in agreement with the FDA risk categorization system in only 18% of consulted women with high risk exposure. Clinical pharmacologists' risk assessment confirming high risk drug exposure had a better positive predictive value for adverse pregnancy outcomes than the FDA X categorization (54% vs 20%, respectively).

Conclusions: Additional evaluation beyond the FDA drug classification is essential, and clinical pharmacologists are ideally placed to consult on how to proceed with a pregnancy following drug exposure to high risk drugs.

POPULATION PHARMACOKINETICS OF SUBCUTANEOUS AND INTRADERMAL GLUCAGON IN PATIENTS WITH TYPE 1 DIABETES

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Background: The closed-loop control system for type 1 diabetes utilizes frequent measurements of blood glucose concentrations and delivery of both an insulin analog and glucagon to achieve automated glucose control. This study aimed to characterize the population pharmacokinetics (PK) of glucagon administered by subcutaneous or intradermal route to facilitate the selection of a desired route of administration.

Methods: This study included 14 patients ≥18 years with type 1 diabetes duration ≥1 year prior to enrollment. Each patient was randomized to receive 50 µg glucagon by 1 route and was crossed over to the other route for 2 repeated visits. Population PK models describing glucagon administered by subcutaneous or intradermal route were developed separately in NONMEM 7.3.

Results: A 2-compartment model with a transit compartment absorption model was selected for subcutaneous glucagon, while a 2-compartment model with first-order absorption was chosen for intradermal glucagon. The population mean (% coefficient of variation [CV%]) for clearance (CL), absorption rate constant (K_a), and central volume of distribution (V_c) of subcutaneous glucagon were 214 L/hr (36.2%), 3.42 hr^{-1} (26.6%), and 29.9 L (76.4%), respectively, scaled by (body weight/median 75.4 kg) to the exponent of 1.78 on CL. For intradermal glucagon, the population mean (CV%) of CL, K_a, and V_c were 237 L/hr (45.4%), 3.52 hr^{-1} (24.8%), and 73.0 L (58.4%), respectively. Age, body size measures, and disease duration did not influence intradermal glucagon PK parameters within the range of covariates studied. The estimated terminal half-life was averagely 25 minutes for both routes.

Conclusion: The population PK models characterized well the PK profiles of glucagon administered by subcutaneous and intradermal routes in patients with type 1 diabetes. No clinically relevant covariates were identified as predictors of glucagon PK, with the exception of body weight on subcutaneous glucagon PK.

RISK OF HOSPITAL ADMISSION FOR LIVER INJURY IN USERS OF NSAIDS AND NON-OVERDOSE PARACETAMOL (EPIHAM)

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Background: The SALT study concluded similar per-user risk of acute liver failure leading to liver transplantation (ALFT) between NSAIDs and a 3- to 4-fold higher rate of ALFT in non-overdose paracetamol (NOP) users.

Objectives: To identify the risks of hospital admission for acute liver injury (ALI) associated with NSAIDs and NOP.

Methods: Case-population study in 1/97 sample of the French population health care database. Cases of ALI were identified in hospital discharge summaries with *ICD-10* codes K71.1, 71.2, 71.6, 71.9 and 72.0 from 01/01/2009 to 31/12/2013 (5 y). Exposure was NSAID or paracetamol dispensation resulting in exposure within 30 days before admission. Population exposure was measured as number of patients using the drugs over the study timeframe as total number of DDD-dispensed and average number of DDD per user.

Results: A total of 75 cases were identified; 15 were exposed to NSAIDs and 27 to paracetamol (alone or combined with opiates). Event rates per million DDD ranged from 0.61 (0.17–1.56) for ketoprofen to 1.43 (0.04–7.97) for diclofenac combinations, 0.49 (0.28–0.81) for all NSAIDs combined, and 0.68 (0.44–1.00) for paracetamol. There was no association with average duration of treatment. Per patient risk ranged from 24 (8–57) for ibuprofen to 101 (3–562) for glucosamine per million users, 43 (24–71) for all NSAIDs combined, and 62 (40–91) for NOP. There was a relation between increasing average duration of treatment and increasing risk.

