DDI-CDS

Drug-Drug Interaction Clinical Decision Support

Improving the Relevance of Drug-Drug Interaction Warnings

Webinar: May 13, 2020

Drug-Drug Interactions with COVID-19 Therapies

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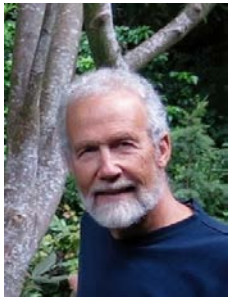

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Webinar and Project Overview

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COLLEGE OF PHARMACY
UNIVERSITY OF UTAH
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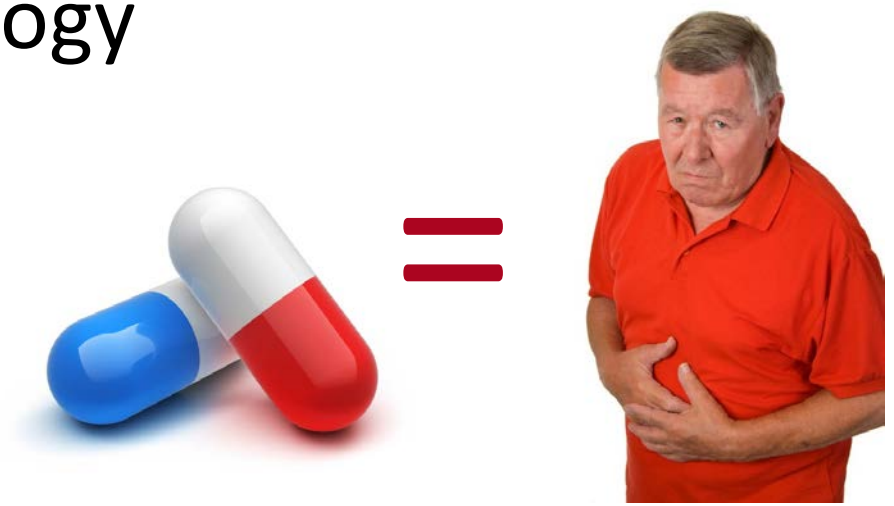
Terminology

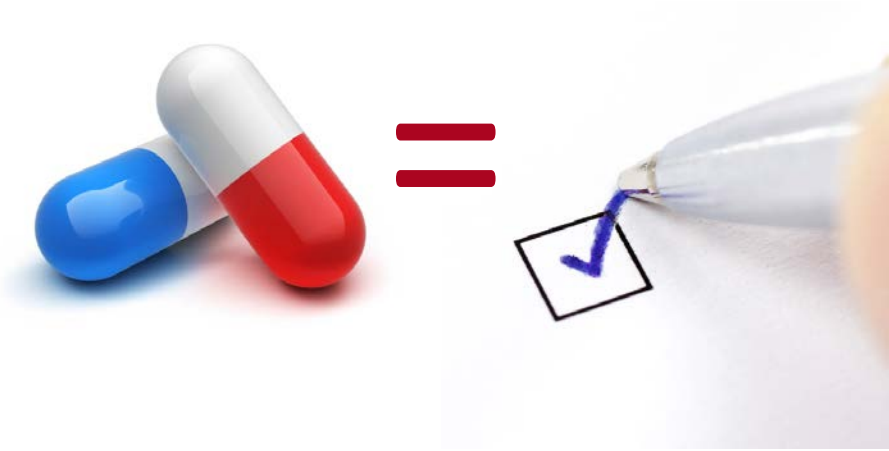
Drug-drug interaction (DDI):

Clinically meaningful alteration in the effect of one drug (*object*) as a result of co-administration of another (*precipitant*)



Potential drug-drug interaction (PDDI):

Co-prescription or co-administration of drugs known to interact, regardless of whether harm ensues



DDI-CDS Webinar Series

- Monthly webinars on specific drug-drug interactions (except today)
- Monthly Webinars Content
  - Clinical pharmacology
  - Mechanism of interaction
  - CDS algorithm
  - Results from testing of the algorithm
  - Programming CDS and related implementation tools
  - Precautions
  - Supporting documentation

- More information available at: https://ddi-cds.org

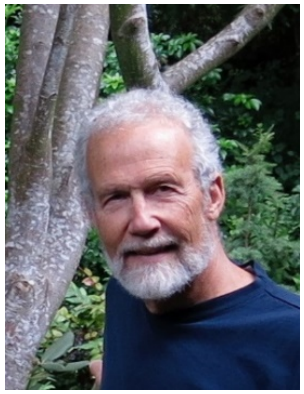
Question: What type of organization best represent your employer?

1. Hospital or hospital-based healthcare system
2. Community pharmacy
3. Third-party drug database
4. Electronic health record software vendor
5. Managed care organization / health insurance organization
6. Academia / University
7. Student / Resident / Fellow
8. Physician group practice
9. Other

Question: How much experience does your organization have with treating COVID-19 patients?

1. None
2. Less than 10 patients
3. 10-20 patients
4. 21 to 100 patients
5. Over 100 patients
6. Unknown
7. Not applicable

