

Open



Systems Pharmacology

Hands-On exercise -
Rifampicin-Midazolam
DDI

Disclaimer:

Examples described herein have been designed to teach physiologically-based pharmacokinetic / pharmacodynamic (PBPK/PD) modeling with PK-Sim® and MoBi®. Cases may have been simplified to focus on relevant didactic aspects and may not necessarily describe the best model variant.

Exercise – Setting up a drug-drug interaction simulation with Rifampicin as a perpetrator and Midazolam as a victim drug.

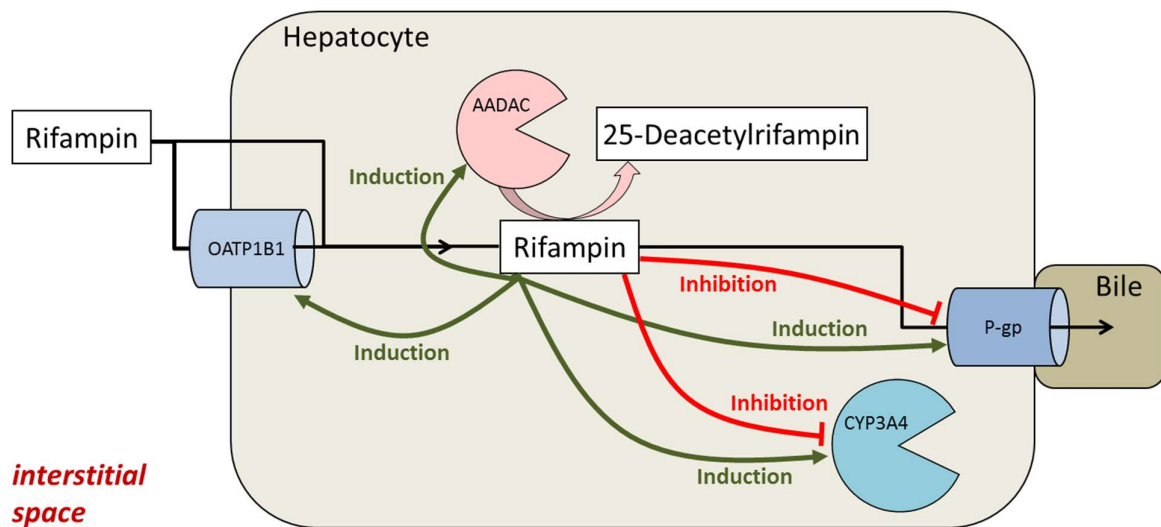
Objectives

Learn to create a simulation with multiple compounds and compare simulation to observed data

Learn to model complex drug-drug interactions with concurrent inhibition and induction of one enzyme and concurrent interactions with transporters by a perpetrator drug

Learn to output additional curves, such as time-varying enzyme concentrations in specific organs.

Features of the Rifampicin PBPK model:



Instructions:

Objective 1:

Evaluate the performance of the midazolam model (open Rifampicin-Midazolam-DDI_1.pksim5).

Make yourself familiar with the compound midazolam. In particular, use the configure simulation function to go through the different features and settings of the simulation.

Objective 2:

Experience the effects of rifampicin pretreatment on midazolam PK using study data from Reitman et al. (2011):

1. Load the compound "Rifampicin" from the compound template database. Make yourself familiar with the compound properties of rifampicin.
2. Create a simulation according to the study of Reitman et al. (2011). To do so, clone the simulation "Midazolam 3 mg PO (solution)" and additionally select the compound "Rifampicin". Make sure that all processes are incorporated into the simulation appropriately! You can add interaction processes by clicking on "Add Interaction", select the "Molecules in the individual" and "Interaction process in compound" for matching. There should be CYP3A4-Templeton 2011, AADAC-assumed, OATP1B1-Dixit 2007 and P-gp-Greiner 1999 induction processes as well as CYP3A4 Kajosaari 2005 and P-gp Reitmann 2011 inhibition by rifampicin. Please use the respective administration protocols for both compounds and the "oral solution" as formulation in both cases.
3. Set the simulation end time to 1344h (under Parameters→Settings)
4. Run the simulation, remove the old observed midazolam data (by right clicking on the data in the simulations window), and drag and drop the midazolam data with rifampicin into the chart. If desired, improve chart layout (e.g. set corresponding simulated and observed data to convenient colors, set min/max for axes, ...)

