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Concurrent clarithromycin and cyclosporin A treatment

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Although macrolides have been associated with significant pharmacokinetic interactions, clarithromycin is considered to have a low interaction capacity. In this study, six transplant recipients treated with cyclosporin A also received clarithromycin. In all patients, the dose of cyclosporin A had to be reduced by a mean of 33% per day depending on the macrolide dose. Normalization of the dosage parameters began on the fourth day after stopping clarithromycin treatment. Co-administration of cyclosporin A and clarithromycin may lead to increases in whole blood cyclosporin levels, and appropriate dose reductions should be considered.

Introduction

Macrolides are potentially useful for treating lower respiratory tract infections in transplant recipients, who may also receive immunosuppresive therapy with cyclosporin A. Cyclosporin A is metabolized primarily in the liver by the microsomal enzymatic system CYP3A4.[1] Interactions between erythromycin and cyclosporin A have been reported,[2] because macrolides bind to oxidized (Fe^{3+}) CYP3A4, and the resulting complex is completely inactivated, thus increasing levels of cyclosporin A. Troleandromycin has the same effect as erythromycin. Roxithromycin and clarithromycin form complexes only *in vitro*,[3] while complexes have not been observed in the case of josamycin, miocamycin and spiramycin. Therefore, clarithromycin would not be expected to have a significant incidence of drug interaction.[2–4]

Here we document clinical interaction between clarithromycin and cyclosporin A in six patients.

Materials and methods

Clarithromycin (Klacid, Abbott Laboratories, Madrid, Spain) was prescribed in four liver transplant and two heart transplant recipients at the University Clinic of Navarre between 1990 and 1996; the dosage was dependent on infection severity. All the patients received triple-drug immunosuppression with cyclosporin A, azathioprine and corticosteroids. Cyclosporin A was administered by mouth twice daily. Cyclosporin A concentrations in whole blood were determined before the morning administration by fluorescence polarization immunoassay (FPIA) with a specific monoclonal antibody (TDx analyser, Abbott Científica, Madrid, Spain). The dosage was adjusted in order to maintain trough concentrations between 150 and 300 μg/L.

Wilcoxon's test was used for intra-individual comparisons between concentrations and dosage of cyclosporin A before and during the macrolide treatment. Spearman's correlation coefficient was also calculated.

Results

The Table shows cyclosporin A concentrations during the study period and details of clarithromycin therapy. In all patients cyclosporin A concentrations were supra-therapeutic, increasing from the second to the fourth day after clarithromycin was commenced. Dosage reduction reduced the cyclosporin A concentrations, and this dose reduction had to be maintained throughout the macrolide therapy. Four to five days following discontinuation of clarithromycin therapy, cyclosporin A dosage had to be increased to maintain target trough blood concentrations in each patient. The Figure shows one of these interactions. Hepatic and renal function were stable throughout the period of antibiotic administration and only patient 6 showed significant impairment of renal function at the end of the macrolide treatment.

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Table. Parameters observed before, during and after clarithromycin treatment

Patient	Transplant type	Time after transplant	Clarithromycin treatment		Cyclosporin A					
					before clarithromycin		during clarithromycin		after clarithromycin	
			dosage (mg/day)	time (days)	dosage (mg/kg/day)	concentration (ng/mL)	dosage (mg/kg/day)	concentration (ng/mL)[c]	dosage (mg/kg/day)	concentration (ng/mL)
1	liver	1 month	1500	10	4.23	228	1.3	216 (415)	2.6	188
2	liver	45 days	500	13	7.93	385	2.84	258 (393)	3.79	237
3	liver	1 month	500	9	12.67	228	2.72	336 (451)	5.24	254
4	liver	2 month	500	24	8.75	317	2.6	257 (395)	3.8	140
5	heart	3 years	1000	11	4.1	162	2.74	241 (362)	3.94	158
6	heart	2 month	1000	17	4.28[a] 3.21[b]	282[a] 341[b]	1.62	245 (399)	–	

[a]Before erythromycin treatment.
[b]During erythromycin treatment.
[c]The highest cyclosporin A concentration found during the interaction is given in brackets.

Statistically significant differences were observed between the values corresponding to the dosage and cyclosporin A concentrations before and during clarithromycin treatment. The cyclosporin A dosage was 1.31 ± 0.66 mg/kg/day lower during clarithromycin treatment ($P = 0.027$), and the trough blood levels were a mean of 205 ± 41 ng/mL higher than before macrolide treatment (mean ± S.D.). An almost statistically significant correlation ($r = 0.77$ with $P = 0.072$) was observed between clarithromycin dosage and the interaction intensity measured by cyclosporin A concentration/dose.

