Week 8 Report: Voriconazole
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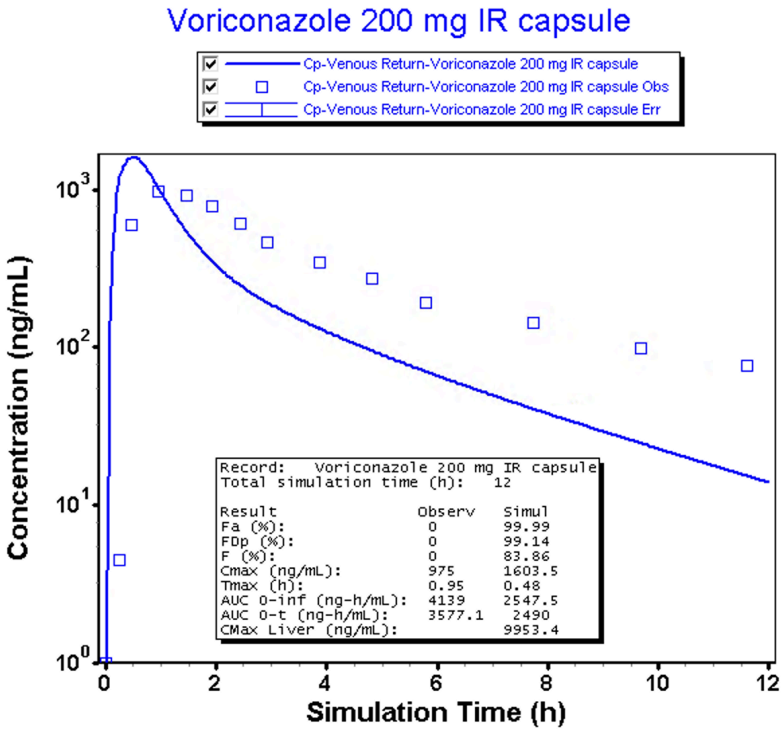
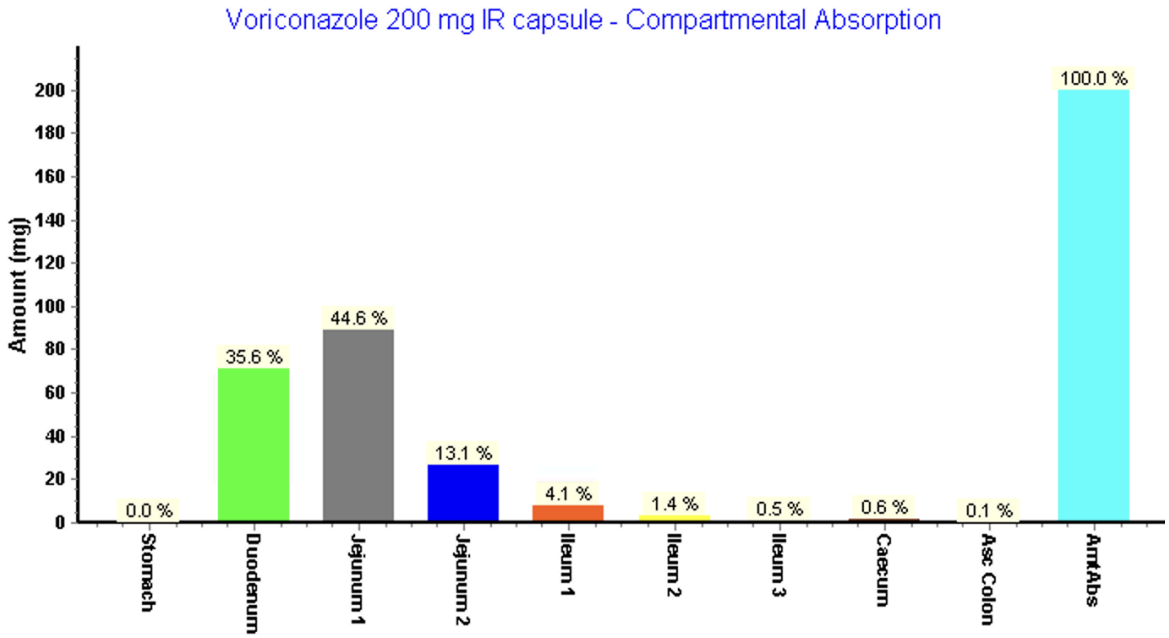
Question 1:

