Trimetazidine does not modify blood levels and immunosuppressant effects of cyclosporine A in renal allograft recipients

Nicolas Simon, Philippe Brunet, Dimitri Roumenov, Bertrand Dussol, Jerome Barre, Jean-Claude Duche, Edith Albengres, Philippe D’Athis, Anne-Marie Chauvet-Monges, Yvon Berland & Jean-Paul Tillement

Service Hospitalo-Universitaire de Néphrologie, Hôpital Sainte Marguerite, F-13009 Marseille, and Service Hospitalo-Universitaire de Pharmacologie, Centre Hospitalier Intercommunal, F-94010 Créteil, France

Aims In renal allograft recipients, trimetazidine (Vastarel®) was proposed to be associated with the classic immunosuppressant treatments because it displays anti-ischaemic effects which may protect against cyclosporine A nephrotoxicity. The objective of this work was to assess the possibility of coadministering cyclosporin A, Sandimmun®, and trimetazidine.

Methods Twelve renal transplant patients were selected on the basis of the stability of their cyclosporine A blood concentrations for the previous 3 months. They received trimetazidine, 40 mg twice daily orally for 5 days. Other coadministered drugs were kept unchanged during the study. Before and after trimetazidine administration, cyclosporine A blood concentrations, plasma interleukin-2 and soluble interleukin-2 receptor levels were measured.

Results The data showed that neither cyclosporin A blood pharmacokinetic parameters, Cmax, tmax, AUC, nor the concentrations of interleukin-2 and soluble interleukin-2 receptors were significantly modified.

Conclusions Therefore, it was suggested that trimetazidine may be coadministered with cyclosporine A without cyclosporine A dosage adjustment.

Keywords: cyclosporine A, trimetazidine, interleukin-2, soluble interleukin-2 receptors

Introduction

Trimetazidine (TMZ), 1-(2,3,4-trimethoxybenzyl)-piperazine dihydrochloride, is an anti-ischaemic drug mainly used in coronary heart disease [1, 2]. Recently, Creagh et al. [3] have shown that TMZ is also able to inhibit the acute nephrotoxic effects of cyclosporine A (CsA) in a canine kidney model. This protective effect of TMZ was attributed to its anti-ischaemic properties. Furthermore, Salducci et al. [4] have demonstrated that TMZ could restore ATP synthesis of isolated rat liver mitochondria previously impaired by a Ca2+ overload either alone or associated to CsA. These data suggest that TMZ may have a beneficial effect on nephrotoxicity induced by CsA.

Our interest in such TMZ properties was recently strengthened by the observation that TMZ did not alter immunosuppressant effects of CsA as shown ex vivo by lymphoproliferative assays on human lymphocytes and in vivo by the delayed hypersensitivity model in mice [5].

However these data needed to be confirmed in vivo in humans. Moreover, the possibility of a pharmacokinetic interaction between the two drugs altering CsA blood levels could not be excluded a priori. Indeed, CsA is thoroughly biotransformed in liver by isoenzymes of the cytochrome P450 (CYP) 3A subfamily [6, 7]. TMZ is also biotransformed in the body but to a lesser extent than CsA [8]. As at least 10 TMZ metabolites have been identified in human urine [8], involvement of CYP3A isoenzymes in TMZ biotransformations was a likely hypothesis. All these data prompted us to run a pilot study in patients to check the outcome of the pharmacokinetics and immunosuppressant effect of CsA when TMZ is given in combination. This work focused on CsA alone, because TMZ has a high therapeutic ratio which prevents the patient from any risk of overdosage. We used renal allograft recipients whose drug dosage regimens were stabilized on the basis of CsA trough concentration measurements. In this pilot study, TMZ was added over a short period of time, although long enough to reach steady-state plasma levels (t1/2 = 6.60 h) [9]. CsA blood levels and concentrations of markers of its immunosuppressant effect, interleukin-2 (IL-2) and soluble interleukin-2 receptors (RIL-2S), were simultaneously measured [10].

