</th>
<th>Treatment</th>
<th>$C_{\text{max}}$ (ng/ml)</th>
<th>$C_{\text{min}}$ (ng/ml)</th>
<th>$T_{\text{max}}$ (h)</th>
<th>$AUC_{0-11\text{h}}$ (ng/ml/h)</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>225</td>
<td>Alone</td>
<td>369</td>
<td>77</td>
<td>2.0</td>
<td>1861</td>
</tr>
<tr>
<td></td>
<td></td>
<td>With mibefradil</td>
<td>598</td>
<td>223</td>
<td>4.0</td>
<td>4021</td>
</tr>
<tr>
<td>2</td>
<td>200</td>
<td>Alone</td>
<td>489</td>
<td>124</td>
<td>2.0</td>
<td>2950</td>
</tr>
<tr>
<td></td>
<td></td>
<td>With mibefradil</td>
<td>1011</td>
<td>279</td>
<td>2.0</td>
<td>5393</td>
</tr>
<tr>
<td>3</td>
<td>100</td>
<td>Alone</td>
<td>464</td>
<td>73</td>
<td>1.0</td>
<td>2131</td>
</tr>
<tr>
<td></td>
<td></td>
<td>With mibefradil</td>
<td>665</td>
<td>232</td>
<td>2.0</td>
<td>4223</td>
</tr>
<tr>
<td>4</td>
<td>225</td>
<td>Alone</td>
<td>500</td>
<td>128</td>
<td>4.0</td>
<td>3295</td>
</tr>
<tr>
<td></td>
<td></td>
<td>With mibefradil</td>
<td>1065</td>
<td>377</td>
<td>2.0</td>
<td>7087</td>
</tr>
<tr>
<td>5</td>
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<td>Alone</td>
<td>521</td>
<td>157</td>
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<td>3170</td>
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<tr>
<td></td>
<td></td>
<td>With mibefradil</td>
<td>1047</td>
<td>379</td>
<td>2.0</td>
<td>7173</td>
</tr>
<tr>
<td>6</td>
<td>325</td>
<td>Alone</td>
<td>518</td>
<td>193</td>
<td>2.0</td>
<td>3264</td>
</tr>
<tr>
<td></td>
<td></td>
<td>With mibefradil</td>
<td>1533</td>
<td>549</td>
<td>2.0</td>
<td>10848</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>212.5 ± 66</td>
<td>Alone</td>
<td>477 ± 57</td>
<td>125 ± 46</td>
<td>2.2 ± 0.98</td>
<td>2778 ± 624</td>
</tr>
<tr>
<td>(n=6)</td>
<td></td>
<td>With mibefradil</td>
<td>986 ± 336*</td>
<td>340 ± 123†</td>
<td>2.3 ± 0.82</td>
<td>6458 ± 2540*</td>
</tr>
</tbody>
</table>

Significantly different from cyclosporin alone (paired t test); *$P < 0.01$; †$P < 0.02$; SD, standard deviation.

![Fig. 2. Whole-blood concentration profile of CsA for Subject 6.](image-url)
Fig. 3. Mean (±SD) plasma mibefradil concentration-time profile on Day 7 of study.

Mibefradil, its hydrolyzed metabolite (Ro 40–5966), and CsA [21,24,25,28] are all substrates for CYP3A4. Additionally, mibefradil and Ro 40–5966 are inhibitors of the CYP3A4 isoenzyme. It is therefore likely that the elevated CsA blood concentrations observed with concomitant mibefradil administration were due to mibefradil inhibition of CYP3A4 in the gut and liver, analogous to inhibition of the same isoenzyme by ketoconazole [26]. The CsA blood assay used in this study was a fluorescence polarization immunoassay utilizing a monoclonal antibody. Although this assay does exhibit some low metabolite cross-reactivity, it does not provide a realistic metric for CsA metabolite blood concentrations. Co-therapy with CAs can change the metabolite profile of CsA [3,5,29,30]. Although some of CsA’s approximately 30 metabolites apparently have an immunosuppressive effect others may increase nephrotoxicity associated with CsA [3,29,30]. Inasmuch as CsA blood metabolites were not quantitated in this study, it is not possible to assess their significance at this time.

Other CAs also interact with CsA, including verapamil [31], diltiazem [32], and nicardipine [33], while among the dihydropyridine CAs (nifedipine, nitrendipine, isradipine, and amlodipine), clinically relevant increases in CsA concentrations are not observed [30,34–38]. However, diltiazem and verapamil increase CsA concentrations less than 50% [4], whereas moderate-dose mibefradil increases CsA blood levels two- to threefold. The elevation of CsA blood concentrations by other CAs has been explained by an analogous metabolism-inhibition mechanism [30,39].

CsA elimination is an excellent model for the in vivo study of CYP 3A4 activity [28]. The finding that 50-mg daily doses of mibefradil elevate steady-state CsA AUC by an average of 2.3-fold confirms that mibefradil has significant CYP3A4 inhibitory activity. Mibefradil blood concentrations were not affected by concomitant administration of CsA. This has the important practical consequence that no adjustment of the mibefradil dose is necessary for patients receiving CsA.

Although the interaction of mibefradil with CsA may at first be seen as a drawback in transplant patients, it could have positive economic value by substantially decreasing the high cost of CsA therapy. Ketoconazole has previously been used for this purpose, but mibefradil may be a more attractive alternative, since it could offer an independent therapeutic contribution in these patients [1]. If CsA and mibefradil are administered concomitantly, a reduced CsA dose and initially frequent monitoring of CsA blood concentrations are necessary. Similarly, if mibefradil were discontinued, monitoring of CsA blood concentrations and an upward adjustment of the CsA dose would probably be necessary.

References
1. Weir M. Therapeutic benefits of calcium channel blockers in cyclosporine-treated organ recipients: blood pressure control
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