Drug Metabolism and Disposition

Supplemental Data

Extrapolation of elementary rate constants of P-glycoprotein mediated transport from MDCKII- hMDR1 to Caco-2 cells

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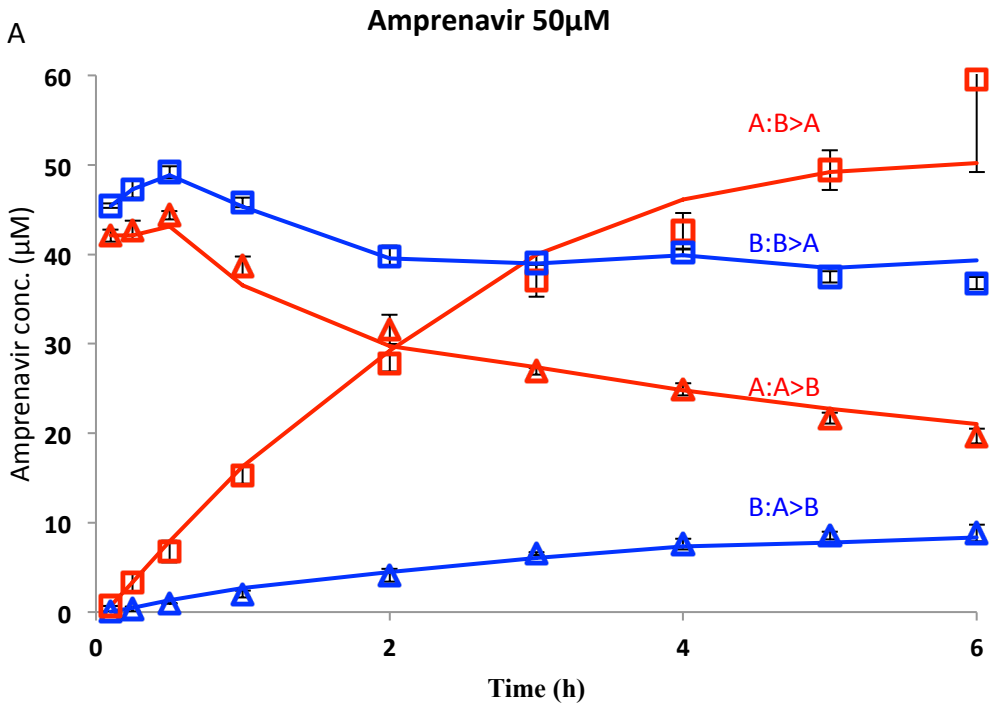
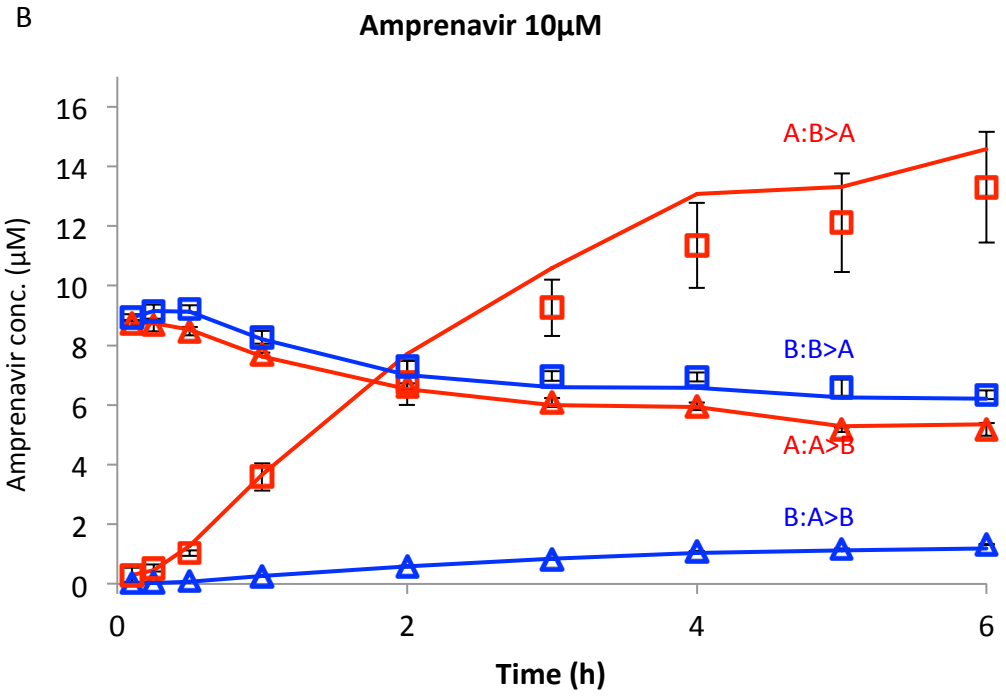
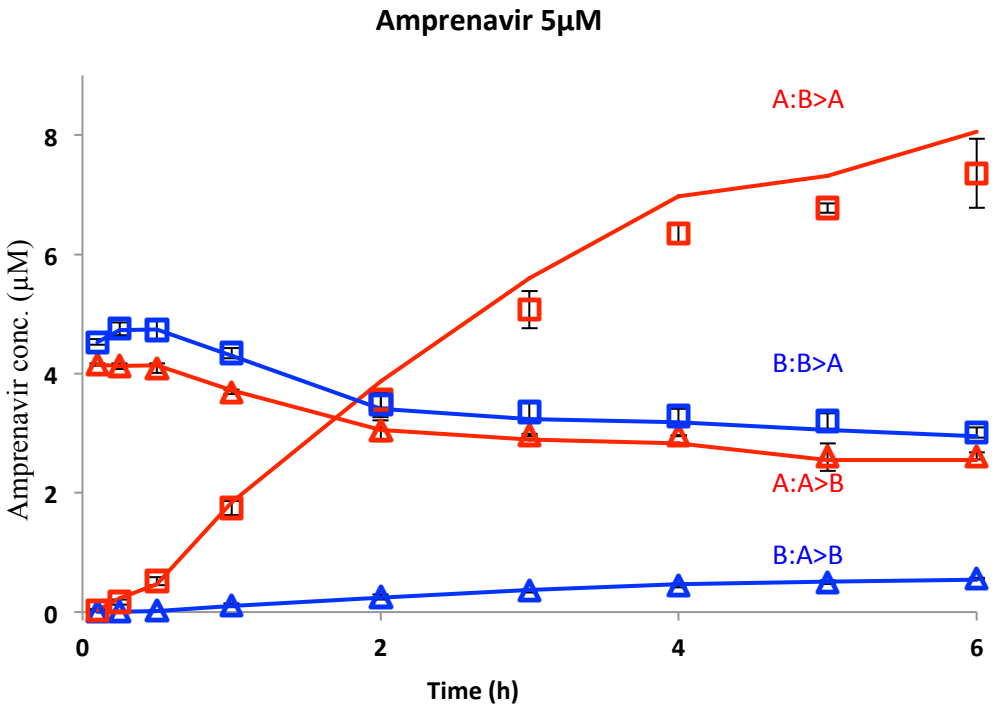
A


Amprenavir 50µM
Amprenavir conc. (µM)
60
50
40
30
20
10
0
0
2
4
6
Time (h)
A:B>A
B:B>A
A:A>B
B:A>B

