Electronic supplementary material *Clinical Pharmacokinetics*

Hyperinflammation reduces midazolam metabolism in critically ill adults with COVID-19

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Model code

; 1. Based on: 001h
; 2. Description: Midazolam
; x1. Author: SDTSassen

$PROBLEM PK model

$INPUT

  CENSOR
  ID
  DROP
  DROP
  TAS
  TAD
  TIME
  AMT=DROP
  AMT ; AMT in mol
  SS
  II
  RATE=DROP
  RATE ; RATE in mol
  DV=DROP
  DV ; DV in mol
  EVID
  MDV
  CMT
  GNDR
  HT
  WT
  AGE
  ALB
  CREA
  CRP
  IL6
  ASAT
  ALAT
  BILI
  TG
  AXA=DROP
  RASS=DROP
  INH=DROP
  IND=DROP

$DATA Mida2_db_230620_min_ery.csv IGNORE=C;

$SUBROUTINES ADVAN5 TRANS1

$MODEL

  NCOMPS=3
  COMP (CENTRAL,DEFDOSE)
  COMP (METAB1)
  COMP (METAB2)

$PK

  IF(CREA.EQ.-99)THEN
      COVCREA= 1
  ELSE
      COVCREA = ((CREA/96)**THETA(9))
  ENDIF

  IF(IL6.EQ.-99)THEN
      COVIL6= 1
  ELSE
COVIL6 = ((IL6/116.5)**THETA(8))

ENDIF

TVV = THETA(2)
V = TVV

TVCL = THETA(3)*COVIL6
CL = TVCL*EXP(ETA(1))

VO = THETA(4)
CLO = THETA(5)*EXP(ETA(3))
VG = THETA(6)

TVCLG = THETA(7)*COVCREA
CLG = TVCLG*EXP(ETA(2))

S1 = V/1000
S2 = VO/1000
S3 = VG/1000

k12 = CL/V
k23 = CLO/VO
k30 = CLG/VG

$THETA
(0, 0.6) ; 1 prop
(0, 130) ; 2 V
(0, 7.91) ; 3 CLM
(0, 200) ; 4 VO
(0, 45) ; 5 CLO
(0, 50) ; 6 VG
(0, 2) ; 7 CLG
(-10, 1) ; 8 IL6
(-10, 1) ; 9 Creat

$OMEGA BLOCK(1) 0.2 ; IIV CL
$OMEGA BLOCK(1) 0.4 ; IIV CLG
$OMEGA BLOCK(1) SAME ; IIV CLO

$SIGMA
1 FIX

$ERROR
IPRED = F
IRES = DV-IPRED
W = IPRED*THETA(1)
IWRES = IRES/W
Y= IPRED+W*ERR(1)

$EST METHOD=1 MAXEVAL=99999 SADDLE_RESET=1 SIG=3 PRINT=5 NOABORT POSTHOC INTERACTION

$COV PRINT= E UNCONDITIONAL
$TABLE ID IPRED TAS TAD IWRES CWRES EVID MDV CMT CREA IL6 CRP TIME NOPRINT ONEHEADER FILE=SDTAB002c
$TABLE ID CL V CLO VO CLG VG ETA1 TAS TIME NOPRINT ONEHEADER FILE=PATAB002c
$TABLE ID NOPRINT ONEHEADER FILE=COTAB002c ; $TABLE ID NOPRINT ONEHEADER FILE=CATAB
Figure S1: Goodness-of-fit plots of the final model. Conditional weighted residuals versus time after midazolam continuous infusion of midazolam, 1-OH-midazolam and 1-OH-midazolam-glucuronide
Figure S2: Goodness-of-fit plots of the final model. Individual weighted residuals versus time after midazolam continuous infusion of midazolam, 1-OH-midazolam and 1-OH-midazolam-glucuronide

Midazolam

1-OH-midazolam

1-OH-midazolam-glucuronide
Figure S3: Goodness-of-fit plots of the final model. Conditional weighted residuals of midazolam versus IL-6 concentrations.
Figure S4: Goodness-of-fit plots of the final model. Conditional weighted residuals of 1-OH-midazolam-glucuronide versus creatinine concentrations.
Figure S5: Individual midazolam clearance versus IL-6 concentrations. This figure is plotted with only IL-6 values were also a midazolam observation has been measured, excluding one outlier of IL-6 2500 pg/mL.
Figure S6: Individual 1-OH-midazolam-glucuronide clearance versus creatinine concentrations