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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($IC_{50}$) 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 pharmacokinetics parameter values between CYA and TAC. The area under the concentration-time curve(AUC), the trough level($C_{min}$), the peak level-($C_{max}$) 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 microemulsion formulation and 7 patient administrated TAC in one month after renal transplant operation.

**Results**: The mean ratio of $IC_{50}$ between CYA and TAC(CYA/TAC of $IC_{50}$) was 25.1. The mean ratio of AUC(CYA/TAC of AUC) was 25.5, the mean ratio of $C_{min}$(CYA/TAC of $C_{min}$) was 13.2, and the mean ratio of $C_{max}$(CYA/TAC of $C_{max}$) was 38.0. The mean ratio of dose per body weight(CYA/TAC of dose/weight) was 25.2. Further their each mean pharmacokinetics parameter ratio values(CYA/TAC of AUC, CYA/TAC of $C_{min}$, and CYA/TAC of $C_{max}$) divided by dose per body weight were 0.95, 0.49, 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 $IC_{50}$, 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 0.95, namely the bioavailability of both drugs was almost same. CYA/TAC of $C_{min}$ was less than CYA/TAC of AUC, oppositely CYA/TAC of $C_{max}$ was more, as CYA had higher peak level and lower trough level than TAC, though the both drug had the same bioavailability. For it was thought that CYA/TAC of $C_{min}$ and CYA/TAC of $C_{max}$ could not reveal actually relative potency.

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### TACROLIMUS VERSUS CYCLOSPORINE: 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 2 g of MMF (PO) and methylprednisolone (IV) as induction therapy. Statistical analysis was performed using t-Test for continuous variables and Chi-square for binomial 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 (p=0,175). There were 3 lost kidneys in the tacrolimus group, 2 primary non-functioning grafts and 1 severe vascular rejection. Four patients died in the Cyclosporine group: 2 cases of systemic infection, 1 PTLD case and 1 case of sudden death. Acute rejection episodes 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<0,05).

**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)-sparing agent. Recently, there is evidence suggesting that blood level of CSA at the second hour ($C_2$) 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 $C_2$, in kidney transplant patients.

**Methods**: Twelve CSA-treated kidney transplant patients with neither diseases nor agents that alter the PK of CSA were enrolled to 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: $AUC_{0-4}$ and $AUC_{0-12}$.

**Results**: Before taking diltiazem, the correlation coefficiency ($r^2$) between $C_0$ with $AUC_{0-4}$ and with $AUC_{0-12}$ were 0.797 and 0.883, respectively (P=0.01), whereas the correlation between $C_2$ with $AUC_{0-4}$ and with $AUC_{0-12}$ were 0.992 and 0.976, respectively (P=0.01). Cmax of CSA was 1.8 hr. After taking diltiazem, the correlation coefficiency ($r^2$) between $C_0$ with $AUC_{0-4}$ and with $AUC_{0-12}$ were 0.654 and 0.707, respectively (P=0.01), and the correlation between $C_2$ with $AUC_{0-4}$ and with $AUC_{0-12}$ were 0.986 and 0.976, respectively (P=0.01). Cmax of CSA was 1.6 hr. The dosage of CSA could be reduced by 28.9% in patients taking diltiazem.

**Conclusions**: $C_2$ had better correlation with AUC than $C_0$ in patients taking diltiazem. This indicates that $C_2$ 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 28.9% after taking diltiazem to maintain the same levels of $C_0$ and $C_2$ 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 CYCLOSPORINE REDUCTION AND CHANGING FROM AZATHIOPRINE TO MYCOPHENOLATE 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