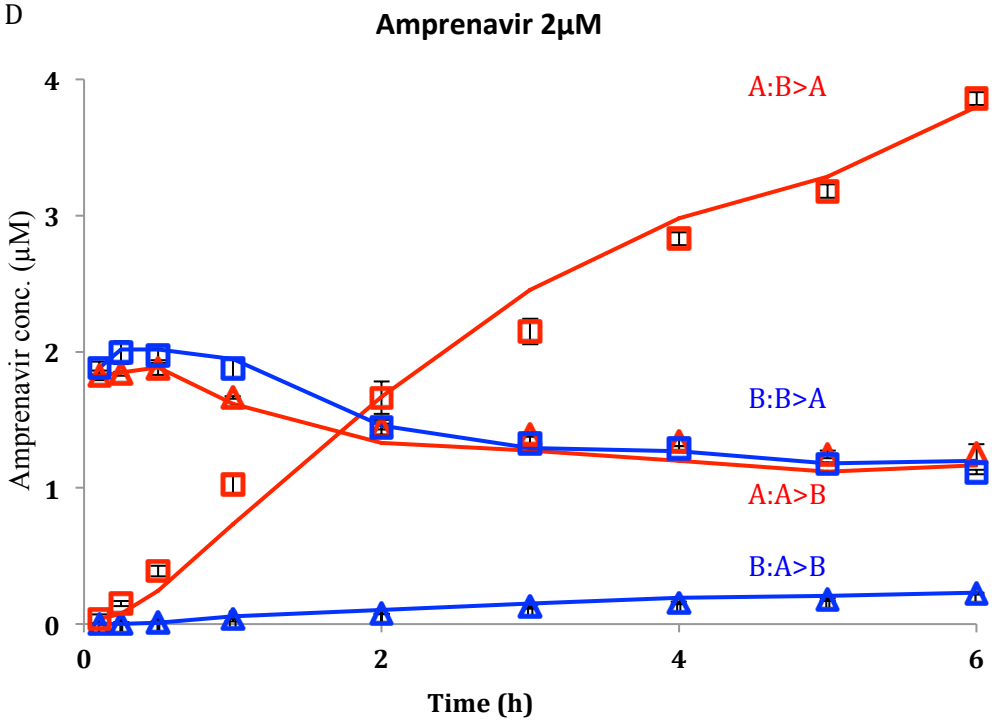
B


Amprenavir 10µM
Amprenavir conc. (µM)
16
14
12
10
8
6
4
2
0
0
2
4
6
Time (h)
A:B>A
B:B>A
A:A>B
B:A>B

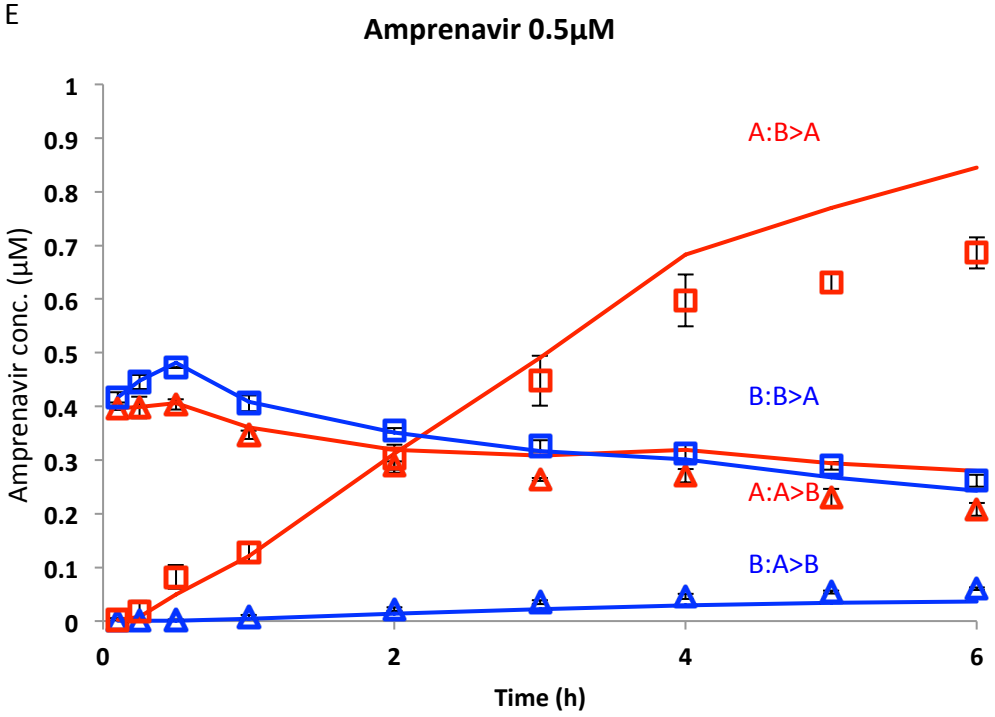
C


Amprenavir 5µM
A:B>A
B:B>A
A:A>B
B:A>B
Amprenavir conc. (µM)
Time (h)
0
2
4
6
8

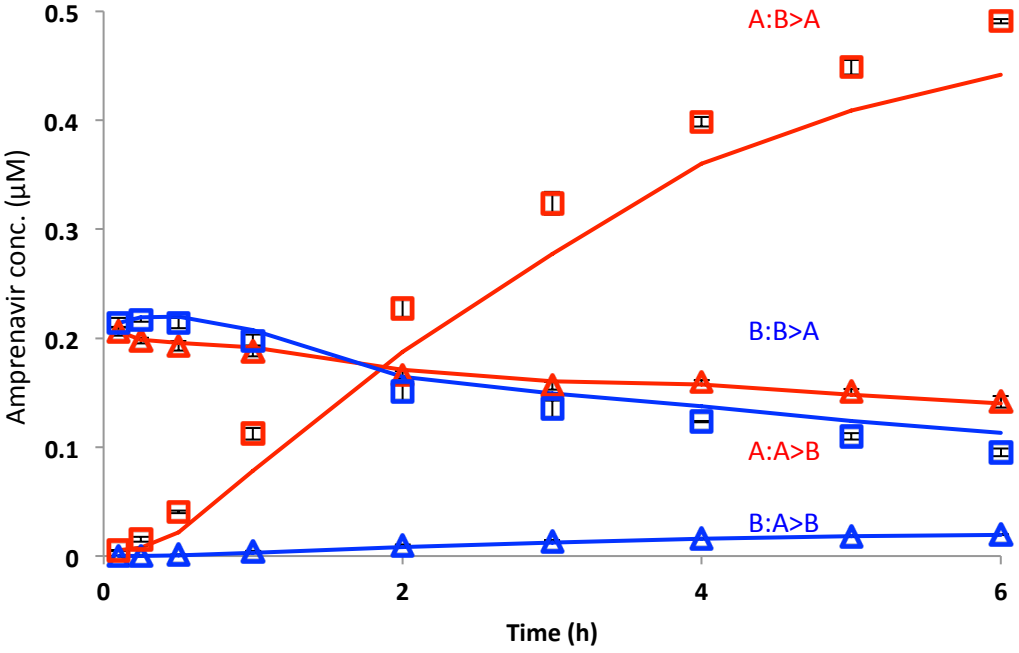
D


Amprenavir 2µM
A:B>A
B:B>A
A:A>B
B:A>B
Amprenavir conc. (µM)
Time (h)
0
1
2
3
4
6

