work is the first stage for determining the design of pharmacology genetics research.

Disclosure of Interest: None declared.

PP189—A PHYSIOLOGICALLY-BASED MECHANISTIC PHARMACOKINETIC MODEL TO ASSESS THE METABOLISM OF OXYCODONE IN HEALTHY VOLUNTEERS: INTERPLAY BETWEEN CYP3A AND 2D6 INHIBITION

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Introduction: Oxycodone undergoes a relatively complicated metabolism producing 3 main metabolites: noroxycodone, oxymorphine, and noroxymorphone. Among these metabolites, oxymorphine is highly related to the pharmacodynamic effect of oxycodone. It is 14 times more potent than the parent compound, and its affinity for the µ opioid receptor is 3 times higher than morphine. Development of a whole-body physiologically based pharmacokinetic (PK) model is an approach to predict in vivo metabolism of oxycodone and PK profile of each metabolite in different drug–drug interaction (DDI) scenarios.

Patients (or Materials) and Methods: The Simcyp simulator was used as a platform and database for simulation of oxycodone’s metabolism in virtual healthy populations. Prior in vitro and in vivo data were combined to build an oxycodone model which was used to predict the PK profile in healthy volunteers. The incorporated parameters were optimized by a top-down approach based on the clinical trial conducted by Samer et al, where PK profile of 0.2 mg/kg single dose oxycodone and its 3 metabolites were monitored in 10 healthy male volunteers (n = 10) previously genotyped for CYP2D6 in 4 scenarios (oxycodone administered alone or coadministered with CYP3A inhibitor ketoconazole (400 mg) and/or CYP 2D6 inhibitor quinidine (100 mg)) (Samer C, Daali Y et al. 2010). The PK data obtained in 3 interaction scenarios of the latter clinical trial were used to test the built model. Simulated trials permitted to evaluate the impact of CYP3A and CYP2D6 inhibitions on the concentration–time profiles of oxycodone and 3 main metabolites. The simulated studies designs were closely matched with the clinical trial and the virtual populations (1 trial of 10 volunteers, and 10 trials of 10 volunteers) were set with the same proportion of each CYP2D6 phenotype as the clinical trial (7 extensive, 1 poor and 2 ultrarapid metabolisers).

Results: Pharmacokinetic profiles of oxycodone and 2 predominant metabolites (oxymorphine and noroxycodone) were closely simulated by the model.

Mean values (SD).

Oxycodone, noroxycodone, and oxymorphine PK profiles were also concordant with the clinical study according to CYP2D6 phenotypic groups. Obtained DDI magnitudes were also in agreement with the clinical data. Noroxymorphone PK profile was less accurately predicted by the model.

Conclusion: The Simcyp developed model for oxycodone is valuable to predict the metabolism of oxycodone and main metabolites, and to simulate DDI involving CYP 3A and 2D6.

PP191—INFLUENCE OF VERAPAMIL ON THE PHARMACOKINETICS OF OXCARBZEPEINE AND 10-HYDROXYCARBZEPEINE ENANTOMERS IN HEALTHY VOLUNTEERS

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Introduction: Oxcarbazepine (OXC) is a drug indicated for the treatment of partial seizures or generalized tonic-clonic seizures in adults and children. It undergoes rapid presystemic reduction with formation of 10-hydroxyoxcarbazepine (MHD), which has a chiral center at position 10, with the enantiomers (S)-(+) and (R)-(−) MHD with similar antiepileptic effects. OXC and MHD are substrates of P-glycoprotein (Pgp), whereas verapamil is an inhibitor of Pgp expressed in various tissues, including the brain. This study aims to evaluate the influence of verapamil on the pharmacokinetics of OXC and MHD enantiomers in healthy volunteers.

