Trimethoprim–sulphamethoxazole does not affect the pharmacokinetics of sirolimus in renal transplant recipients

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Aims

The influence of the trimethoprim–sulphamethoxazole combination on the steady-state pharmacokinetics of sirolimus, a potent macrocyclic immunosuppressant, was studied in renal transplant recipients.

Methods

Fifteen kidney transplant recipients were treated with sirolimus 8–23 mg m⁻² in combination with azathioprine and prednisolone from the day of transplantation. Whole blood sirolimus AUC and C_{max} were determined on days 6 and 7 after transplantation. On day 7, sirolimus was coadministered with the first dose of trimethoprim (80 mg) and sulphamethoxazole (400 mg).

Results

On day 6, the mean (95% confidence interval) whole blood sirolimus AUC_(0–24 h) was 1040 (846, 1234) ng ml⁻¹ and mean C_{max} was 109 (88, 129) ng ml⁻¹. Corresponding values on day 7 were AUC_(0–24 h) 1060 (826, 1293) ng ml⁻¹ and C_{max} mean 107 (87, 127) ng ml⁻¹. The mean difference in the dose-corrected AUC_(0–24 h) was 0.40% (–9.4, +10).

Conclusions

A single dose of trimethoprim–sulphamethoxazole does not affect the pharmacokinetics of sirolimus in renal transplant patients.

Introduction

Sirolimus is one of the newer immunosuppressants used for the prevention of acute rejection in kidney transplantation. Compared with ciclosporin, sirolimus has shown similar efficacy, but appears to have the advantage of a lesser risk for nephrotoxicity. Known concentration-dependent side-effects include hyperlipidaemia, thrombocytopenia and leucopenia. Its pharmacokinetics have previously been shown to be variable, both within and

between patients, partly due to a low oral bioavailability of about 14% [1–3]. Sirolimus is a substrate for both intestinal and liver CYP3A enzymes, as well as the drug transporter P-glycoprotein. Elimination of the drug occurs mainly through metabolism via CYP3A4 and biliary excretion [4, 5]. Drug interactions have been reported with agents that affect CYP3A4 and/or P-glycoprotein activity, e.g. erythromycin, diltiazem, ketoconazole and rifampicin [6, 7].

The trimethoprim–sulphamethoxazole combination (cotrimoxazole) is routinely used as prophylaxis against opportunistic infections during the first 3–6 months after kidney transplantation. Cotrimoxazole has been reported to interfere with the elimination of several other drugs by various mechanisms. *In vitro* data suggest that trimethoprim, at low concentrations, selectively inhibits CYP2C8, whereas sulphamethoxazole inhibits CYP2C9, findings that can explain reported drug interactions with, for example, warfarin and phenytoin [8–10]. At higher *in vitro* concentrations, both trimethoprim (above 100 µM) and sulphamethoxazole (above 500 µM) lost their selectivity, and also inhibited CYP3A4 [8]. Furthermore, the tubular secretion of digoxin and methotrexate seems to be decreased by cotrimoxazole [11]. A reversible increase in serum creatinine in renal transplant recipients has also been reported during concomitant treatment with ciclosporin and sulphamethoxazole–trimethoprim [12].

We have investigated the steady-state pharmacokinetics of sirolimus in 15 kidney transplant recipients before and during the first day of prophylactic treatment with trimethoprim–sulphamethoxazole, beginning 1 week after transplantation.

Patients and methods

Fifteen kidney transplant recipients, 12 men and three women, from three Swedish transplantation centres, were included in the study, which was part of an international multicentre trial comparing sirolimus-based therapy with ciclosporin [1]. The participants gave their written informed consent, and the study was approved by the Karolinska Institute research ethics committee. Patients were aged 32–67 years, with a mean age of 52 for men and 58 for women. Reasons for transplantation included polycystic kidney disease, nephrosclerosis, chronic glomerulonephritis, diabetes mellitus, IgA nephritis and malformation in two cases each and chronic pyelonephritis, chronic renal insufficiency and sponge kidney in three cases, respectively.

Patients were treated with an oral solution of sirolimus 8–23 mg m⁻² (Rapamune; Wyeth, Collegeville, PA, USA) given once daily, in combination with azathioprine and prednisolone from the day of transplantation. On day 7, sirolimus was coadministered with the first oral dose of trimethoprim (80 mg) and sulphamethoxazole (400 mg) in a combination tablet (Bactrim®; F.Hoffmann-La Roche Ltd, Basel, Schweiz). Blood samples were collected for whole blood sirolimus determinations at 0, 1, 2, 4, 6, 12 and 24 h after administration on days 6 and 7 after transplantation. Sirolimus AUC during the 24-h dose interval (calculated as the

linear trapezoidal area under the whole blood concentration curve until $C_{\max}$, and as the log-linear trapezoidal area after $C_{\max}$) and $C_{\max}$ were determined. Whole blood sirolimus concentrations were analysed by reverse-phase high-performance liquid chromatography with ultraviolet detection. The lower limit of quantification was 6.5 ng ml⁻¹ and the mean between-assay coefficient of variation was ≤6.6% [13]. Pharmacokinetic measurements were compared by the paired *t*-test on untransformed data (based on the Shapiro–Wilk test of normality on the differences in pharmacokinetics between day 6 and day 7).

