The Impact of COVID-19 Mediated Bidirectional Dysregulation of CYP3A4 on Systemic and Pulmonary Candidate Drug Concentrations

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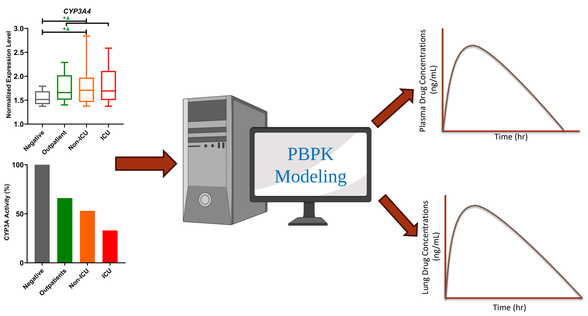
Introduction

- Several clinical studies have reported disease – drug interactions involving CYP3A4 in hospitalized COVID-19 patients[1,2,3].
- COVID-19 downregulates and upregulates CYP3A4 in the liver and nasopharynx, respectively, with potential effects on systemic and pulmonary drug concentrations[1,2,3,4].

Objective

- To investigate how simultaneous hepatic downregulation and pulmonary upregulation of CYP3A4 impacts systemic and pulmonary drug concentrations, as well as therapeutic outcomes.

Method



Model Verification

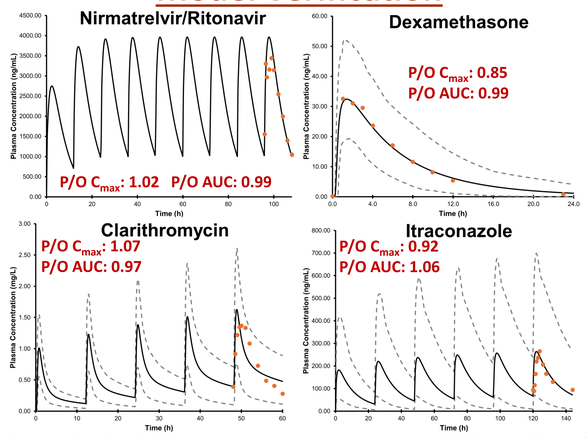
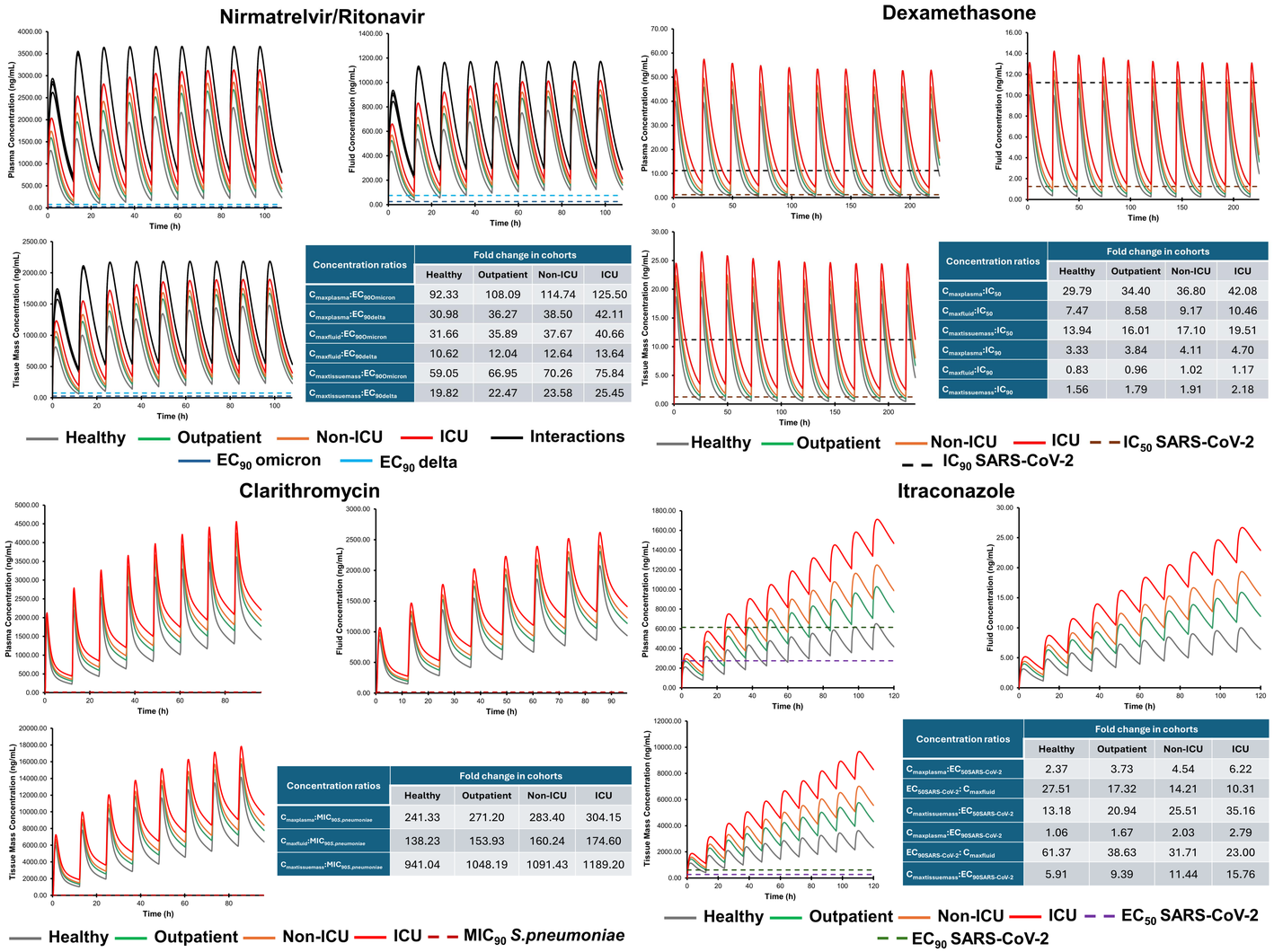