Patients (or Materials) and Methods: The study was conducted in 2 phases and included 12 adult healthy volunteers. In the Phase I, they were treated with 300 mg/12 hours OXC during 5 days. On the fifth day, after the last dose, serial blood samples were collected up to 12 hours. In the Phase II, the same healthy volunteers were treated with OXC (300 mg/12 hours during 5 days) associated with verapamil (80 mg/8 hours during 5 days). On the fifth day, after the last OXC dose, serial blood samples were collected up to 12 hours. Plasma concentrations of OXC and MHD enantiomers were evaluated by LC-MS/MS coupled with a chiral phase Chiralcel® OD-H column. Pharmacokinetic analysis was performed using the software WinNonlin and statistical tests were conducted with the significance level set at P < 0.05.

Results: The following pharmacokinetic parameters for OXC were obtained in Phase I (median): maximum plasma concentration (Cmax) of 1.35 mg/mL in 1.0 hour, area under the plasma concentration versus time curve (AUC0–12) of 3.98 µg·h/mL and half-life of 2.45 hours. The kinetic disposition of MHD was enantioselective, with observation of a higher proportion for the enantiomer S-(+) than R-(−) MHD compared with R-(−)-MHD (AUC0–12S/(+)R-(−) of 4.10). Verapamil treatment (Phase II) decreased the mean residence time (3.83 vs 4.71 hours) and the apparent volume of distribution (Vd) (2.86 vs 3.78 L/kg) of OXC. Concerning MHD enantiomers, the verapamil treatment increased Cmax, AUC and Css for both enantiomers.

Conclusion: Verapamil treatment reduced OXC Vd and increased AUC of both MHD enantiomers probably due to the Pgp inhibition.

Disclosure of Interest: None declared.
**PP192—PHARMACOKINETICS OF SELEXIPAG IN SUBJECTS WITH SEVERE RENAL IMPAIRMENT COMPARED WITH HEALTHY SUBJECTS**

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**Introduction:** Selexipag is a new prostacyclin receptor agonist, which is being investigated in Phase III studies for the treatment of pulmonary arterial hypertension (PAH). Renal function impairment can alter the disposition of a large number of drugs and since PAH patients may have impaired renal function, the aim of this study was to assess how severe renal function impairment (SRFI) may affect the pharmacokinetics (PK), safety, and tolerability of selexipag and its active metabolite (ACT-333679).

**Patients (or Materials) and Methods:** Sixteen subjects were enrolled in this 2-group Phase I study. Groups A and B were composed of 8 subjects with SRFI and 8 healthy subjects, respectively. Subjects in Group B were matching with those in Group A, based on age, sex, race, and body mass index. Subjects received a single oral dose of 400 µg selexipag and were monitored for 144 h (Group A) or 72 h (Group B). PK samples were analyzed by liquid chromatography coupled to tandem mass spectrometry. PK parameters of selexipag and ACT-333679 were explored using ratios of geometric means and their 90% CIs.

**Results:** PK results (geometric mean (95% CI)) are presented in the table below:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group A</th>
<th>Group B</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Selexipag</td>
<td>ACT-333679</td>
</tr>
<tr>
<td>Cmax [ng/mL]</td>
<td>6.2 (3.2–11.8)</td>
<td>7.7 (5.1–11.9)</td>
</tr>
<tr>
<td>Tmax [h]</td>
<td>1.2 (0.8–1.8)</td>
<td>1.4 (1.0–2.2)</td>
</tr>
<tr>
<td>1/C t1/2</td>
<td>0.6 (0.4–1.0)</td>
<td>0.8 (0.5–1.2)</td>
</tr>
<tr>
<td>AUC0–∞ [ng*h/mL]</td>
<td>17.6 (13.4–22.5)</td>
<td>21.6 (17.0–26.3)</td>
</tr>
</tbody>
</table>

1peak concentration, 2time to reach Cmax, median (range), 3terminal half-life, 4exposure from 0 to ∞.

No relevant differences in plasma protein binding of selexipag and ACT-333679 were observed between both groups. Five subjects reported 17 adverse events (AEs): 8 in Group A, 9 in Group B. Headache was the most frequently reported AE in both groups (4 each in each group). No clinically significant changes in mean vital signs, electrocardiograms, clinical laboratory variables, including estimated glomerular filtration rate and urinalysis, were observed. No deaths or serious adverse events were reported.