Discussion

Transplant patients may suffer from infections which could be treated with macrolides. Some of these antibiotics interact with cyclosporin A by inhibiting the cytochrome P450, CYP3A4 isozyme, which metabolizes cyclosporin A. Clarithromycin is structurally similar to erythromycin, with 14 carbon atoms, but is thought unlikely to interact with cyclosporin A because it does not seem to form a nitrosoalkane complex with cytochrome P450.[2] However, increases in cyclosporin A concentrations have been observed during clarithromycin treatment,[5,6] as well as concentrations of tacrolimus (FK506), theophylline and carbamazepine.[7,8]

We believe that clarithromycin has a clinically important capacity to interact with cyclosporin A. All the patients who received clarithromycin in our study needed a temporary dosage reduction as a result of increases in cyclosporin A concentrations.

Alterations in cyclosporin A concentrations could not be attributed to improvements in bioavailability of the drug resulting from the patients' length of time post-transplant.[9] One patient had their transplant over 3 years previously, and this patient had received the same cyclosporin A dose for a long time without alterations in the trough blood level.

The extent of the interaction seems to depend on the clarithromycin dosage, as observed with other macrolides like josamycin.[10] The highest cyclosporin A dosage reduction was in patient 1, who was receiving the highest dose, but, in patient 6, there were two other factors which may have complicated the situation: (i) previous erythromycin administration and (ii) renal dysfunction.

Cyclosporin A concentrations increased between the second and fourth days after clarithromycin treatment was started. In two patients, whose cyclosporin A levels were monitored daily, the dose was observed to normalize on the fifth day in one patient and on the eighth day in the other. In patient 6, resolution of the interaction disappeared later, and the concentration increase was higher than observed in the other patients. This probably resulted from the impairment in renal function.

These observations show the importance of the clinical

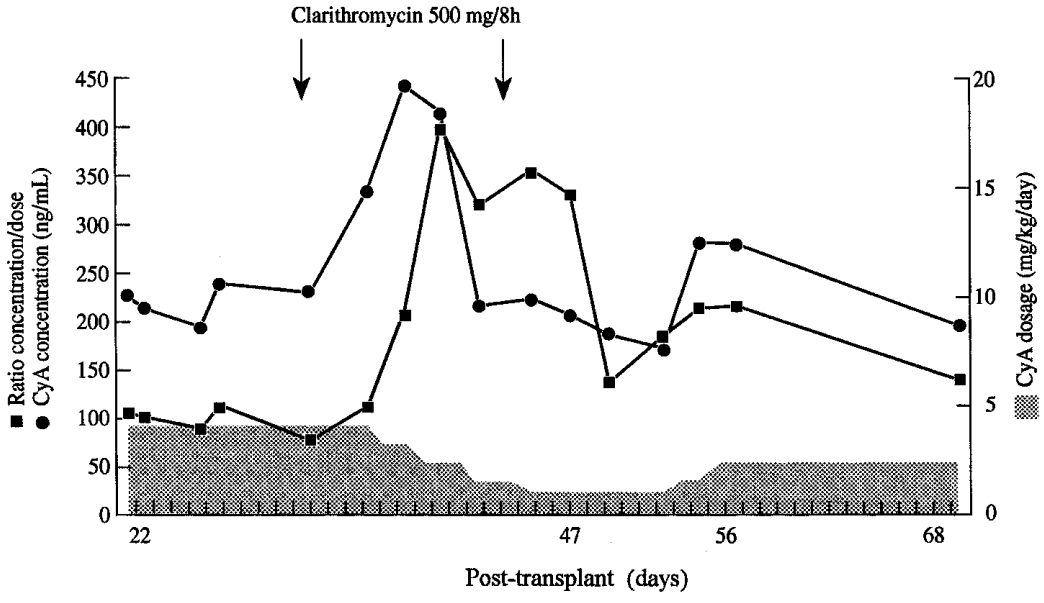

Figure. Interaction evolution in patient 1.

interaction between clarithromycin and cyclosporin A, probably at the level at which is it is metabolized by CYP3A4. Cyclosporin A dosage should be reduced during the administration of clarithromycin from the second day of the macrolide treatment, and adjusted according to the cyclosporin A concentration.

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