E

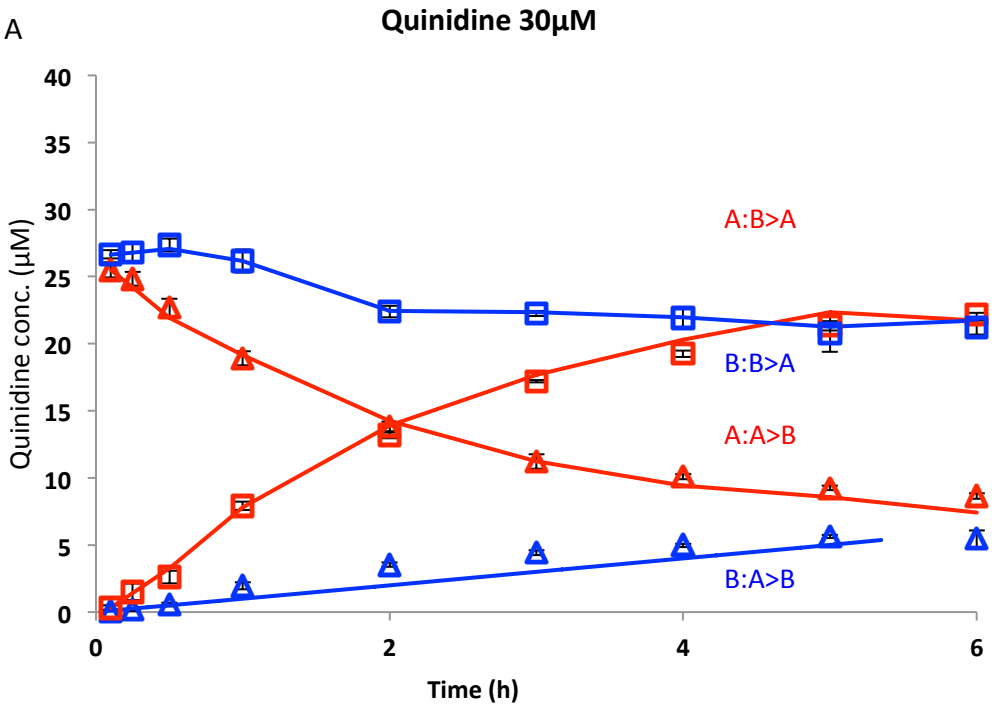

Amprenavir 0.5µM
Amprenavir conc. (µM)
Time (h)
A:B>A
B:B>A
A:A>B
B:A>B
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1
0
2
4
6

F

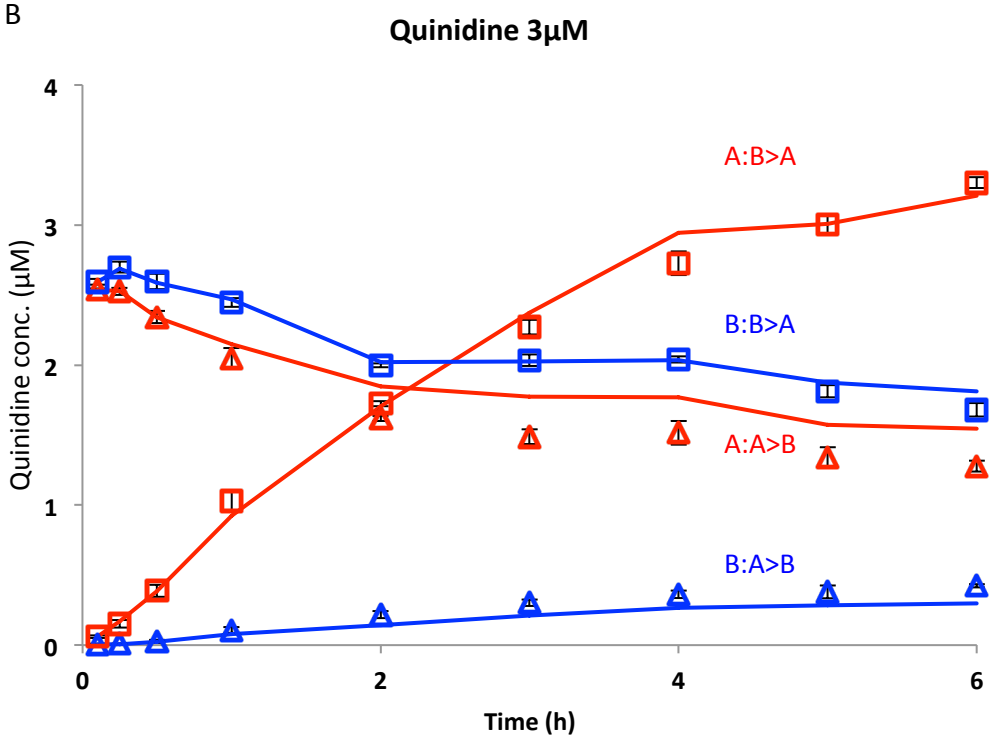

Amprenavir 0.2µM
Amprenavir conc. (µM)
Time (h)
A:B>A
B:B>A
A:A>B
B:A>B
0
0.1
0.2
0.3
0.4
0.5
0
2
4
6

Supplemental Figure 1: Transport data of amprenavir with initial concentration of 50μM (A), 10μM (B), 5μM (C), 2μM (D), 0.5μM (E) and 0.2μM (F) over 6 hours and their fitted curves across Caco-2 cell monolayers. The symbols show the data points with error bars showing the standard deviation of triplicate experimental measurement. The lines show the best fits for drugs assuming there are no other transporters. A:B>A denotes the substrate concentration in the apical chamber when the basolateral chamber is the donor, while B:B>A denotes the substrate concentration remaining in the donor basolateral chamber. The A:B>A transport is high because P-gp actively effluxes drug into the apical chamber. The B:A>B denotes the substrate concentration in the basolateral chamber when apical chamber is the donor, while A:A>B denotes the substrate concentration remaining in the donor apical chamber.

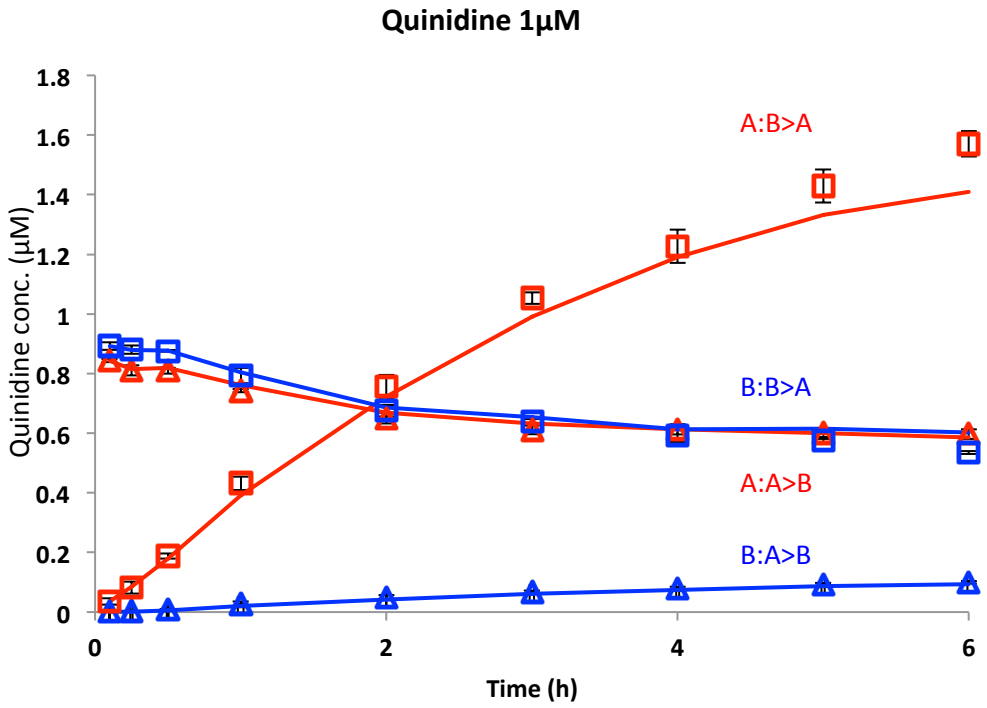
A


Quinidine 30µM
Quinidine conc. (µM)
Time (h)
A:B>A
B:B>A
A:A>B
B:A>B
0
5
10
15
20
25
30
35
40
0
2
4
6