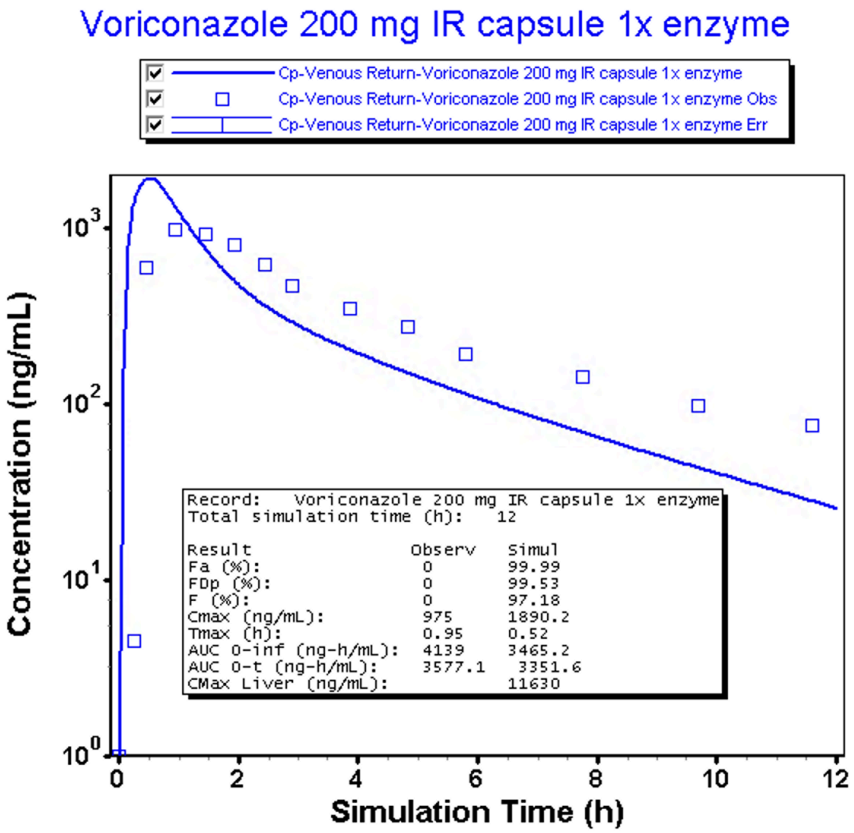
Niki's simulation (x7 fold enzyme Vmax):



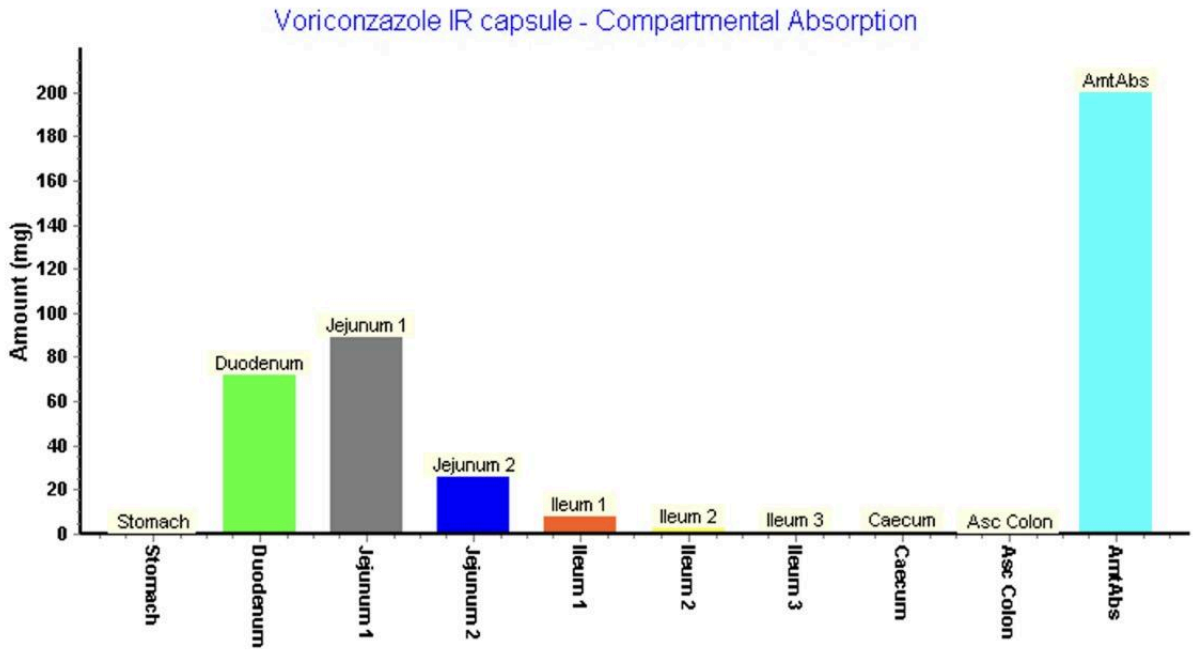
Regional absorption



Jiaqi's simulation (x1 fold enzyme Vmax):



Regional absorption



AUC and Cmax bias(x7 fold enzyme Vmax)

200mg Oral		Observation	Adding Solubility Factor and new physiology/ Percentage difference(%)
	AUC(ng-h/ml)	3577.1	2490 / -30.39%
	Cmax(ng/ml)	975	1603.5 / +64.46%

AUC and Cmax bias(x1 fold enzyme Vmax)

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

Analysis:

While increasing the Vmax (7X) of the enzymes involved in Voriconazole's metabolism helped to create a better model fit for the IV drug record, it has actually worsened the fit for the oral drug record (more bias from the observed AUC). However, a few things are true of both models. The simulated data shows that Voriconazole is being absorbed too fast and cleared too quickly. Absorption data might be off because we do not have any permeability data inputted yet. As for the higher clearance in the simulation, this could be because the model is overpredicting the extent of metabolism that occurs in the gut. Although all the enzymes that metabolize Voriconazole are present in the gut, most of Voriconazole's clearance is reported to occur in the liver. Thus, the lowered enzyme Vmax (1X) might be a better predictor of clearance in the oral model.

In terms of regional absorption, we may assume that Voriconazole (pKa = 1.76) will be charged in the stomach where the pH is approximately 1 and therefore be dissolved. But also, because of the hydrophobic nature of the molecule, most of it will be available once it reaches the gut. Therefore, it makes sense that absorption in the gut is high. In fact, that does match with data on Voriconazole, which is known to be highly absorbed and have a bioavailability of up to 96% (Geist et al., 2013). This paper also suggests that steady-state absorption is not achieved with a dose of 200 mg, which may contribute to the variability in the AUC data.

<u>Question 2</u>:

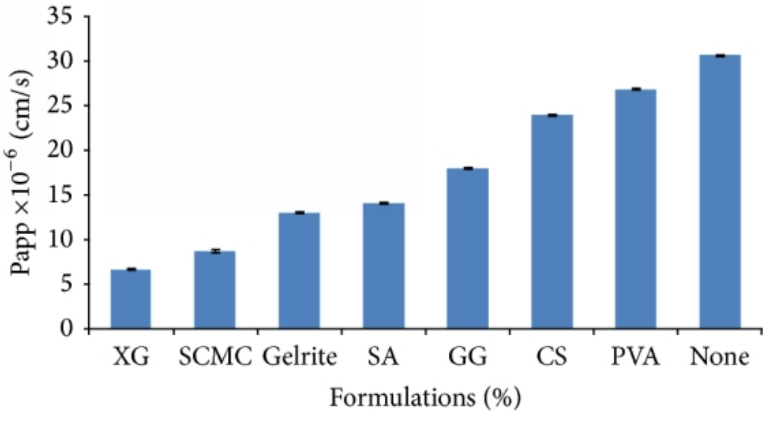
Permeability data for Voriconazole is limited to studies in which the dosing formulation of Voriconazole is as an eyedrop, therefore it is a bit harder to predict what the permeability of a tablet will be. However, there are papers that suggest that administering Voriconazole with a low viscosity solvent yields a Papp ~= 30 cm/s. See the figure below from a paper by Malhotra et al. (2014) where 'None' represents a Voriconazole solution without viscosity modifiers. Again, the tissue tested here was corneal and may not be the best representation of Voriconazole's permeability. There are limited papers on Voriconazole permeation as a tablet/capsule.

Table 1. Details of the BCS and rDCS classification of voriconazole

Drug substance BCS Classification[a,b]		**Class II**
24 h buffer solubility [mg/mL]	pH 1.2	2.89 ± 0.12
	pH 4.5	0.959 ± 0.010
	pH 6.8	0.874 ± 0.022
Dose-to-solubility (D/S) ratio [mL][a]	pH 1.2	138 ± 6
	pH 4.5	417 ± 4
	pH 6.8	458 ± 12
Permeability	Absolute bioavailability [%][a]	> 85% [7, 8]
Drug product dissolution performance[c]		**Very rapid**
% dissolved after 15 minutes	pH 1.2	90.2 ± 6.0
	pH 4.5	93.9 ± 1.5
	pH 6.8	89.0 ± 3.6
Drug substance rDCS Classification[a,d]		**Class I_{400mg}**
24 h biorelevant solubility [mg/mL]	FaSSGF pH 1.6	1.62 ± 0.01
	FaSSIF-V1 pH 6.5	0.827 ± 0.006
Dose-to-solubility (D/S) ratio [mL][a]	FaSSGF pH 1.6	247 ± 1
	FaSSIF-V1 pH 6.5	484 ± 3
Disk IDR [mg/min/cm^2]	FaSSGF pH 1.6	0.159 ± 0.005
	FaSSIF-V1 pH 6.5	0.0848 ± 0.0014
Permeability	*In vitro* Caco-2 P_{app} [x 10^{-6} cm/s]	27.3 ± 1.8
	Estimated human P_{eff} [x 10^{-4} cm/s]	4.30
Target particle size [µm][e]	Dissolution/transit balance	≤ 516
	Dissolution/permeation balance	≤ 118

[a]*Based on the highest single oral dose (400 mg)*
[b]*Based on the lowest buffer solubility in the pH range 1.2-6.8, high solubility D/S cut-off = 250 mL*
[c]*VFEND® 200 mg film-coated tablets*
[d]*Based on the FaSSIF-V1 solubility, high solubility D/S cut-off = 500 mL*
[e]*Calculated from solubility, IDR, and permeability data according to Beran et al. [4]*

Nevertheless, we did find a poster abstract reporting permeability of voriconazole tablet form (VFEND® 200 mg film-coated tablets). Permeability was assessed using the Caco-2 cell assay with pH gradients mimicking the pH changes in GI tract; the apparent permeability (Papp) values were calculated from the apical membrane to the basolateral membrane. After obtaining a series of Papp values, the average Papp value was calculated, and it was converted to effective human permeability (Peff). See values in the below figure[1]:



References:

Geist, M. J., Egerer, G., Burhenne, J., Riedel, K. D., Weiss, J., & Mikus, G. (2013). Steady-state pharmacokinetics and metabolism of voriconazole in patients. *The Journal of antimicrobial chemotherapy*, *68*(11), 2592–2599.

Malhotra S, Khare A, Grover K, Singh I, Pawar P. Design and Evaluation of Voriconazole Eye Drops for the Treatment of Fungal Keratitis. J Pharm (Cairo). 2014;2014:490595.

2023 PharmSci 360 Meeting.

https://aaps2023.eventscribe.net/fsPopup.asp?efp=Uk9MQVBBV1ExOTMxMg&PosterID=591048&rnd=0.4579715&mode=posterInfo.