Pharmacokinetic Drug Interactions with COVID-19 Therapies



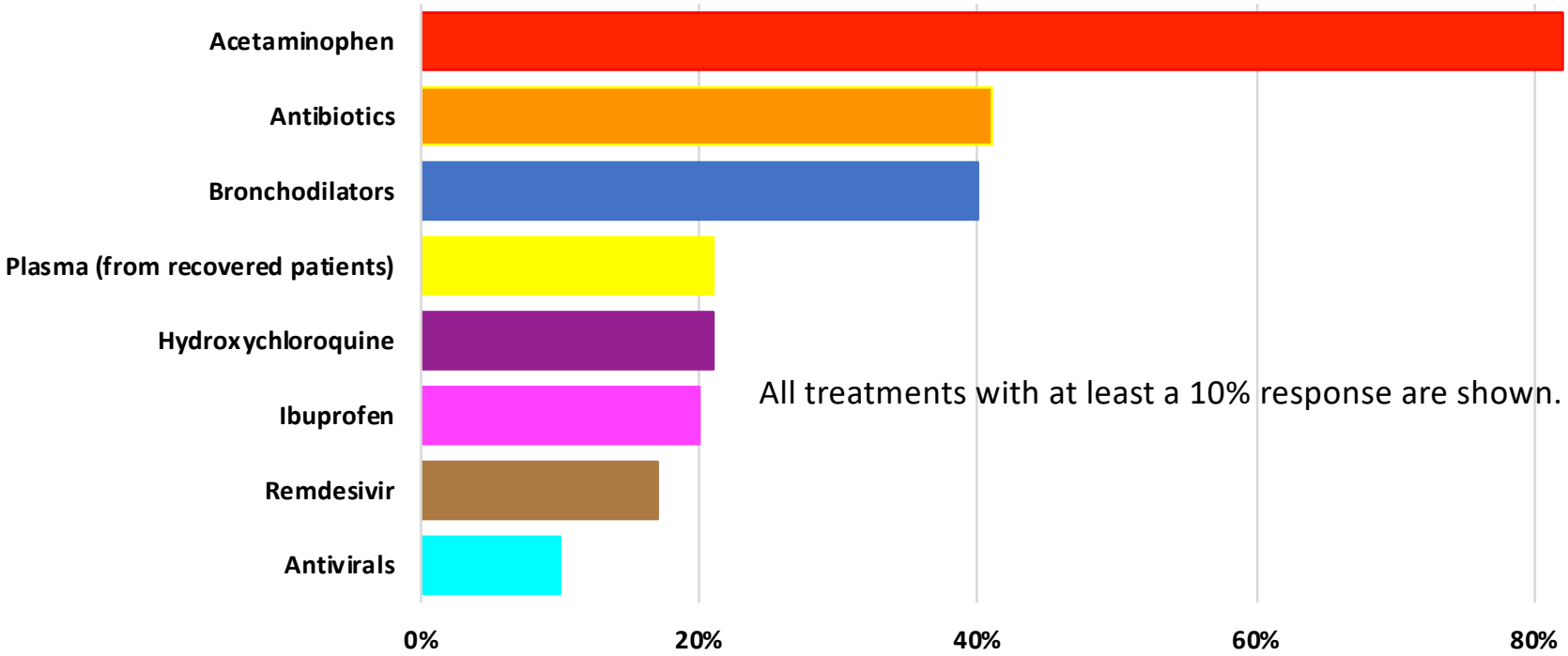
Dr. Philip Hansten, PharmD

Professor Emeritus

UNIVERSITY of WASHINGTON

Medications Used for Covid-19

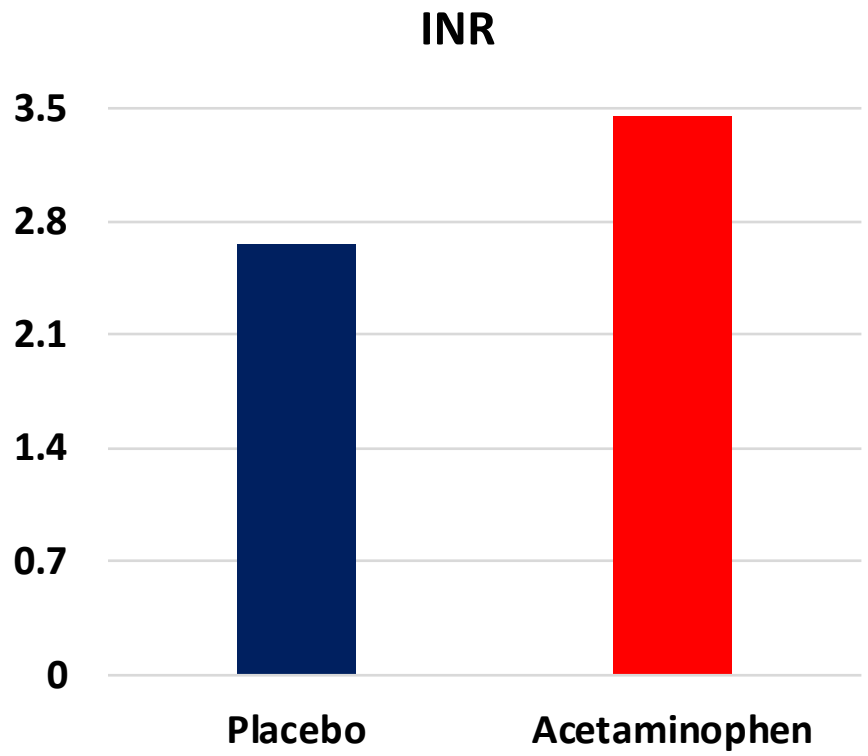
Leading treatments prescribed to patients with COVID-19



Note: Survey of 203 physicians with frontline care roles was conducted April 14-15.
Source: InCrowd

Acetaminophen + Warfarin

- 20 patients on stable doses of warfarin randomized to receive acetaminophen 4g/d or placebo for 14 days in a double-blind, crossover study
- Maximum INR increase from baseline over 2 times larger following acetaminophen
- Later study from same group found increased INR with acetaminophen 2g or 3g/day (but effect was smaller)



Mahe I et al. Haematologica 2006;91:1621-1627.

Paracetamol (acetaminophen) warfarin interaction: NAPQI, the toxic metabolite of paracetamol, is an inhibitor of enzymes in the vitamin K cycle

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Summary

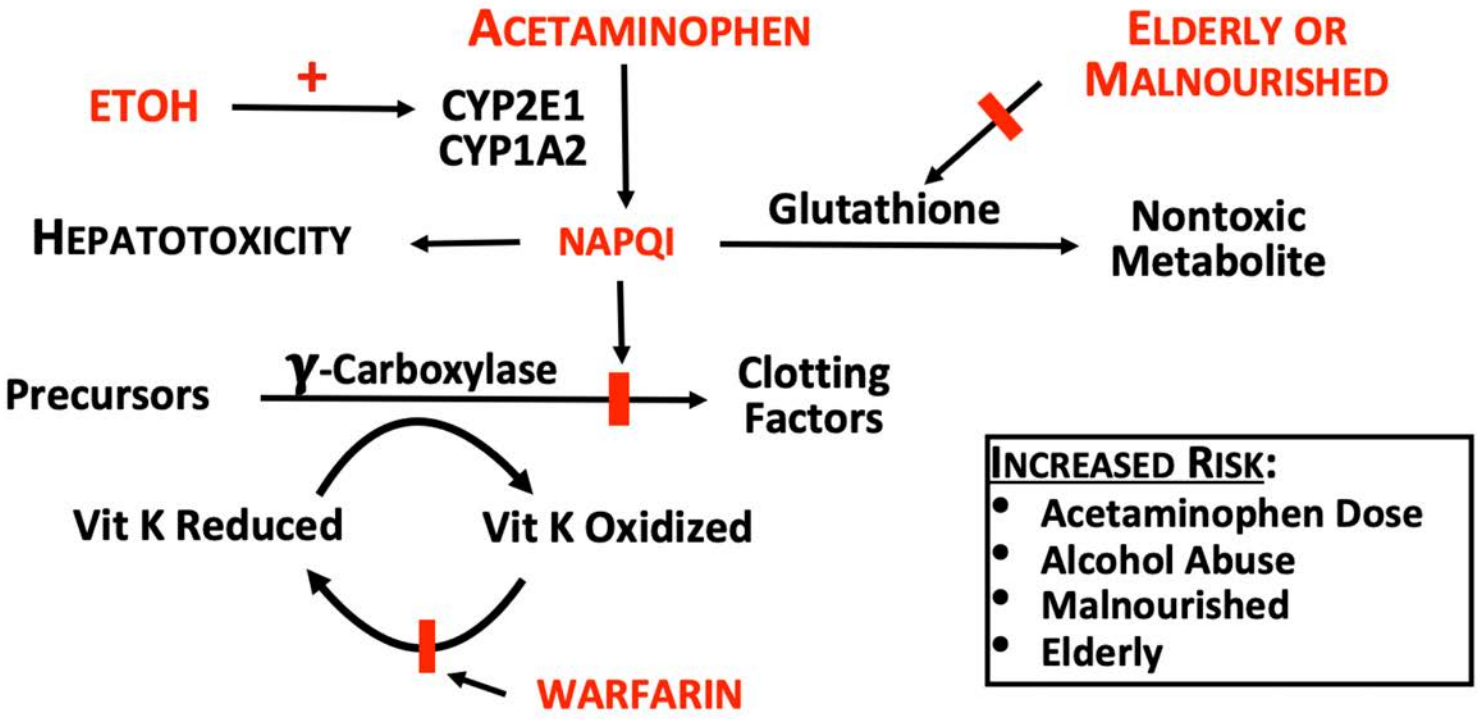
Paracetamol (acetaminophen) is generally considered to be the analgesic of choice for patients undergoing oral anticoagulant therapy. Occasionally, however, interactions have been reported with therapeutic doses of the analgesic, e.g. if the drug is taken for a longer period of time. The mechanism of this interaction is not clearly understood. We investigated the effects of paracetamol and its toxic metabolite N-acetyl-para-benzoquinone-imine (NAPQI) on *in vitro* vitamin K-dependent γ-carboxylase (VKD-carb) and vitamin K epoxide reductase (VKOR) activities. Paracetamol had no effect in either enzymatic reactions. NAPQI, on the other hand, appeared to interfere with VKD-carb activity via two mechanisms; 1) oxidation of the cofactor vitamin K-hydroquinone, 2) inactivation of the enzyme. The inactivation, in micromolar ranges, is not reversible and may be the result of covalent binding of NAPQI with functional amino acids. NAPQI also inhibited VKOR, but at higher concentrations. Unexpectedly, N-acetylcysteine was found to inhibit VKOR activity at concentrations that are obtained during rescue therapy of paracetamol intoxication. We conclude that, the potentiation of the oral anticoagulant effect by paracetamol is likely to result from NAPQI-induced inhibition of enzymes of the vitamin K cycle, particularly VKD-carb.

