Solution – Drug-Drug interaction Itraconazole/Midazolam

Objectives

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

Learn to couple parent and metabolite

Learn to model drug-drug interaction

Learn that predefined compound properties, like defining Ki values and type of inhibition or defining a certain compound as a metabolite, will be taken automatically into account when creating a simulation

Learn how to retrieve AUC Ratio and Cmax Ratio in drug-drug interaction simulations

Open **Exercise_DDI_ITZ_1.pksim5**.

Objective 1: Evaluate the performance of the itraconazole (+ hydroxy-itraconazole) model

Set up a Simulation

- Upload the compounds itraconazole and hydroxy-itraconazole from the compound template database. This is done by a right click on "Compounds" in the Building Block window. Select "Load from Template …". A new window opens displaying available compound templates. Select "Itraconazole". You will be asked "Do you also want to load the metabolite(s) of this compound?" Click on "yes".
- Make yourself familiar with the compound properties. In particular, go to the "ADME" properties tab in the compound "Itraconazole", Select Metabolism → Metabolizing Enzymes → CYP3A4 → Optimization. Please note that the metabolite defined here ("Hydroxy_Itraconazole") is a compound defined in the compound building block. Have a look at Inhibition → CYP3A4 → Optimization. These properties will be automatically taken into account when creating a simulation.
- Make yourself familiar with the Administration Protocol "Barone 93 BID", i.e. an advanced administration protocol.
- Click "**Simulation**" in the "**Create**" Group of the "**Modeling**" ribbon tab. Create a simulation according to the study of Barone et al. (1993) (use this as name), i.e. use the provided "European standard male" individual and the compounds Itraconazole and

Hydroxy_Itraconazole. Furthermore, use the "Barone 93 BID" administration protocol, "oral solution" formulation and add a standard meal at t=0h as an event.

- Set simulation end time to 800h under Parameters → Settings.

Check and Run Simulation

- Make yourself familiar with the "Reaction Diagram" on the respective tab and, if desired, rearrange the symbols to improve overview. Check if parent-metabolite coupling and inhibition is properly placed in the diagram and, hence the simulation is properly established.
- Run the simulation

Compare to Observed Data

- Compare the simulated results to observed data from Barone et al. (1993). To do so, drag and drop the observed data "Barone_93_15days_MD_ITZ" and "Barone_93_15days_MD_OH-ITZ" from the observed data building block onto the chart.
- Open the chart editor and improve chart layout: set corresponding simulated and observed data to the same color, set min/max for Y-axes, try different legend positions

In case you wish to enter the exercise after this step and you did not perform the exercise described above, please open file **Ex_DDI_ITZ_2.pksim5**.

Objective 2: Experience the effects of itraconazole coadministration on midazolam PK using study data from Olkkola et al. (1996):

Simulate midazolam control:

Set up a Simulation

- Upload the compound "Midazolam" from the compound template database. This is done by a right click on "Compounds" in the Building Block window. Select "Load from Template …". A new window opens displaying available compound templates. Select "Midazolam".
- Make yourself familiar with the compound properties.
- Make yourself familiar with the Administration Protocol "Olkkola et al. Midazolam", i.e. an advanced administration protocol including oral and intravenous administration.
- Click "**Simulation**" in the "**Create**" Group of the "**Modeling**" ribbon tab. Name the new simulation "Olkkola et al. (1996) Control". Use the provided "European standard male", the "midazolam" compound, the "Olkkola et al. midazolam" application protocol and the "Midazolam tablet" formulation.

Run Simulation

- Run the simulation

Compare to Observed Data

- Compare the simulated results to observed data from Olkkola et al. (1996). To do so, drag and drop the observed data "Olkkola 1996 control" from the observed data building block onto the chart.
- Open the chart editor and improve chart layout: set corresponding simulated and observed data to the same color, set min/max for Y-axes, try different legend positions

In case you wish to enter the exercise after this step and you did not perform the exercise described above, please open file **Ex_DDI_ITZ_3.pksim5**.

Simulate midazolam-itraconazole interaction:

Set up a Simulation

- Make yourself familiar with the Administration Protocol "Olkkola et al. Itraconazole", i.e. once-daily administration.
- Click "**Simulation**" in the "**Create**" Group of the "**Modeling**" ribbon tab. Name the new simulation "Olkkola et al. (1996) Treatment". Use the provided "European standard male", the compounds "midazolam", "itraconazole" and "hydroxy-itraconazole" (check boxes), the "Olkkola et al. midazolam" application protocol and the "Midazolam tablet" formulation for midazolam as well as "Olkkola et al. itraconazole" application protocol for itraconazole.

Check and Run Simulation

- Make yourself familiar with the "Reaction Diagram" on the respective tab and, if desired, rearrange the symbols to improve overview. Check if parent-metabolite coupling and inhibition is in place in the diagram and, hence the simulation is properly established.
- Run the simulation

Compare to Observed Data

- Compare the simulated results to observed data from Olkkola et al. (1996 and 1994). To do so, drag and drop the observed data "Olkkola 1996 Treatment" and "Olkkola 1994 Itraconazole" from the observed data building block onto the chart.
- Open the chart editor and improve chart layout: set corresponding simulated and observed data to the same color, set min/max for Y-axes, try different legend positions,

remove Hydoxy_Itraconazole peripheral venous blood concentrations from the chart by unchecking the box “visible”.

In case you wish to enter the exercise after this step and you did not perform the exercise described above, please open file **Ex_DDI_ITZ_4.pksim5**.

Compare the Simulations:

Create a Comparison Chart

- Click “**Compare Results**” in the “**Analyses**” Group of the “**Run & Analyze**” ribbon tab.
- Drag and drop the **Simulations** “Olkkola et al (1996) Control” and “Olkkola et al. (1996) Treatment” and their corresponding **Observed Data** into the white field. In the **Chart Editor** select the curves you wish to be displayed.
- Rename comparison chart to “Olkkola et al. (1996) Treatment vs. Control” by a right click on comparison chart in the Simulations window. Select “Rename”.
- Open the chart editor and improve chart layout: set corresponding simulated and observed data to the same color, set min/max for Y-axes, try different legend positions

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