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 how to retrieve AUC Ratio and C_{max} Ratio in drug-drug interaction simulations

Open **Ex_DDI_ITZ_1.pksim5**.

Task 1: Evaluate the performance of the itraconazole model

Set up a Simulation

- Upload the compounds itraconazole and its metabolites 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 from the OSP GitHub Cloud. Select "Itraconazole".
- Make yourself familiar with the compound properties. In particular, go to the "ADME" properties tab in the compound "Itraconazole", Select Metabolism → Metabolizing Enzymes → CYP3A4. Please note that the first metabolite defined here ("Hydroxy-Itraconazole") is a compound defined in the compound building block. Have a look at Inhibition → CYP3A4. These properties will be automatically taken into account when creating a simulation. Try to find out what are the next metabolites after Hydroxy-Itraconazole.
- Make yourself familiar with the Administration Protocol "Itraconazole PO MD 200 mg", i.e. an advanced administration protocol.
- Click "**Simulation**" in the "**Create**" Group of the "**Modeling**" ribbon tab. Create a simulation according to a study design of 5 applications of 200 mg itraconazole once daily. Use the provided "European" individual and the compounds Itraconazole and all its metabolites. Furthermore, use the "Itraconazole PO MD 200 mg" administration protocol and "ITZ Capsule fasted" as formulation.
- Choose in the "Compounds" tab for Itraconazole "Capsule fasted" as option for Solubility.
- Check in the "Processes" tab that the inhibition processes for all 4 compounds are activated.

- Check if the simulation end time is set to 120h 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 couplings and inhibition are properly placed in the diagram and, hence the simulation is properly established.
- Run the simulation (and choose all 4 compounds in Peripheral Venous Blood as Curve Selection)

Compare to Observed Data

- Compare the simulated results to observed data from 3 different studies. To do so, drag and drop the observed data in the itraconazole subfolder within "Observed Data" 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**.

Task 2: Experience the effects of itraconazole coadministration on midazolam PK

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 from the OSP GitHub Cloud. Select "Midazolam".
- Make yourself familiar with the compound properties.
- Make yourself familiar with the Administration Protocols "Olkkola 1994 - Midazolam - 7.5 mg (Control)".
- Click "**Simulation**" in the "**Create**" Group of the "**Modeling**" ribbon tab. Name the new simulation "Olkkola 1994 - Midazolam - 7.5 mg (Control)". Use the provided "European",

the “midazolam” compound, the “Olkkola 1994 - Midazolam - 7.5 mg (Control)” application protocol and the “Tablet (Dormicum)” formulation.

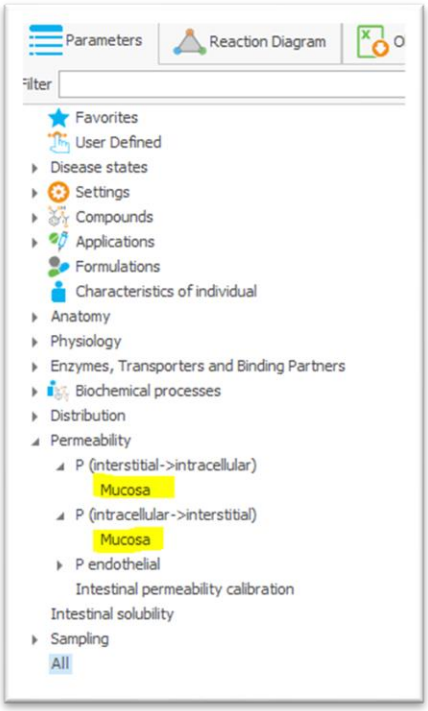
Run Simulation

- Run the simulation

Compare to Observed Data

- Compare the simulated results to observed data from Olkkola et al. 1994. To do so, drag and drop the observed data “Olkkola 1994 - po Control (Perpetrator Placebo) - Midazolam - PO - 7.5 mg - Plasma - agg. (n=9)” 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.

You will notice that the observed data are not well described by the simulation. Midazolam undergoes extensive first pass gastrointestinal metabolism. This needs to be reflected in a compound-specific simulation parameters: the interstitial to intracellular and vice versa permeability in the mucosa. You can modify these parameters in the “Parameters” tab of you simulation. Switch to “Advanced” mode at the bottom.



Put in a value for all 22 parameters of 0.0019242177595 cm/min. More details can be found here: https://github.com/Open-Systems-Pharmacology/OSP-PBPK-Model-Library/blob/v11.2/Midazolam/midazolam_evaluation_report.md

Rerun the simulation and compare again to the observed data.

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 1994 - Midazolam - 7.5 mg (with Itraconazole)" and "Olkkola 1994 - Itraconazole - 200 mg OD 4 days".
- Right-click the Simulation "Olkkola 1994 - Midazolam - 7.5 mg (Control)" from the previous step and choose "Clone…". Name the new simulation "Olkkola 1994 - Midazolam - 7.5 mg (with Itraconazole)".
- Add itraconazole and its metabolites.
- Choose in the "Compounds" tab for Itraconazole "Capsule fasted" as option for Solubility.
- Add in the "Processes" tab all the CYP3A4 inhibition processes for all 4 compounds.
- Exchange the administration protocol for midazolam to "Olkkola 1994 - Midazolam - 7.5 mg (with Itraconazole)"
- Add the administration protocol "Olkkola 1994 - Itraconazole - 200 mg OD 4 days" for itraconazole. Choose "ITZ Capsule fasted" as formulation.
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Check and Run Simulation

- Check if the simulation end time is set to 96h under Parameters → Settings.
- Delete the observed data from the previous step (right-click on the observed data building block under the simulation in the Simulations window.
- 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.
- Click on "Define Settings and Run". Choose midazolam and itraconazole peripheral venous blood plasma as output for selected curves.

Compare to Observed Data

- Compare the simulated results to observed data. To do so, drag and drop the observed data "Olkkola 1994 - po with Perpetrator (Itraconazole) - Midazolam - PO - 7.5 mg - Plasma - agg. (n=9)" and "Olkkola 1994 - po with Perpetrator (Itraconazole) - Itraconazole - PO - 200 mg - Plasma - agg. (n=9)" 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, etc.

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**.

Task 3: Basic PK-Analysis on AUC and C_{max}

- Click on "Show PK-Analysis" below the latest figure.
- Click on the button AUC Ratio (AUCR) below Midazolam.
- Interpret the results for midazolam.

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**.