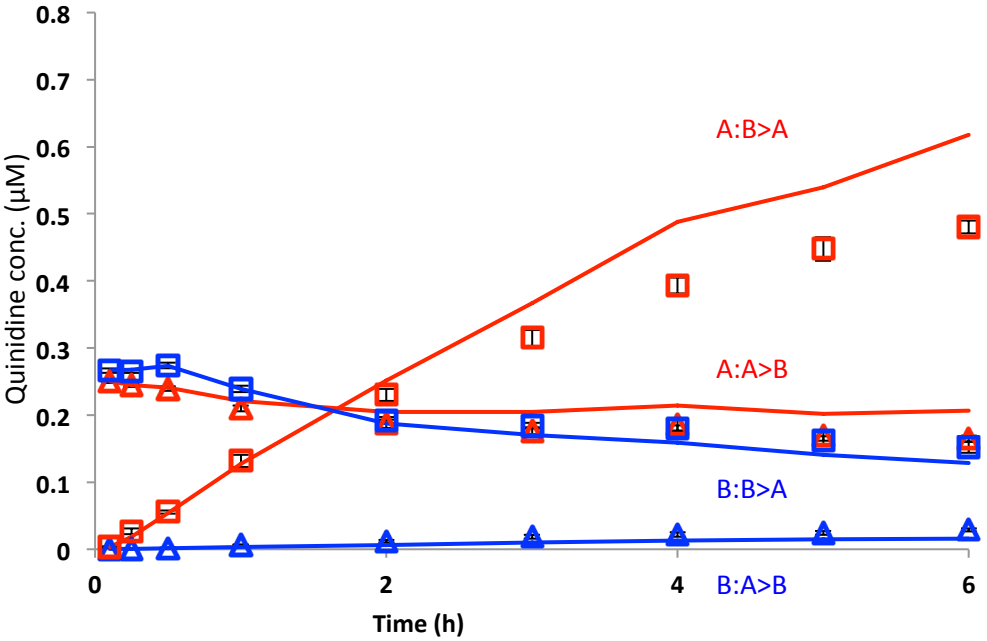
B

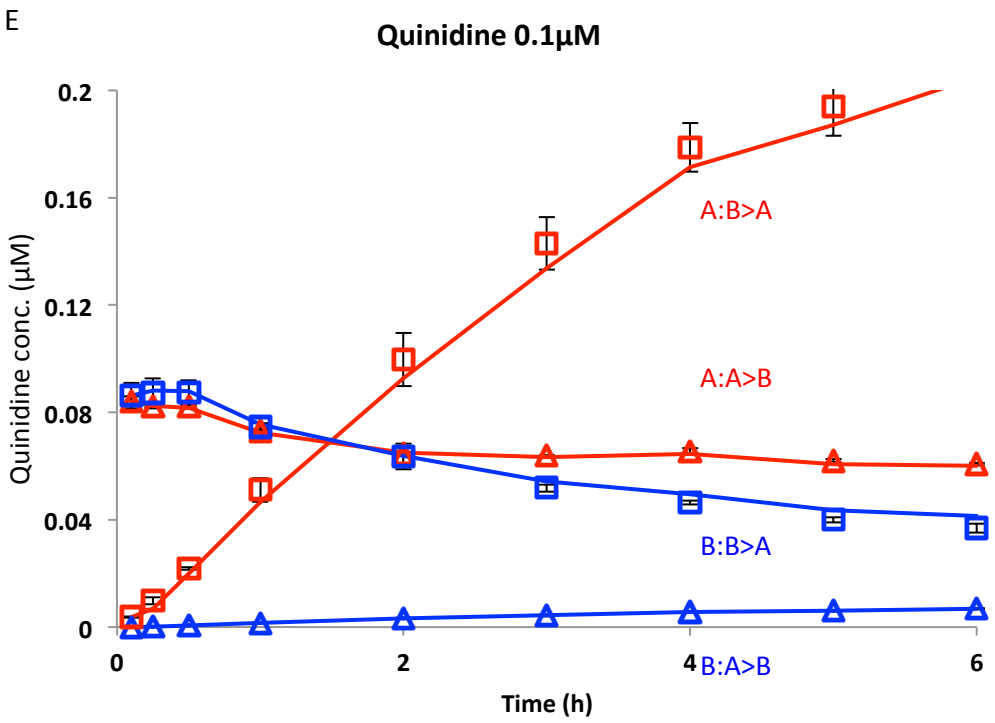

Quinidine 3µM
Quinidine conc. (µM)
Time (h)
A:B>A
B:B>A
A:A>B
B:A>B
0
1
2
3
4
0
2
4
6

C

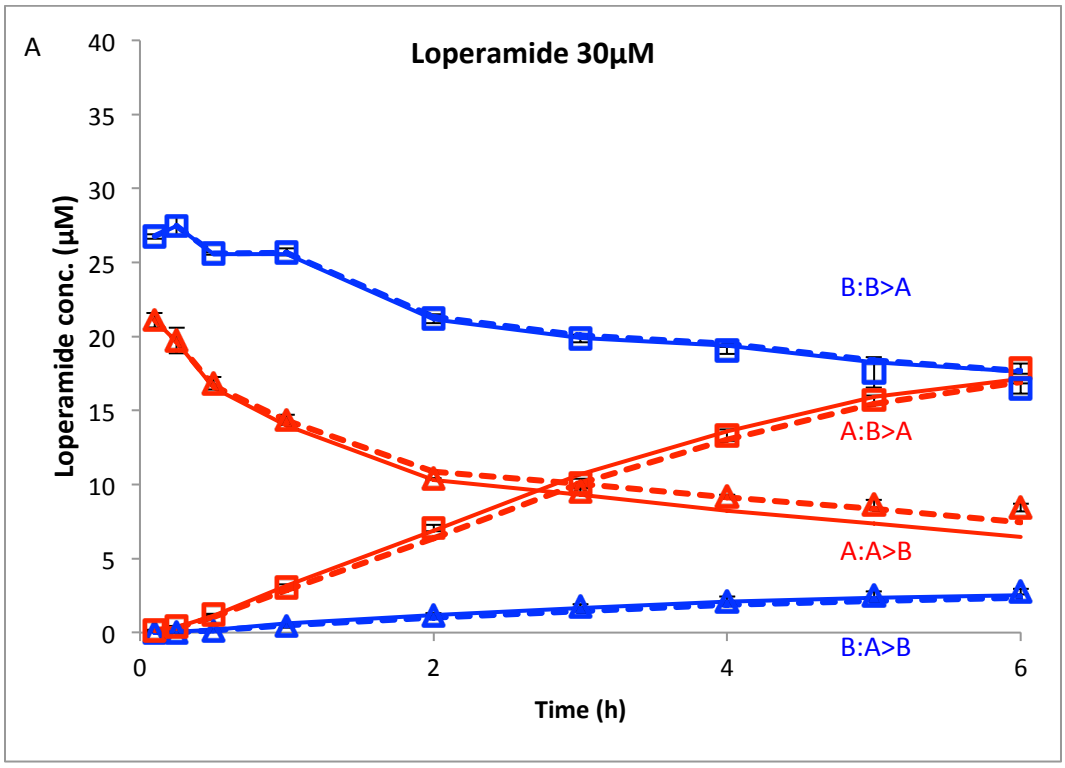

Quinidine 1µM
Quinidine conc. (µM)
Time (h)
A:B>A
B:B>A
A:A>B
B:A>B
0
0.2
0.4
0.6
0.8
1
1.2
1.4
1.6
1.8
0
2
4
6

