Week 9 Report: Voriconazole
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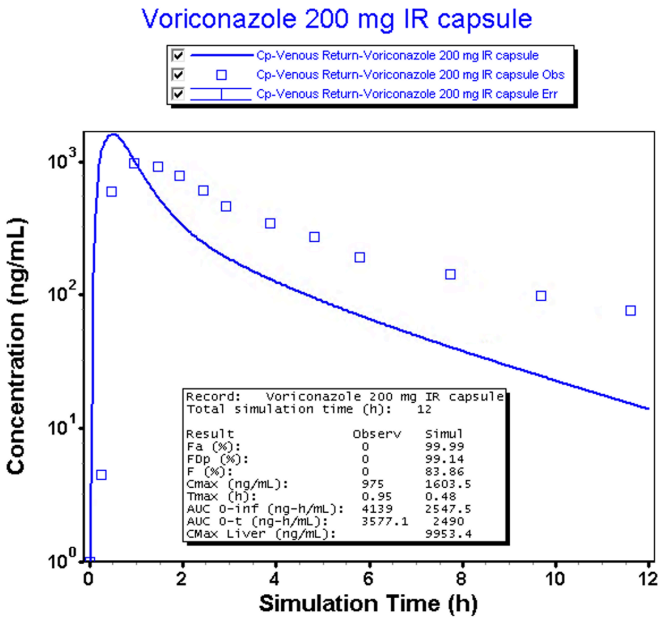
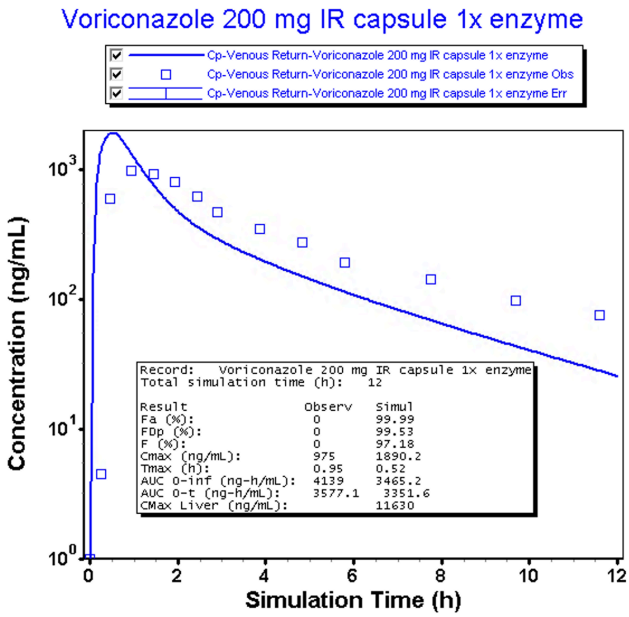
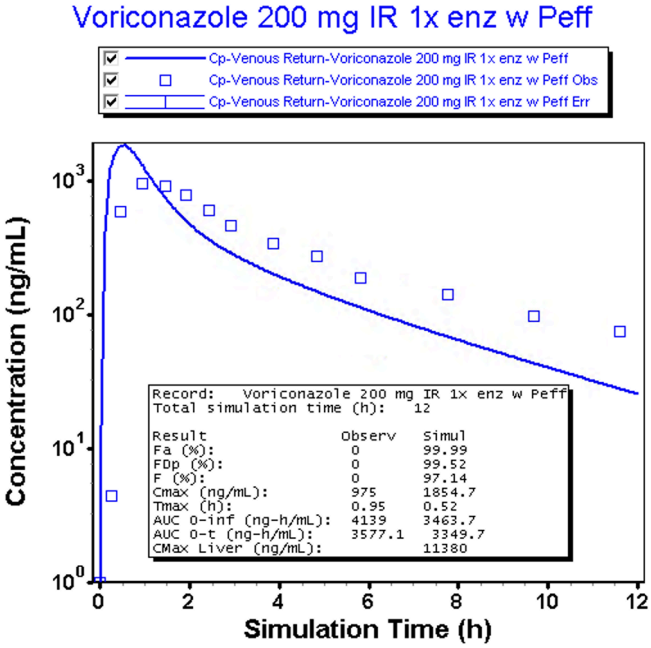
In our IV model, we decided to increase the Vmax of the enzymes in our table by 7x to help produce a better fit for the model, however we were curious to see if we would get a better fit for the oral dose if we changed the enzyme Vmax back to the original unit converted value.

x7 fold enzyme Vmax (left) vs. x1 fold enzyme Vmax (right):





Changing the values to 1x enzyme Vmax (the raw unit-converted values) does a better job predicting for the oral model than the 7-fold enzyme Vmax (even though it's still overpredicting Cmax and underpredicting AUC). Therefore, for the next data set, we used the 1x enzyme Vmax model. One other note is that the bioavailability increases from 83.86% to 97.18% which is more in line with the literature values. The 7-fold enzyme Vmax model was likely overpredicting the extent of gut metabolism.