Keywords

Oral anticoagulation, paracetamol, drug interaction, vitamin K-dependent factors

Thromb Haemost 2004; 92: 797–802

Acetaminophen: Clotting Factors



Thijssen HH et al. Thromb Haemost 2004;92:797-802.

Colchicine for Covid-19: Rationale

- Patients with Covid-19 often develop acute respiratory distress syndrome and lung injury
- Inflammasome NLRP3 is thought to be a major factor in pathophysiology of ARDS
- Various Interleukins may also be involved in Covid-19 pathology
- Colchicine appears to suppress Interleukins (IL-1b, IL-18 and IL-6) through inhibition of Inflammasome NLRP3

Deftereos SG et al. Hellenic J Cardiol. March 27, 2020

Colchicine Drug Interactions

- CYP3A4/P-glycoprotein inhibitors may lead to colchicine toxicity, fatalities have occurred
- Colchicine toxicity can occur soon after interacting drug is given (days)
- Major findings in colchicine toxicity include pancytopenia, multiple organ failure, and myopathy

Dogukan A et al. *Clinical Nephrology*. 2001;55:181

Colchicine + Clarithromycin

- Pharmacokinetic study found clarithromycin caused a 282% mean increase in colchicine AUC (but one subject had an almost 9-fold increase)
- Case series in which 18% of patients on colchicine who had more than 2 days clarithromycin overlap died from colchicine toxicity
- 20 published case reports of colchicine toxicity with concurrent clarithromycin administration (19 were rated “Probable” on DIPS)
- FDA’s Adverse Event Reporting System search revealed 30 deaths reported from this DDI

Villa-Zapata L et al. Drug Saf. (2020) https://doi.org/10.1007/s40264-020-00930-7

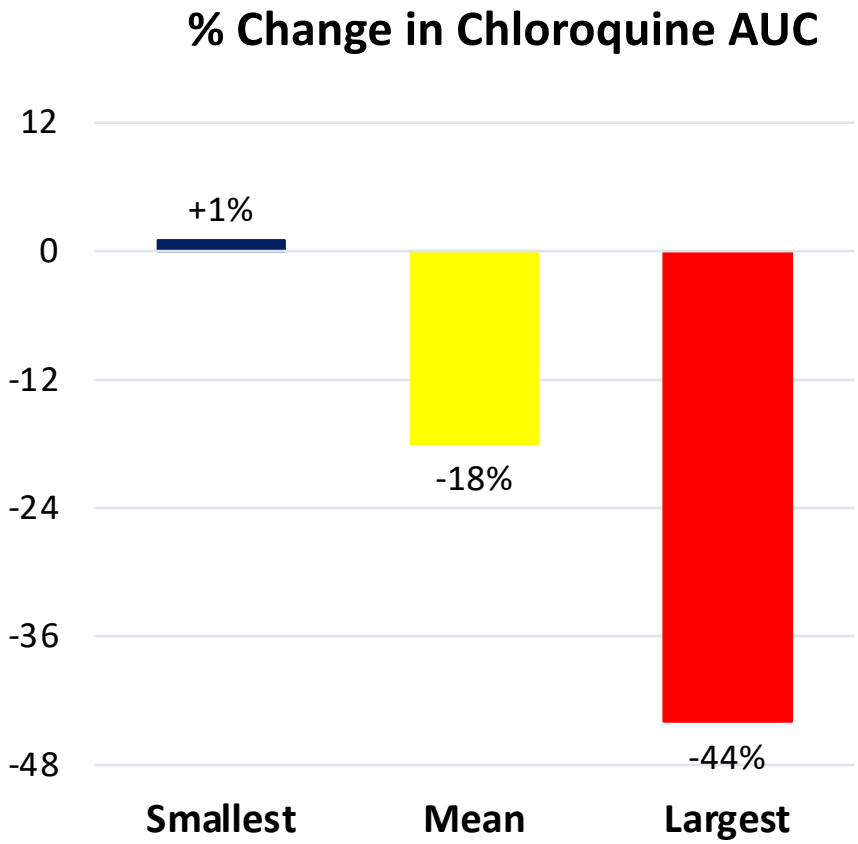
Remdesivir Drug-Drug Interactions

- All DDI information is from *in vitro* studies
- *In vitro*, remdesivir is a substrate for CYP2C8, CYP2D6, OATP1B1 P-gp
- *In vitro* studies suggest remdesivir is an inhibitor of CYP3A4, OAT1B1, OAT1B3, BSEP, MRP4, and NTCP, but rapid clearance of remdesivir minimizes risk of harm from DDI
- Remdesivir may induce CYP1A2 and CYP2B6, but not CYP3A4
  - Remdesivir metabolites do not produce enzyme induction
- Remdesivir is rapidly hydrolyzed to active form, hence manufacturer suggests risk of DDI is low.
  - No known information on metabolites.

European Medicines Agency. Remdesivir Gilead, Summary on Compassionate Use, April 3, 2020

