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RELATIVE POTENCY BETWEEN CYCLOSPORINE AND TACROLIMUS EVALUATED FROM LYMPHOCYTE SUPPRESSION TEST IN VITRO AND CLINICAL PHARMACOKINETICS PARAMETER
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Aims: We evaluated clinical relative potency between cyclosporine (CYA) and tacrolimus (TAC) with point of view of pharmacodynamics and pharmacokinetics to find out the most suitable converting dose between both drugs.
Methods: The relative pharmacodynamics potency between CYA and TAC was examined for reciprocal of mean ratio of concentrations of CYA and TAC that gave 50% inhibition of in vitro blastogenesis of mitogen stimulated lymphocyte (IC50) obtained 66 chronic renal failure (CRF) patients waiting renal transplantation. The relative potency estimated from clinical pharmacokinetics parameters was examined for reciprocal of mean ratio of each pharmacokinetic parameter values between CYA and TAC. The area under the concentration-time curve (AUC), the trough level (Cmin), the peak level (Cmax) and their parameter values divided by dose per body weight dose as pharmacokinetics parameter were measured by 12-hours monitoring of blood concentrations on 7 patients administrated CYA micromolar formulation and 7 patient administrated TAC in one month after renal transplantation operation.
Results: The mean ratio of IC50 between CYA and TAC (CYA/TAC of IC50) was 25.1. The mean ratio of AUC (CYA/TAC of AUC) was 25.5, the mean ratio of Cmax (CYA/TAC of Cmax) was 15.2, and the mean ratio of Cmin (CYA/TAC of Cmin) was 25.0. The mean ratio of dose per body weight (AUC/TAC of dose/weight) was 25.2. Further their each mean pharmacokinetics parameter ratio values (AUC/TAC of AUC, Cmax/TAC of Cmax, and Cmin/TAC of Cmin) divided by dose per body weight were 1.07, 1.03, and 1.44 respectively.
Conclusions: It is usually thought that AUC of calcineurin inhibitor is pharmacokinetics parameters being related to the most clinical efficacy. The relative potency that estimated from the AUC between CYA and TAC was almost equal to the relative pharmacodynamics potency estimated from IC50. Further CYA/TAC of dose/weight also. Therefore we concluded that the potency of TAC was 25-fold superior to CYA and the relative potency value could useful to convert between both drugs. CYA/TAC of AUC divided by dose per body weight was 0.96, namely the bioavailability of both drugs was almost same. CYA/TAC of Cmax was less than CYA/TAC of AUC, oppositely CYA/TAC of Cmin was more, as CYA had higher peak level and lower trough level than TAC, though the both had the same bioavailability. For it was thought that CYA/TAC of Cmin and CYA/TAC of Cmax could not reveal actually relative potency.

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TACROLIMUS VERSUS CYCLOSPORIN: A STUDY ABOUT TWO IMMUNOSUPPRESSIVE REGIMENS
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Aims: The purpose of this study was to compare the use of tacrolimus versus cyclosporine in triple immunosuppressive protocols with mycophenolate mofetil and prednisone, for renal transplantation, in what concerns the incidence of side effects, graft function and acute rejections.
Methods: Data on 103 patients submitted to solitary renal transplantation at Coimbra University Hospital, between January 2001 and December 2003, were analysed. While 52 patients received cyclosporine 8 mg/Kg, 51 patients received tacrolimus 0.15 to 0.2 mg/Kg, and all were administered 4 mg of MMF (PO) and mycophenolate mofetil (IV) as induction therapy. Statistical analysis was performed using the X2 test for continuous variables and Chi-square for binominal variables.
Results: No statistically significant differences were found between the two groups in what concerns baseline variables such as time of discharge from the hospital, plasma creatinine at 1, 6 and 12 months post-transplant, patient age, sex, cold ischemia time, HLA incompatibilities, panel reactive antibodies, CMV serology and primary renal disease. Delayed graft function was found in 2 patients in Tacrolimus group versus 6 in cyclosporine group. 1 patient in Tacrolimus group and 3 in cyclosporine group had rejection grade 3a or 4. No patients had rejection grade 5. Acute rejection occurred in 17.6% of the patients in the Tacrolimus group versus 32.7% in cyclosporine group (p=0.062). We observed a difference in post-transplant diabetes: 7 cases requiring insulin in the tacrolimus group (14.2%) and only one case, not requiring insulin, in the cyclosporine group (p=0.005).
Conclusions: In triple immunosuppressive protocol, there was a trend to statistically significant differences in the incidence of acute rejection between Tacrolimus and Cyclosporine groups. Four patients in the CsA group and 3 in the tacrolimus group lost their kidneys. The incidence of post-transplant diabetes was significantly higher in the patients receiving tacrolimus.

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EFFECTS OF DILTIAZEM UPON THE PHARMACOKINETICS OF CYCLOSPORINE A IN KIDNEY GRAFT RECIPIENTS
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Aims: It has been shown that diltiazem might be used as a cyclosporine (CSA)-saving agent. Recently, there is evidence suggesting that blood level of CSA at the second hour (C2) is the best single point blood sampling for monitoring CSA therapeutic level. We, therefore, would like to study the effects of diltiazem on the pharmacokinetics (PK) of CSA, including C0, in kidney transplant patients.
Methods: Twelve CSA-treated kidney transplant patients with neither diabetes nor agents that alter the PK of CSA were included in this study. The PK of CSA were studied in all patients before and 2 weeks after diltiazem. Area under the curve (AUC) of CSA was obtained by 2 methods: AUC04 and AUC012.
Results: Before taking diltiazem, the correlation coefficient (r2) between C0 with AUC04 and with AUC012 were 0.787 and 0.893, respectively (P<0.01), whereas the correlation between C0 with AUC04 and with AUC012 were 0.992 and 0.976, respectively (P<0.01). Cmax of CSA was 1.8 hr. After taking diltiazem, the correlation coefficient (r2) between C0 with AUC04 and with AUC012 were 0.854 and 0.707, respectively (P<0.01), and the correlation between C0 with AUC04 and with AUC012 were 0.996 and 0.976, respectively (P<0.01). Cmax of CSA was 1.8 hr. The dosage of CSA could be reduced by 38.8% in patients taking diltiazem.
Conclusions: C0 had better correlation with AUC than C0 in patients taking diltiazem. This indicates that C0 should be used to monitor the therapeutic levels of CSA in kidney transplant patients who are taking diltiazem. Obviously, we found that the dosage of CSA could be reduced up to 29.6% after taking diltiazem to maintain the same levels of C0 and Cmax in the same patients before taking diltiazem. Therefore, it is anticipated that diltiazem might play some roles in reducing the long-term toxicities of CSA, in term of nephrotoxicity and metabolic complications, in kidney transplant patients.

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CHRONIC ALLOGRAFT NEPHROPATHY: IMPACT OF CYCLOSPORIN REDUCTION AND CHANGING FROM AZATHIOPRINE TO MYCOPHENOLET MOFETIL RESULTS AT TWO YEARS.
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Aims: Chronic allograft nephropathy (CAN) is a major cause of graft failure. Cyclosporine (CyA) is involved in the development of CAN due to overproduction of TGF-beta. This study was initiated to test the hypothesis that patients with CAN might be ameliorated by

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