Interaction between Ciclosporin and Diltiazem in Renal Transplant Patients

J.M.		Campistol
F.		Oppenheimer
J.		Vilardell
M.J.		Ricart
A.		Alcaraz
E.		Ponz
J.		Andreu

Renal Transplant Unit, Hospital Clinic, Barcelona, Spain

J.M. Campistol, Renal Transplant Unit, Hospital Clinic i Provincial, C. Villarreal 170, E-08036 Barcelona (Spain)

Dear Sir,

Recently, ketoconazole has been proposed to associate with ciclosporin immunosuppressive therapy because of the inhibitory effect on ciclosporin liver metabolism by inhibition P-450 microsomal enzymes, and the financial consequences of this pharmacological interaction [1]. Ciclosporin is extensively metabolized by the liver and excreted via the bile into the feces. Several drugs, besides ketoconazole, have been demonstrated to increase ciclosporin plasma levels by inhibiting the drug metabolism in the liver, such as erythromycin, androgens, cimetidine, rifampicine, diphenylhydantoin, and the calcium channel blocker, diltiazem [2]. We present here our preliminary results of this interaction between ciclosporin and diltiazem in renal transplant patients.

Between January 1988 and January 1989, 82 cadaveric renal transplants were performed in our unit. To determine the protective effect of diltiazem on posttransplant acute tubular necrosis and the inhibition of liver ciclosporin metabolism, we randomized 12 patients with ciclosporin plus diltiazem and 25 with ciclosporin alone. Patients with posttransplant acute tubular necrosis and patients treated with other pharmacological interaction (rifampicine, cimetidine, erythromycin) were excluded from the diltiazem-ciclosporin study. Renal function (serum creatinine), ciclosporin doses (mg/kg/day) and ciclosporin blood levels (RIA-specific monoclonal) were evaluated in both groups at 3, 6, 12 months postkidney transplant. No differences were observed between the two groups in age, weight and sex distribution.

Graft survival was 100% at 1 year in both groups, without differences in plasma creatinine at 3, 6 and 12 months posttransplant. Ciclosporin doses were lower during the entire follow-up in the group with diltiazem,

300
250
200
150
100

5 6 7 8 9 10

Posttransplant period, months

12

Dose Blood levels

○ Cs alone □ Cs alone

• Csa + diltiazem ■ Csa + diltiazem

Fig. 1. Interaction between ciclosporin and diltiazem. Follow-up of ciclosporin dose and blood levels.

although without statistical significance: at 3 months, 4.12 vs. 4.70 mg/kg/day; at 6 months 3.53 vs. 4.02 mg/kg/day, and at 12 months 3.38 vs. 3.93 mg/kg/day (fig. 1). In the diltiazem group, the ciclosporin dose was 18–25% less than in the ciclosporin only group. In spite of lower doses, ciclosporin blood levels were higher in the diltiazem group at 3 and 6 months postkidney transplant, and similar at 1 year: at 3 months 249 vs. 186 mg/ml ($p < 0.03$), at 6 months 162 vs. 135 mg/ml ($p < 0.06$), and at 1 year 127 vs. 130 mg/ml. The incidence of rejection episodes was similar in both groups: 0.6 rejection episode/patient in the diltiazem group vs. 0.68 rejection episode/patient in the other group.

Ciclosporin represents the most important advance in recent years in immunosuppression of organ transplantation. The main disadvantages are its nephrotoxicity and the high cost of this drug at long-term follow-up [3]. Ciclosporin is exclusively metabolized by the liver,

242

Campistol/Oppenheimer/Vilardell/Ricart/Alcaraz/Ponz/Andreu

via cytochrome P450 hepatic enzymes. Several drugs could interfere with ciclosporin metabolism, modifying blood levels in both ways, with higher risk of nephrotoxicity or lower degree of immunosuppression and higher risk of graft rejection.

First et al. [1] proposed the utilization of ketoconazole associated with ciclosporin trying to decrease ciclosporin doses and cost. In this study ciclosporin doses could be decreased at 75% of the initial doses, without side effects and with good renal function. Our study demonstrated also the inhibitory effect of diltiazem in ciclosporin liver metabolism with reduction in ciclosporin doses and without side effects. Certainly that ketoconazole has a more intense inhibitory effect on ciclosporin liver metabolism than diltiazem and ciclosporin could be decreased to a greater extent, although we think that diltiazem has several advantages over ketoconazole. First, diltiazem is a calcium channel blocker agent with a vasodilatation action on renal arterial circulation preserving the kidney from ciclosporin nephrotoxicity secondary to renal artery vasoconstriction. Second, several studies demonstrated the beneficial effect of diltiazem to prevent posttransplant acute tubular necrosis [4]. Third, inhibition of ciclosporin metabolism is less intense with diltiazem than with ketoconazole; therefore, the ciclosporin dose could be arranged more easily with diltiazem. Fourth, ketoconazole is an antifungal antibiotic and long-term resist-

ances could appear. For all these reasons we think that diltiazem is a good option to inhibit ciclosporin liver metabolism, decrease the ciclosporin dose and reduce cost.

References

First MR, Schroeder TJ, Weiskittel P, Myre SA, Alexander JW, Pesce AJ: Concomitant administration of cyclosporin and ketoconazole in renal transplant recipients. *Lancet* 1989;ii: 1198–1200.

Cohen DJ, Loertscher R, Rubin MF, Tilney L, Carpenter CB, Strom TB: Cyclosporine: A new immunosuppressive agent for organ transplantation. *Ann Intern Med* 1984;101:667–682.

Greenberg A, Egel JW, Thompson ME, Hardesty RL, Griffith B, Bahnson HT, Bernstein RL, Hastillo A, Hess ML, Puschett JB: Early and late of ciclosporine nephrotoxicity: Studies in cardiac transplant recipients. *Am J Kidney Dis* 1987;9:12–22.