Chloroquine + Antacids

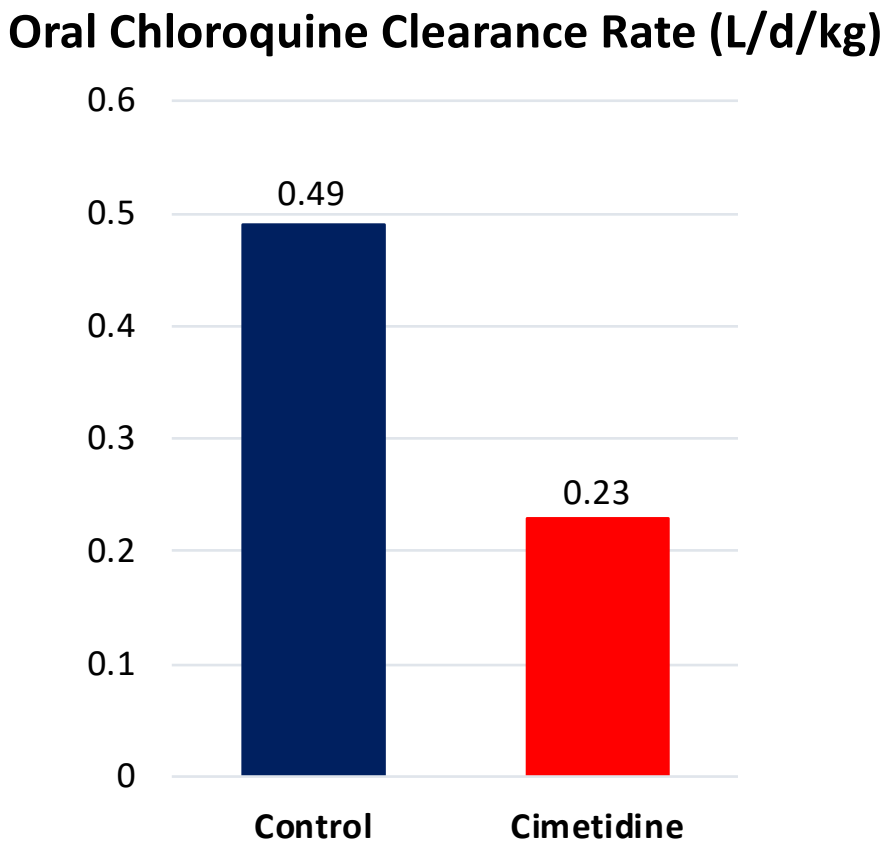
- 6 healthy subjects- single dose of chloroquine 250 mg alone or combined with 1 gram magnesium trisilicate
- Magnesium trisilicate reduced chloroquine AUC by 18%, but there was high variability (+1% to -44%)



McElnay JC, et al. J Trop Med Hyg. 1982;85:159-163

Chloroquine + Cimetidine

- 10 healthy subjects received chloroquine 300 mg; 5 were pretreated with cimetidine 400 mg/day for 4 days
- Cimetidine associated with 53% reduction in chloroquine clearance
- Chloroquine half-life increased by 49%
- Ranitidine did not affect chloroquine in another study



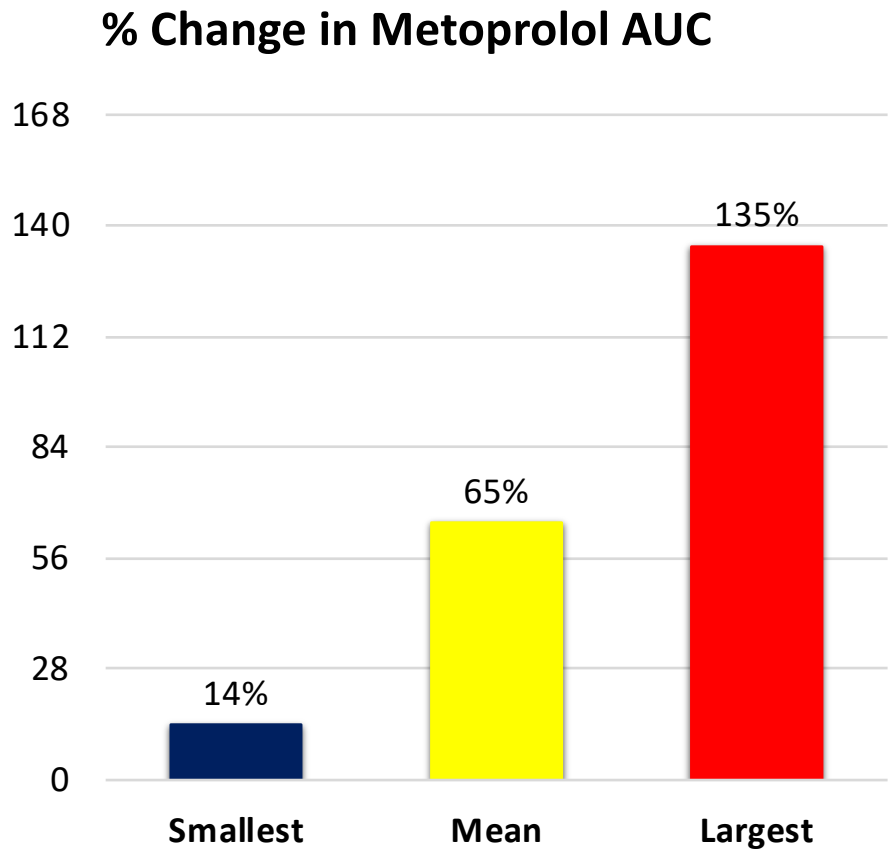
Ette EI, et al. J Clin Pharmacol. 1987;27:813-816.

Possible Chloroquine DDIs

Drug	Effect	Significance
Cyclosporine	Increased cyclosporine concentrations	Isolated case reports. Clinical importance not established
Digoxin	Increased digoxin serum concentrations	Poorly documented. Based on study in dogs and isolated reports of digoxin toxicity from hydroxychloroquine
Statins	Possible increased risk of statin-induce myopathy	Chloroquine may inhibit OATP1B1 resulting in increased risk of myopathy from pitavastatin, rosuvastatin, and pravastatin. Based on in vitro data and FAERS case reports.
Thyroxine	Reduced thyroxine effect	Poorly documented. Case report not convincing.

Hydroxychloroquine + Metoprolol

- 6 healthy subjects were given a single dose of metoprolol 250 before and after hydroxychloroquine 400 mg/day for 8 days
- All 6 were CYP2D6 EMs
- Hydroxychloroquine increased metoprolol AUC by a mean of 65%
- In addition, another subject (7th subject) who was CYP2D6 IM was made a PM by hydroxychloroquine



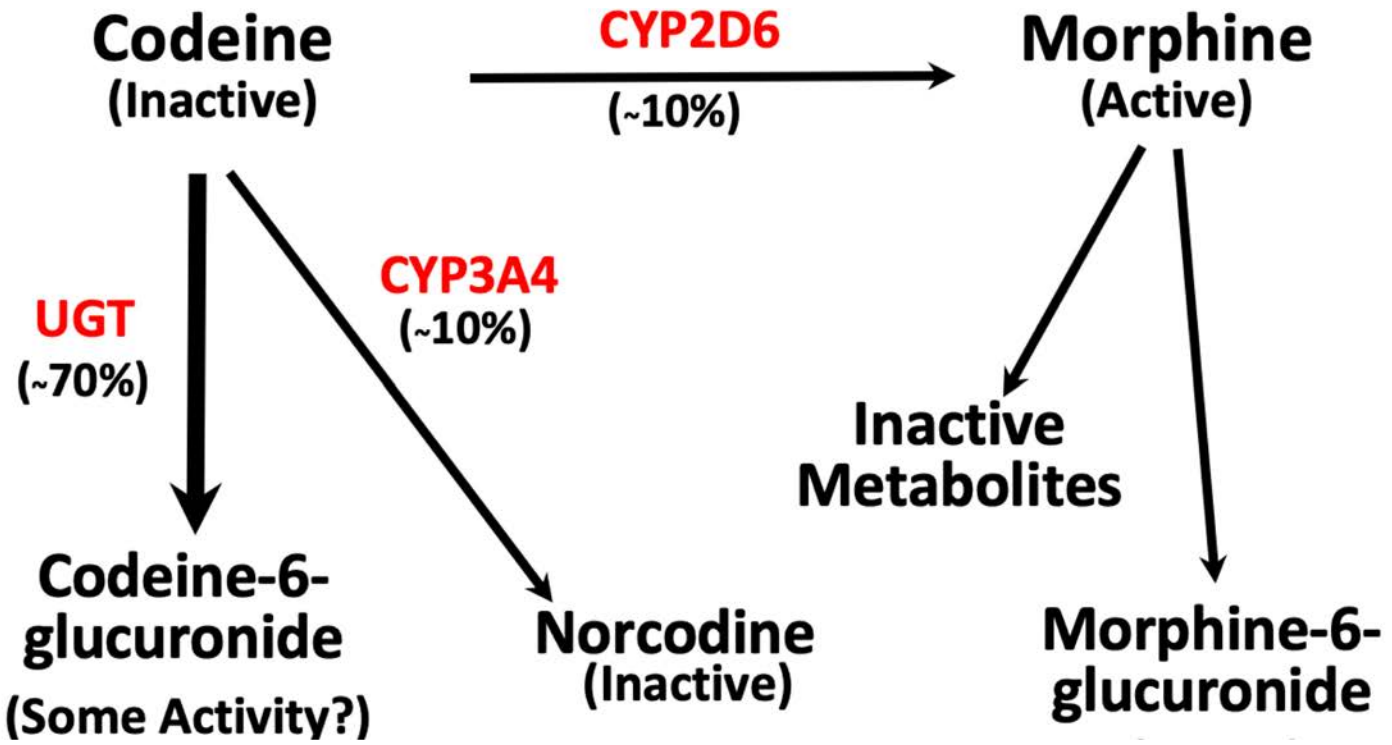
Somer M, et al. Br J Clin Pharmacol. 2000;49:549-554.

