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Background: Cisplatin is highly effective in the treatment of testicular cancer. Cisplatin-induced ototoxicity (CIO), which occurs in 10-25% of adult patients, is an important complication of this treatment. Although clinical variables contribute to the occurrence of CIO, they do not completely explain the observed inter-individual variability.

Objective: To identify pharmacogenomic variants that contribute to the occurrence of CIO.

Methods: Discovery and replication cohorts of adult testicular cancer patients previously treated with cisplatin were recruited and extensive clinical data were collected to facilitate case-control designation. All samples were genotyped for 7,907 variants using a custom pharmacogenomic genotyping panel. Logistic regression was performed to identify variants that were significantly associated with CIO and functional validation assays were utilized to substantiate these findings.

Results: Association and fine-mapping analyses identified one significantly associated variant in SLC16A5 (combined cohort: $P = 2.17x10^{-7}$; OR = 0.06; 95% CI: 0.02-0.22) that conferred protection against CIO. Functional validation of this transporter gene revealed that in vitro SLC16A5-silencing significantly altered cellular responses to cisplatin treatment ($P < 0.0001$), thereby providing suggestive evidence of a role for SLC16A5 in the development of CIO.

Conclusions: This study has identified a strong association with a synonymous variant in SLC16A5 and protection against CIO. This variant could be used to better predict which patients are at risk of CIO before therapy begins. These findings also provide insight into the molecular mechanisms of CIO in adult cancer patients with implications for potential otoprotectant strategies.

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0010

Role of Oxidative Stress in the Pathophysiology of Sulfonylarylamines Hypersensitivity Reactions

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Sulfonylarylamines (SAAs) are a group of very important and useful medications. However, SAAs are associated with a major adverse reaction – hypersensitivity reaction (HR) – with a rate that ranges between 2% to 4% in the general population but can occur in nearly 50% in HIV patients. The pathophysiology of sulfonylarylamine-induced HRs is not understood but accumulation of toxic reactive metabolites is thought to be a major factor. These RMs contribute, in part, to the formation of reactive oxygen species (ROS), which can cause cellular damage and induce cell death through apoptosis and necroptosis. In this study we collected blood samples from suspected SAAs HS patients (n = 26), health volunteers (HV, n = 13) and sulfonamide-tolerant patients (ST, n = 6). We then isolated peripheral blood monocytes (PBMCs) and blood platelets and measured the induction of cell death in these cells upon in vitro challenge with different concentrations of the sulfamethoxazole (SMX) reactive metabolite, sulfamethoxazole hydroxylamine (SMX-HA). We then compared the degrees of cell death with accumulation of ROS, lipid peroxidation, level of formation of carbonyl protein, another marker of cellular oxidative stress, and cellular glutathione contents. When challenged with the RM in vitro, cells isolated from SSA HS patients exhibited significantly ($p<0.05$) higher degrees of cell death, ROS accumulation and lipid peroxidation and carbonyl protein levels than HV and ST groups. These findings clearly indicate the role of oxidative stress in the pathophysiology of SAAs hypersensitivity reactions.

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0011

Agonist-Antagonist Transition in CXCR4 Ligands

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The chemokine CXCL12 and it's cognate receptor CXCR4 are of high importance in normal physiology but also in diseases like cancer and HIV. As such, this system is of much interest as drug target but, due to its important physiological roles, important side effects are present when this system is pharmacologically blocked. Agonistic drugs could have a much more acceptable pharmaceutical profile but all available synthetic compounds are antagonists/inverse agonists. Junction of inverse CXCR4 agonists T140 with N-terminal CXCL12 oligopeptides has produced the first nanomolar synthetic CXCR4 agonists (ACS Med.Chem.Lett. 2011; 2, 597-602.). In those agonists the inverse-agonistic portion provides affinity whereas the N-terminal CXCL12 sequence provides receptor activation. Different CXCR4 crystal structures exist from two inverse-agonist occupied CXCR4 and we therefore attempted to produce another CXCL12 oligopeptide combination with the small molecule inverse agonist IT1t. For this purpose a primary amino group was introduced as anchoring point for the oligopeptide graft by total synthesis into one of the methyl groups of IT1t producing MEX4. The introduction of the oligopeptides on MEX4 however yielded antagonist instead of agonist and displayed relatively low affinities. It appears that IT1t blocks the activation site in CXCR4. Alkylation, acylation and guanylation of MEX4 reduced or abolished affinity of those compounds. On the other hand, the amino-substituted analogue of IT1t, MEX4, was a potent inverse agonist with an IC50 of 2.8 nM (Gαi) compared to the IC50 of IT1t of

8nM. MEX4 is hitherto the most potent inverse agonist of CXCR4 reported so far.

