PP208—DEOXYCHOLIC ACID AS A MODIFIER OF THE BLOOD BRAIN BARRIER PERMEATION IN RAT

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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 permeation promoter of lipophilic molecules through BBB as well as other biological membranes.

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Key words: deoxycholic acid bile acid gliclazide blood barrier permeability

Disclosure of Interest: None declared.

PP209—MoLAR DOSING FOR THE BLOOD BRAIN BARRIER Penetration of Bile Acids: An In-vitro Study

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Introduction: Paracetamol (APAP) 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 analgescics 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 I 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

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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 of 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.
Patients (or Materials) and Methods: The study was conducted in 12 healthy volunteers. Each participant received a 1-g single dose intravenously of sulbactam, after which PK studies were carried out, using a Monte Carlo simulation to determine the probability of attaining a specific pharmacodynamic target.

Results: The population PKs of sulbactam were; \( k12 = 0.637 \times 10^{-2} \) h\(^{-1} \), \( k21 = 0.663 \times 10^{-1} \) h\(^{-1} \), \( k13 = 8.626 \times 10^{-3} \) h\(^{-1} \), \( k31 = 5.424 \times 10^{-3} \) h\(^{-1} \), \( k1 \) \( ke = 3.223 \times 10^{-1} \) h\(^{-1} \), \( CL = 11.903 \times 10^{-3} \) L/h and \( V = 3.693 \times 10^{1} \) L. The PTAs for selected regimens over a range of MICs were as follows:

<table>
<thead>
<tr>
<th>Dosage regimen</th>
<th>MIC (mg/L)</th>
<th>PTA of T&gt;MIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 g q8h (1/2/3/4 h infusion)</td>
<td>1</td>
<td>0.17/0.99/0.99/0.99</td>
</tr>
<tr>
<td>2 g q8h (1/2/3/4 h infusion)</td>
<td>2</td>
<td>0.00/0.21/0.99/0.99</td>
</tr>
<tr>
<td>3 g q8h (1/2/3/4 h infusion)</td>
<td>3</td>
<td>0.00/0.99/0.99/0.99</td>
</tr>
<tr>
<td>4 g q8h (1/2/3/4 h infusion)</td>
<td>4</td>
<td>0.00/0.99/0.99/0.99</td>
</tr>
<tr>
<td>3/6/9/12 g q24h (continuous infusion)</td>
<td>5</td>
<td>0.11/0.46/0.99/0.99</td>
</tr>
</tbody>
</table>

Conclusion: The concurrent administration of piperine with domperidone to rats produced a significant increase in the plasma levels of the latter. However, further studies are needed to determine the possible mechanism(s) involved in this pharmacokinetic interaction.

Disclosure of Interest: None declared.

PP212—BIOAVAILABILITY OF DIGOXIN TABLETS, LOW THERAPEUTIC INDEX DRUG, DETERMINED BY EMIT
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Introduction: Introducing of a standard drug monitoring for digoxin, a digitalis glycoside using in heart failure, considerably reduce the incidences of digoxin toxicity. The need for measurement of digoxin concentrations and knowledge about bioavailability of the given preparation arise from the low therapeutic index of digoxin and its concentration-dependent toxicity. The recommended therapeutic range (1.0–2.5 nmol/L) reflects significant increase in the risk of toxicity that occurs with serum concentrations over 2.6 nmol/L. Choosing a proper analytical method for digoxin bioavailability evaluation is essential due to digoxin-like immunologic factor (DLIF) and others interfering substances that overestimate serum digoxin concentration which may be a significant clinical problem.

Patients (or Materials) and Methods: The study was performed on 24 healthy volunteers in accordance with GCP and legal requirements. Digoxin tablets were administered as a single dose of 0.5 mg. Pharmacokinetic profiles were plotted up to 60 hours after dosing. Determination of digoxin concentration in serum samples was performed by immunoenzymatic method by using the Emit® 2000 Digoxin Assay (Siemens Healthcare Diagnostics). EMIT is a homogeneous enzyme immunoassay intended for use in the quantitative analysis of digoxin in human serum or plasma. The method was fully validated according to the international guidelines. Original solutions of digoxin were used as calibration standards. Lower limit of quantification was set at the concentration of 0.1 ng/mL that is sufficient for human pharmacokinetic evaluation. Standard pharmacokinetic and bioavailability parameters in single-dose regimen (AUC, AUCinf, Cmax, Tmax, MRT, t1/2) were calculated by a noncompartamental method.