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Methods

Clinical

Twelve renal transplant patients (seven men and five women, mean age 42 years, range 19–66), 8 to 53 months post-kidney transplantation, participated in this study. They were asked to maintain their usual eating, drinking and smoking habits throughout the study. All patients had a three-drug course of immunosuppressive therapy consisting of CsA,
concentrations. Aliquots of plasma were obtained after 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, and 12 h after the morning dosing for the determination of plasma RIL-2S, trough (pre-dose) CsA concentrations and calculated creatinine clearance were by ANOVA. 95% confidence intervals of the differences in means of all these parameters were also calculated. Coefficients of variation for inter- and intraindividual variability were computed using the analysis of variance tables, including between-subjects and between-periods sources of variation, obtained successively with and without TMZ therapy.

Results

The steady-state blood CsA concentration vs time profiles over a 12 h dosing interval during period A (control period and on day 4 (period A) and day 8 (period B) are listed in Table 1. Statistical analysis did not show any significant differences between the two periods for any parameter. Coefficients of variation for inter- and intraindividual variability are the following: 62.88%, 39.37% without TMZ, and 56.81%, 29.67% with TMZ respectively.

In addition, creatinine clearance measured at day 1 and 10 was not significantly modified (D1: 42.0 ± 11.5 ml min⁻¹, D10: 41.2 ± 10.6 ml min⁻¹, P > 0.05).
Table 1 Mean (s.d.) steady-state cyclosporine A parameters without and with trimetazidine.

<table>
<thead>
<tr>
<th></th>
<th>Without trimetazidine</th>
<th>Cyclosporine A parameters with trimetazidine</th>
<th>P value</th>
<th>95% CI*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Cmax (µg l−1)</td>
<td>AUC(0, 12h) (µg l−1 h−1)</td>
<td>Cmin (µg l−1)</td>
</tr>
<tr>
<td>Mean (s.d.)</td>
<td></td>
<td>2.9 (2.0)</td>
<td>1188 (3.0)</td>
<td>5829 (832)</td>
</tr>
<tr>
<td>Minimum (min)</td>
<td></td>
<td>3.3 (1.7)</td>
<td>1133 (498)</td>
<td>251 (91)</td>
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<tr>
<td>Maximum (max)</td>
<td></td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>95% CI</td>
<td></td>
<td>−45.3 to 74.7%</td>
<td>−20.6 to 26.5%</td>
<td>−17.7 to 14.3%</td>
</tr>
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Discussion

These data show that neither CsA blood concentrations, nor plasma levels of markers of its immunosuppressant effect such as IL-2 and RIL-2S, are significantly modified by TMZ 80 mg day−1. From a pharmacokinetic point of view, these results suggest that TMZ biotransformations should not be CYP 3A4 dependent and thus should not interfere with the metabolic pathways of CsA at the selected dosages of each drug. The CsA concentrations measured in this study were subject to a wide intra- and interindividual variability. However, such variability is similar to that previously reported for CsA itself [13, 14].

As no sign of transplant rejection was observed during the trial, the evaluation of CsA immunosuppressant effect was based on the measurements of T-cells functional markers [15–17]. In our patients, IL-2 and RIL-2S concentrations were similar to those of a population without any lymphocyte activation (0.4 u ml−1 and 0.8 pmol/l for IL-2 and RIL-2S respectively). Inhibition of lymphocyte activation by CsA remained unchanged under TMZ + CsA treatment as shown by the stability of IL-2 and RIL-2S concentrations. As the inhibition of IL-2 production by CsA occurs 4 to 12 h after the CsA intake, the two periods of the survey were long enough to see a variation in these parameters [10]. When we considered each patient alone, no progressive rise (>20% patient’s baseline) of IL-2 and RIL-2S in two or more consecutive samples were found. Confidence intervals of the difference in means of IL-2 and RIL-2S concentrations, between the two phases of the study confirm the absence of any modification (Table 1). This conclusion is in accordance with previous data showing the lack of modification of CsA ability to inhibit T-cell activation, when it is associated to TMZ [8].

In summary, our data indicate that under our experimental conditions TMZ had no significant effect either on the pharmacokinetic parameters of CsA or on IL-2 and RIL-2S concentrations. Therefore, our results suggest that both drugs may be coadministered and that there is no need for additional CsA dosage adjustment when they are given in combination.

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