The role of therapeutic monitoring of mycophenolic acid in diabetic patients receiving a pancreas-kidney transplant

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Among the immunosuppressive agents, mycophenolate mofetil (MMF) is widely used for the prophylaxis of graft rejection in renal, pancreas and liver transplantation. MMF is a prodrug for mycophenolic acid (MPA) that acts by inhibiting the inducible isoform of inosine-monophosphate dehydrogenase (IMPDH II; Alison and Eugui, 2000). The drug decreases the incidence of acute rejections and improves the long-term graft survival in solid organ transplantation (Sollinger, 2004), allowing the reduction/withdrawal of calcineurin inhibitors and steroids. However, MMF administration is characterized by the occurrence of gastrointestinal toxicities in 40% of patients (Neerman and Boothe, 2003), and the use of a standard dose may produce consistent differences in plasma levels in transplant recipients. Noteworthy, polymorphisms in glucuronosyltransferase, concomitant medications, as well as cyclosporine and tacrolimus, the functionality of transplanted organs and underlying diseases (i.e., diabetes) may significantly affect MPA pharmacokinetics (Kobayashi et al, 2004; Pisapuati et al, 2005). Data from clinical studies demonstrated that pre-dose MPA plasma concentrations and area under the time/concentration curve (AUC) values of 1-3.5 μg/ml and 36-60 h´μg/ml, respectively, are associated with the lower incidence of both graft rejection and toxicity (David-Neto et al, 2005). Therefore, the aim of the present retrospective study was to evaluate the correlation between MPA disposition after MMF administration and side effects in diabetic patients receiving a pancreas-kidney transplantation. MPA plasma levels were monitored in 11 men and 11 women (median age and range, 37 and 28-50 years, respectively) before (C_0), 1 (C_1) and 2 h (C_2) after MMF administration over a median period of 27.3 months (range, 7.9-40.2 months). Standard immunosuppressive therapy consisted of MMF (1-2 g/day) in association with tacrolimus (12 patients) or cyclosporine (10 patients). Daily doses of calcineurin inhibitors were adjusted on the basis of their respective therapeutic ranges (tacrolimus, 8-12 ng/ml, cyclosporine C_0 and C_2 ranges of 140-200 and 800-1000 ng/ml, respectively). A total of 744 plasma samples were obtained and a validated HPLC method with UV detection was used to measure MPA plasma concentrations. Area under the time/concentration curve from 0 to 12 h ($AUC_{0\rightarrow12h}$) was calculated by a limited sampling model based on the following equation $AUC_{0\rightarrow12h}=11.55+7.25´C_0+3.35´C_2$. Clinical signs of toxicity (i.e., diarrhoea) and laboratory findings of leucopenia, thrombocytopenia and anemia were recorded. Receiver-operating control (ROC) analysis was performed to identify optimal cut off values. In 6 women experiencing leukopenia or diarrhoea, C_0 (mean±SD, 2.65±2.08 mg/L), C_1 (9.60±6.99 mg/L) and $AUC_{0\rightarrow12h}$ (61.57±35.04 h´μg/ml) were significantly higher than those measured in 16 patients who tolerated the treatment (C_0, 1.65±1.26, C_1, 7.42±4.93 μg/ml, $AUC_{0\rightarrow12h}$, 33.90±15.11 ´μg/ml). ROC analysis on dose-normalized results demonstrated that cut-off value of 2.65 μg/ml/MMF dose for C_0 was significantly associated with sensitivity and specificity and good test performance. Furthermore, in tacrolimus-treated patients MPA plasma levels at C_0 (2.28±1.74 μg/ml, 95% CI 2.02-2.54 μg/ml) were significantly higher than in subjects given cyclosporine (1.10±0.90 μg/ml, 95% CI 0.90-1.29 μg/ml). In conclusion, the definition of a threshold value of 2.65 μg/ml/MMF dose for MPA C_0 may be useful to prevent treatment-induced toxicities in diabetic pancreas-kidney transplant recipients receiving MMF.

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