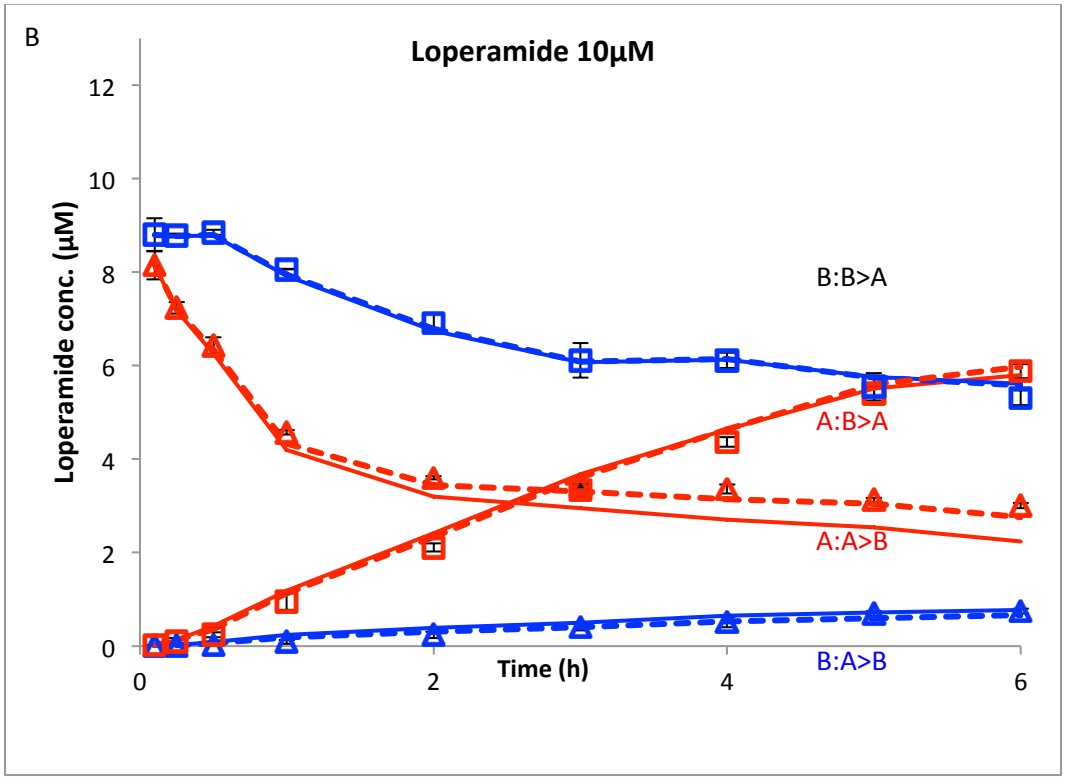
D

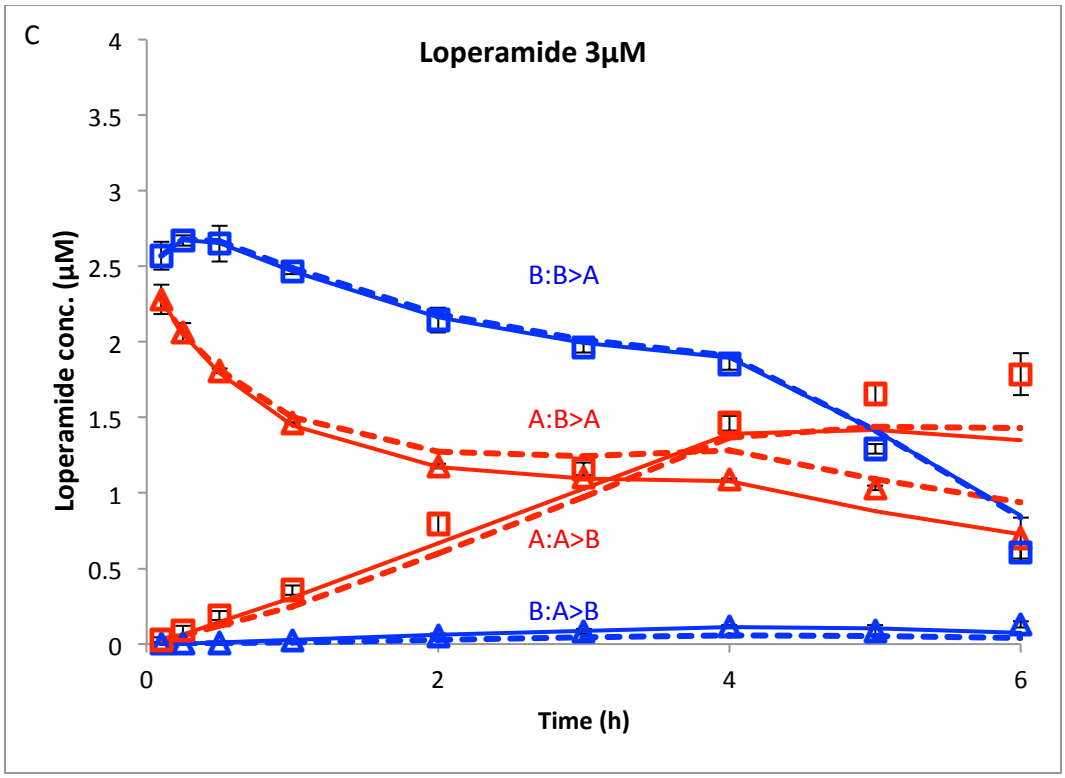

Quinidine 0.3µM
Quinidine conc. (µM)
Time (h)
A:B>A
A:A>B
B:B>A
B:A>B
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0
2
4
6