Results: Study results, including t1/2 and other bioavailability parameters, were in agreement with the reference data. Mean AUCinf was 33.42 (10.13) ng*h/mL, while AUCt was 23.93 (6.70) ng*h/mL. Cmax was observed as 3.24 (0.77) ng/mL but occurred at different Tmax (range, 0.5–2.5 hours). The intersubject variability was similar in case of AUC and Cmax (range, 23.80%–30.31%). The high variability of Tmax was observed (49.33%). Cmax exceed the recommended therapeutic ranges in most cases due to administration of a high dose of the tested drug. Digoxin tablets elimination half-life in healthy volunteers, even after single dose administration is high (32.78 (6.48) hours) as well as MRT (44.14 (8.34) hours).

Conclusion: The study results have confirmed that the EMI T method was appropriate for assessment digoxin bioavailability and can be used not only as reliable screening test but also in bioavailability and bioequivalence evaluation.

Disclosure of Interest: None declared.

PP211—PIPERINE INCREASES PLASMA DOMPERIDONE CONCENTRATIONS IN THE RAT
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Introduction: Piperine is the main pungent alkaloid present in the fruits of black pepper (Piper nigrum) and long pepper (Piper longum). In traditional medicine, black pepper has been used as an analgesic and anti-inflammatory agent and in the treatment of epilepsy and snake venom poisoning. Piperine also has been reported as an inhibitor against several cytochrome P-450–mediated pathways and Phase II metabolism as well as P-glycoprotein. This study was carried out to investigate the effect of piperine on the pharmacokinetics of domperidone after acute and chronic administration in rats.

Patients (or Materials) and Methods: Animals received a single dose of domperidone (20 mg/kg, p.o.) alone or together with piperine (60 mg/kg, p.o.). Similarly, the same doses of domperidone alone or when it was given together with piperine were administered to rats chronically for 5 days. Plasma samples were collected at 0.25, 0.5, 1.0, 2.0, 3.0, 4.0, 6.0, 8.0, 10.0, and 12.0 hours after drug administration. The concentrations of domperidone in the plasma were measured using an HPLC method.

Results: The concomitant administration of piperine with domperidone acutely or chronically resulted in a significant (\( P < 0.05 \)) increase in the maximum plasma concentration (Cmax), the mean area under the plasma concentration–time curve (AUC), and the elimination half-life (t\( _{1/2} \)) of domperidone compared with those obtained for domperidone alone.

Disclosure of Interest: None declared.

PP213—CORRELATION OF DISSOLUTION DATA WITH CLINICAL EFFICACY OF TWO LAMOTRIGINE TABLET FORMULATION
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Introduction: Evaluation of a drug product in the manufacturing stage as well as in clinical practice is essential due to the low therapeutic ratio of lamotrigine and potential interactions with other drugs.

Patients (or Materials) and Methods: The study was performed on 24 healthy volunteers in accordance with GCP and legal requirements. Lamotrigine tablets were administered as a single dose of 150 mg. Pharmacokinetic profiles were plotted up to 60 hours after dosing. Determination of lamotrigine concentration in serum samples was performed by immunoenzymatic method by using the Emit® 2000 Lamotrigine Assay (Siemens Healthcare Diagnostics). EMIT is a homogeneous enzyme immunoassay intended for use in the quantitative analysis of lamotrigine in human serum or plasma. The method was fully validated according to the international guidelines. Original solutions of lamotrigine were used as calibration standards. Lower limit of quantification was set at the concentration of 0.1 ng/mL that is sufficient for human pharmacokinetic evaluation. Standard pharmacokinetic and bioavailability parameters in single-dose regimen (AUC, AUCinf, Cmax, Tmax, MRT, t1/2) were calculated by a noncompartamental method.

Results: Study results, including t1/2 and other bioavailability parameters, were in agreement with the reference data. Mean AUCinf was 33.42 (10.13) ng*h/mL, while AUCt was 23.93 (6.70) ng*h/mL. Cmax was observed as 3.24 (0.77) ng/mL but occurred at different Tmax (range, 0.5–2.5 hours). The intersubject variability was similar in case of AUC and Cmax (range, 23.80%–30.31%). The high variability of Tmax was observed (49.33%). Cmax exceed the recommended therapeutic ranges in most cases due to administration of a high dose of the tested drug. Lamotrigine tablets elimination half-life in healthy volunteers, even after single dose administration is high (32.78 (6.48) hours) as well as MRT (44.14 (8.34) hours).

Conclusion: The study results have confirmed that the EMI T method was appropriate for assessment lamotrigine bioavailability and can be used not only as reliable screening test but also in bioavailability and bioequivalence evaluation.

Disclosure of Interest: None declared.