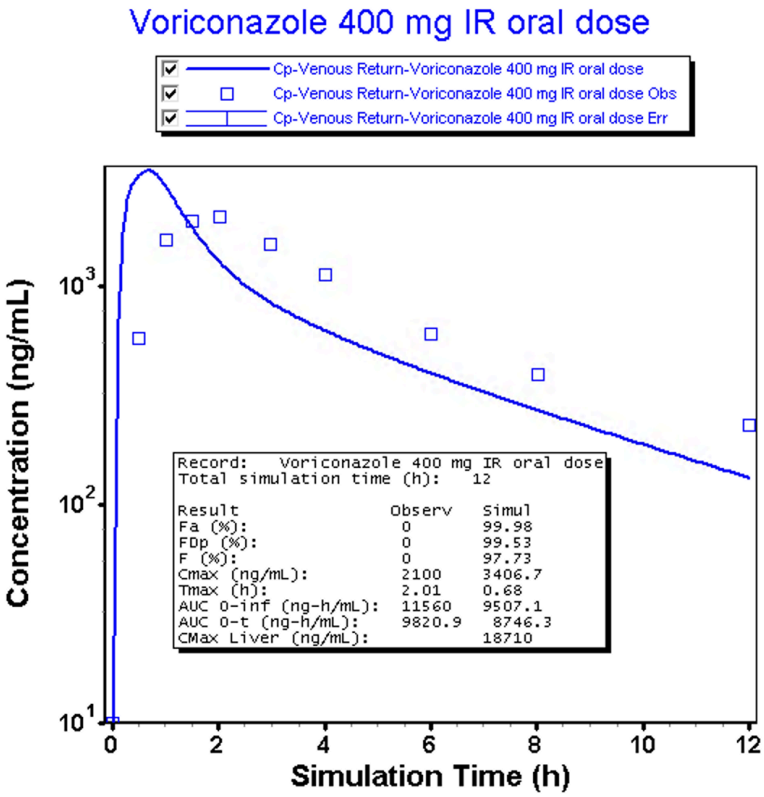


200mg Oral		Observation	Before adding Peff/ Percentage difference(%)	After adding Peff/ Percentage difference(%)
	AUC(ng-h/ml)	3577.1	3351.6 / -6.30%	3349.7 / -6.36%
	Cmax(ng/ml)	975	1890.2 / +93.86%	1854.7 / +90.22%

After modifying Peff (from 4.57x10-4 cm/s to experimental data - 4.3x10-4 cm/s), the AUC is approximately the same as the one modifying Peff; while

Cmax dropped a little. Tmax changed from 0.48 h to 0.52 h (with lower Peff). Though the changes are not significant (likely because it was only a small shift), this indicates that the rate of absorption of Voriconazole is limited by permeation. The higher the Peff, the higher the Cmax and the lower the Tmax.

400 mg oral dose from the latest paper & 1x enzyme Vmax with Peff



		Observation	Adding Peff and X1 Vamx of enzymes/ Percentage difference(%)
400mg Oral			
	AUC(ng-h/ml)	9820.9	8746.3 / -10.95%
	Cmax(ng/ml)	2100	3406.7 / +62.22%

When the dose level changes to 400mg, the AUC increases by 174.55% and the Cmax increases by 115.38% compared to the 200mg dose level, indicating greater absorption and clearance. This is in line with what the literature suggests, that overall the pharmacokinetics of a 400 mg oral dose are more favorable than that of a 200 mg oral dose.

