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

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Introduction: Acute rejection (AR) and delayed graft function (DGF) are two main adverse early posttransplant events that one would like to avoid. DGF conventionally defined as requirement for dialysis during the first postoperative week is a form of acute renal failure that results in posttransplant oliguria, 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 into 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.

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 \[127\] \( \mu \)g/L vs 170 \[72\] \( \mu \)g/L; \( P = 0.0002 \)) while C2 and AUCO-4 were lower (698 \[320\] \( \mu \)g/L vs 919 \[412\] \( \mu \)g/L, 2162 \[380\] \( \mu \)g*h/L vs 2610 \[1002\] \( \mu \)g*h/L; \( P < 0.01 \)). The highest concentrations differences were found in AM4N metabolite: C0 \( 66.5 \[61\] \( \mu \)g/L vs 7.5 \[7.4\] \( \mu \)g/L, C2 \( 111 \[93\] \( \mu \)g/L vs 41 \[34\] \( \mu \)g/L, C4 \( 134 \[131\] \( \mu \)g/L vs 32 \[22\] \( \mu \)g/L, AUCO-4 \( 415 \[352\] \( \mu \)g*h/L vs 121 \[91\] \( \mu \)g*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, AUCO-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

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

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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

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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
core body temperatures can drop to as low as approximately −3°C. This is followed by a state with full restoration of metabolism and body temperature called “arousal” without reperfusion injury or other ill effects. It has been recently reported that cooling of hamster cells increases endogenous production of H2S through cystathionine-β-synthase (CBS) enzyme, which prevents apoptotic cell death. Therefore, in this study, we investigate the role of CBS and H-2S in the induction of torpor and organ preservation during hibernation by blocking CBS with the compound aminooxyacetic acid (AOAA).

**Patients (or Materials) and Methods:** Male Syrian golden hamsters (Mesocricetus auratus) were housed in cages in a climate-controlled chamber at 5°C under dim red light to induce torpor. Movement of all animals was continuously monitored with passive infrared detectors. Osmotic mini-pumps filled with saline or AOAA (100 mg/kg/d) were implanted IP during torpor after a bolus injection of AOAA (10 mg) under 2.5% isoflurane anesthesia. At 4 days after implantation of pumps, hamsters were aroused by handling for 4 hours and euthanized under pentobarbital anesthesia. Blood samples were taken and kidneys of the hamsters were obtained. Summer euthermic hamsters served as controls.

**Results:** In contrast to saline infusions, infusion of AOAA prevented hamsters from re-entry into torpor. Infusion of AOAA also induced excess renal damage as indicated by high expression of kidney injury marker as well as changes in renal morphology. In contrast, renal morphology was well preserved during hibernation in the saline and nonhibernating summer control groups.

**Conclusion:** Blocking CBS during hibernation precludes animals from entering torpor and counteracts up-regulation of CBS enzyme in the kidney, thus inducing kidney damage. Endogenous H2S production by activation or up-regulation of CBS may be instrumental to alleviate kidney damage in several clinically relevant conditions such as deep hypothermia, organ storage for transplantation, and ischemia-reperfusion.

**Disclosure of Interest:** None declared.

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**PP283—MOTOR AND BEHAVIORAL CHANGES IN MICE WITH CISPLATIN-INDUCED ACUTE RENAL FAILURE**

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**Introduction:** Acute renal failure (ARF) is a state of rapid loss of kidney function. We have previously shown that chronic renal failure in rats induces changes in motor activity and behavior. There are no reports on the central nervous system after induction of nephrotoxicity of cisplatin (CP) in mice. This is the subject matter of the current work.

**Patients (or Materials) and Methods:** CP was injected intraperitoneally (IP) in a single dose of 20 mg/kg to induce a state of ARF, and 3 days later, its effects on motor activity, thermal and chemical nociceptive tests, neuromuscular coordination, pentobarbitone-sleeping time, and exploration activity, and 2 depression models were investigated.

The platinum concentration in the kidneys and brains of treated mice was also measured. The occurrence of CP nephrotoxicity was ascertained by standard physiological, biochemical, and histopathologic methods.

**Results:** CP induced all the classical biochemical, physiological, and histopathologic signs of nephrotoxicity. The average renal platinum concentration of CP-treated mice was 5.16 ppm. However, no measurable concentration of platinum was found in the whole brains of CP-treated mice. CP treatment significantly decreased motor and exploration activities, and decreased immobility time in depression models, possibly suggesting a depression-like state. Also, the time taken by the treated mice on the hot plate and tail flick tests was significantly prolonged compared with the control, indicating possible anti-nociceptive action of CP. There was also a significant decrease in neuromuscular coordination in CP-treated mice.

**Conclusion:** CP, given at a nephrotoxic dose, induced several adverse motor and behavioral alterations in mice. Further behavioral tests and molecular and biochemical investigations in the brains of mice with CP-induced ARF are warranted.

**Disclosure of Interest:** None declared.

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**PP284—EFFECT OF DIESEL EXHAUSTS PARTICLES ON CISPLATIN-INDUCED TOXICITY ON HUMAN KIDNEY CELLS, AND THE INFLUENCE OF CURCUMIN THEREON**

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**Introduction:** Particulate air pollution with particle diameter <2.5 μm contributes to respiratory and extra-respiratory morbidity and mortality. We have recently reported the first in vivo experimental evidence that diesel exhaust particles (DEP) in the lung aggravated the renal, pulmonary, and systemic effects of cisplatin (CP)-induced acute renal failure in rats. This in vitro study sought to determine whether and to what extent does DEP exposure exacerbate the effects of CP-induced oxidative stress in human embryonic kidney (HEK-293) cells, and to examine if these effects could be mitigated/prevented with curcumin (the yellow pigment isolated from turmeric).

**Patients (or Materials) and Methods:** Cells viability, cysteine uptake, and oxidative stress indices (glutathione [GSH], total antioxidant capacity [TAC]), and antioxidant enzymes (catalase; glutathione peroxidase; superoxide dismutase) were evaluated by standard methods in all study groups.

**Results:** DEP aggravated the CP-induced HEK-293 cells toxicity as evidenced by decreasing cells viability and inducing oxidative stress (GSH depletion, TAC impairment, and antioxidant enzymes inhibition). DEP selectively inhibited the cysteine uptake; meanwhile, CP had no effect. Curcumin significantly prevented the observed DEP and CP-induced cellular insults.

**Conclusion:** DEP augmented the CP-induced toxicity in HEK-293 cells. Curcumin protected the cells against DEP and CP-induced toxicity through its potent antioxidant action.

**Disclosure of Interest:** None declared.