Conclusions: The risk profiles of NSAIDs and NOP concerning hospital admissions for ALI were similar and indicative of a type A (pharmacological or toxicological) reaction, in contrast with the ALFT, which had a pattern suggestive of type B (genetic or allergic) reactions. The 3-fold higher risk with paracetamol for ALFT was not found for ALI. Event rates for ALI were not predictive of risk of ALFT. ALI and ALFT probably have different mechanisms and risks, even if one may be the prelude to the other.

HIGH DOSE FAVIPIRAVIR: FIRST EXPERIENCE IN A PATIENT WITH EBOLA

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Background: On October 2014, the first case of human-to-human transmission of Ebola virus (EVOB) outside Africa was admitted in our hospital. Patient received supportive treatment and experimental treatment with convalescent plasma and antiviral was considered. Favipiravir (Toyama-Chemical) is a RNA polymerase inhibitor approved in Japan for the treatment of influenza, but with no previous experience in human EVOB infected patients.

Methods: The rational for favipiravir dose and schedule was based on recent in vitro and in vivo data in mice (Oesterech, 2014) showing an EBOV-IC90: 17 µg/mL and therapeutic efficacy: 300 mg/kg/d. Preclinical toxicology studies in monkeys settled a NOAEL of 100 mg/kg/d. Also pharmacokinetic data in healthy volunteers (loading dose/maintenance: 1200/600 BID) provided by Company was took in consideration: C_{max}: 30–56 µg/mL, $t_{1/2}$: 3.4–5.8 hr and plasma albumin binding: 53%. Based on this limited information, we decided a loading dose of 50 mg/kg BID (3 doses) and maintenance dose of 25 mg/kg TID. This schedule aimed to maintain a free C_{min} above IC_{90} and as close as possible to 60 µg/mL of total concentration. Similar doses had been recommended after our decision (Mentré, 2014).

Results: Favipiravir was initiated on day 9 of illness (DOI-9) and stopped on DOI-20 after two consecutive undetectable EBOV plasma viral loads. Despite the high doses used, favipiravir was well tolerated, without adverse events clearly related to the drug. The patient fully recovered and was discharged on DOI-34.

Conclusions: The contribution of favipiravir to disease resolution is difficult to ascertain because the use of other therapies (convalescent plasma and supportive treatment) and the spontaneous evolution of the disease, which can all be related to the cure of our patient. However, considering the time to treatment initiation, the severity of the disease, and the high viral load, contribution of favipiravir to the outcome of our patient must be considered and support its role as experimental therapy.

PRESCRIBING PATTERN FOR MALARIA IN INDIA: A NATIONWIDE SURVEY USING ADR COHORT EVENT MONITORING FORM

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Background: The present study aimed to assess the prescribing pattern of antimalarial drugs and their concordance with national malaria treatment guidelines, as an adjunct to ongoing cohort event monitoring.
Methods: A prospective, observational cohort study was carried out using modified WHO cohort event monitoring form. The study population comprised patients of all age, gender, and pregnancy status who were diagnosed with falciparum, vivax, or mixed infection malaria and receiving treatment from any peripheral or community health center or government sector hospital in India.
Results: A total of 1050 ADR forms were received from 243 reporters from 23 districts in 9 states. Previous self-treatment was observed in 9.3% patients in the form of antibiotics (31) and antimalarials (37), primarily chloroquine. For analysis, the patients were divided into chloroquine primaquine (CQPQ, 64%) and artesunate-sulfadoxine-pyrimethamine (ACT, 29%) groups. Inappropriate antimalarials were prescribed in 7% patients (ie, chloroquine alone, primaquine alone, artemisinin monotherapy, and chloroquine with ACT). Patients in the CQPQ group were younger, smaller in height, and lighter in weight. There were more males in the CQPQ group. Significantly more patients in the ACT group had higher total number of symptoms as compared to patients in CQPQ group ($P < 0.001$). Fever disappeared significantly faster in the ACT group (median fever duration 2 days vs 3 days; $P < 0.001$). For the reported malaria episode, the national programme recommended dose and duration of treatment was observed in 46% and 59% patients, respectively.
Conclusion: With increasing resistance and drying pipeline of drugs for malaria, high prevalence of inappropriate prescribing observed in the study is unacceptable and requires stringent monitoring.

