Week 5 Report: Voriconazole
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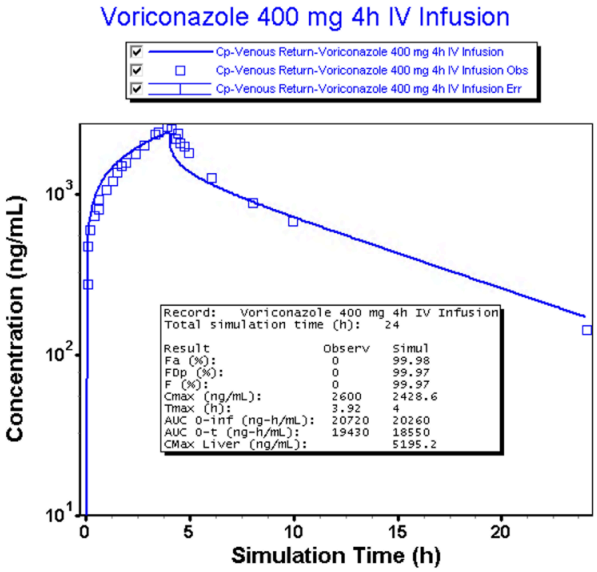
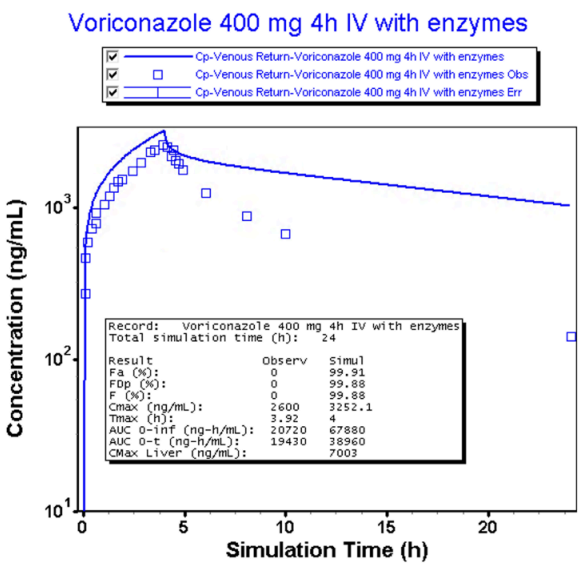
Week 4



Week 5



Enzyme Table

Generic	Enzyme	Location	Data Source	Vmax (mg/s) or (mg/s/mg-enz)	Km (mg/L)
Voriconazole 400 mg 4h IV wi	2C19	PBPK	Microsomes	0.0000406	0.947
Voriconazole 400 mg 4h IV with e	2C9	PBPK	Microsomes	0.00000587	5.409
Voriconazole 400 mg 4h IV with e	3A4	PBPK	Microsomes	0.0000142	63.55

Note: For this week's assignment we are showing one dosing level, but in the future we will apply the changes to all dosing levels. One of our papers discussed the role of FMOs (Flavin-Containing Monooxygenases) and their role in Voriconazole metabolism, however we need to determine hepatic expression of these enzymes and introduce them into the PBPK model before we can include the data.

Assessment without statistics:

As is plain to see, the addition of the CYP enzyme Vmax and Km data has altered the output to a significant extent. This could partially be because we don't have the most accurate information for all of the routes of metabolism yet (re: FMO1 and 3 roles). What is most notable when comparing observed to simulation output is the change in the AUC (see specific statistics down below). Given the relationship between AUC and clearance, this means that clearance rate has lowered. A possible explanation is that not all clearance is being accounted for. On the other hand, the concentration of the drug at the end of the simulation is much lower, showing that the addition of metabolism and clearance data does perhaps give a more accurate estimate of the amount of drug remaining. It's not as obvious why Cmax increased after inputting enzyme kinetics.

The following figure shows the WEEK 3 results: AUC and Cmax bias from the observation data, before and after adding NAC CL model: Observation AUC value is 20620 ng-h/ml; Cmax is 2600 ng/ml.