Figure 1. Predicted versus observed pharmacokinetic profile of nirmatrelvir/ritonavir, dexamethasone, clarithromycin, and itraconazole in the plasma compartment. Simcyp 22.1 simulated plasma concentrations for nirmatrelvir/ritonavir (10 subjects, 8.3% females, 300 mg/100 mg twice daily for 5 days with a 2 mg midazolam dose on day 5), dexamethasone (8 subjects, 87.5% females, 4.5 mg single dose), clarithromycin (6 subjects, 50% females, 250 mg every 12 hours for 5 doses), and itraconazole (8 subjects, no female, 200 mg daily for 6 days). Black lines: simulated data; orange points: observed data; gray lines: 5th and 95th percentiles.

COVID-19's Impact on CYP3A4 Puts ICU Patients at Higher Risk of Drug Overexposure



Concentration ratios	Fold change in cohorts			
	Healthy	Outpatient	Non-ICU	ICU
$C_{maxplasma}$:$EC_{90Omicron}$	92.33	108.09	114.74	125.50
$C_{maxplasma}$:$EC_{90delta}$	30.98	36.27	38.50	42.11
$C_{maxfluid}$:$EC_{90Omicron}$	31.66	35.89	37.67	40.66
$C_{maxfluid}$:$EC_{90delta}$	10.62	12.04	12.64	13.64
$C_{maxtissuemass}$:$EC_{90Omicron}$	59.05	66.95	70.26	75.84
$C_{maxtissuemass}$:$EC_{90delta}$	19.82	22.47	23.58	25.45

Concentration ratios	Fold change in cohorts			
	Healthy	Outpatient	Non-ICU	ICU
$C_{maxplasma}$:IC_{50}	29.79	34.40	36.80	42.08
$C_{maxfluid}$:IC_{50}	7.47	8.58	9.17	10.46
$C_{maxtissuemass}$:IC_{50}	13.94	16.01	17.10	19.51
$C_{maxplasma}$:IC_{90}	3.33	3.84	4.11	4.70
$C_{maxfluid}$:IC_{90}	0.83	0.96	1.02	1.17
$C_{maxtissuemass}$:IC_{90}	1.56	1.79	1.91	2.18

Concentration ratios	Fold change in cohorts			
	Healthy	Outpatient	Non-ICU	ICU
$C_{maxplasma}$:$MIC_{90S.pneumoniae}$	241.33	271.20	283.40	304.15
$C_{maxfluid}$:$MIC_{90S.pneumoniae}$	138.23	153.93	160.24	174.60
$C_{maxtissuemass}$:$MIC_{90S.pneumoniae}$	941.04	1048.19	1091.43	1189.20

Concentration ratios	Fold change in cohorts			
	Healthy	Outpatient	Non-ICU	ICU
$C_{maxplasma}$:$EC_{50SARS-CoV-2}$	2.37	3.73	4.54	6.22
$EC_{50SARS-CoV-2}$:$C_{maxfluid}$	27.51	17.32	14.21	10.31
$C_{maxtissuemass}$:$EC_{50SARS-CoV-2}$	13.18	20.94	25.51	35.16
$C_{maxplasma}$:$EC_{90SARS-CoV-2}$	1.06	1.67	2.03	2.79
$EC_{90SARS-CoV-2}$:$C_{maxfluid}$	61.37	38.63	31.71	23.00
$C_{maxtissuemass}$:$EC_{90SARS-CoV-2}$	5.91	9.39	11.44	15.76

Figure 2. Pharmacokinetic profile of nirmatrelvir/ritonavir, dexamethasone, clarithromycin, and itraconazole in the plasma compartment, fluid, and tissue mass compartments of the right lung lower lobe.

