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A LIMITED NUMBER OF PRESCRIBED DRUGS ACCOUNT FOR THE MAJORITY OF CLINICALLY RELEVANT DRUG INTERACTIONS

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Introduction: Drug-drug interactions constitute a predictable and in many cases avoidable cause of adverse drug reactions and therapeutic failure. We conducted a register-based study to investigate the prevalence of prescribed combinations of interacting drugs in the whole Swedish population (Holm et al. Eur J Clin Pharmacol. 2014).
Material and Methods: A retrospective, cross-sectional register study was conducted, covering four months in 2010. Data from the Prescribed Drug Register on all dispensed drug prescriptions in Swedish pharmacies from January 1 to April 30 were linked to the drug-drug interaction database SFINX. The analysis focused on drug interactions classified in the database as clinically relevant that can be handled, e.g. by dose adjustments (C-interactions), and clinically relevant interactions that should be avoided (D-interactions). Interactions were categorized according to clinical consequence and drug type and prevalences of interacting drug combinations were described. The study was approved by the Regional Ethics Committee.
Results: About half of the population were dispensed at least one drug prescription. Mean (SD) number of dispensed drugs was 3.8 (3.4). About 2.5 million potentially interacting drug combinations were identified in the study population of 9.3 million people. Among detected interactions 38% were classified as C-interactions and 3.8% as D-interactions. About half of all C- and D-interactions were combinations of drugs with potential to cause therapeutic failure. The 15 most prevalent combinations accounted for 80% of D-interactions. The 10 most prevalent individual drugs were involved in 94% of all D-interactions.
Conclusions: A limited number of drugs and a few specific drug combinations account for the majority of D-interactions, i.e. clinically relevant interactions that should be avoided, in Sweden. About half of interacting drug combinations among C- and D-interactions potentially leads to treatment failure.

CHARACTERIZATION OF URACIL CATABOLISM VARIABILITY IN HEALTHY VOLUNTEERS

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Uracil catabolism is crucial for the pharmacokinetics of the chemotherapeutic 5-fluorouracil (5-FU) since 5-FU is degraded by the same pathway. Decreased activity of the first catabolizing enzyme, dihydropyrimidine dehydrogenase (DPD), is a major predictor of 5-FU toxicity with known risk variants in the DPD gene (*DPYD*) accounting for ~30% of toxicities. However, not all toxicity cases can be explained by *DPYD* risk variants. To date, the phenotypic variability in the catabolism downstream of DPD by dihydropyrimidinase (DHP) and β-ureidopropionase (bUP), potentially contributing to 5-FU toxicity, has not been investigated. Thus, we aimed to characterize the baseline phenotypic variability of endogenous metabolites and metabolic ratios of 5-FU catabolism enzymes and to correlate the phenotype with genetic variation in the DHP and bUP genes (*DPYS* and *UPB1*).
Material and Methods: Three variants in *DPYS* and *UPB1* previously associated with 5-FU toxicity were genotyped in 320 healthy volunteers and their plasma uracil, dihydrouracil (UH_2), β-ureidopropionic acid (UPA), and β-alanine (BAL) concentrations were determined by LC-MS/MS.
Results and Conclusions: High inter-individual variability in all metabolic ratios was observed. Sex-dependent differences were detected at each enzymatic step in the uracil catabolism pathway, with lower metabolite levels ($P \leq 0.007$) in women. Moreover, lower UPA/UH_2 ratios ($P < 0.001$) were observed in women, suggesting that reduced 5-Fluoro-UH_2 catabolism may contribute to higher fluoropyrimidine toxicity rates observed in females. Furthermore, volunteers carrying *DPYS* variant c.265-58T>C had lower UH_2 plasma levels ($P = 0.033$) and higher UPA/UH_2 ratios ($P = 0.036$) and carriers of the *UPB1* variant c.1-80C>G showed lower BAL plasma levels ($P = 0.004$). These initial results are in agreement with the previously observed reduced fluoropyrimidine toxicity in c.265-58C carriers and increased toxicity in carriers of c.1-80G, indicating a possible functional effect related to these variants.