PHARMACOKINETIKS OF ATOMOXETINE IN PLASMA AND ORAL FLUID IN PEDIATRIC PATIENTS WITH ATTENTION DEFICIT/HYPERACTIVITY DISORDER

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Introduction: Atomoxetine (ATX) is the first non-psychostimulant drug indicated for the treatment of attention-deficit hyperactivity disorder (ADHD) in pediatric patients as an alternative to methylphenidate. The aim of this study was to describe the pharmacokinetic profile of ATX in oral fluid in comparison to plasma in paediatric patients with ADHD.

Material and Methods: The protocol was approved by the local research committee. Child's parent or legal representative signed an informed consent (with assent) before inclusion. Participants were 5 children (2 girls and 3 boys, mean age: 8 y) and 6 adolescents (2 girls and 4 boys, mean age: 14 y) diagnosed as having ADHD and treated with different oral doses of ATX (60, 40, 35, 25, and 18 mg/d). Samples of blood and oral fluid were obtained before and post-dose (along 24 h). Concentrations of ATX and its metabolites 4-hydroxyatomoxetine (4-OH-ATX) and N-desmethylatomoxetine (N-des-ATX) were determined using liquid chromatography–tandem mass spectrometry in plasma and oral fluid.
Results: ATX, 4-OH-ATX, and N-des-ATX were found in plasma, but only ATX and 4-OH-ATX were detected in oral fluid samples. Mean ATX was found in plasma and oral fluid at a peak concentration of 589.6 and 19.72 ng/mL with a mean t_{max} of 1.4 and 2.7 h, respectively. For 4-OH-ATX detected in oral fluid, peak concentration was approximately half that in plasma (7.4 vs 13.8) with a mean t_{max} of 2.6 h in oral fluid and 2.1 in plasma. A good correlation between ATX and 4-OH-TX in plasma and saliva was achieved.
Conclusion: The correlations between ATX and 4-OH-ATX concentrations in the 2 biological fluids indicate that oral fluid concentrations may be an alternative to plasma concentrations.

NEW INSIGHTS ON THE PIOGLITAZONE RISK-BENEFIT RATIO IN EUROPEAN POPULATION

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Background: The benefit from antidiabetic drugs in T2DM lies on poorly powered clinical trials with high risk of bias and inconclusive meta-analysis results. While pioglitazone and metformin have been suggested to lower cardiovascular risk, some thiazolinediones have been associated with an increase in myocardial infarction and heart failure. Evidence on increased bladder cancer risk led to withdrawal of pioglitazone in France. However, both EMA and FDA withheld from action arguing that risk-benefit ratio might still be favorable in a limited population that could not benefit from other treatments. We aimed to investigate whether risks from pioglitazone outweighed the benefit.
Material and Methods: We conducted a simulation study using a French Realistic Virtual Population of type 2 diabetic individuals to evaluate the efficacy and safety of pioglitazone. Risk scores allowed estimating risk of non-fatal MI, stroke, and bladder cancer. Virtual patients without bladder cancer received pioglitazone by 3 years (pioglitazone effect: OR = 0.84 for cardiovascular events; OR = 1.22 for bladder cancer). We computed the NNT and the number needed to harm (NNH) by sex and age categories.
Results: Pioglitazone might prevent 47 non-fatal MI and 20 strokes while it could provoke 2 bladder cancers for every 10,000 individuals treated over 3 years. The overall NNT was 148 and the NNH was 4758. The number of cardiovascular events prevented was greater than the number of bladder cancers whatever the subgroup studied, with a ratio ranging from 21 in men over 65 years to 539 in women under 45 years. The absolute benefit is higher in men, especially at higher baseline cardiovascular risk levels and ages.
Conclusions: Risk-benefit ratios allow identifying specific T2DM subgroups that could take more benefit than harm from pioglitazone. Evidence from RCT should use modeling approaches as additional support to decide about the relevance of treatments applied on a given population structure.