

Enteric reabsorption: influence on drug pharmacokinetics depending on the underlying mechanism

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SUPPLEMENTARY INFORMATION

1. TABLES

Table Ia – Parameters implemented for the sensitivity analysis in the EHR model. Included as: mean values (standard deviation). A log-normal distribution was assumed for all rate constants. The volume of distribution for the central compartment was set to 10 L.

Drug	k_h (h^{-1})	k_g (h^{-1})	k_r (h^{-1})	k_a (h^{-1})	k_{ch} (h^{-1})	k_{hc} (h^{-1})	k_{cg} (h^{-1})	k_{gh} (h^{-1})	k_{hb} (h^{-1})
A	1.1 (0.2)	0.06 (0.2)	0.01 (0.2)	1.5 (0.3)	0.3 (0.1)	2.5 (0.1)	0.2 (0.1)	0.2 (0.1)	1.0 (1.0)
B	7.0 (0.2)	0.2 (0.2)	0.07 (0.2)	1.5 (0.3)	1.0 (0.1)	1.5 (0.1)	0.2 (0.1)	1.0 (0.1)	3.0 (1.0)
C	0.35 (0.2)	0.0	0.4 (0.2)	1.5 (0.3)	1.0 (0.1)	2.5 (0.1)	0.2 (0.1)	0.5 (0.1)	1.0 (1.0)

Table Ib – Parameters implemented for the sensitivity analysis in the EGR model. Included as: mean values (standard deviation). A log-normal distribution was assumed for all rate constants. The volume of distribution for the central compartment was set to 10 L.

Drug	k_h (h^{-1})	k_g (h^{-1})	k_r (h^{-1})	k_a (h^{-1})	k_{ch} (h^{-1})	k_{hc} (h^{-1})	k_{cg} (h^{-1})	k_{gh} (h^{-1})	k_s (h^{-1})	k_{sc} (h^{-1})	k_{cs} (h^{-1})	k_{sh} (h^{-1})
A	1.0 (0.2)	0.25 (0.2)	0.03 (0.2)	1.5 (0.3)	1.0 (0.1)	2.5 (0.1)	0.2 (0.1)	0.1 (0.1)	0.5 (1.0)	0.5 (0.1)	0.15 (0.1)	0.1 (0.1)
B	5.0 (0.2)	0.5 (0.2)	0.15 (0.2)	1.5 (0.3)	1.0 (0.1)	1.5 (0.1)	0.2 (0.1)	1.0 (0.1)	0.5 (1.0)	0.5 (0.1)	1.5 (0.1)	0.1 (0.1)
C	0.3 (0.2)	0.0	0.4 (0.2)	1.5 (0.3)	1.0 (0.1)	2.5 (0.1)	0.2 (0.1)	0.1 (0.1)	0.5 (1.0)	0.5 (0.1)	0.15 (0.1)	0.1 (0.1)