CYP3A4 Dysregulation Alters Drug Distribution in Systemic and Pulmonary Compartments

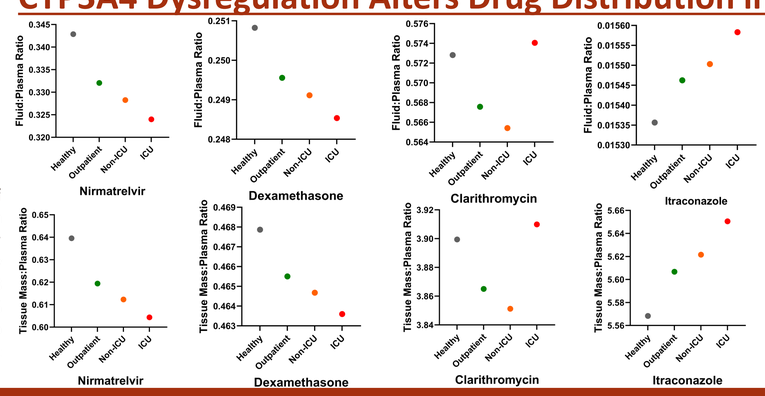


Figure 3. Fluid: plasma (top) and tissue mass: plasma (bottom) ratios of nirmatrelvir, dexamethasone, clarithromycin, and itraconazole. Simcyp version 22.1 was used to simulate the systemic and pulmonary concentrations of nirmatrelvir/ritonavir, dexamethasone, clarithromycin, and itraconazole. The nirmatrelvir/ritonavir trial (12 participants, 8.3% females, 21 – 50 years) received 300 mg/100 mg twice daily for 5 days; dexamethasone trial (100 participants, 50% females, 18 – 60 years) received 6 mg daily for 10 days; clarithromycin trial (200 participants, 50% females, 20 – 50 years) received 500 mg every 12 hours for 8 doses; itraconazole trial (260 participants, 50% females, 23 – 50 years) received 200 mg twice daily for 10 doses. Participants were classified into healthy (light gray), outpatient (green), non-ICU (orange), and ICU (red) cohorts. In these participant cohorts, their CYP3A4 abundance levels were downregulated in the liver and upregulated in the lung according to the clinical COVID-19 – CYP3A4 expression and activity data[3,4]. Permeability-limited lung model was activated with the primary goal of accounting for lung CYP3A4 metabolism without altering permeability parameters.

Conclusions

- Systemic and pulmonary drug concentrations are mainly influenced by hepatic CYP3A4 metabolism, with pulmonary CYP3A4 having a lesser role.
- COVID-19 – CYP3A4 interactions in the liver may be useful for guiding the design of personalized dosing regimens that achieves optimal systemic and pulmonary drug concentrations for at risk COVID-19 patients[5,6].
- Dexamethasone, nirmatrelvir, and clarithromycin showed overexposure in both systemic and pulmonary compartments, posing potential safety risks, particularly for ICU patients.
- Itraconazole was underexposed in the lung fluid compartment, partly explaining it's limited efficacy for COVID-19 treatment[7].

References

1. Gregoire M et al. Lopinavir pharmacokinetics in COVID-19 patients. *J Antimicrob Chemother.* 2020;75(9):2702-2704. doi:10.1093/jac/dkaa195

2. Salerno DM et al. SARS-CoV-2 infection increases tacrolimus concentrations in solid-organ transplant recipients. *Clin Transplant.* 2021;35(3):e14193. doi:10.1111/ctr.14193

3. Le Carpentier EC et al. Impact of Inflammation on Midazolam Metabolism in Severe COVID-19 Patients. *Clin Pharmacol Ther.* 2022;112(5):1033-1039. doi:10.1002/cpt.2698

4. Nwabufo CK et al. COVID-19 Severity Gradient Differentially Dysregulates Clinically Relevant Drug Processing Genes in Nasopharyngeal Swab Samples. *Brit J Clinical Pharma.* Published online 26 April 2024:bcp.16124. doi:10.1111/bcp.16124

5. Nwabufo CK, Bendayan R. Pharmacokinetic considerations to optimize clinical outcomes for COVID-19 drugs. *Trends Pharmacol Sci.* 2022;43(12):1041-1054. doi:10.1016/j.tips.2022.09.005

6. Nwabufo CK. Mirvetuximab soravtansine in ovarian cancer therapy: expert opinion on pharmacological considerations. *Cancer Chemother Pharmacol.* Published online 18 August 2023. doi:10.1007/s00280-023-04575-y

7.Liesenborghs L et al. Itraconazole for COVID-19: preclinical studies and a proof-of-concept randomized clinical trial. *eBioMedicine*. 2021;66:103288. doi:10.1016/j.ebiom.2021.103288

Acknowledgments

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