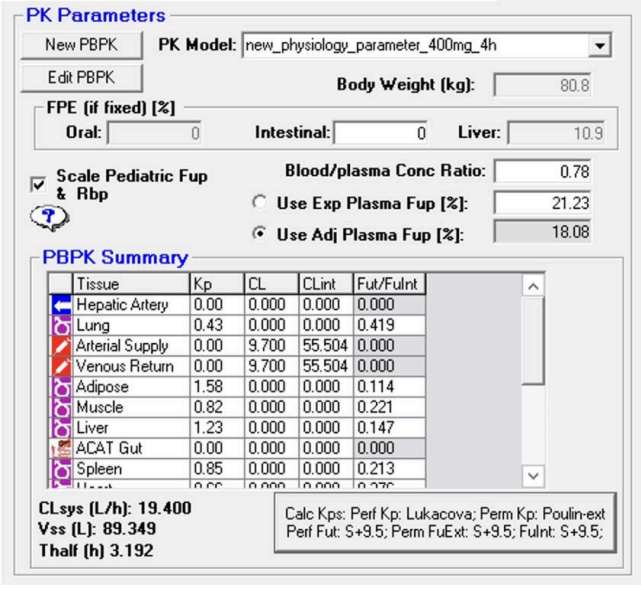
	Before adding NCA CL value/ Percentage difference(%)	After adding NCA CL value/ Percentage difference(%)
AUC(ng-h/ml)	40240 / +95.15%	20010 / -2.96%
Cmax(ng/ml)	3069.3 / +18.05%	3205.8 / +23.3%

The following figure shows a comparison of bias after adding the Fup model and after adding Vmax and Km model.

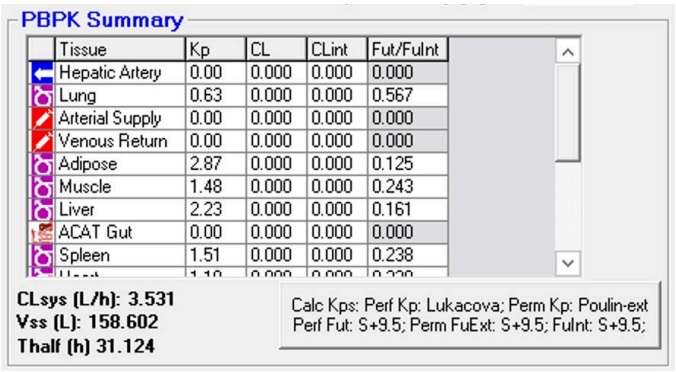
400mg 4h		Observation	After adding Fup value/ Percentage difference(%)	After adding Vmax and Km/ Percentage difference(%)
	AUC(ng-h/ml)	19430	18550 / -4.53%	38960 / +100.51%
	Cmax(ng/ml)	2600	2428.6 / -6.59%	3252.1 / +25.08%

1. Inputting enzyme kinetics of the CYP enzymes, the AUC increased by 105.04% (100.51%+4.53%) when adding the Fup value; while Cmax increased by 31.67% (25.08%+6.59%). Introducing metabolic enzymes to the model should have caused a better clearance, which means that the total drug amount in the plasma should be lower (AUC as well as Cmax should have decreased), this is contradictory to what we obtained from the data analysis as explained above.

2. Compared to the model with just the NCA CL value, we see the bias of Cmax are approximately the same, while the AUC is increased by almost 100%. We have almost entirely reverted back to the model before adding the Fup data. The CL value we added for liver in the NCA CL model is 9.7L/h, and GastroPlus automatically calculates CLint is 55.5L/h:



However, during this week's assignment, we set the CL to 0, thus the CLint in the PBPK model is 0:



And the actual CL value that GastroPlus used in this week's model can be calculated based on the following formulation:

$$CL_{int,in\ vitro} \approx \frac{V_{max}}{K_m}$$

Enzyme Table	Vmax(mg/s)	Km(mg/L)	CLint(L/h)
CYP2C9	0.00000587	5.409	0.0039
CYP2C19	0.0000406	0.947	0.154
CYP3A4	0.0000142	63.55	0.0008

The CLint used for this week is too low compared to the CLint value in the NCA CL model - 55.5 L/h, which could be the reason that clearance does not work in our model.