Interaction Between Roxithromycin and Cyclosporin in Heart Transplant Patients

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Summary

Cyclosporin is an immunosuppressive agent commonly used in transplant patients. It is actively metabolised by the cytochrome P450 system and interactions with drugs metabolised by the same system are predictable. This is particularly relevant since cyclosporin has a low therapeutic index and its renal toxicity is concentration-related.

Roxithromycin, a new, well-tolerated macrolide with a weak interactive profile, uses the same isoenzyme of the P450 system as cyclosporin. To evaluate its interaction potential in clinical practice, 8 heart transplant recipients treated with cyclosporin for at least 1 month received roxithromycin for 11 days (150mg twice daily). Bi-weekly controls of plasma cyclosporin concentrations and creatinine levels were carried out before, during and after roxithromycin treatment. A slight nonsignificant rise in cyclosporin concentrations was observed, but creatinine levels remained stable during roxithromycin treatment. Values of cyclosporin concentrations diminished after withdrawal of roxithromycin. Cyclosporin dosage adjustment was not necessary. There was a minor pharmacokinetic interaction, which can be considered safe for the usual therapeutic dosage of roxithromycin used.

Cyclosporin is an immunosuppressive agent commonly administered to transplant patients. It has a low therapeutic index and its nephrotoxicity is concentration-related. Since it is mainly metabolised by the cytochrome P450 system (Le Bigot et al. 1987), interactions between cyclosporin and drugs metabolised by this system are predictable.

One such interaction may occur with macrolide antibiotics, often used to treat the respiratory pathology encountered in transplant recipients. However, the fact that macrolides are highly metabolisable by the hepatic cytochrome P450 system may mean that their potential for interaction with cyclosporin is very strong. *In vitro* studies (Fabre et al. 1988) using human or animal liver microsome fractions have shown that among these macrolides troleandomycin, erythromycin, josamycin, pristinamycin and roxithromycin use the same metabolic isoenzyme as cyclosporin, but that spiromycin does not. Their interactive potential *in vitro* varies from intense for troleandomycin to insignificant for roxithromycin. Troleandomycin is seldom used clinically in hospitals, but marked increases in the concentrations of plasma cyclosporin and creatinine have been reported after administration of erythromycin (Hourmant et al. 1985;
Ptachcinski et al. 1985), and may persist for several days after its withdrawal. The present authors found smaller increases with josamycin (Kreft-Jais et al. 1987) and the same phenomenon was observed by others for pristinamycin (Garraffo et al. 1987). In practice, the degree of inhibition of the metabolism of cyclosporin by macrolides seems to vary with the different antibiotic molecules. Thus, in a previous study, it was shown that in heart transplant patients there was no evidence of an interaction between spiramycin and cyclosporin (Guillemain et al. 1989), and the same has been reported for renal transplant recipients (Kessler et al. 1988).

The authors were therefore interested in assessing, in the present work, the interaction in humans between cyclosporin and roxithromycin, a new macrolide which is well tolerated and exhibits only mild clinical interactions with other drugs (Saint-Salvi et al. 1987).

**Patients and Methods**

**Patients**

Eight heart transplant patients receiving cyclosporin treatment were studied. They comprised 6 men and 2 women (mean age 49 ± 7 years, mean weight 62 ± 9kg) who had recently undergone transplants (<2 months) and were taking cyclosporin for at least 1 month. All patients were well equilibrated under this treatment with a trough plasma cyclosporin concentration [taken as the baseline, T(0)] of 150 to 250 μg/L, and a concentration 4 hours after administration [T(4)] of 300 μg/L. They were followed up for cyclosporin concentration and creatinine level before, during and after 11 days of treatment with roxithromycin.

**Treatment**

Patients were given cyclosporin orally 3 times daily at the dose necessary to equilibrate plasma concentrations, and this dosage (8.0 ± 1.7 mg/kg/day) was kept stable throughout the study. In addition, roxithromycin was given orally for 11 days in 2 daily doses, each of 150mg. Immunosuppression was completed by administering corticosteroids (prednisolone 12 ± 2 mg/day) and azathioprine (112 ± 35 mg/day).

During this study, patients received the usual heart transplant medication, except for drugs known to produce pharmacokinetic (or renal pharmacodynamic) interactions with cyclosporin.

**Assay**

Roxithromycin administration was checked by intermediate microbiological measurements using *Sarcina lutea*, at trough concentration [T(0)] and peak time plus 2 hours [T(2)].

Plasma cyclosporin concentrations were measured twice a week before, during and after roxithromycin treatment, at T(0) and T(4). For these determinations, a nonspecific radioimmunoassay (polyclonal RIA, Sandoz) was used on plasma samples. The limit of detection was 25 μg/L. Within-batch and between-batch coefficients of variation were < 10% in the range 75 to 1000 μg/L. Plasma was separated under standardised conditions at 22°C.

Renal function was evaluated from plasma creatinine levels.

**Statistics**

Results were analysed using the analysis of variance (ANOVA) method (p < 0.05) and were expressed as the mean (± SD) of 3 determinations during each period for cyclosporin concentration and creatinine level.

**Results**

All patients completed the study, which lasted for 4 weeks. Roxithromycin was introduced 42 ± 19 days after transplantation, and the treatment period was 11 ± 2 days. Therapeutic roxithromycin concentrations ranged between 3.8 ± 1.0 mg/L at T(0) and 5.7 ± 1.6 mg/L at peak time, i.e. T(2). These values displayed very small intra- and interindividual variations.

Other treatments comprised a very few common agents, known to have no influence on cyclo-