2. R-SCRIPTS AND MLXTRAN CODE TO IMPLEMENT SIMULATIONS FOR MODELS EHR AND EGR AFTER ORAL AND INTRAVENOUS ADMINISTRATION

R-script enterohepatic reabsorption model

```
### Enterohepatic reabsorption model (EHR) ###
```

```
library(mlxR)
```

```
# Defining parameter values for the following constant rates (h-1)
```

```
k41 <- 1.5    # absorption & reabsorption from the gastrointestinal compartment
```

```
k40 <- 0.06   # intestinal elimination
```

```
k42 <- 0.2    # hepatic uptake of drug coming from the gastrointestinal compartment through  
portal venous blood
```

```
k12 <- 0.3    # hepatic drug uptake from systemic circulation
```

```
k14 <- 0.2    # enterocyte uptake from systemic circulation
```

```
k10 <- 0.01   # renal elimination
```

```
k21 <- 2.5    # liver-to-central transference
```

```
k20 <- 1.1    # hepatic elimination
```

```
k23 <- 1      # hepatobiliary secretion
```

```
Bb <- 50      # gallbladder release
```

```
# Defining value for the volume of distribution of the central compartment (L)
```

```
V1 <- 10
```

```
# Steps for gallbladder release
```

```
d1 <- 8
```

```
d2 <- 0.2
```

```
d3 <- d1+d2
```

```
step1 <- list(time=seq(d1,300,by=d3), amount=1, adm=1)
```

```
step2 <- list(time=seq(d3,300,by=d3), amount=-1, adm=1)
```

```
# Defining treatment
```

```
dose <- list(time=0, amount=100, adm=2)
```

```
# Parameter vector for inclusion in simulx
```

```
p <- c(ka = k41,
```

```
      kel_g = k40,
```

```
      kg_l = k42,
```

```

kc_l = k12,
kc_g = k14,
kel_r = k10,
kl_c = k21,
kel_l = k20,
khb = k23,
B = Bb,
Vc = V1
)
# Output definition
f <- list(name = c('Ac','Cc','Agb','Aliv','Agut','AUCgut','Fr','AUC','Eren','Eliv','Egut','Relgb'),
          time=seq(0,96,by=0.1))
# Performing simulation for intravenous bolus administration
IV_EHC <- simulx(model= "Supp_EHCmodel_IV.txt",
                 treatment= list(step1, step2, dose),
                 parameter = p,
                 output = f)
# Ploting
A <- cbind(IV_EHC$Ac, IV_EHC$Agb['Agb'], IV_EHC$Aliv['Aliv'],IV_EHC$Agut['Agut'])
D <- melt(A, id="time", value.name = "amount", variable.name = "compartment")
ggplot(data=res$Relgb) + geom_line(aes(x=time, y=Relgb), size=1, color="red") # Gallbladder
release pattern
ggplot(D, aes(time, amount,colour=compartment)) + geom_line() +
  facet_wrap(~compartment,scales="free") +
  labs(x="Time (h)", y="Amount (mg)") # Amounts vs time

# Performing simulation for oral administration
PO_EHC <- simulx(model= "Supp_EHCmodel_PO.txt",
                 treatment= list(step1, step2, dose),
                 parameter = p,
                 output = fo)

```

Mlxtran code for intravenous administration into the EHR model (Supp_EHCmodel_IV.txt)

[LONGITUDINAL]

input= {ka, kel_g, kg_l, kc_l, kl_c, kel_l, khb, kc_g, kel_r, B, Vc}

PK:

compartment(cmt=1, amount=Relgb)

compartment(cmt=2, amount=Ac)

iv(adm=1, cmt=1)

iv(adm=2, cmt=2)

EQUATION:

odeType = stiff

t0 = 0

Relgb_0 = 0

ddt_Relgb=0

$$\text{ddt_Agut} = \text{Relgb} \cdot B \cdot \text{Agb} + \text{kc_g} \cdot \text{Ac} - (\text{ka} + \text{kg_l} + \text{kel_g}) \cdot \text{Agut}$$

$$\text{ddt_Ac} = \text{ka} \cdot \text{Agut} + \text{kl_c} \cdot \text{Aliv} - (\text{kc_l} + \text{kel_r} + \text{kc_g}) \cdot \text{Ac}$$

$$\text{ddt_Aliv} = \text{kg_l} \cdot \text{Agut} + \text{kc_l} \cdot \text{Ac} - (\text{kel_l} + \text{kl_c} + \text{khb}) \cdot \text{Aliv}$$

$$\text{ddt_Agb} = \text{khb} \cdot \text{Aliv} - \text{Relgb} \cdot B \cdot \text{Agb}$$

$$\text{ddt_Eren} = \text{kel_r} \cdot \text{Ac}$$

$$\text{ddt_Egut} = \text{kel_g} \cdot \text{Agut}$$

$$\text{ddt_Eliv} = \text{kel_l} \cdot \text{Aliv}$$

$$\text{ddt_Fr} = \text{ka} \cdot \text{Agut}$$

$$\text{Cc} = \text{Ac} / \text{Vc}$$

$$\text{ddt_AUCgut} = \text{Agut}$$

$$\text{ddt_AUC} = \text{Cc}$$

Mlxtran code for oral administration into the EHR model

(Supp_EHCmodel_PO.txt)