**Conclusion:** Selexipag 400 µg was generally well tolerated in all subjects. Compared with healthy subjects, a 1.7-fold increase in Cmax and AUC to selexipag was observed in subjects with SRFI. Similar results were obtained for ACT-333679, i.e., a 1.4-fold increase in Cmax and an approximately 1.7-fold increase in AUC in subjects with SRFI compared with healthy subjects.

**Disclosure of Interest:** None declared.

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**PP193—SIMULTANEOUS LC-MS/MS QUANTIFICATION OF P-GLYCOPROTEIN AND CYTOCHROME P450 PROBE SUBSTANCES AND THEIR METABOLITES IN DRIED BLOOD SPOTS**

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**Introduction:** Modifications in cytochrome P450 (CYP) and/or transporter activities (such as P-glycoprotein [P-gp]) can result in important pharmacokinetic variability and are the underlying mechanisms of many drug–drug interactions. CYP and P-gp activity can be assessed by the in vivo administration of a cocktail of probe drugs each of which is metabolized by 1 specific cytochrome or transported by P-gp.

**Patients (or Materials) and Methods:** In this study, a single HPLC-MS/MS method has been developed for the simultaneous quantification of P-gp (fexofenadine) and CYP probe substances (caffeine for CYP1A2, bupropion for CYP2B6, flurbiprofen for CYP2C9, omeprazole for CYP2C19, dextromethorphan for CYP2D6 and midazolam for CYP3A4), and their metabolites in dried blood spots (DBS). Substances were extracted from DBS (10 µL) using methanol. HPLC analysis was performed using a LC-MSSMS system consisting of a 5500QTrap® triple quadrupole linear ion trap (QqQLT) mass spectrometer equipped with a TurboIon SprayTM interface and an Ultimate 3000 RS instrument as LC system.

**Results:** The method was validated according to international criteria. The intermediate precision was <10% and the accuracy was in the interval (92.2%–111.1%) for all substances and all concentrations tested. A linear response was observed for the following concentration ranges: 1 to 200 ng/mL for bupropion, hydroxybuproprion, and fexofenadine; 0.1 to 100 ng/mL for midazolam; 0.2 to 200 ng/mL for omeprazole, hydrometrexoprazole, hydroxymidazolam, and dextromethorphan; 0.5 to 500 ng/mL for dextrophen; 50 to 10,000 ng/mL for caffeine and paraxanthine; 50 to 2500 ng/mL for flurbiprofen and 5 to 1000 ng/mL for hydroxyflurbiprofen. All substances were stable in DBS stored at room temperature for at least 15 days. The method has been successfully applied to a pharmacokinetic study where healthy male volunteers have received a low-dose cocktail of the here described P-gp and CYP probe substances. Metabolic ratios were determined for all CYP probe drugs and a good correlation was observed when drug concentrations in capillary DBS samples were compared with venous plasma samples.

**Conclusion:** DBS is a suitable sampling method for cytochromes and P-glycoprotein phenotyping.

**Disclosure of Interest:** None declared.

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**PP194—PHARMACOKINETICS OF SELEXIPAG IN SUBJECTS WITH MILD, MODERATE, OR SEVERE HEPATIC IMPAIRMENT COMPARED WITH HEALTHY SUBJECTS**

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**Introduction:** Selexipag is a new prostacyclin receptor agonist, which is being investigated in Phase III studies for the treatment of pulmonary arterial hypertension (PAH). Selexipag is eliminated for >90% by the liver and because PAH patients may suffer from liver impairment, the aim of this study was to assess how different degrees of liver impairment may affect the pharmacokinetics (PK), safety, and tolerability of selexipag and its active metabolite (ACT-333679).

**Patients (or Materials) and Methods:** Twenty-six subjects were enrolled in this 4-group Phase I study. Group A, B, C, and D were composed of 8 subjects with mild liver impairment, 8 subjects with moderate liver impairment, 2 subjects with severe liver impairment, and 8 healthy subjects, respectively. Subjects of Group D were matching with those of Group B, based on age, sex, body weight, and height. Subjects received a single oral dose of selexipag (400 µg for