Chloroquine and Hydroxychloroquine: CYP2D6 Inhibition

- Chloroquine and hydroxychloroquine are moderate inhibitors of CYP2D6
- Many drugs are metabolized by CYP2D6, but the risk of concurrent use of hydroxychloroquine or chloroquine or probably less than with potent inhibitors of CYP2D6 such as paroxetine.
- Possible problems with 2D6 substrates

Laporte S, et al. Pharmacol Res. 2017;118:19-32.
Yuet WC, et al. J Am Osteopath Assoc. 2019;119:102-111

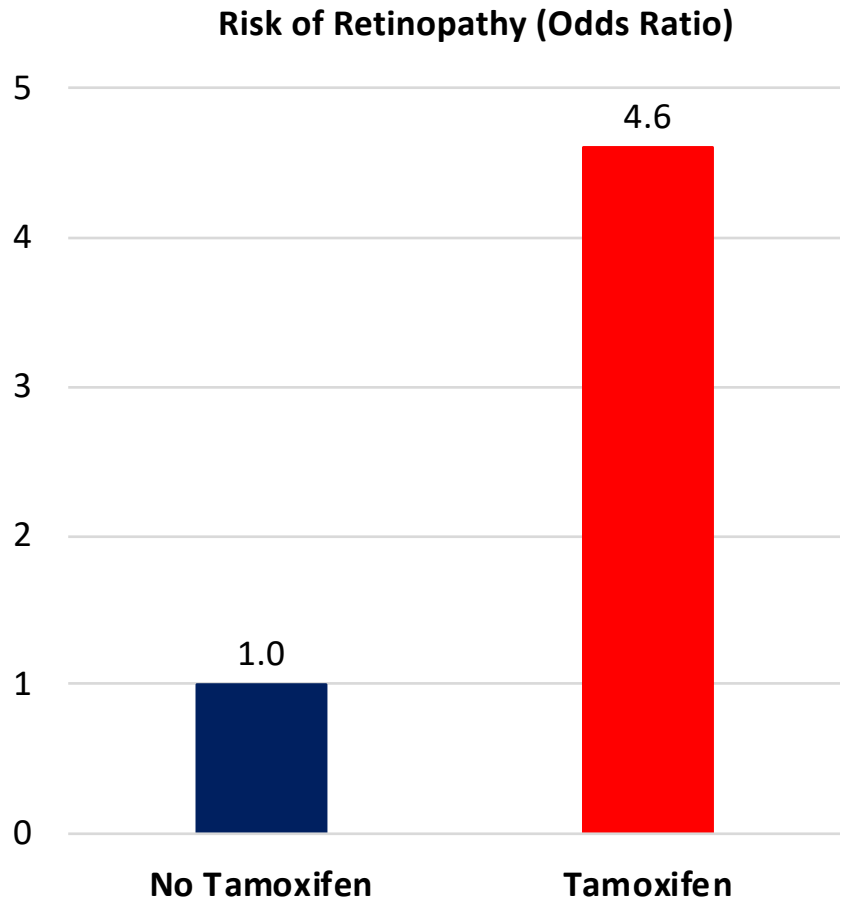
Codeine Metabolism*



* In Extensive Metabolizer (most people)

Hydroxychloroquine + Tamoxifen

- Case-control study of 2361 patients on at least 5 years of hydroxychloroquine
- Risk of retinopathy was increased by long-term use, larger doses, renal disease, and concurrent use of tamoxifen
- Hydroxychloroquine may also inhibit the efficacy of tamoxifen due to inhibition of CYP2D6



Melles RB et al, JAMA Ophthalmol. 2014;132;1453-1460.
Hansten PD. Eur J Drug Metab Pharmacokinet. 2018;43:495.

Possible Hydroxychloroquine DDIs

Drug	Effect	Significance
Anticonvulsants	Increased Seizure Risk	Warning in hydroxychloroquine label. Clinical importance not clear
Digoxin	Increased digoxin serum concentrations	Limited data. Two case reports with positive dechallenge, but causal relationship not established
Proton Pump Inhibitors	Reduced effect of hydroxychloroquine	Based on theoretical considerations. Clinical importance not clear.
Rifampin	Reduced effect of hydroxychloroquine	Based on single case report. Possibly due to rifampin enzyme induction

Ritonavir: A Potent Drug Interaction Precipitant

- Acute dosing inhibits multiple CYPs; e.g., CYP3A4, CYP2D6 and transporters; e.g., P-gp, OAT
- Chronic dosing can induce pregnane X receptor (PXR) resulting in modest induction of CYP1A2, CYP2B6, CYP2C9, CYP3A4 and glucuronidation
- Net effect on object drugs will depend on the balance of inhibition / induction and elimination pathways

Kharasch ED et al. Antimicrob Agents Chemother. 2008;52:1663-9;
Marzolini C et al. J Antimicrob Chemother. 2016;71:1755-8;
Kirby BJ et al. Drug Metab Dispos. 2011;39:2329-37.