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0012

The Risk of Adverse Pregnancy Outcome After First Trimester Exposure to H1 Antihistamines: A Systematic Review and Meta-analysis

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Introduction: H1-antihistamines are used for the treatment of nausea and vomiting during pregnancy, as well as the symptomatic relief of asthma, urticaria, allergy, and common cold. Although they are overall felt to be safe in pregnancy, recently several studies challenged this assumption, as millions of women are exposed to them in the first trimester.

Methods: Following the guidelines of Meta-Analysis of Observational Studies in Epidemiology group, a systematic review was performed to retrieve all published articles involving H1-antihistamines exposure during pregnancy. Electronic databases including PubMed, SCOPUS, and EMBASE were searched for possibly relevant articles published in any language up to December 2015.

Results: After removing duplicate publications, excluding animal studies, case studies; and review articles without original data, 56 articles were reviewed in detail and 37 studies fulfilled the inclusion criteria for the meta-analysis. In cohort studies the risk of congenital malformation in the offspring of women exposed to H1-antihistamines was not higher than that of the control population (OR 1.067; 95% CI 0.979-1.162). The Q-statistic for heterogeneity of effects was not significant ($P > 0.05$, $I2 < 25\%$) and there was no evidence of publication bias. Similar results were achieved with case-control studies (OR 1.053; 95% CI 0.899-1.232). Similarly, H1-antihistamines were not associated with more prematurity (OR 0.956 (0.764-1.198), miscarriage (OR 0.996 (0.826-1.201), low birth weight (OR 1.202 (0.630-2.294).

Conclusions: The safety of H1 blockers has been confirmed with over 1.3 million exposed and controls.

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0013

Marked Interpatient and Sex-Dependent Variation in Rivaroxaban and Apixaban Plasma Levels in Routine Care

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Background: Direct oral anticoagulants (DOACs) are widely prescribed for the prevention of stroke in patients with atrial fibrillation. There is increasing concern relating to the safety and effectiveness of DOACs in the post-market clinical setting.

Objective: To determine the extent of interpatient variation in the plasma rivaroxaban and apixaban concentrations among real-world atrial fibrillation patients.

Methods: DOAC plasma level analysis was determined from blood collected from patients prescribed rivaroxaban or apixaban for atrial fibrillation during routine clinic visits. Patients were prospectively invited to participate in this observational cohort study. Subjects were enrolled if they had been taking these medications for greater than 4 days at the recommended dosing cycle for rivaroxaban (once daily) and apixaban (twice daily) to ensure drug levels were at steady-state.

Results: Among 243 patients (rivaroxaban, n = 94; apixaban, n = 149), the interpatient variation was far greater than reported in clinical trials, with approximately 40% of both rivaroxaban and apixaban patients outside of the predicted concentration profiles observed in clinical trials. Higher rivaroxaban and apixaban levels were observed in females compared to males after dose and weight adjustment. Females were more likely to attain rivaroxaban levels in excess of the predicted 95th percentile of that observed in clinical trials (Relative Risk 3.22, 95% confidence interval 1.29 – 8.08).

Conclusions: Therapeutic drug monitoring in some patients coupled with the availability of lower dose strengths may help to further optimize and individualize DOAC dosing and potentially reduce bleeding risk.

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0014

Prevalence of Gastrointestinal Symptoms in Renal Transplant Children Receiving Mofetil Mycophenolate

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Background: Gastrointestinal symptoms (GIS) are common in renal transplant recipients. It has been related to immunosuppressant drugs such as mofetil mycophenolate and steroids.

Objectives: The aim was to estimate the prevalence and severity of GIS in renal transplant children with the use of the Gastrointestinal Symptom Rating Scale (GSRS).

Methods: We applied the Gastrointestinal questionnaire Symptom Rating Scale (GSRS) to pediatric renal transplant recepients receiving mycophenolate as prophylactic treatment for organ rejection in the transplant outpatient clinic during a three month period.

Results: 39 patients were included, mean age 12.9 ± 3.9 years, median post-transplant a time of 13 months (25th, 75th percentile 8, 27), 19 were female (47.5%), all were receiving mofetil mycophenolate, tacrolimus and steroids. Median total GSRS score 6 (range 0,36). 16 had a total GSRS score higher than 10 (41%). The most frequent symptom was sucking sensations in the epigastrium in 17 patients (43.5%), followed by borborygums in 17 (43.5%) and flatulence in 18 (46.15%). Two patients switched mycophenolate brand or dosing regime due to GIS, and one patient was switched to azathioprine due to GIS after questionnaire evaluation. There was no significant correlation between post-transplant time and age vs. total GSRS score.

Conclusion: Adverse drug reactions (ADRs) are common in transplant recipents. Moderate to severe GIS were found in 41% of