Model Structure
 Compounds
 Processes
 Administration
 Events
 Observers

Inhibition / Induction

Add Interaction

Molecule in individual	Interaction process in compound		
CYP3A4	Rifampicin CYP3A4-Kajosaari 2005		
P-gp	Rifampicin P-gp-Reitman 2011		
CYP3A4	Rifampicin CYP3A4-Templeton 2011		
AADAC	Rifampicin AADAC-Assumed		
P-gp	Rifampicin P-gp-Greiner 1999		
OATP1B1	Rifampicin OATP1B1-Dixit 2007		

Midazolam

Metabolism

	Enzyme in individual	Enzymatic process	Metabolite			
	CYP3A4	CYP3A4-Optimized	Sink		+	
	AADAC	<None>	Sink		+	
	UGT1A4	UGT1A4-Optimized	Sink		+	

Transport & Excretion

	Systemic process	Data source
	Glomerular Filtration	Optimized

Specific Binding

	Protein in individual	Binding process	
	CYP3A4	<None>	
	AADAC	<None>	
	P-gp	<None>	
	OATP1B1	<None>	
	ATP1A2	<None>	
	UGT1A4	<None>	
	GABRG2	GABRG2-Buhr 1997	

Rifampicin

Metabolism

	Enzyme in individual	Enzymatic process	Metabolite			
	CYP3A4	<None>	Sink		+	
	AADAC	AADAC-Nakajima 2011	Sink		+	
	UGT1A4	<None>	Sink		+	

Transport & Excretion

	Systemic process	Data source
	Glomerular Filtration	GFR

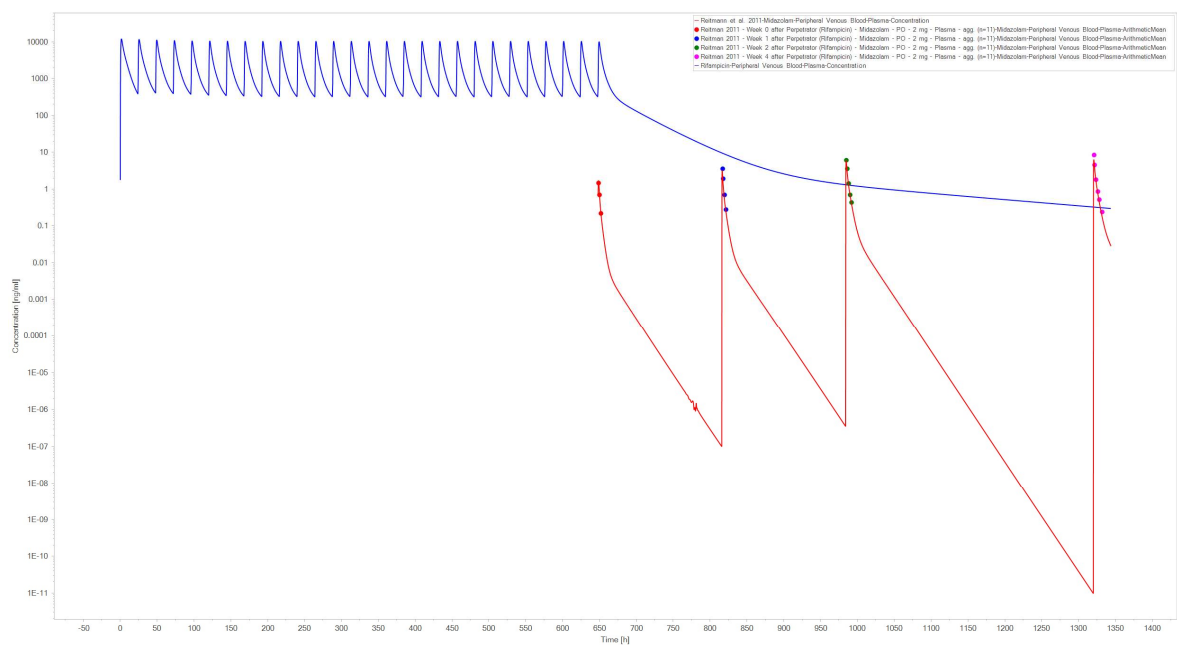
	Transporter in individual	Transport process	
	P-gp	P-gp-Collett 2004	
	OATP1B1	OATP1B1-Tirona 2003	

Previous

Next

OK

Cancel



Objective 3:

Experience the effects of rifampicin treatment on the time-course of CYP3A4 abundance in the liver (if you start from here, open the file “Rifampicin-Midazolam-DDI_2.pksim5”:

Assess time-course of CYP3A4 abundance in hepatocytes to visualize the effect of induction: Create new “Time Profile Analyses” tab. Click “Define Settings and run simulation” and include “Liver periportal|intracellular|CYP3A4”. Check “Liver periportal|intracellular|CYP3A4” concentrations in the “Chart Editor” to be displayed.