Inhibition of CYP3A4 by Antiviral Agents

- Amprenavir
- Atazanavir
- Boceprivir
- Cobicistat
- Darunavir
- Delavirdine
- Fosamprenivir
- Indinavir
- Letermovir
- Nelfinavir
- Ritonavir
- Saquinavir
- Simeprevir
- Telaprevir
- Voxilaprevir

Hansten PD, Horn JR. The Top 100 Drug Interactions, 2019

Pharmacodynamic Drug Interactions with COVID-19 Therapies

John Horn, PharmD

Professor

UNIVERSITY of WASHINGTON

FDA Guideline for Thorough QT Study

- Endpoint: max time-matched, placebo and baseline corrected change in QTc. (ΔΔQTc)
- Include clinical and supra-therapeutic doses and positive control (eg, moxifloxacin)
- Threshold of regulatory concern is 5 milliseconds (10 milliseconds upper bound 95% CI)
- Drug is potential QT prolongator if threshold reached at any dose, any time point
- Normal QT variability far exceeds these values

Shah RR et al Early Investigation of QTc Liability. Drug Saf. 2012;35:695-709

Assessing the Risk of QTc Changes: Variability of QTc in Healthy Men

- 20 healthy subjects, 25 – 53 years with 24-hour Holter monitor
- Average QTc: 404 ± 34 milliseconds (ms)
- QTc variability over 24 hrs: 76 ± 19 ms (35-108)
- 55% had one or more QTc > 440 ms
- 5% had one or more QTc > 500 ms

Morganroth et al. Am J Card. 1991;67:774

QT Interval Changes: Relevance to Drug Interactions

- European Agency for Evaluation of Medicinal Products (EMEA) guidelines to assess QT prolongation

  < 30 milliseconds (ms) unlikely to be clinically significant

  30 – 60 ms likely drug effect; potential concern

  > 60 ms or QTc > 500 ms concern about risk of arrhythmias

ECG Abnormalities With CQ or HCQ Treatment of Connective Tissue Diseases

Author	N	QTc prolonged	Other conduction abnormalities
McGhie	453 SLE	0.7%	15.7%
Costedoat-Chalumeau	85 SLE and other CTD	none	3%
Teixeira	317 SLE	3.1%	9.7%

SLE = systemic lupus erythematosus; CTD = connective tissue diseases

McGhie TK. Clin Exper Rheum 2018;36:545; Costedoat-Chalumeau N. Rheumatology. 2007;46:808; Teixeira RA. Europace. 2014;16:887

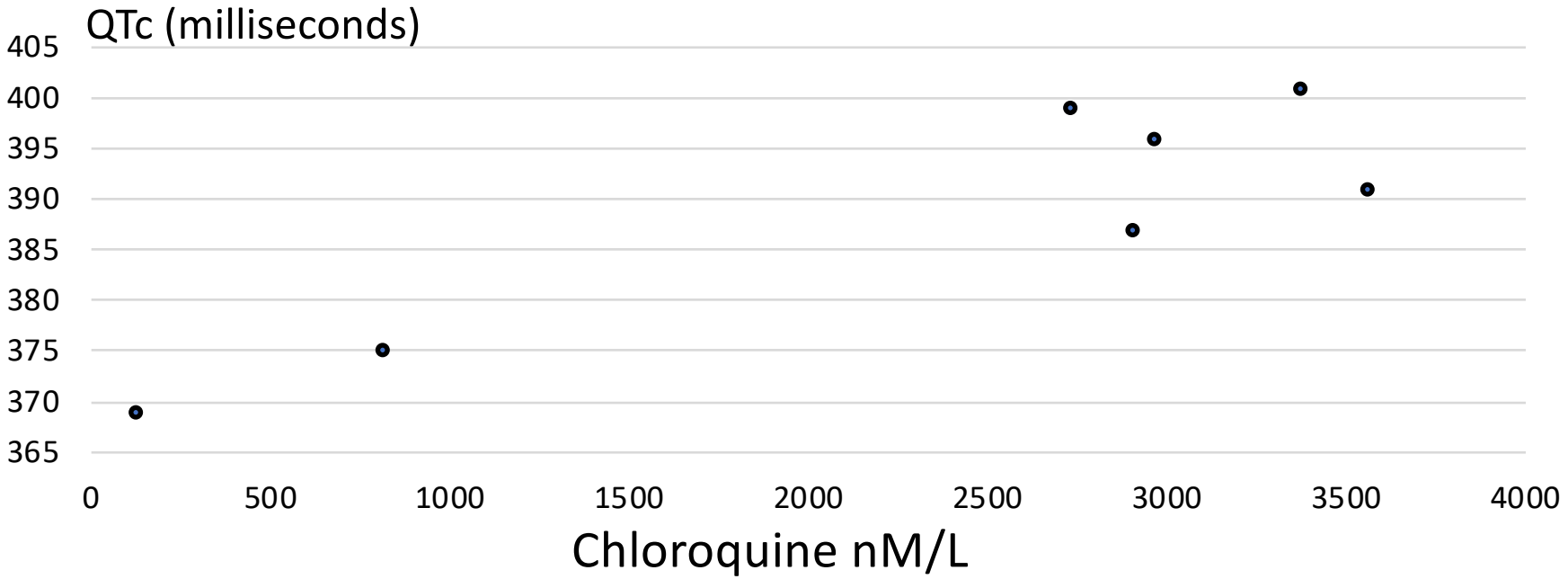
Chloroquine Concentration Effect on QTc in Healthy Subjects

Dose / Day (mg)	Cmax (uM)	ΔQTc day 1 vs baseline (milliseconds)	ΔQTc day 3 (milliseconds)	ΔQTc day 14 (milliseconds)
600 x 1	1.8	15		-3
600 x 2, 300 x 1	3.4	16	21	16

QTcB at 4-5 hr post-dose
N=24 @ 600mg/d; N=14 @ 500/d x 3

Mzayek F. PLoS Clin Trials 2007; 2(1):e6.doi:10.1371/journal.pctr.0020006

QTc vs Chloroquine Concentration in Children



Chloroquine dose: 10 mg/kg BID x 2 days then 5 mg/kg BID x 1 or 2 days; N=30. Max changes in QTc (ΔQTc) 15 milliseconds

Ursing. Antimicrob Agents Chemother. 2020;64:e01846-19

Chloroquine Effect on QTc

Reference	Dose	N	ΔQTc (milliseconds)
PLoS Clin Trials 2007; 2(1):e6.doi:10.1371/journal.pctr.0020006	300 mg bid x 1 day	126 healthy	15
PLoS Clin Trials 2007; 2(1):e6.doi:10.1371/journal.pctr.0020006	300 mg bid x 2 days, 300 mg x 1 day	126 healthy	21
Antimicrob Agents Chemother 2020;64: e01846-19	50 mg/kg or 70mg/kg x 3 days	15 malaria	15
Am J Trop Med Hyg 1997;56:494-7	10 mg/kg x 3 days	139 malaria	20
Br J Clin Pcol. 1986;22:31-6	3mg/kg IV 10 min	12 healthy	NC
Antimicrob Agent Chemother 2014;58:3354-9	600 mg single dose	12 healthy	6
Clin Pharmacol Ther. 2018;105:943-63	1000 mg day 1, 500 mg day 2, 1000 mg day 3	60 healthy	30-50

