Supplementary material

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Paxlovid-Tacrolimus Drug-Drug Interaction in a 23-Year Old Female Kidney Transplant Patient with COVID-19

Short title: Paxlovid-Tacrolimus drug-drug interaction in a kidney transplant patient with Covid-19

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Supplementary Material

The prior model used for Bayesian maximum aposteriori probability (MAP):

1- Mean values of pharmacokinetic parameters adjusted to fat free mass (FFM)

Clearance (CL) = 11.3 L/h
Volume of Central compartment (Vc) = 82.23 L
Intercompartmental clearance (Q) = 15.8 L/h
Absorption rate = 1.01 h^{-1}
Volume of Peripheral compartment= 422.73L
Lag time on absorption= 0.41 h

Clearance, Volume of Central compartment and Intercompartmental clearance were modeled as random effects, and absorption rate, Volume of Peripheral compartment were modeled as fixed effects.

2- Ω matrix (Variance-covariance matrix for random effects)

$$\begin{matrix} 0.63 & & \\ 0.29 & 0.73 & \\ 0.44 & 0 & 0.79 \end{matrix}$$

Elements on the diagonal are variances of CL [1,1] ,Vc [2,2] and Q [3,3]. Elements [2,1] and [3,1], are the covariance of CL with Vc, CL with Q, respectively.

R code for bayseian MAP estimation:

```
library(MASS)
library(mrgsolve)
library(mapbayr)

code <- "
$PARAM @annotated
TVCL:  11.3 : Clearance
TVVC: 82.23 : Central volume
V2  : 422.73 : Peripheral volume of distribution
TVQ   :  15.8 : Intercompartmental clearance
KA   : 1.01 : Absorption rate (h-1)
TVALAG1: 0.41 : lag time on absorption

ETA1: 0 : Clearance (L/h)
ETA2: 0 : Central volume (L)
ETA3: 0: Intercompartmental clearance



$OMEGA @block
0.63
0.29 0.73
0.44 0    0.79

$SIGMA
0.149 // proportional
0 // additive
$CMT @annotated
DEPOT : Depot () [ADM]
CENTRAL: Central (mcg/L)[OBS]
PERIPH: Peripheral compartment ()
$TABLE
double DV = (CENTRAL/VC) * (1 + EPS(1)) + EPS(2);

$MAIN
double CL = TVCL * exp(ETA1 + ETA(1)) ;
double VC  = TVVC  * exp(ETA(2) + ETA2) ;
double Q  = TVQ  * exp(ETA(3) + ETA3) ;


double K12 = Q / VC  ;
double K21 = Q / V2  ;

double K10 = CL / VC ;
$ODE
dxdt_CENTRAL   = KA * DEPOT+ K21 * PERIPH - (K10 + K12) * CENTRAL ;
dxdt_PERIPH =  K12 * CENTRAL - K21 * PERIPH ;
dxdt_DEPOT   = -KA * DEPOT;
$CAPTURE DV CL VC Q
"
my_model <- mcode("tac", code)
## Building tac ... done.
my_est <- my_model %>%
  adm_lines(time = 0, amt = 1500) %>%
  adm_lines(time = 12, amt = 1500) %>%
  adm_lines(time = 24, amt = 1000) %>%
  adm_lines(time = 48, amt = 1000) %>%
  adm_lines(time = 60, amt = 1000) %>%
  adm_lines(time = 72, amt = 1000) %>%
  adm_lines(time = 84, amt = 1000) %>%
```

```
adm_lines(time = 96, amt = 500) %>%
adm_lines(time = 108, amt = 500) %>%
adm_lines(time = 120, amt = 500) %>%
adm_lines(time = 144, amt = 500) %>%
obs_lines(time = 71, DV = 48.5) %>%
obs_lines(time = 95, DV = 100) %>%
obs_lines(time = 119, DV = 85.8) %>%
obs_lines(time = 143, DV = 62) %>%
mapbayest()
plot(my_est)
```