POLYPHARMACY AND POTENTIALLY INAPPROPRIATE MEDICATION IN ELDERLY OF NORTHERN PORTUGAL

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Introduction: The growing aging of population and increasing prevalence of chronic diseases require the simultaneous use of drugs, lead to the issue of polypharmacy and potentially interactions and inappropriate use.
Aim: To characterize polymedicated elderly and related factors, identify potentially interactions and inappropriate medication in elderly.
Material and Methods: This cross-sectional study was based on a questionnaire applied to 69 elderly (≥65 years) from northern Portugal. It was considered as polymedicated seniors taking ≥5 drugs. Beers list and the Delafuente classification were used to evaluate the therapeutic and possible interactions. It was used descriptive statistics and a model of binary regression, with a significance of 5%. The study was approved by Ethics Committee.
Results: The sample consisted mainly of males (53.6% vs. 46.4%), aged between 66 and 99 years (mean 82.01), while 65.2% have more than 80 years. However, most elderly are not polymedicated (58%), on average 4.61 different drugs are administered per day (maximum=19), antihypertensives (36.2%) and antacids (30.04%) are the most prescribed. Hypertension and depression increase the risk of polymedication eightfold ($P = 0.004$) and fivefold ($P = 0.011$) respectively. Female gender seems increase the risk of polypharmacy threefold, although not statistically significant ($P = 0.102$), and regarding age, the older age group (>85 years) seems reduces the risk of polypharmacy in 0.6 fold, but also not statistically significant. According with Delafuente classification, 1.4% of elderly has potentially drug interactions (Omeprazole and Iron salts). According to the list of Beers, 5.8% of seniors take drugs that classified as having some indications (hydroxyzine, amitriptyline).
Conclusions: Regarding polypharmacy, 42% of elderly are polymedicated with an average of about 5 different drugs per day, antihypertensives and antacids the most prescribed. Hypertension and depression are highly associated with polypharmacy. We identified

one potentially drug interaction and about 6% of elderly taking drugs that classified as having some indications.

Key words: Beers list, Delafuente classification, Elderly, Inappropriate medication in elderly, Medication interactions, Polypharmacy.

INNOVATIVE APPROACH TO BLOOD SAMPLING USING DRIED BLOOD SPOTS. APPLICATION TO PHARMACOKINETICS AND CYTOCHROME P450 PHENOTYPING

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Background: The use of dried blood spots (DBS) has gained in popularity in the last few years over conventional whole blood or plasma sampling for PK or drug monitoring. In order to overcome the impact that haematocrit has on the spreading of the applied drop of blood, precise knowledge of the collected volume is crucial for the determination of drug/metabolites concentrations.

Material and Methods: Although the collection of an accurate capillary volume using a volumetric micropipette is simpler than venous blood collection, it still needs to be conducted by trained technicians using dedicated instruments. To simplify this process a new capillary blood collection device has been developed. The prototype integrates a patented microfluidic plate (WO/2013/144743) allowing for accurate volume control and a conventional filter paper card for blood storage.

The concentrations and pharmacokinetic profiles of a P-glycoprotein (P-gp) and six cytochrome P450 (CYP) probes and their metabolites obtained with the new sampling device have been compared with a conventional volumetric micropipetting method in a clinical trial including 30 volunteers who have received the Geneva cocktail for CYP and P-gp phenotyping. The quantification was done using a previously validated LC/MS-MS method.

Results: Concentrations obtained with the new microfluidic sampling device showed excellent correlation with conventional micropipetting concentrations with slopes values close to 1 (0.91 – 1.03) and determination coefficients R^2>0.90 for all of the 13 analysed substances. Sampling could be successfully performed by the volunteers themselves with almost no previous training.

Conclusion: DBS technique combined with an innovative sampling device and a sensitive analytical method can be used as a self-test for CYP and P-gp phenotyping The use of this technique can be further enlarged to the quantification of other substances for PK studies and therapeutic drug monitoring.