[LONGITUDINAL]

input= {ka, kel_g, kg_l, kc_l, kl_c, kel_l, khb, kc_g, kel_r, B, Vc}

PK:

compartment(cmt=1, amount=Relgb)

compartment(cmt=2, amount=Ac)

compartment(cmt=3, amount = Agut)

iv(adm=1, cmt=1)

iv(adm=2, cmt=3)

EQUATION:

odeType = stiff

t0 = 0

Relgb_0 = 0

ddt_Relgb=0

$$\text{ddt_Agut} = \text{Relgb} \cdot B \cdot \text{Agb} + \text{kc_g} \cdot \text{Ac} - (\text{ka} + \text{kg_l} + \text{kel_g}) \cdot \text{Agut}$$

$$\text{ddt_Ac} = \text{ka} \cdot \text{Agut} + \text{kl_c} \cdot \text{Aliv} - (\text{kc_l} + \text{kel_r} + \text{kc_g}) \cdot \text{Ac}$$

$$\text{ddt_Aliv} = \text{kg_l} \cdot \text{Agut} + \text{kc_l} \cdot \text{Ac} - (\text{kel_l} + \text{kl_c} + \text{khb}) \cdot \text{Aliv}$$

$$\text{ddt_Agb} = \text{khb} \cdot \text{Aliv} - \text{Relgb} \cdot B \cdot \text{Agb}$$

$$\text{ddt_Eren} = \text{kel_r} \cdot \text{Ac}$$

$$\text{ddt_Egut} = \text{kel_g} \cdot \text{Agut}$$

$$\text{ddt_Eliv} = \text{kel_l} \cdot \text{Aliv}$$

$$\text{Cc} = \text{Ac} / \text{Vc}$$

$ddt_AUC_{gut} = A_{gut}$

$ddt_AUC = C_c$

R-script enterogastric reabsorption model

Enterogastric reabsorption model (EGR)

library(mlxR)

Defining parameter values for the following constant rates (h⁻¹)

$k_{51} <- 1.5$ # absorption & reabsorption from the gastrointestinal compartment

$k_{50} <- 0.25$ # intestinal elimination

$k_{52} <- 0.1$ # hepatic uptake of drug coming from the gastrointestinal compartment through portal venous blood

$k_{12} <- 1$ # hepatic drug uptake from systemic circulation

```

k15 <- 0.2    # enterocyte uptake from systemic circulation
k10 <- 0.03   # renal elimination
k21 <- 2.5    # liver-to-central transference
k20 <- 1      # hepatic elimination
k23 <- 1      # hepatobiliary secretion
k13 <- 0.15   # parietal cell uptake from cental compartment
k31 <- 0.5    # parietal cell-to-central transference
k34 <- 0.5    # secretion of drug into the gastric lumen
k32 <- 0.1    # hepatic uptake from arterial irrigation
Bb <- 50      # stomach release

# Defining value for the volume of distribution of the central compartment (L)

V1 <- 10

# Steps for stomach release

d1 <- 8
d2 <- 0.2
d3 <- d1+d2
step1 <- list(time=seq(d1,50,by=d3), amount=1, adm=1)
step2 <- list(time=seq(d3,50,by=d3), amount=-1, adm=1)

# Defining treatment
dose <- list(time=0, amount=100, adm=2)

# Parameter vector for inclusion in simulx

p <- c(ka = k51,
      kgut = k50,