Hydroxychloroquine Effect on QTc

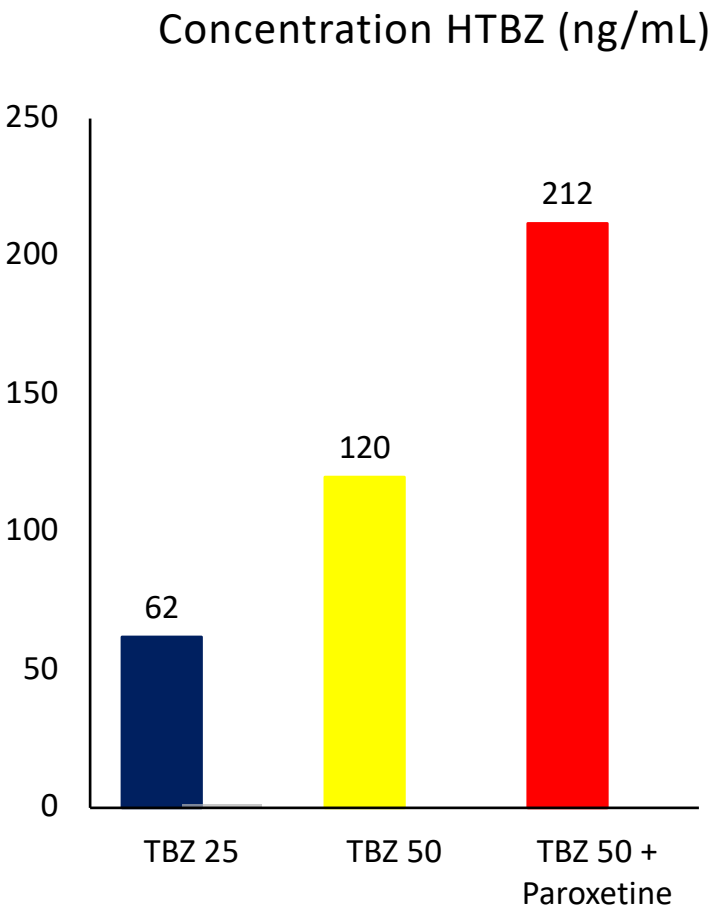
Reference	Dose	N	QTc (milliseconds)
Rheumatology 2007;46:808-10	200 HCQ mg qd or bid for average of 8 years	85 CTD	QTc 410 (349-464)
Clin Exper Rheumatology 2018;36:545-51	HCQ or QC mean cumulative dose 1525 grams	453 SLE	QTc abnormal in 0.7%
Drug Safety 2018;41:919-31	Mean cumulative dose 1235 grams HCQ and 803 grams CQ	127 CTD	No ↑QTc; other conduction disorders common
JAMA Cardiol. doi:10.1001/jamacardio.2020.1834	HCQ 400mg bid x 1, 400mg x 4d alone and with Azith 500mg x1, 250mg/d x4	37 HCQ, 53 HCQ+Azith COVID-19	HCQ: 5.5; HCQ + Azithromycin: 23

HCQ= hydroxychloroquine; CQ= chloroquine; SLE = systemic lupus erythematosus; CTD = connective tissue diseases

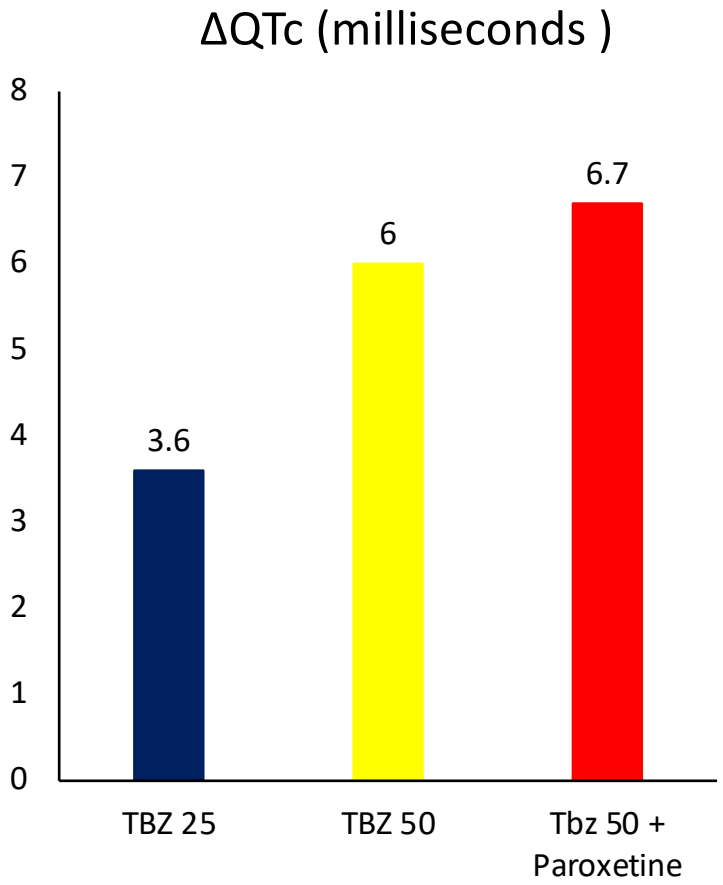
Azithromycin Effect on QTc

Reference	Dose	N	ΔQTc (milliseconds)
Clin Ther 2001;23:451-66	500 mg x 1 dose, 250 mg/day x4 days	90 healthy	-0.1
Cystic Fibrosis 2016;15:192-5	250 and 500 mg/day chronic	56 cystic fibrosis	1
Clin Pharmacol Ther 1995;58:310-5	500 mg x 1 dose, 250 mg x 4 days + Terfenadine 60 mg bid or placebo	24 healthy	Terfenadine = 8; Terfenadine + Azithromycin = 11
Clin Ther 2001;23: 451-66	500 mg x 1 dose, 250 mg/day x 4 days + Desloratadine 5 mg x 7 days	90 healthy	Desloratadine = -6.3; Azithromycin = -0.1; Desloratadine + azithromycin = -4.2
Azithromycin Label	500mg, 1000mg, 1500 mg/day + Chloroquine 1000mg	116 healthy	Chloroquine + Azithromycin = 5-7 vs Chloroquine alone
Am J Trop Med Hyg. 2006;74:407-12	1000 mg/day x 3 days + Chloroquine 600 mg/day x 2 days then 300mg x 1 day	39 healthy	Chloroquine = 13.7, Chloroquine + Azithromycin = 19.9

Tetrabenazine / Paroxetine: PK and PD

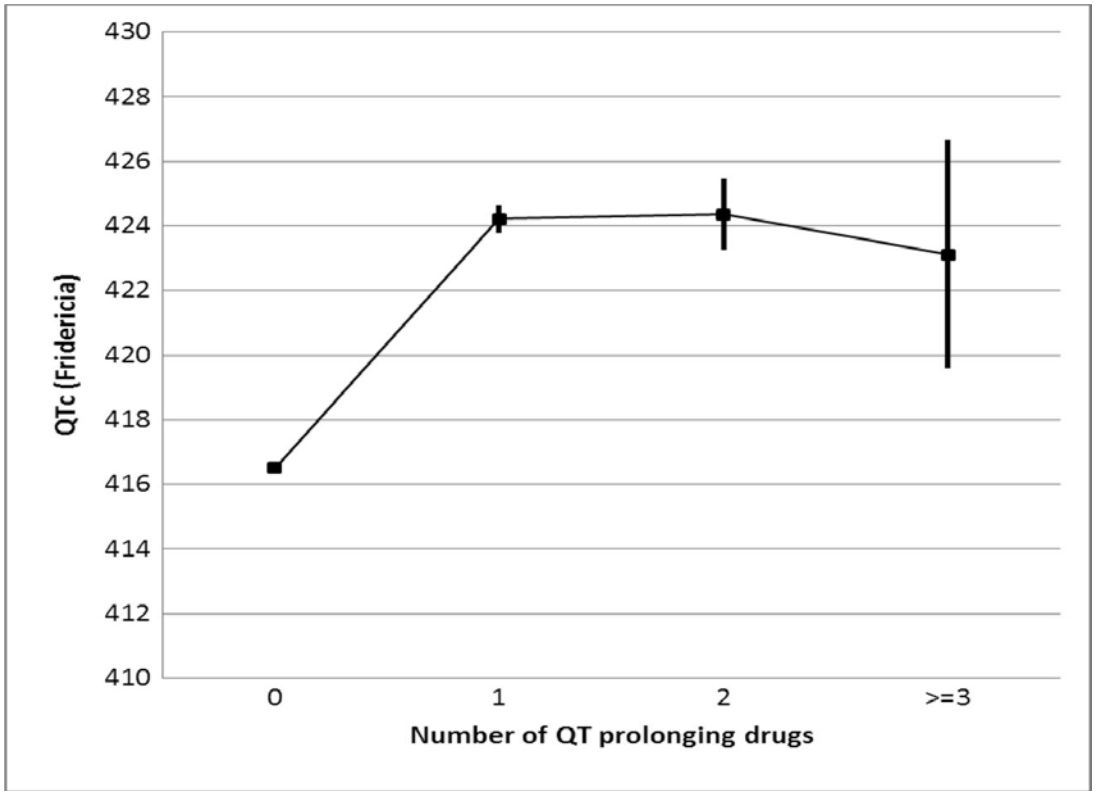


HTBZ = dihydrotetrabenazine;
TBZ = Tetrabenazine



Source: Tetrabenazine New Drug Application

Effect of Multiple QT Prolongating Drugs



133,359 ECGs from 40,037 patients.