If desired, open the chart editor and improve chart layout e.g., by selecting only rifampicin and CYP3A4 concentrations in the repository of available outputs, setting the scale of the Y-axis to linear etc.

Individual Simulation Settings: Curve Selection

Select the curves that will be generated by the simulation.

Number of curves to generate for this simulation : 3 Deselect All

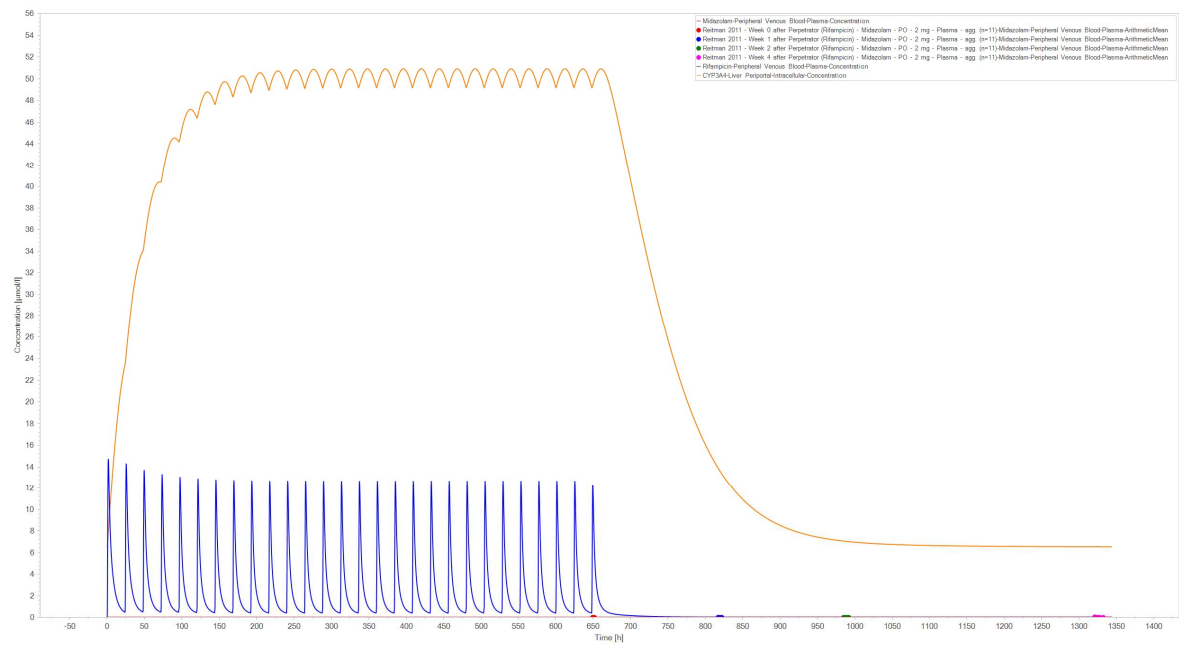
Organ ▲

Compartment	Molecule	Name	Selected
Interstitial	Midazolam-GABRG2-Buhr 199...	Concentration	<input type="checkbox"/>
Interstitial	Midazolam-GABRG2-Buhr 199...	Fraction of dose-Midazolam	<input type="checkbox"/>
Interstitial	Midazolam-GABRG2-Buhr 199...	Receptor Occupancy-Midazolam-G...	<input type="checkbox"/>
Interstitial	Rifampicin-AADAC-Nakajima ...	Fraction of dose-Rifampicin	<input type="checkbox"/>
Intracellular	CYP3A4	Concentration	<input checked="" type="checkbox"/>
Intracellular	AADAC	Concentration	<input type="checkbox"/>
Intracellular	P-gp	Concentration	<input type="checkbox"/>
Intracellular	OATP1B1	Concentration	<input type="checkbox"/>
Intracellular	ATP1A2	Concentration	<input type="checkbox"/>
Intracellular	UGT1A4	Concentration	<input type="checkbox"/>
Intracellular	GABRG2	Concentration	<input type="checkbox"/>
Intracellular	Midazolam	Concentration	<input type="checkbox"/>

Organ ▲

Compartment	Molecule	Name	Selected
Liver Periportal			
Intracellular	CYP3A4	Concentration	<input checked="" type="checkbox"/>
Peripheral Venous Blood			
Plasma	Midazolam	Concentration	<input checked="" type="checkbox"/>
Plasma	Rifampicin	Concentration	<input checked="" type="checkbox"/>

Save Settings into OK Cancel



*In case you wish to enter the exercise after this step and you did not perform the exercise described above, please open file **Rifampicin-Midazolam-DDI End.pksim5**.*