```

```

kg_l = k52,
kc_l = k12,
kc_g = k15,
kr = k10,
kl_c = k21,
kliv = k20,
kc_s = k13,
ks_c = k31,
ks_l = k32,
ks = k34,
B = Bb,
Vc = V1
)

# Output definition

f <- list(name = c('Ac', 'As', 'Aliv', 'Aig', 'Agut', 'AUCgut', 'AUC', 'Eren', 'Eliv', 'Egut', 'Relgb'),
          time=seq(0,50,by=0.1))

# Performing simulation for intravenous bolus administration

IV_EGC <- simulx(model= "Supp_EGCmodel_IV.txt",
                 treatment= list(step1, step2, dose),
                 parameter = p,
                 output = f)

# Ploting

A <- cbind(res$Ac, res$As['As'], res$Aliv['Aliv'], res$Agut['Agut'], res$Aig['Aig'])

```

```
D <- melt(A, id="time", value.name = "amount", variable.name = "compartment")
```

```
ggplot(data=res$Relst) + geom_line(aes(x=time, y=Relst), size=1, color="red") # Stomach release  
pattern
```

```
ggplot(D, aes(time, amount, colour=compartment)) + geom_line() +  
  facet_wrap(~compartment, scales="free") +  
  labs(x="Time (h)", y="Amount (mg)") # Amounts vs time
```

```
# Performing simulation for oral administration
```

```
PO_EGC <- simulx(model= "Supp_EGCmodel_PO.txt",  
  treatment= list(step1, step2, dose),  
  parameter = p,  
  output = fo)
```

Mlxtran code for intravenous administration into the EHR model

(Supp_EGCmodel_IV.txt)

[LONGITUDINAL]

```
input= {ka, kgut, kg_l, kl_c, kliv, kc_l, kc_g, kc_s, ks_c, ks_l, ks, B, Vc, kr}
```

PK:

```
compartment(cmt=1, amount=Relst)
```

```
compartment(cmt=2, amount=Ac)
```

```
iv(adm=1, cmt=1)
```

```
iv(adm=2, cmt=2)
```

EQUATION:

odeType = stiff

t0 = 0

Relgb_0 = 0

ddt_Relst=0

ddt_Agut = -(ka+kgut+kg_l)*Agut + Relst*B*Ajg + kc_g*Ac

ddt_Ac = ka*Agut+kl_c*Aliv+ks_c*As-(kc_l+kc_g+kc_s+kr)*Ac

ddt_Aliv = kc_l*Ac +ks_l*As - (kl_c+kliv)*Aliv + kg_l*Agut

ddt_As = kc_s*Ac - (ks_c+ks_l+ks)*As

ddt_Ajg = ks*As- Relst*B*Ajg

Cc = Ac / Vc

ddt_AUCgut = Agut

ddt_AUC = Cc

ddt_Eren = kr*Ac

ddt_Egut = kgut*Agut

ddt_Eliv = kliv*Aliv

Mlxtran code for oral administration into the EHR model

(Supp_EGCmodel_PO.txt)

[LONGITUDINAL]

input= {ka, kgut, kg_l, kl_c, kliv, kc_l,kc_g,kc_s,ks_c,ks_l, ks, B, Vc, kr}

PK:

compartment(cmt=1, amount=Relst)

compartment(cmt=2, amount=Ac)

compartment(cmt=3, amount = Agut)

iv(adm=1, cmt=1)

iv(adm=2, cmt=3)

EQUATION:

odeType = stiff

t0 = 0

Relst_0 = 0

ddt_Relst=0

ddt_Agut = -(ka+kgut+kg_l)*Agut + Relst*B*Ajg + kc_g*Ac

ddt_Ac = ka*Agut+kl_c*Aliv+ks_c*As-(kc_l+kc_g+kc_s+kr)*Ac

ddt_Aliv = kc_l*Ac +ks_l*As - (kl_c+kliv)*Aliv + kg_l*Agut

ddt_As = kc_s*Ac - (ks_c+ks_l+ks)*As

ddt_Ajg = ks*As- Relst*B*Ajg

Cc = Ac / Vc

ddt_AUCgut = Agut

ddt_AUC = Cc

ddt_Eren = kr*Ac

ddt_Egut = kgut*Agut

ddt_Eliv = kliv*Aliv