N :
0 drug – 102,227
1 drug – 26,162
2 drugs – 4476
≥ 3 drugs – 444

Heemskerk CPM et al. Europ J Clin Pharmacol. 2018;74:183

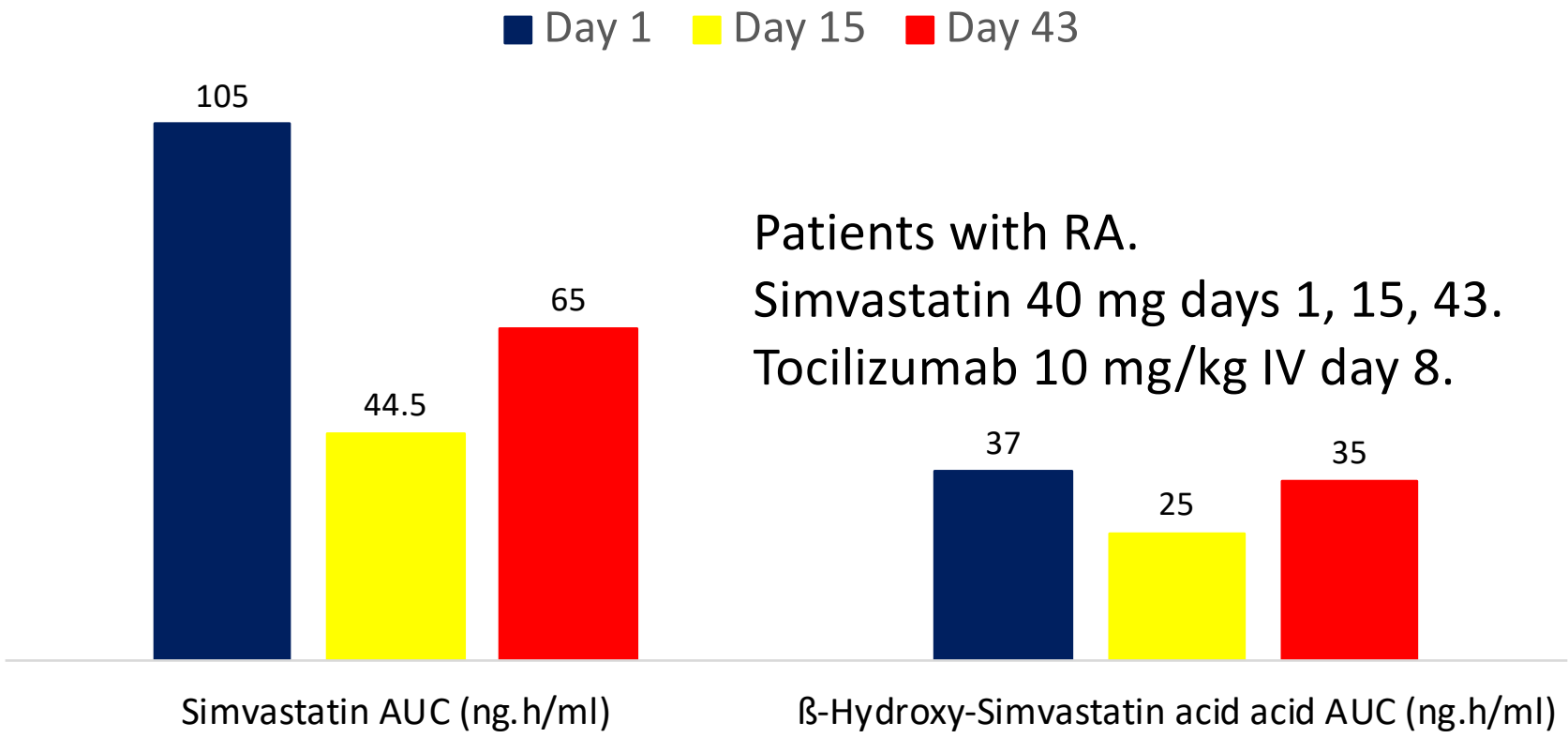
Effect of Hydroxychloroquine on HbA1c in Diabetics with Rheumatic Disease

	HCQ n=45	MTX n=37	P value
Pretreatment	7.71%	7.38%	0.35
Lowest within 12 mos	7.05%	7.27%	0.49
Change pretreat – lowest	0.66%	0.11%	0.04

HCQ= hydroxychloroquine; MTX= methotrexate

Rekedal L. Arthritis & Rheumatism. 2010;62:3569-3573

Tocilizumab / Simvastatin



Schmitt et al.. Clin Pharmacol Thera. 2011;89:735-740

Effects of Cytokines on CYP450 Enzymes

Cytokine	CYP1A2	CYP2B6	CYP2C8	CYP2C9	CYP2C19	CYP3A4
IL-1	↓	↓ ↔	↓	↔	↔	↓
IL-2	↓	↓		↓	↓	↓
IL-4	↓	↑				↑ ↔
IL-6	↓	↓	↓	↓	↓	↓
TNF-α	↓	↓ ↑	↓	↔	↓ ↔	↓
INF-γ	↓	↓	↔	↔	↔	↓
TGF	↓	↓ ↑	↓	↓	↓	↓

Adapted from Shah et al. Drug Metab Dispos. 2015;43:400

Pathophysiological Effects of Cytokines

- Increase atherogenesis, endothelial dysfunction, susceptibility of plaque to rupture, inflammation-based thrombus formation
- Prolong action potential duration by enhancing L-type calcium influx and impairing hERG potassium channel
- Patients with rheumatoid arthritis (RA) greater risk of ischemic heart disease, congestive heart failure, sudden cardiac death vs general population.
- Patients with RA increased QT dispersion and QTc that appears associated with cytokine levels; decreased QTc, TNFα, and C-reactive protein observed following tocilizumab
- Patients with RA have increased risk of atrial fibrillation

Lazzerini PE. Europ Heart J. 2017;38:1717, Aromolaran AS. Plos One doi.org/10.1371/journal.pone.0208321

Question: What products leading to drug-drug interactions are you **most concerned** about related to COVID19 treatments

1. Chloroquine
2. Hydroxychloroquine
3. Azithromycin
4. Tocilizumab
5. Colchicine

How to engage with us?

Access and use our resources: https://ddi-cds.org

- Other DDI algorithms
- Connect with us using our discussion forum

Acknowledgements

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