PP208—DEOXYCHOLIC ACID AS A MODIFIER OF THE BLOOD BRAIN BARRIER PERMEATION IN RAT
M. Lalic-Popovic1; S. Golocorbin-Kon1,2; V. Vasovic1; B. Milijasavic1; and M. Mikov1,3
1Department of Pharmacy, Faculty of Medicine, Novi Sad, Serbia; 2Faculty of Pharmacy, University of Montenegro, Podgorica, Montenegro; and 3Department of Pharmacology, Toxicology and Clinical Pharmacology, Faculty of Medicine, Novi Sad, Serbia
Introduction: Major problem for diabetic patients represents damage of blood vessels and the oxidative stress of the brain cells due to increased concentration of free radicals and poor nutrition of brain cells. Gliclazide has antioxidative properties and poor blood brain barrier (BBB) penetration. Bile acids are known for their hypoglycemic effect and as promoters of drug penetration across biological membranes.
Aim: The aim of this study is to investigate whether the bile acid (deoxycholic acid) can change the permeation of gliclazide, through the blood brain barrier of a rat model type-1 diabetes.
Patients (or Materials) and Methods: Twenty-four male Wistar rats were randomly allocated to 4 groups, of which 2 were given alloxan intraperitoneally (100 mg/kg) to induce diabetes. One diabetic group and 1 healthy group were given a bolus gliclazide intra-arterially (20 mg/kg), while the other 2 groups apart from gliclazide got deoxycholic acid (4 mg/kg) subcutaneously. Blood samples were collected 30, 60, 150, and 240 seconds after dose, brain tissues were immediately excised, and blood glucose and gliclazide concentrations were measured.
Results: Penetration of gliclazide in groups without deoxycholic acid pretreatment was increased in diabetic animals compared with healthy animals. Also in both, healthy and diabetic animals, deoxycholic acid increased the permeation of gliclazide through that in BBB. Deoxycholic acid pretreatment also changed the pattern of blood glucose level increase after gliclazide application in diabetic as well as in healthy animals.
Conclusion: Deoxycholic acid promotes gliclazide penetration across BBB in diabetic and in healthy animals. In addition, deoxycholic acid alters some pharmacokinetic properties of gliclazide in both healthy and diabetic rats. Thus, deoxycholic acid should be more investigated in the treatment of diabetes mellitus and as penetration promoter of lipophilic molecules through BBB as well as other biological membranes.
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Key words: deoxycholic acid bile acid gliclazide blood brain barrier permeability
Disclosure of Interest: None declared.

PP209—MODEL-BASED ANALYSIS OF THE PHARMACOKINETICS OF A MODIFIED RELEASE FORMULATION OF PARACETAMOL AFTER TWICE DAILY DOSING AND POTENTIAL IMPLICATIONS FOR THE RISK OF HEPATOTOXICITY IN OSTEOARTHRITIS PATIENTS
O. Della Pasqua1; K. Bergman2; and J. de Jongh2
1Clinical Pharmacology Modelling & Simulation, GlaxoSmithKline, Uxbridge, United Kingdom; and 2LAP&P Consultants, Leiden, the Netherlands
Introduction: Paracetamol (AP) is recommended as the initial pharmacologic treatment of choice for the management of osteoarthritis (OA). However, inadequate compliance with the prescribed regimen can lead to reduced efficacy. This may in turn prompt patients to switch to other analgesics with increased safety risks. Panadol 1 g sustained release (P12) tablet is a twice-daily sustained released formulation that provides 4 g of paracetamol per day that could dramatically enhance patient’s compliance and reduce the possibility of switching to less well-tolerated drugs. The main objective of this investigation was to evaluate the maximum paracetamol concentration in plasma (Cmax) after a twice-daily dosing (BID) regimen with P12 compared with the currently marketed immediate-release (IR) formulation. In addition, we apply pharmacokinetic-pharmacodynamic concepts to assess the time that APAP levels remain above the minimum effective concentration (MEC) and evaluate the potential impact of differences in exposure between the 2 formulations on the risk of hepatotoxicity in osteoarthritis patients.
Patients (or Materials) and Methods: A population PK model was developed using data from 3 Phase 1 studies and 1 study in patients with type 2 diabetes to explore the effects of demographic covariates. Using the nomogram line as reference to assess the risk of APAP-induced hepatotoxicity, different dosing scenarios were simulated taking into account the effects of age, sex, and body weight. Peak concentrations (Cmax) were used as measure of interest to assess the probability of liver toxicity. APAP concentrations were assumed to be the primary driver of toxicity.
Results: Our results show that there is no difference in the risk of hepatotoxicity between the regimens when APAP is taken at therapeutic doses or after an unintentional overdose of 4 tablets. After an unintentional overdose with 10 tablets, hepatotoxicity is predicted for 1 of 10,000 patients taking the IR formulation under fasted conditions and for none of the patients taking the P12 formulation. After overdose with 10 tablets, patients with low body weight are likely to exceed the toxic threshold by no more than 0% to 0.94% for the IR and by 0.04% to 0.15% for P12 formulation.
Conclusion: In conclusion, the risk of hepatotoxicity after BID dosing appears to be similar to the standard regimen. Our analysis also reveals that the proportion of patients who stay above the MEC is higher for P12 when APAP is taken under fasting conditions. These results illustrate the relevance of clinical trial simulations before the implementation of a clinical trial protocol. Our approach illustrates what should be considered best-practice in the evaluation of drug safety in late clinical development.
Disclosure of Interest: None declared.

PP210—PHARMACOKINETICS AND PHARMACODYNAMICS MODELING TO OPTIMIZE DOSAGE REGIMENS OF SULBACTAM
S. Jaruratanasirikul1; W. Wongpoowarak1; N. Aeinlang1; and M. Jullangkoon1
1Department of Medicine, Faculty of Medicine, Prince of Songkla University; and 2Department of Pharmaceutical Technology, Faculty of Pharmaceutical Sciences, Prince of Songkla University, Hat Yai, Songkla, Thailand
Introduction: In the current situation of worldwide spreading of multidrug-resistant A. baumannii and only a few effective antimicrobial agents currently available, sulbactam is a potentially useful alternative treatment option for this pathogen. This agent is characterized by time-dependent antimicrobial activity and the exposure time during which the free drug concentration remains above the MIC (T>MIC) is the pharmacokinetic/pharmacodynamic (PK/PD) index that best correlates with efficacy.
Objectives: The aims of the study were to: (1) reveal a population pharmacokinetic (PK) model to describe the disposition of sulbactam; and (2) assess the efficacy of various dosage regimens of sulbactam in achieving the probability of target attainment (PTA) of this agent over a range of MICs.