PP280—BLOOD LEVELS OF CYCLOSPORINE A AND ITS FIRST LINE METABOLITES DURING AN EARLY FASE AFTER RENAL TRANSPLANTATION IN PATIENTS WITH NORMAL AND DELAYED GRAFT FUNCTION

M. Grundmann[1*]; P. Halvova[2]; H. Brozmanova[1]; J. Dedochova[3]; and A. Martinek[3]

[1]Dept. of Clinical Pharmacology, Faculty of Medicine University of Ostrava; [2]Dept. of Clinical Pharmacology; and [3]Dept. of Internal Medicine, University Hospital Ostrava, Ostrava, Czech Republic

Introduction: Acute rejection (AR) and delayed graft function (DGF) are 2 main adverse early posttransplant events that one would like to avoid. DGF conventionally defined as requirement for dialysis during the first postperative week is a form of acute renal failure that results in posttransplant oligouria, increases risk of AR, and decreases graft survival. Higher incidence of DGF in renal transplant recipients treated by CsA was described previously, but the mechanism of this effect has not been explained yet. The aim of this study was to compare blood concentrations of CsA and its metabolites AM1, AM9, and AM4N in patients with immediate and DGF renal function.

Patients (or Materials) and Methods: Fourteen adult renal transplant recipients (8 males) were prospectively observed during the first 3 months. The therapy was based on CsA microemulsion (Sandimun Neoral® or Equoral®) in combination with mycophenolate and prednisone and was adapted in accordance with guidelines and clinical outcomes. First dose of CsA (4–8 mg/kg) was administered in the day of transplantation. On the basis of clinical status confirmed by serum creatinine level and creatinine clearance the subjects were divided in to 2 groups with immediate graft function (IF-7 patients) and with DGF (7 patients). The CsA and the metabolites C0, C2, and C4 concentrations were analyzed using LC-MS/MS method in days 1 to 7, 14, 21, and 28.[1]

Results: Significant higher creatinine levels and significant lower creatinine clearance were found in DGF group ($P < 0.05$). During the first month the CsA C0 were significantly higher (237 [127] µg/L vs 170 [72] µg/L; $P = 0.0002$) while C2 and AUC0-4 were lower (698 [320] µg/L vs 919 [412] µg/L, 2162 [830] µg*h/L vs 2610 [1002] µg*h/L; $P < 0.01$). The highest concentrations differences were found in AM4N metabolite: C0 (66.5 [61] µg/L vs 7.5 [7.4] µg/L), C2 (111 [93] ug/L vs 41 [34] ug/L), C4 (134 [131] µg/L vs 32 [22] ug/L), AUC0–4 (415 [352] µg*h/L vs 121 [91] µg*h/L). AM4N/CsA ratio: C0 (0.3 [0.28] vs 0.05 [0.04]), C2 (0.19 [0.17] vs 0.05 [0.04]), C4 (0.25 [0.25] vs 0.06 [0.04]). All results were significant for $P < 0.0001$. Similarly C0, C2, C4, AUC0–4 of AM1 and AM1/CsA ratio were significantly lower in DGF group ($P < 0.001$). The graft function in DGF group recovered between 1 week and 2 months and the differences of CsA and metabolites concentrations disappeared.

Conclusion: Metabolismus of CsA in patients with IF and DGF was different. Higher concentrations of AM4N and AM1 should be cause or markers.Therefore, TDM of CsA in combination with fenotypization is recommended.

Disclosure of Interest: None declared.

Reference

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PP281—INTRAVENOUS STREPTOMYCIN DOSING REGIMEN IN A PATIENT UNDERGOING HEMODIALYSIS: PLASMA LEVEL MONITORING AND PHARMACOKINETIC SIMULATION

H. Chtioui[1*]; D. Zbinden[2]; O. Manuel[2]; J. Entenza[3]; L.A. Decosterd[4]; and T. Buclin[1]

[1]Division of Clinical Pharmacology; [2]Infectious Diseases Service, University Hospital (CHUV) - Lausanne, Switzerland; [3]Department of Fundamental Microbiology, University of Lausanne; and [4]Biomedicine Service, University Hospital (CHUV) - Lausanne, Switzerland, Lausanne, Switzerland

Introduction: Streptomycin, as other aminoglycosides, exhibits concentration-dependent bacterial killing but has a narrow therapeutic window. It is primarily eliminated unchanged by the kidneys. Data and dosing information to achieve a safe regimen in patients with chronic renal failure undergoing hemodialysis (HD) are scarce. Although main adverse reactions are related to prolonged, elevated serum concentrations, literature recommendation is to administer streptomycin after each HD.

Patients (or Materials) and Methods: We report the case of a patient with end-stage renal failure, undergoing HD, who was successfully treated with streptomycin for gentamicin-resistant *Enterococcus faecalis* bacteremia with prosthetic arteriovenous fistula infection. Streptomycin was administered intravenously 7.5 mg/kg, 3 hours before each dialysis (3 times a week) during 6 weeks in combination with amoxicillin. Streptomycin plasma levels were monitored with repeated blood sampling before, after, and between HD sessions. A 2-compartment model was used to reconstruct the concentration time profile over days on and off HD.

Results: Streptomycin trough plasma-concentration was 2.8 mg/L. It peaked to 21.4 mg/L 30 minutes after intravenous administration, decreased to 18.2 mg/L immediately before HD, and dropped to 4.5 mg/L at the end of a 4-hour HD session. Plasma level increased again to 5.7 mg/L 2 hours after the end of HD and was 2.8 mg/L 48 hours later, before the next administration and HD. The pharmacokinetics of streptomycin was best described with a 2-compartment model. The computer simulation fitted fairly well to the observed concentrations during or between HD sessions. Redistribution between the 2 compartments after the end of HD reproduced the rebound of plasma concentrations after HD. No significant toxicity was observed during treatment. The outcome of the infection was favorable, and no sign of relapse was observed after a follow-up of 3 months.

Conclusion: Streptomycin administration of 7.5 mg/kg 3 hours before HD sessions in a patient with end-stage renal failure resulted in an effective and safe dosing regimen. Monitoring plasma levels along with pharmacokinetic simulation document the suitability of this dosing scheme, which should replace current dosage recommendations for streptomycin in HD.

Disclosure of Interest: None declared.

PP282—THE ROLE OF CBS AND H2S IN THE INDUCTION OF TORPOR AND ORGAN PRESERVATION DURING HIBERNATION

G.J. Dugbartey[*]; and Prof. Dr. Robert H. Henning

Clinical Pharmacology, University Medical Center Groningen, Groningen, the Netherlands

Introduction: Mammalian hibernation is characterized by profound reductions in metabolism and body temperature. As a result, hibernating animals enter a state of suspended animation called "torpor," where