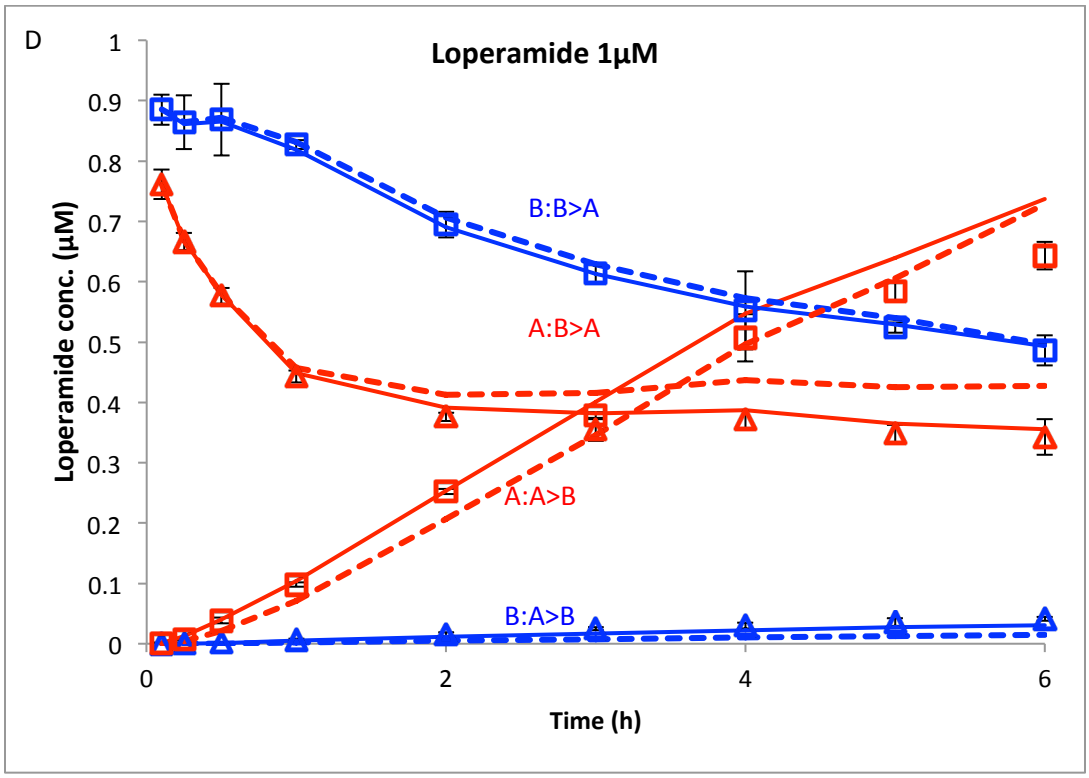


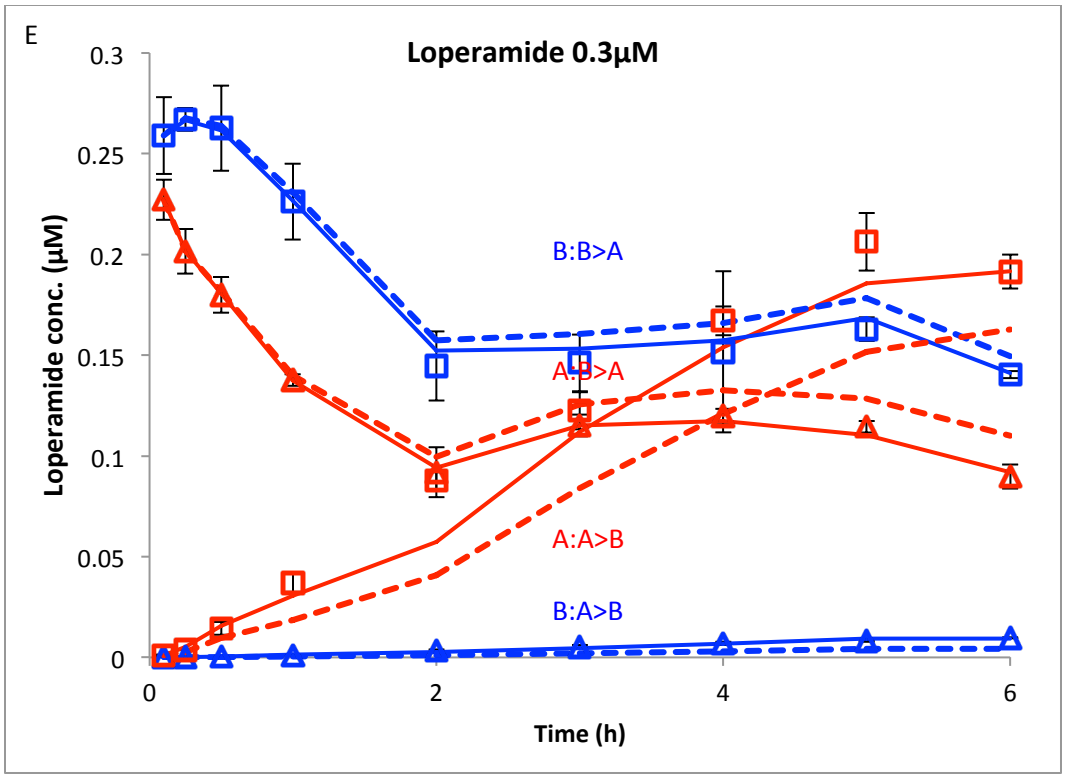
Supplemental Figure 2: Transport data of quinidine with initial concentration of 30µM (A), 10µM (B), 1µM (C), 0.3µM (D) and 0.1µM (E) over 6 hours and their fitted curves across Caco-2 cell monolayers. The symbols show the data points with error bars showing the standard deviation of triplicate experimental measurement. The lines show the best fits for drugs assuming there are no other transporters. A:B>A denotes the substrate concentration in the apical chamber when the basolateral chamber is the donor, while B:B>A denotes the substrate concentration remaining in the donor basolateral chamber. The A:B>A transport is high because P-gp actively effluxes drug into the apical chamber. The B:A>B denotes the substrate concentration in the basolateral chamber when apical chamber is the donor, while A:A>B denotes the substrate concentration remaining in the donor apical chamber.

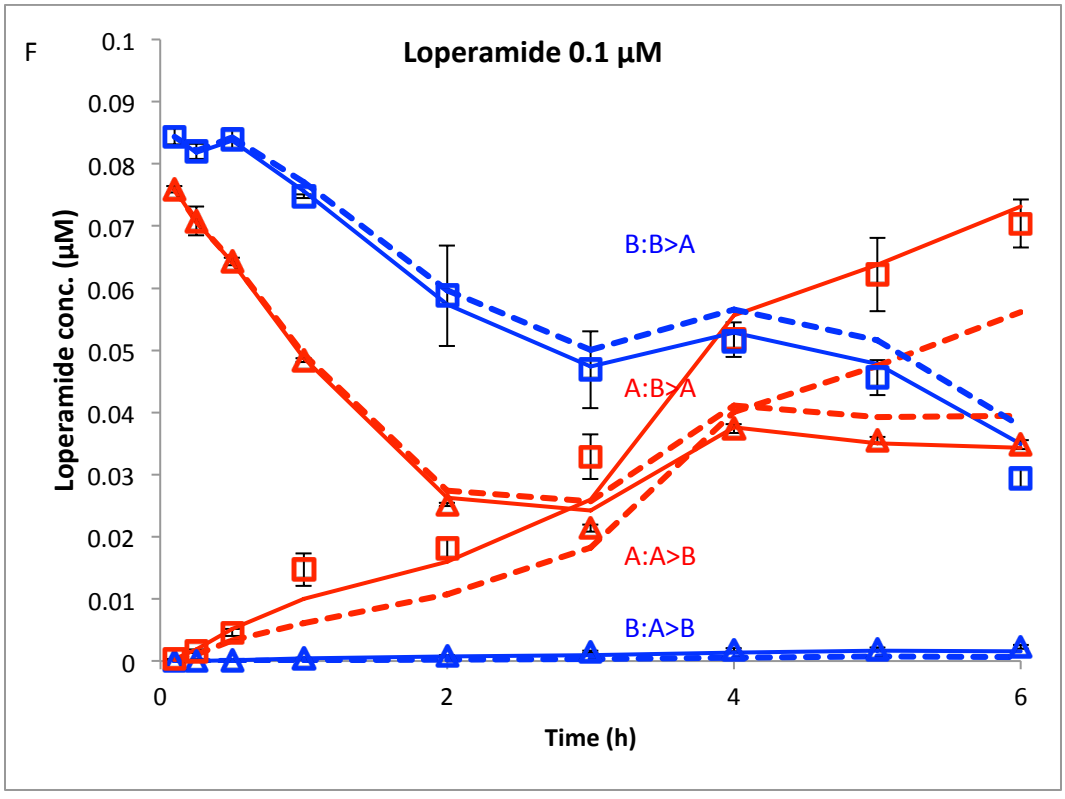

A
Loperamide 30µM
Loperamide conc. (µM)
Time (h)
B:B>A
A:B>A
A:A>B
B:A>B
0
5
10
15
20
25
30
35
40
0
2
4
6


B
Loperamide 10µM
Loperamide conc. (µM)
Time (h)
B:B>A
A:B>A
A:A>B
B:A>B
0
2
4
6
8
10
12
0
2
4
6

