SUPPLEMENTAL MATERIALS

Investigational treatments for COVID-19 may increase ventricular arrhythmia risk through drug interactions

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Supplemental material for this manuscript consists of links to model code and 3 supplemental tables that provide additional methodological information.

Availability of model code

Mathematical models that were used to generate this manuscript's results were implemented in MATLAB (Figures 1, 3, and 4) or R (Figure 2). These source files have been placed at the first author's github repository and are freely available for download:

https://github.com/meeravarshneya1234/COVID19Drugs_ArrhythmiaRisk

Table S1: Drug Channel Block Characteristics

Drug	IC_{50} I_{Kr} (nM)	IC_{50} I_{CaL} (nM)	IC_{50} I_{Na} (nM)	IC_{50} I_{NaL} (nM)	IC_{50} I_{Ks} (nM)	IC_{50} I_{K1} (nM)	IC_{50} I_{to} (nM)
Azithromycin	70796	-	-	189128	470131	-	88764
Chloroquine	6889	-	-	-	-	10595	-
Lopinavir	5170	15601	-	-	-	-	-
Ritonavir	5157	8228	-	7175	-	-	-

Drug	EFTPC (nM)	h I_{Kr}	h I_{CaL}	h I_{Na}	h I_{NaL}	H I_{Ks}	h I_{K1}	h I_{to}
Azithromycin	1937	0.5	-	-	1.9	1.4	-	0.5
Chloroquine	249.5	0.6	-	-	-	-	0.8	-
Lopinavir	703.7	1.2	1	-	-	-	-	-
Ritonavir	436.9	1	1.3	-	0.7	-	-	-

IC_{50} values and Hill coefficients taken from a study that measured block of 7 cardiac ion channels by 30 drugs under standardized conditions.[1]

Table S2: Phenotypic group parameterization

The model parameters in Table S1 were used to describe the healthy male phenotype while the remaining three groups were scaled based on published data. The healthy female scaling factors were taken from Yang et al.,[2] while the heart failure male were taken from Gomez et. al.[3] The heart failure female group was formed by multiplying the healthy female and heart failure male groups.

Parameter	Healthy Male	Healthy Female	Heart Failure Male	Heart Failure Female
$\overline{G}_{Na,fast}$	1	1	1	1
$\overline{G}_{Na,late}$	1	1	1.8	1.8
$\overline{G}_{to}$	1	0.64	0.4	.256
$\overline{G}_{Kr}$	1	0.79	1	0.79
$\overline{G}_{Ks}$	1	0.83	1	0.83
$\overline{G}_{K1}$	1	0.86	0.68	0.5848
$\overline{G}_{NaCa}$	1	1	1.75	1.75
$\overline{G}_{Kb}$	1	1	1	1
P_{Ca}	1	1	1	1
$\overline{I}_{NaK}$	1	0.79	0.7	0.5530
P_{Nab}	1	1	1	1
P_{Cab}	1	1	1	1
$\overline{G}_{pCa}$	1	1	1	1
$SERCA_{total}$	1	1.15	0.5	0.5750
RyR_{total}	1	1	1	1
$Trans_{total}$	1	1	1	1
$Leak_{total}$	1	1	1.3	1.3
K_{CaMK}	1	1	1.5	1.5

Model Parameters

Table S3: Channel Conductance Parameters varied in O'Hara Model[4]

Parameter	Definition	Baseline value[1]
$\overline{G}_{Na,fast}$	Maximal Na^+ conductance	75 mS/μF
$\overline{G}_{Na,late}$	Maximal late Na^+ conductance	0.0075 mS/μF
$\overline{G}_{to}$	Maximal transient outward K^+ conductance	0.02 mS/μF
$\overline{G}_{Kr}$	Rapid delayed rectifier K^+ conductance scaling factor [1]	0.046 mS/μF
$\overline{G}_{Ks}$	Slow delayed rectifier K^+ conductance scaling factor [2]	0.0034 mS/μF
$\overline{G}_{K1}$	Inward rectifier K^+ conductance scaling factor [1]	0.1908 mS/μF
$\overline{G}_{NaCa}$	Maximal Na^+-Ca^{2+} exchange current	0.0008 μA/μF
$\overline{G}_{Kb}$	Maximal conductance of background K^+	0.003 mS/μF
P_{Ca}	L-type Ca^{2+} current permeability	0.0001 cm/s
$\overline{I}_{NaK}$	Scales the Na^+-K^+ ATPase current	30
P_{Nab}	Background Na^+ current permeability	3.75e-10 cm/s
P_{Cab}	Background Ca^{2+} current permeability	2.5e-8 cm/s
$\overline{G}_{pCa}$	Maximal sarcolemmal Ca2+ pump current	0.0005 mS/uF
$SERCA_{total}$	SR Ca^{2+} release scaling factor [4]	1
RyR_{total}	SR Ca^{2+} uptake (SERCA) scaling factor[4]	1
$Trans_{total}$	NSR to JSR Ca^{2+} translocation[4]	1
$Leak_{total}$	Ca^{2+} Leak from the NSR[4]	1

Notes

[1]The scaling factors for I_{K1} and I_{Kr} are not formally maximal conductance, since each is multiplied by $\sqrt{K_o}/5.4$ and can therefore be greater than this value. Changing this factor scales the current at all values of extracellular $[K^+]$ while maintaining the dependence on this variable.

[2]The scaling factor for I_{Ks} is multiplied by a function of intracellular $[Ca^{2+}]$. This value is therefore not precisely the current's maximal conductance.

[3]$\overline{I}_{NaK}$ was not labeled in the original paper and have been given these names to keep to terminology consistent.

[4]Parameters controlling the magnitude of these channels are an introduced unitless multiplier with baseline value equals to 1.00.

REFERENCES

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