Results

No statistically significant differences were seen in a comparison of whole blood sirolimus pharmacokinetics before (day 6) and after (day 7) the start of cotrimoxazole prophylaxis. The confidence intervals (CIs) for the differences in $C_{\max}$, AUC and dose-corrected AUC did not exceed 20% of the mean in either direction. Individual and mean sirolimus concentrations vs. time on days 6 and 7 are shown in Figure 1, and the corresponding values for $C_{\max}$ and AUC_(0–24 h) in Figure 2. On day 6 after transplantation, the mean (95% CI) whole blood sirolimus pharmacokinetic parameters were C_0 27 (22, 33) ng ml⁻¹, $C_{\max}$ 109 (88, 129) ng ml⁻¹, $T_{\max}$ 1.5 (1.0, 2.0) h, and AUC_(0–24 h) 1040 (846, 1234) ng ml⁻¹ h⁻¹. The corresponding values when sirolimus was given concomitantly with cotrimoxazole were C_0 29 (21, 36) ng ml⁻¹, $C_{\max}$ 107 (87, 127) ng ml⁻¹, $T_{\max}$ 1.0 (1.0, 1.0) h, and AUC_(0–24 h) 1060 (826, 1293) ng ml⁻¹ h⁻¹.

One patient received a higher sirolimus dose on day 7 (12 mg m⁻²) compared with day 6 (8 mg m⁻²), whereas two patients received slightly lower doses on day 7 (20

Figure 1

Individual (thin lines) and mean (thick line) whole blood sirolimus concentration curves before (0–24 h) and after (24–48 h) a single dose of cotrimoxazole

Figure 2

Whole blood sirolimus $C_{\max}$ and $AUC_{(0-24\text{ h})}$ values on day 6, before cotrimoxazole and on day 7, after the first dose of cotrimoxazole. Diamonds represent individual patients, with the three patients with dose changes marked with closed symbols. Closed boxes are mean ($\pm$ SE) values

and 7 mg m^{-2}) compared with day 6 (23 and 8 mg m^{-2} , respectively). The mean dose for the whole group (11.5 mg m^{-2}) did not change from day 6 to day 7. In addition, the mean AUC values corrected for dose were similar for days 6 and 7 [99 ($77\text{--}121$) vs. 96 ($79\text{--}113$) $\text{ng ml}^{-1}\text{ h}^{-1}\text{ mg}^{-1}\text{ m}^{-2}$]. The intraindividual change in dose-corrected AUC values from day 6 to day 7 varied from -21% to $+35\%$ (mean 0.40% , 95% CI -9.4 , $+10$), and that in $C_{\max}$ varied from -32% to $+88\%$ (mean -2.1% , 95% CI -16 , $+20$).

No clinically significant differences were observed in serum creatinine values before and after administration of cotrimoxazole. In all but one patient, there was a continuous decrease in serum creatinine concentration during the first week after transplantation, from a mean of $565\text{--}219\text{ }\mu\text{mol l}^{-1}$. However, in nine of the 15 patients, a slight increase in serum creatinine was seen on the day after beginning cotrimoxazole treatment (day 8 after transplantation). The increase in serum creatinine varied from 1 to $50\text{ }\mu\text{mol l}^{-1}$. The mean change in all 15 patients was a 4.3% (95% CI -0.56 , $+9.1$) increase (corresponding to $6.0\text{ }\mu\text{mol l}^{-1}$). One patient had a borderline rejection episode at this time, according to biopsy. During the second week after transplantation, serum creatinine concentrations stabilized around $220\text{ }\mu\text{mol l}^{-1}$ in all the patients.

Discussion

Administration of a single dose of trimethoprim–sulphamethoxazole did not affect the pharmacokinetics of sirolimus in 15 renal transplant recipients. Based on the pharmacokinetics of the two drugs, and data from earlier interaction studies, the risk of an interaction is probably low. However, the combination is used routinely in seriously ill patients who might have impaired renal function and who are likely to be treated with many different drugs. The main limitation of the study is that the pharmacokinetics of sirolimus was monitored for only 24 h

after a single dose of cotrimoxazole, whereas the half-life of the former is approximately 60 h. However, as the general status of patients changes rapidly in the post-transplantation period and concomitant drug treatment, including that of sirolimus, is often altered on a daily basis, studying its pharmacokinetics for a longer period would not be possible. Despite this limitation, a large change in the bioavailability of sirolimus, an important concern for this drug, would still have been detected with the present study design.

A reversible increase in serum creatinine in renal transplant recipients has been reported during concomitant treatment with ciclosporin and sulphamethoxazole–trimethoprim and was observed in the present study. This effect has been attributed to a reversible inhibition of the tubular secretion of creatinine by trimethoprim [12].

In conclusion, a single dose of sulphamethoxazole–trimethoprim does not affect the pharmacokinetics of sirolimus in renal transplant recipients. However, the possibility that longer-term treatment with cotrimoxazole may lead to increased sirolimus concentrations cannot be excluded, especially in patients with poor renal function, who might be at risk of cotrimoxazole accumulation.

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