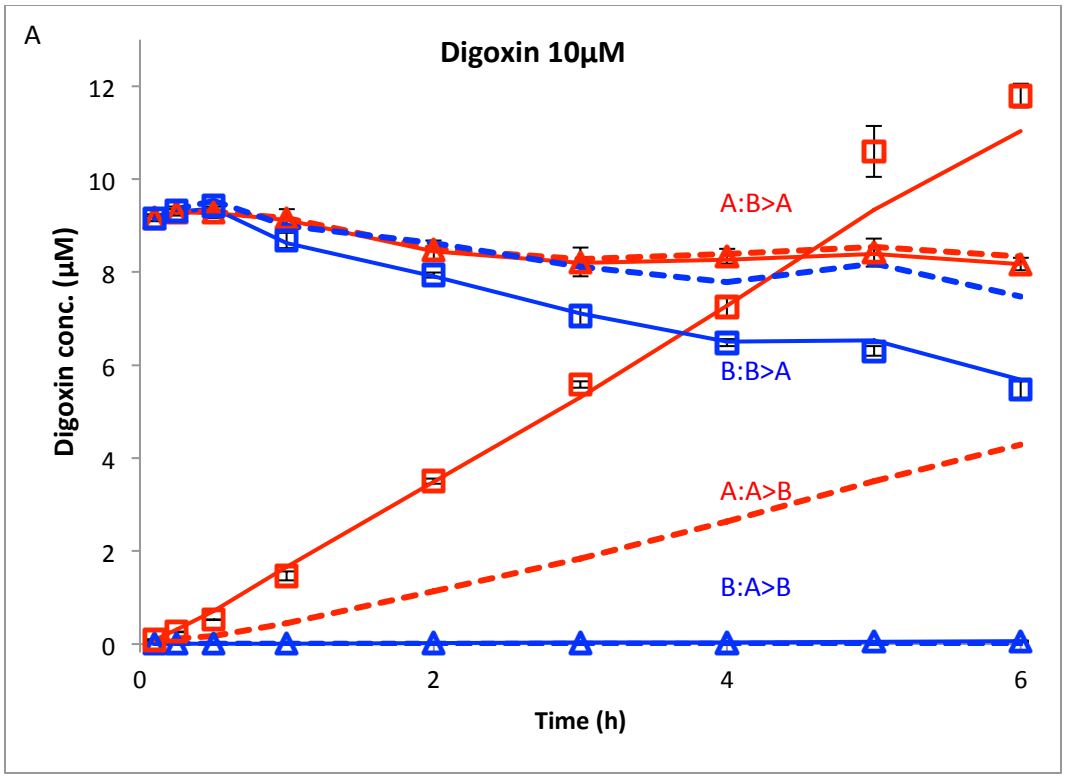

C
Loperamide 3µM
Loperamide conc. (µM)
Time (h)
B:B>A
A:B>A
A:A>B
B:A>B
0
0.5
1
1.5
2
2.5
3
3.5
4
0
2
4
6

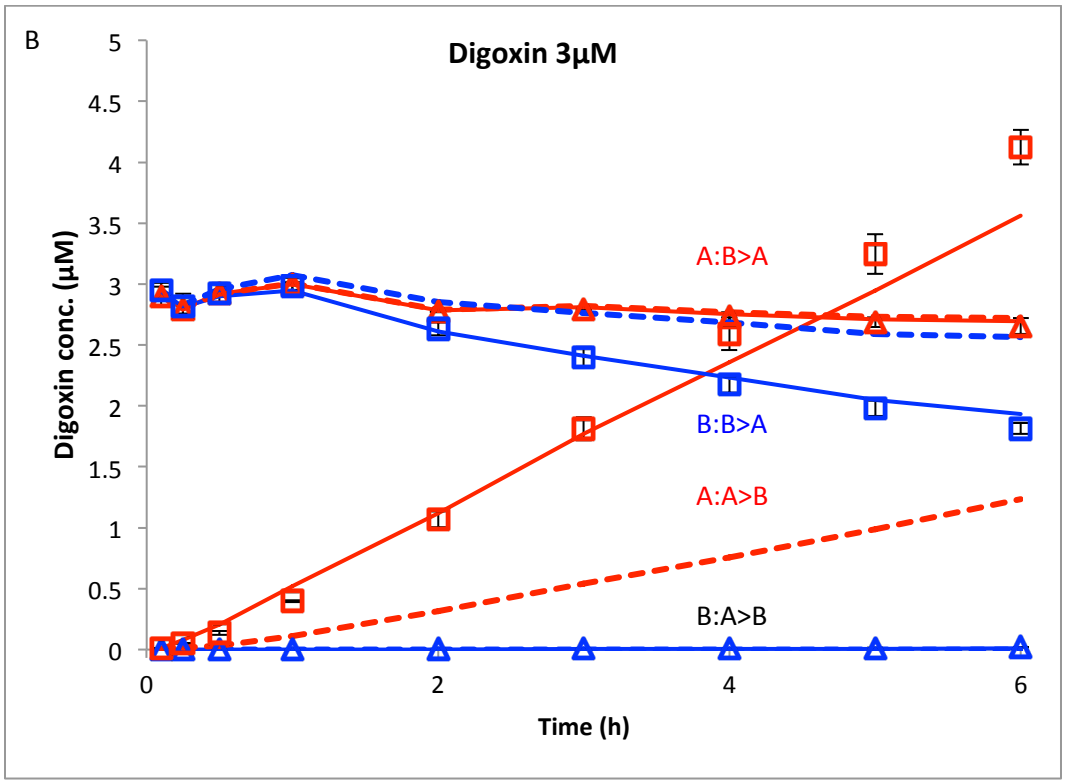

D
Loperamide 1µM
Loperamide conc. (µM)
Time (h)
B:B>A
A:B>A
A:A>B
B:A>B
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1
0
2
4
6

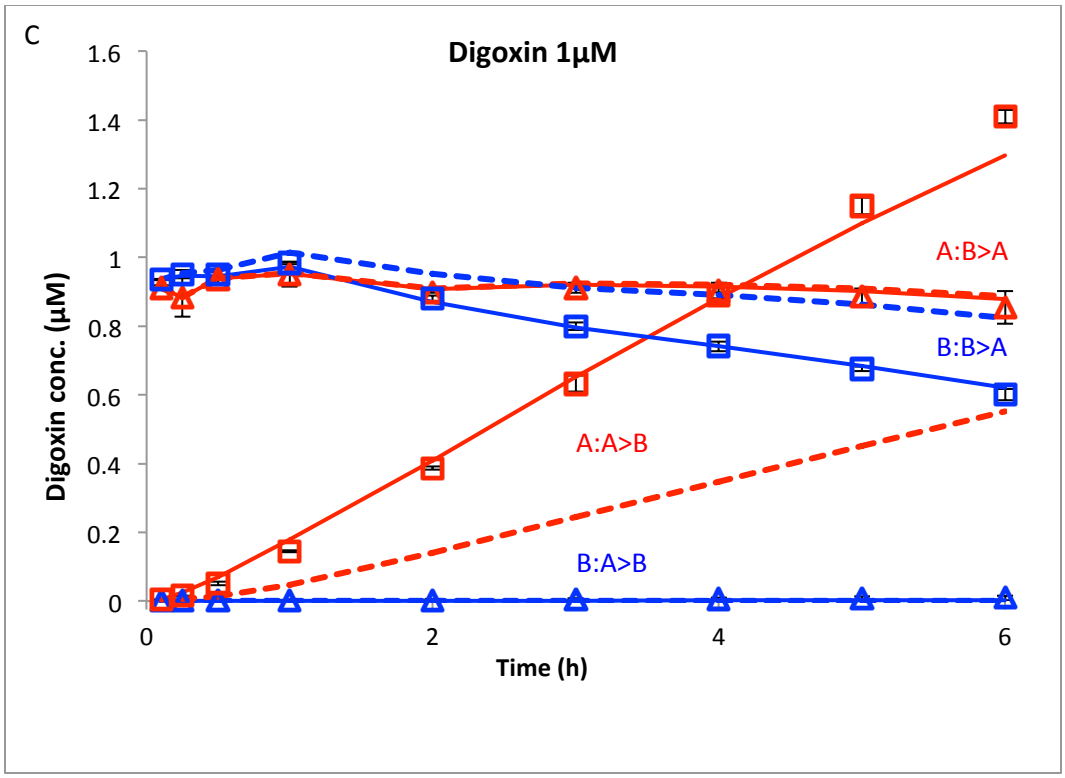

E
Loperamide 0.3µM
Loperamide conc. (µM)
0.3
0.25
0.2
0.15
0.1
0.05
0
0
2
4
6
Time (h)
B:B>A
A:B>A
A:A>B
B:A>B