THERAPEUTIC DRUG MONITORING FOR ANTIDEPRESSANTS AND ANTIPSYCHOTICS – A LONGITUDINAL PREVALENCE ANALYSIS

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Background: Therapeutic drug monitoring (TDM) can help clinicians to optimize dosing of medicines. Evidence on the use of this service in psychiatry mainly refers to questionnaire studies. The aim of this study was to use register data to describe the prevalence of TDM for antidepressants and antipsychotics during 2006-2013.

Material and Methods: The study population consisted of individuals, ≥5 years of age, residing in the Stockholm County. The prevalence of TDM for each study year was calculated with the number of individuals in whom TDM had been performed as nominator (extracted from the TDM database at Karolinska University Laboratory) and the number of treated individuals as denominator (extracted from the Swedish Prescribed Drug Register). The prevalence of TDM was compared between substances according to the level of TDM recommendation by guidelines.

Results: In 2006, 641 in 133,275 (0.48%) individuals on antidepressants were subjected to TDM. In 2013, the corresponding figure was 580 in 162,998 (0.36%). In 2013, the most frequently analysed antidepressants were nortriptyline (6.2%) and clomipramine (4.5%). For patients on antipsychotics, the prevalence of TDM increased between 2006 and 2013, from 729 in 31,463 (2.3%) to 1,338 in 32,534 (4.1%). In 2013, the most frequently analyzed antipsychotics were clozapine (29%) and perphenazine (22%). For both antidepressants and antipsychotics, TDM was more common in men than in women. A trend to a greater prevalence was found for substances strongly recommended for TDM than for substances with a lower level of recommendation (5.6% vs. 1.1%; $P = 0.063$).

Conclusions: Each year, less than one in 200 patients on antidepressants and less than one in 20 patients on antipsychotics have their treatment personalized by means of TDM. The use of TDM is increasing for antipsychotics but not for antidepressants. Men are more frequently monitored by plasma concentrations than women.

HOSPITALISATIONS BY DRUG INTERACTIONS WITH NSAIDS IN ELDERLY POLY-TREATED PATIENTS: OUTCOME RESEARCH ON ADMINISTRATIVE DATABASES

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Background: Elderly patients are highly susceptible to poly-pharmacy, which may cause drug–drug interactions and relevant hospitalisations. These often involve NSAIDs (Non- Steroidal-Anti-Inflammatory-Drugs), which are inappropriately prescribed. This study aimed to investigate the risk of kidney injury and bleeding following various NSAIDs interactions in the elderly poly-treated population.

Material and Methods: An historic cohort study based on administrative databases of the Local Health Authority of Bologna (866,000 inhabitants) was performed. Patients with at least a NSAID prescription in the first semester of 2012 were selected among elderly (≥65 years) poly-treated (>4 different drugs) subjects. Co-prescriptions of NSAIDs + ACE- Inhibitors (or sartans), NSAIDs + diuretics, NSAIDs + ACE-Inhibitors (or sartans) + diuretics (triple whammy), NSAIDs + metformin, NSAIDs + SSRIs, NSAIDs + corticosteroids and NSAIDs + warfarin were considered as potential interactions. Kidney injury and bleeding hospitalisations represented the outcome measures. Kaplan-Meier curves and Cox regression model were used to estimate the risk of two outcomes following interactions. Hazard Ratios (HRs), with 95% Confidence Interval (95CI), were adjusted for gender, age and concomitant drugs.

Results: Out of 34,353 elderly poly-treated patients, 7,420 subjects received NSAIDs (60.8% female, 76.9 average age). Among these, 85.7% was exposed to NSAIDs + ACE-Inhibitors(or sartans), 69.9% to NSAIDs + diuretics, 32.8% to triple whammy, 21.6% to NSAIDs + metformin, 20.1% to NSAIDs + SSRIs, 17.1% to NSAIDs + corticosteroids and 8.2% to NSAIDs + warfarin. A significant risk of kidney injury was found only for triple whammy (adjHR: 1.33; 95CI: