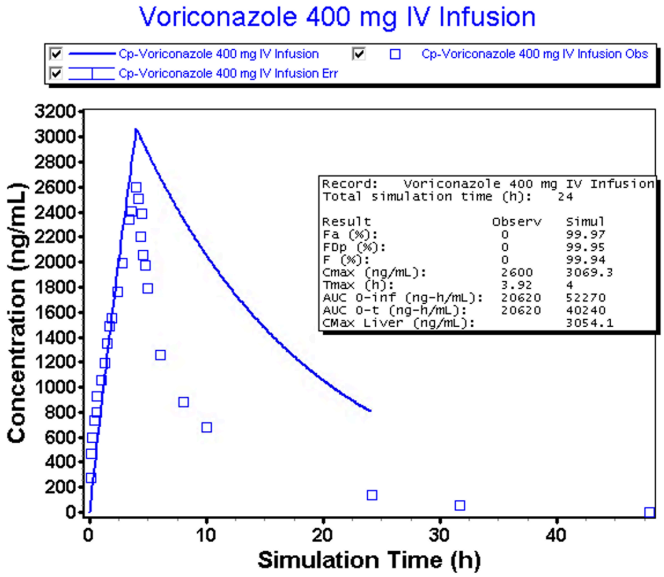
Week 3 Report: Voriconazole
Jiaqi Fu and Nicole Mohajer

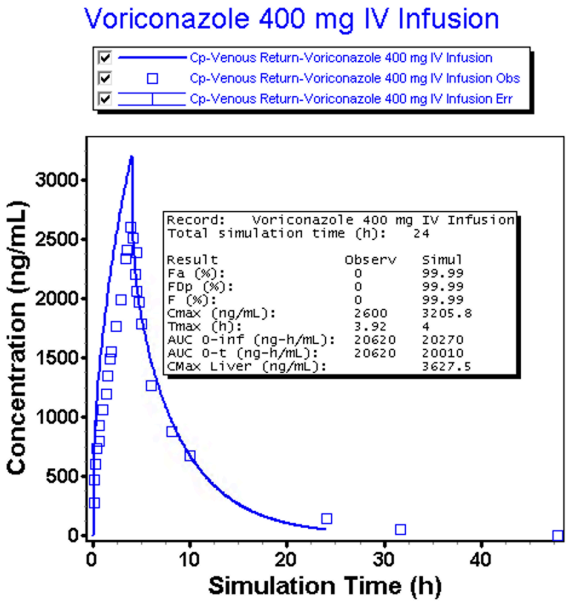
Part 1: PEAR Physiology model + NCA CL

400 mg dose 4h infusion time

Week 2:



Week 3:



Analysis:

(1). Comparison of AUC and Cmax: 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%

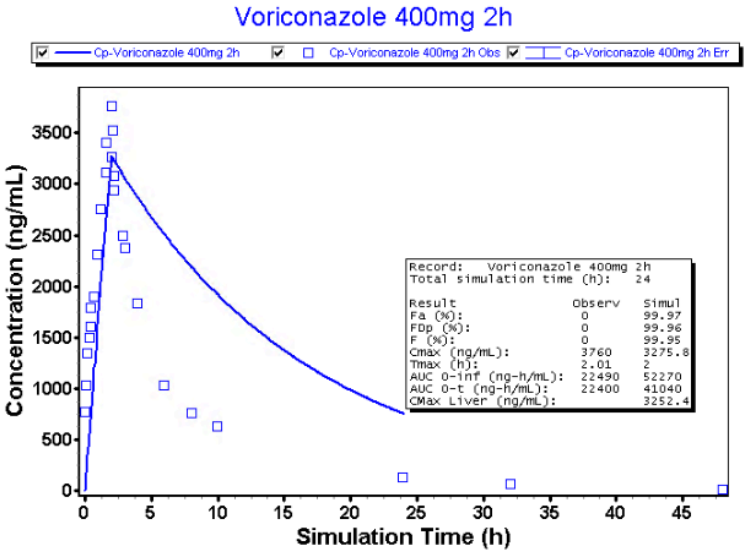
(2). Based on observation of the two figures and after calculating percentage difference (%), we see that the NCA CL value contributed a lot to creating a better fit between simulated curve and observation data. The NCA CL analysis showed a lower, but insignificantly different, predicted AUC than the observed one (-2.96%). However, after adding the NCA CL value, the simulation of the Cmax still has a significant bias compared to the observed value (+ 23.3%), even more so than the previous one (+18.05 %).

In the right panel, the steep slope indicates a rapid decrease in concentration due to distribution being the dominant process. However, in the left panel, we observe that the concentration decreases at a more consistent rate over time, indicating that the clearance is the dominant process.

Cmax liver refers to the maximum concentration of drug in the liver tissue. **Cmax Liver after adding the NCA CL value (3627.5 ng/ml) is higher than the previous (3054.1 ng/ml). This is in line with the conclusion that the right panel is a distribution dominant process.**

400 mg dose 2h infusion time

Week 2:



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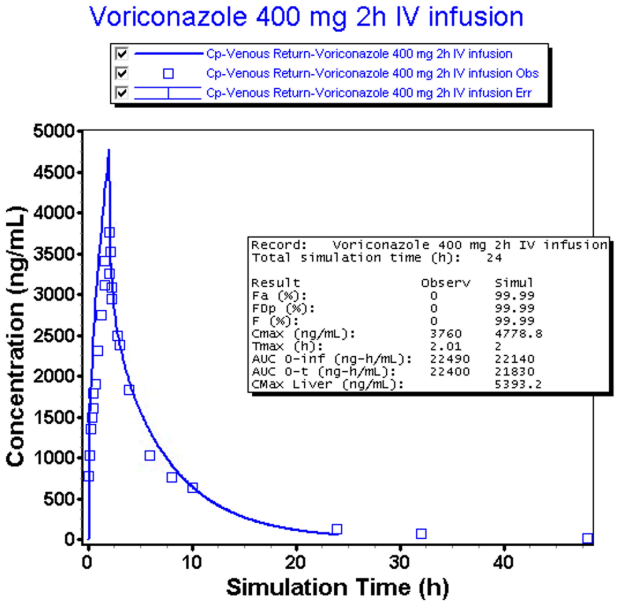


Analysis:

(1). Comparison of AUC and Cmax: Observation AUC value is 22400 ng-h/ml; Cmax is 3760 ng/ml.

	Before adding NCA CL value/ Percentage difference(%)	After adding NCA CL value/ Percentage difference(%)
AUC(ng-h/ml)	41040 / +83.21%	21830 / -2.54%
Cmax(ng/ml)	3275.8 / -12.88%	4478.8 / +19.11%

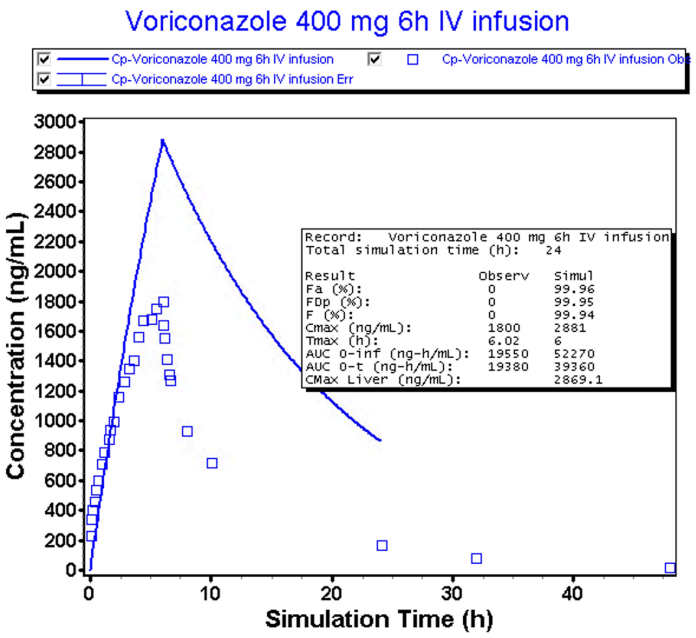
(2). Based on the observation of the two figures and calculated percentage difference (%), we see that the NCA CL value contributed a lot to making a better fit between simulated curve and observation data. We observe a lower, but insignificantly different, predicted AUC than the observed one (-2.54%). However, even after adding the NCA CL value, the simulation of the Cmax still has a significant bias compared to the observed value. **Moreover, the 400mg dose injected over 2h is different from the other three conditions - It has a smaller Cmax predicted(-12.88%) before adding NCA CL value.**

In the right panel, the steep slope indicates a rapid decrease in concentration due to distribution being the dominant process. However, in the left panel, we observe that the concentration decreases at a more consistent rate over time, indicating that the clearance is the dominant process.

Cmax Liver after adding the NCA CL value(5393.2 ng/ml) is higher than the previous (3252.4 ng/ml). This is in line with the conclusion that the right panel is a distribution dominant process. (Because it means more drugs distributed into the liver tissue)

400 mg dose 6h infusion time

Week 2:



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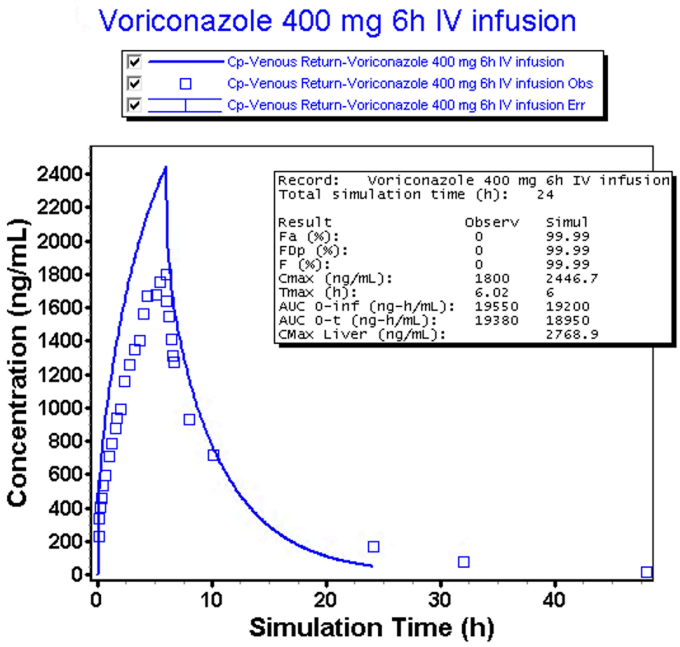


Analysis:

(1). Comparison of AUC and Cmax: Observation AUC value is 19380 ng-h/ml; Cmax is 1800 ng/ml.

	Before adding NCA CL value/ Percentage difference(%)	After adding NCA CL value/ Percentage difference(%)
AUC(ng-h/ml)	39360 / +103.10%	18950 / -2.22%
Cmax(ng/ml)	2881 / +60.06%	2446.7 / +35.93%

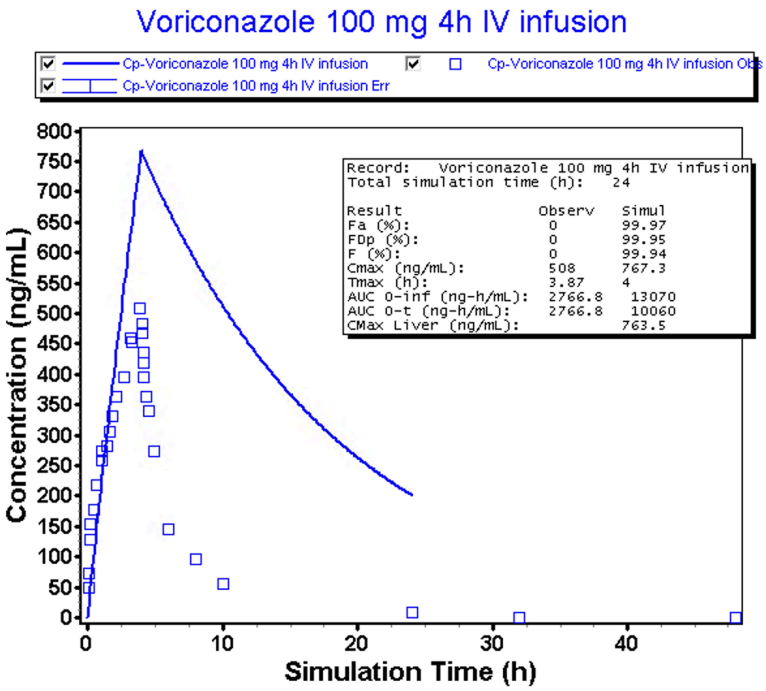
(2). Based on the observation of two figures and calculation on percentage difference (%), the NCA CL analysis contributed to creating a better fit between the simulated curve and the observation data. Moreover, we observed a lower, but insignificantly varying, predicted AUC than the observed one (-2.22%). However, after adding the NCA CL value, the simulation of the Cmax still has a significant bias compared to the observed value (+ 35.93%); nevertheless, for this dose it seems that adding NCA CL indeed creates a better fit for the Cmax calculation (the bias shrinked from +60.6% to +35.93%).

In the right panel, the steep slope indicates a rapid decrease in concentration due to distribution being the dominant process. However, in the left panel, we could observe that the concentration decreases at a more consistent rate over time, indicating that the clearance is the dominant process.

Cmax Liver after adding the NCA CL value (2768.9 ng/ml) is lower than the previous (2869.1 ng/ml). This is *contradictory* with the conclusion that the right panel is a distribution dominant process.

100 mg dose 4h infusion time

Week 2:



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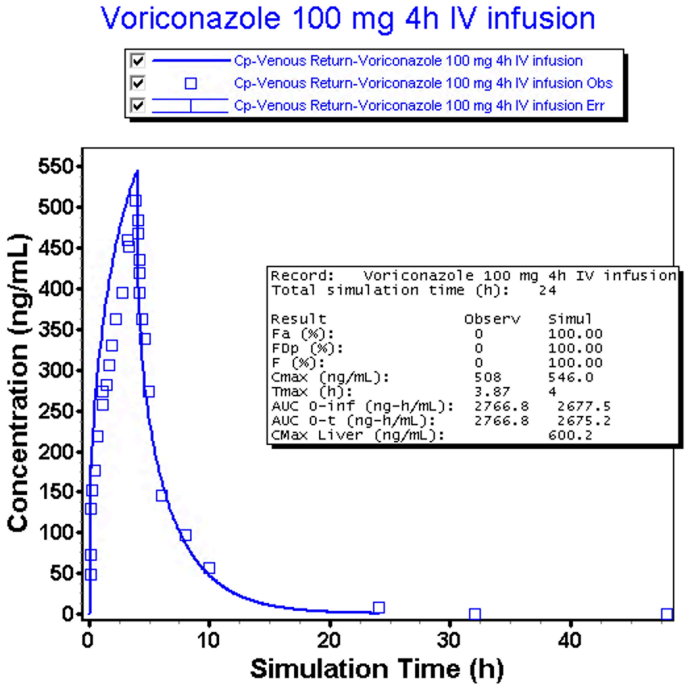


Analysis:

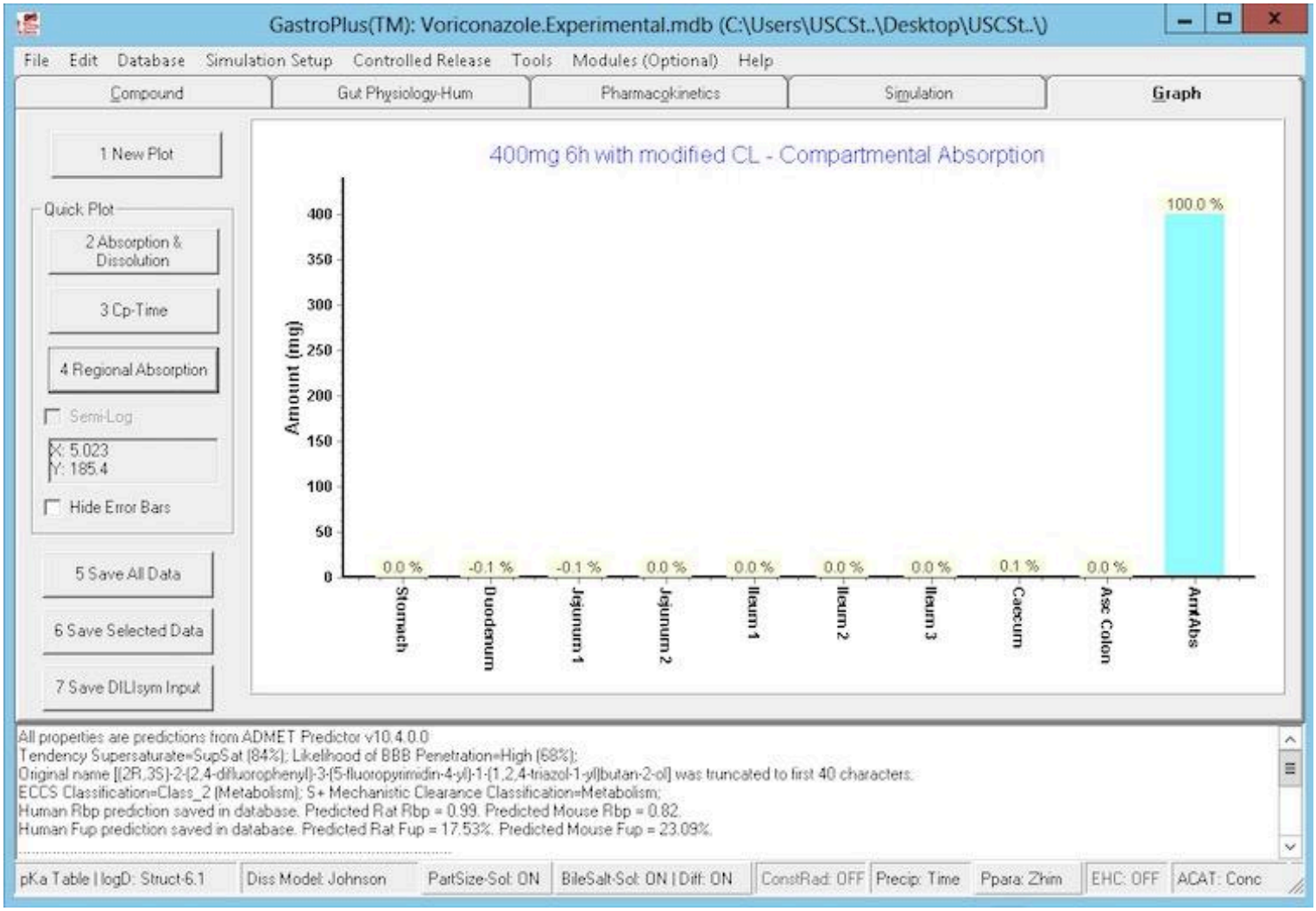
(1). Comparison of AUC and Cmax: Observation AUC value is 2766.8 ng-h/ml; Cmax is 508 ng/ml.

	Before adding NCA CL value/ Percentage difference(%)	After adding NCA CL value/ Percentage difference(%)
AUC(ng-h/ml)	10060 / +263.60%	2675.2 / -3.31%
Cmax(ng/ml)	767.3 / +51.04%	546 / +7.48%

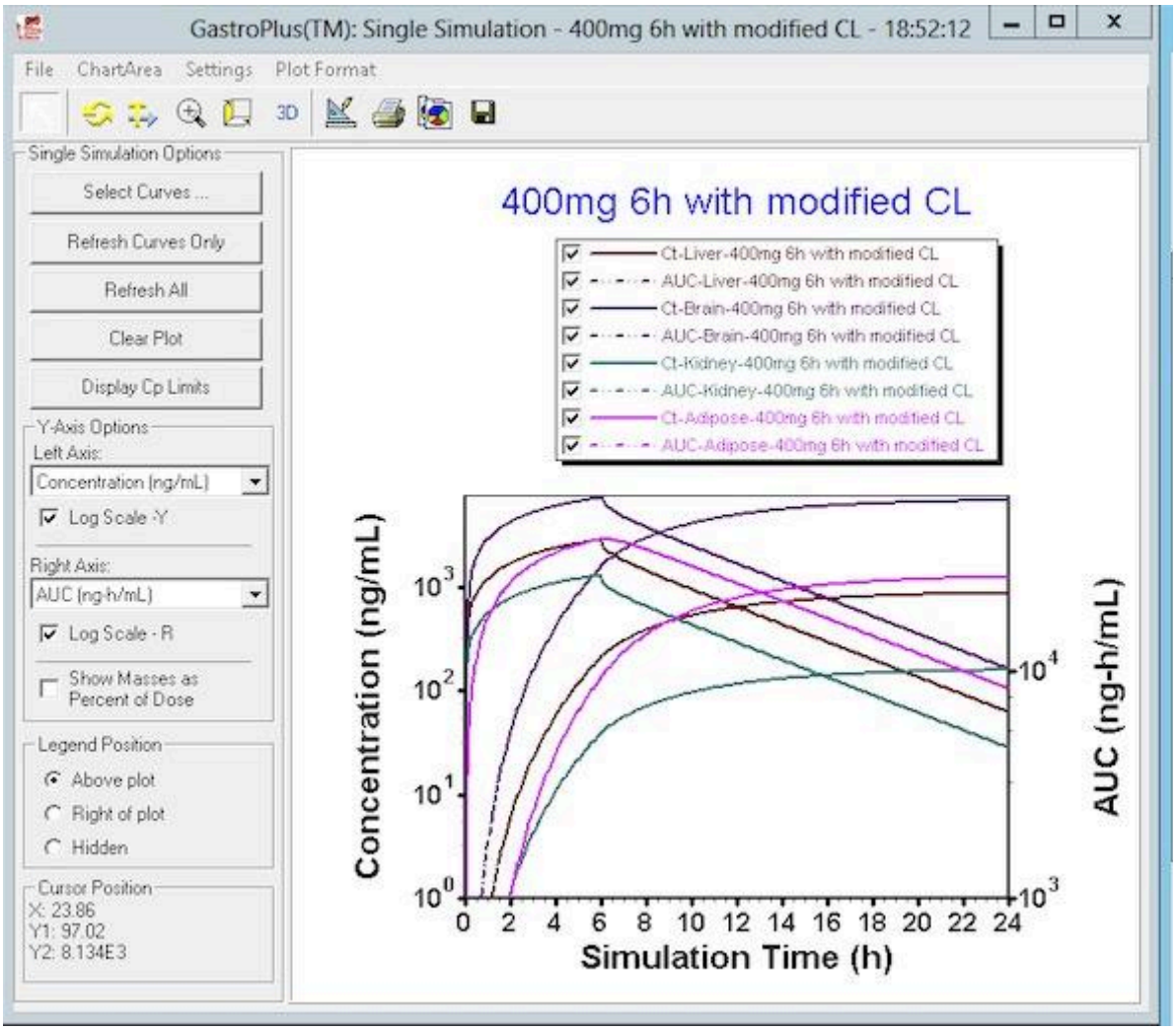
(2). Based on the observation of two figures and calculation on percentage difference (%), the NCA CL analysis contributed to creating a better fit between simulated curve and observation data. Moreover, we observed a lower, but insignificantly different, predicted AUC than the observed one (-3.31%). For this dose, it seems that adding the NCA CL data indeed gives a better fit for the Cmax (percentage difference controlled under 10%).

In the right panel, the steep slope indicates a rapid decrease in concentration due to distribution being the dominant process. However, in the left panel, we observe that the concentration decreases at a more consistent rate over time, indicating that the clearance is the dominant process.

Cmax Liver after adding the NCA CL value(600.2 ng/ml) is lower than the previous(763.5 ng/ml). This is in line with the conclusion that the right panel is a distribution dominant process.



The Regional Absorption figure indicates that 100% of drugs entered into systemic circulation, which is in line with the fact that the drug is given by injection.



This figure describes the concentration and AUC of the drug within different organs, along with simulation time. We chose four tissues: brain, liver, kidney, and adipose tissue. It is observed that the concentration reaches a maximum at ~6 hours, because the duration of injection lasts for 6 hours. The sequence of the amount of drug that enters each tissue is: brain > adipose ~= liver > kidney. Given the logP value is 2.13, we may rationalize the sequence:

The brain is rich in lipid content, which means for a moderate logP, the drug would choose to enter into the brain rather than gather in the adipose tissue (body fat) which is highly lipophilic. The amount of drug that enters into the liver and kidney is not related to the logP, it is related to the cardiac output. Perhaps more drug reaches the liver because it is where it is metabolized.

Part 2: Fraction unbound in plasma (f_u) and blood plasma concentration ratio (RBP)

As we know, the f_u, or fraction of unbound drug in the plasma, is one measurement of a drug's therapeutic potential since it is assumed that this fraction has reached its target tissue. Florent et al. (2014) calculated an f_u of 23% for Voriconazole. Given the hydrophobic nature of the drug, an f_u of less than 50% seems low considering hydrophobic molecules tend to distribute to tissue rather than hang on plasma proteins. Other studies, using higher throughput methods found a median f_u of approximately 49.6% (Vanstraelen et al., 2015). This data could possibly explain the discrepancies between the simulation versus what is observed. Because the simulation is basing the data off of the structure of the molecule and is likely more accurate, distribution of the drug (based on the AUC) seems higher than what is observed with less precise mechanisms. Interestingly, other papers by this lab suggest that Voriconazole tends to bind to albumin, and that by decreasing albumin concentration, f_u of Voriconazole increases (Vanstraelen et al., 2014). Despite being a relatively hydrophobic drug, much of the data suggests that Voriconazole may have issues distributing to tissue; maybe due to an affinity for albumin. Data on the ratio of blood vs. plasma concentration seems to be scant, however, the minimum plasma concentration required to observe a therapeutic effect is consistent between a range of 1 to 6 μg/mL (Hicks et al., 2015). This value suggests that perhaps a higher dose is required to achieve a therapeutic effect compared to other more hydrophobic drugs. It is also likely why Voriconazole is administered as an IV dose.

References:

1. Florent, A., Gandia, P., Seraissol, P., Chatelut, E., & Houin, G. (2014). Determination of plasma unbound fraction of voriconazole in patients treated with a prophylactic or a curative treatment. Therapeutic drug monitoring, 36(6), 752–758.
2. Vanstraelen, K., Wauters, J., Vercammen, I., de Loor, H., Maertens, J., Lagrou, K., Annaert, P., & Spriet, I. (2014). Impact of hypoalbuminemia on voriconazole pharmacokinetics in critically ill adult patients. Antimicrobial agents and chemotherapy, 58(11), 6782–6789.
3. Vanstraelen, K., Pauwels, S., Oyaert, M., Maertens, J., & Spriet, I. (2015). Key Elements in Determining Voriconazole Protein Binding Characteristics: Comment on "Determination of Plasma Unbound Fraction of Voriconazole in Patients Treated With a Prophylactic or a Curative Treatment". Therapeutic drug monitoring, 37(4), 551–553.