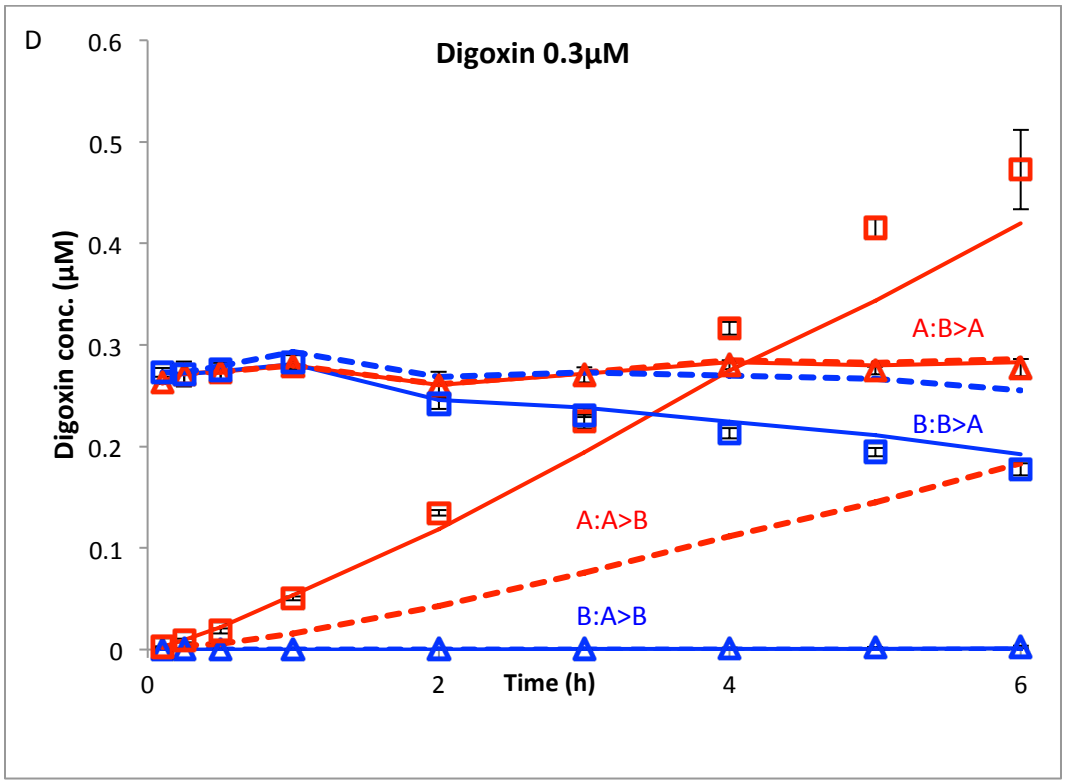

F
Loperamide 0.1 µM
Loperamide conc. (µM)
0.1
0.09
0.08
0.07
0.06
0.05
0.04
0.03
0.02
0.01
0
0
2
4
6
Time (h)
B:B>A
A:B>A
A:A>B
B:A>B

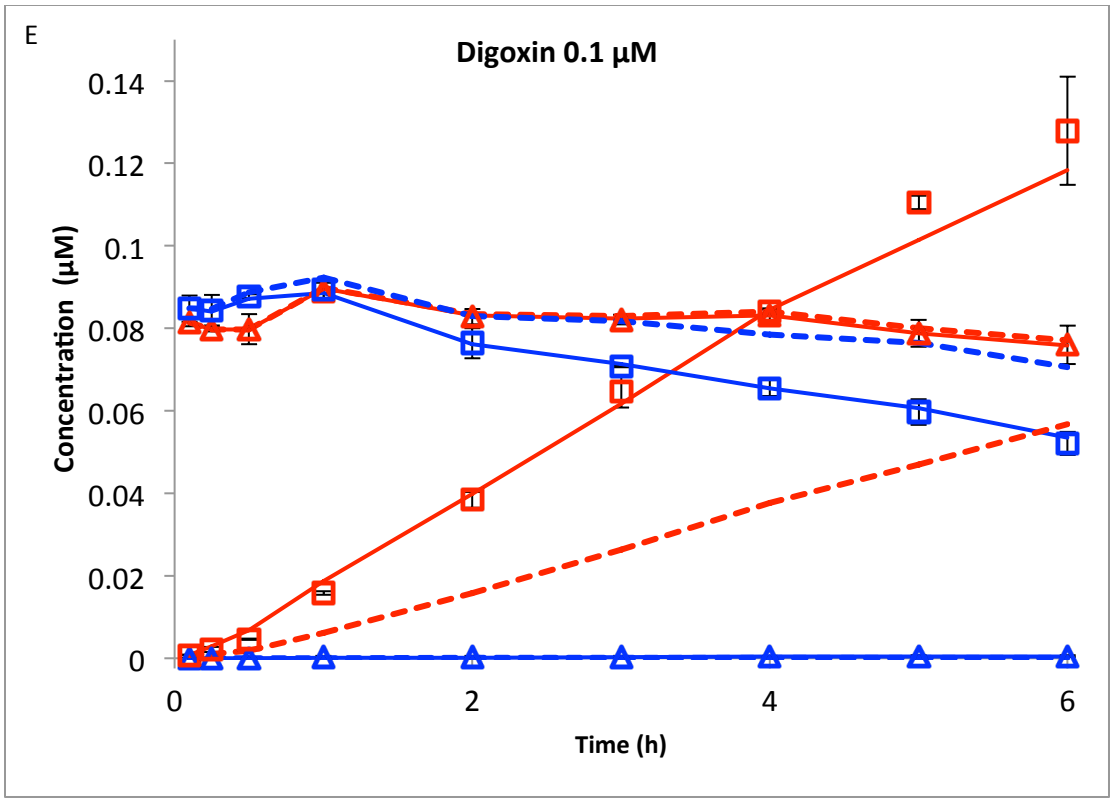
Supplemental Figure 3: Loperamide transport data with initial concentrations of 30μM (A), 10μM (B), 3μM (C), 1μM (D), 0.3μM (E) and 0.1 μM (F) fitted with and without a basolateral transporter. The symbols show the data points with error bars showing the standard deviation of triplicate measurements. The fits for P-gp alone are shown by a dashed line, whereas the solid line shows the effect of adding a basolateral uptake transporter modeled with first-order clearance. Loperamide shows an underestimate of the data for P-gp alone.


A
Digoxin 10µM
Digoxin conc. (µM)
Time (h)
A:B>A
B:B>A
A:A>B
B:A>B
0
2
4
6
8
10
12


B
Digoxin 3µM
Digoxin conc. (µM)
Time (h)
A:B>A
B:B>A
A:A>B
B:A>B
0
0.5
1
1.5
2
2.5
3
3.5
4
4.5
5


C
Digoxin 1µM
Digoxin conc. (µM)
Time (h)
A:B>A
B:B>A
A:A>B
B:A>B
0
0.2
0.4
0.6
0.8
1
1.2
1.4
1.6
0
2
4
6


D
Digoxin 0.3µM
Digoxin conc. (µM)
Time (h)
A:B>A
B:B>A
A:A>B
B:A>B
0
0.1
0.2
0.3
0.4
0.5
0.6
0
2
4
6



Supplemental Figure 4: Digoxin transport data with initial concentrations of 10µM (A), 3µM (B), 1µM (C), 0.3µM (D) and 0.1µM (E) fitted with and without a basolateral transporter. The symbols show the data points with error bars showing the standard deviation of triplicate measurements. The fits for P-gp alone are shown by a dashed line, whereas the solid line shows the effect of adding a basolateral uptake transporter modeled with first-order clearance. Digoxin show an underestimate of the data for P-gp alone.