Compartmental Parameters

Voriconazole IR 400mg capsule with Peff

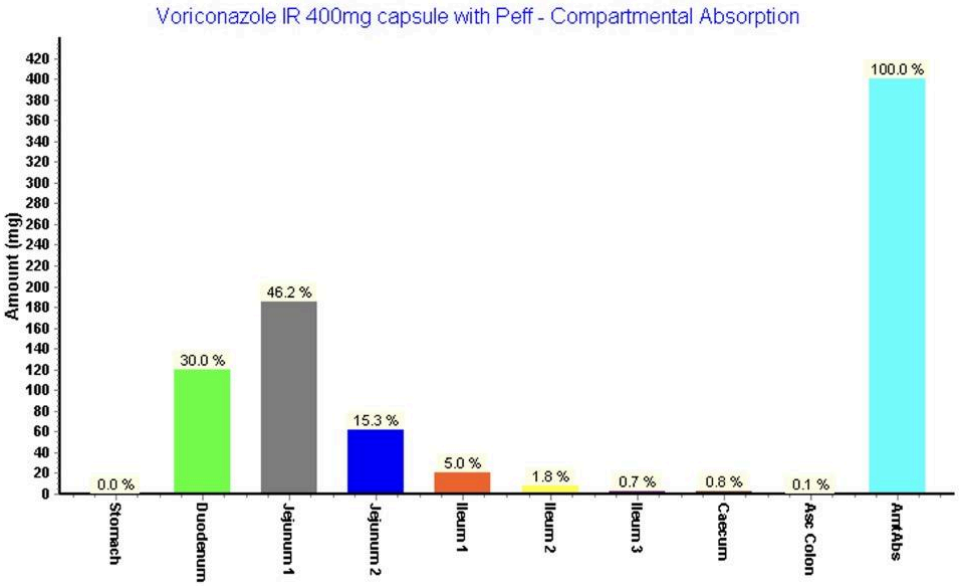
Reset All Values

Excrete all

Zero-order

Compartment Data

Compartment	Peff	ASF	pH	Transit Time (h)	Volume (mL)	Length (cm)	Radius (cm)	SEF	Bile Salt (mM)
Stomach	0	0.0	1.30	0.25	50.00	30.00	10.00	1.000	0.0
Duodenum	0	2.673	6.00	0.26	48.25	15.00	1.60	4.235	2.800
Jejunum 1	0	2.658	6.20	0.95	175.3	62.00	1.50	3.949	2.330
Jejunum 2	0	2.629	6.40	0.76	139.9	62.00	1.34	3.489	2.030
Ileum 1	0	2.592	6.60	0.59	108.5	62.00	1.18	3.029	1.410
Ileum 2	0	2.568	6.90	0.43	79.48	62.00	1.01	2.569	1.160
Ileum 3	0	2.505	7.40	0.31	56.29	62.00	0.85	2.109	0.140
Caecum	0	1.223	6.40	4.50	52.92	13.75	3.50	1.790	0.0
Asc Colon	0	2.373	6.80	13.50	56.98	29.02	2.50	2.480	0.0

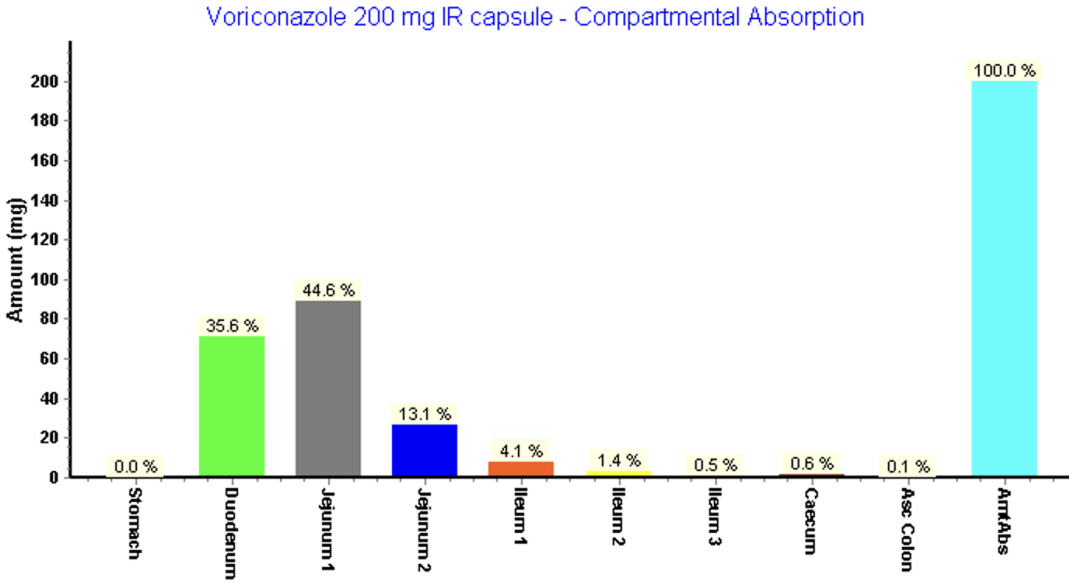


Based on the figure in the upper left, we see the sequence of ASF is:
Duodenum > Jejunum 1 > Jejunum 2 > ileum 1 > ileum 2 > ileum 3 > Asc Colon > Caecum

However, according to the compartmental absorption figure, the sequence of the amount of absorption should be:
Jejunum 1 > Duodenum > Jejunum 2 > ileum 1 > ileum 2 > ileum 3 > Caecum > Asc Colon

This sequence is contradictory to the sequence of ASF in four compartments:
Jejunum 1 > Duodenum; Caecum > Asc Colon

Overall, however, regional absorption is not dose-dependent since the differences between the 200 mg and 400 mg dose are not significant:



Here is the reason that may cause the contradiction between ASF and compartmental absorption:

The jejunum has a larger surface area because of the existence of villi and microvilli on the surface, even if the absorption scaling factor is lower than the duodenum, the larger surface area will cause a larger amount of absorption.