

Electronic supplementary material *Clinical Pharmacokinetics*

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

Tim JL Smeets¹, Abraham J Valkenburg², Mathieu van der Jagt², Birgit CP Koch¹,
Henrik Endeman², Diederik AMPJ Gommers², Sebastian DT Sassen¹, Nicole GM
Hunfeld^{1,2}

¹ Department of Hospital Pharmacy, Erasmus MC University Medical Center
Rotterdam, Doctor Molewaterplein 40, 3015 GD Rotterdam, the Netherlands

² Department of Intensive Care Adults, Erasmus MC University Medical Center
Rotterdam, Doctor Molewaterplein 40, 3015 GD Rotterdam, the Netherlands

Corresponding author: t.smeets@erasmusmc.nl

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= 96  
ELSE  
    COVCREA = ((CREA/96)**THETA(9))  
ENDIF  
  
IF(IL6.EQ.-99)THEN  
    COVIL6= 116.5  
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)

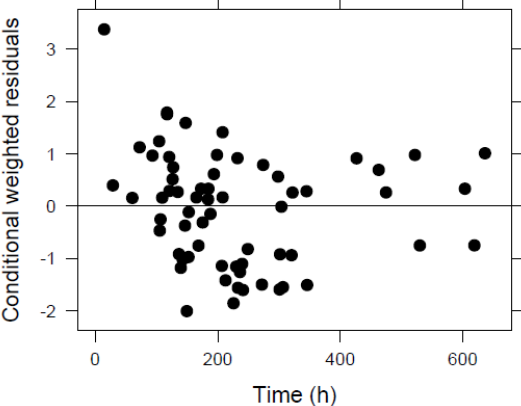
$EST METHOD=1 MAXEVAL=99999 SADDLE_RESET=1 SIG=3 PRINT=5 NOABORT POSTHOC
INTERACTION

$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

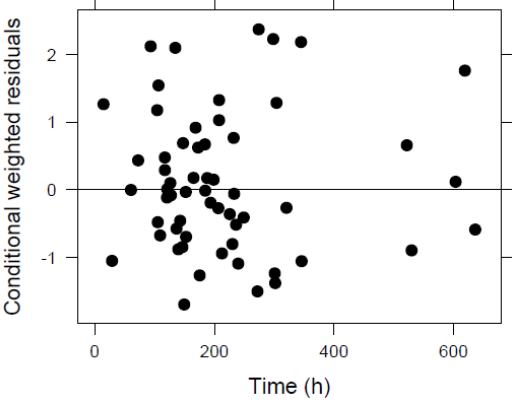
```

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

Midazolam



1-OH-midazolam



1-OH-midazolam-glucuronide

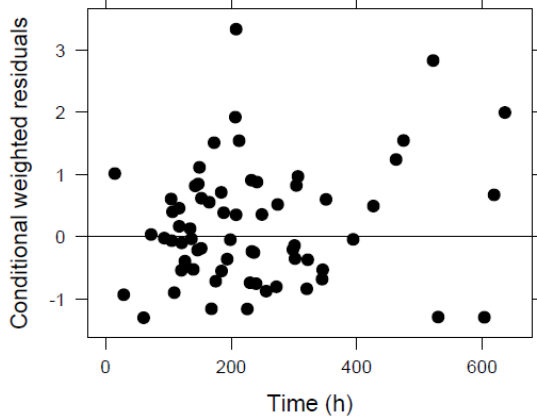
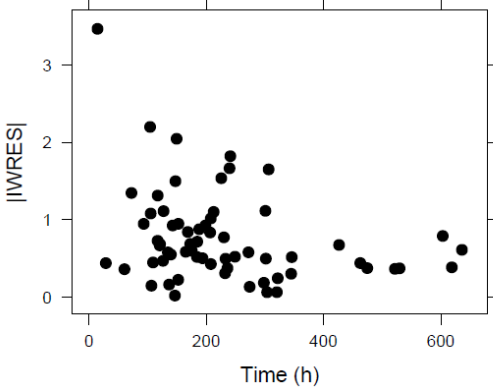
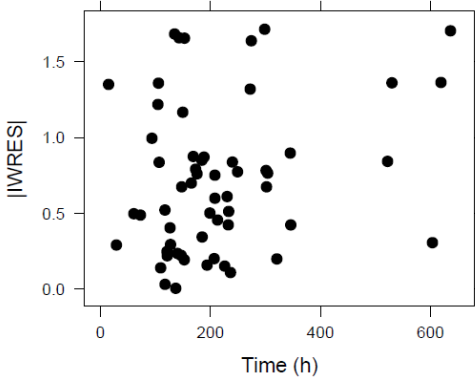


Figure S2: Goodness-of-fit plots of the final model. Individual weighted residuals versus time after midazolam continuous infusion of midazolam, 1-OH-midazolam and 1-OH-midazolam-glucuronide

Midazolam



1-OH-midazolam



1-OH-midazolam-glucuronide

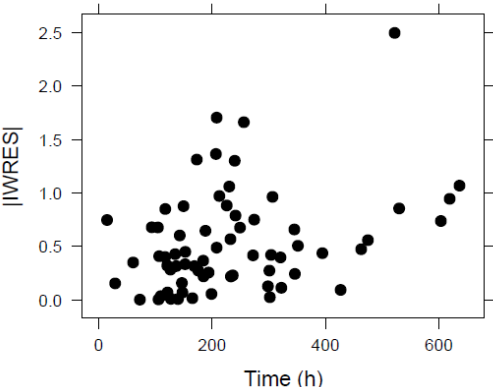


Figure S3: Goodness-of-fit plots of the final model. Conditional weighted residuals of midazolam versus IL-6 concentrations

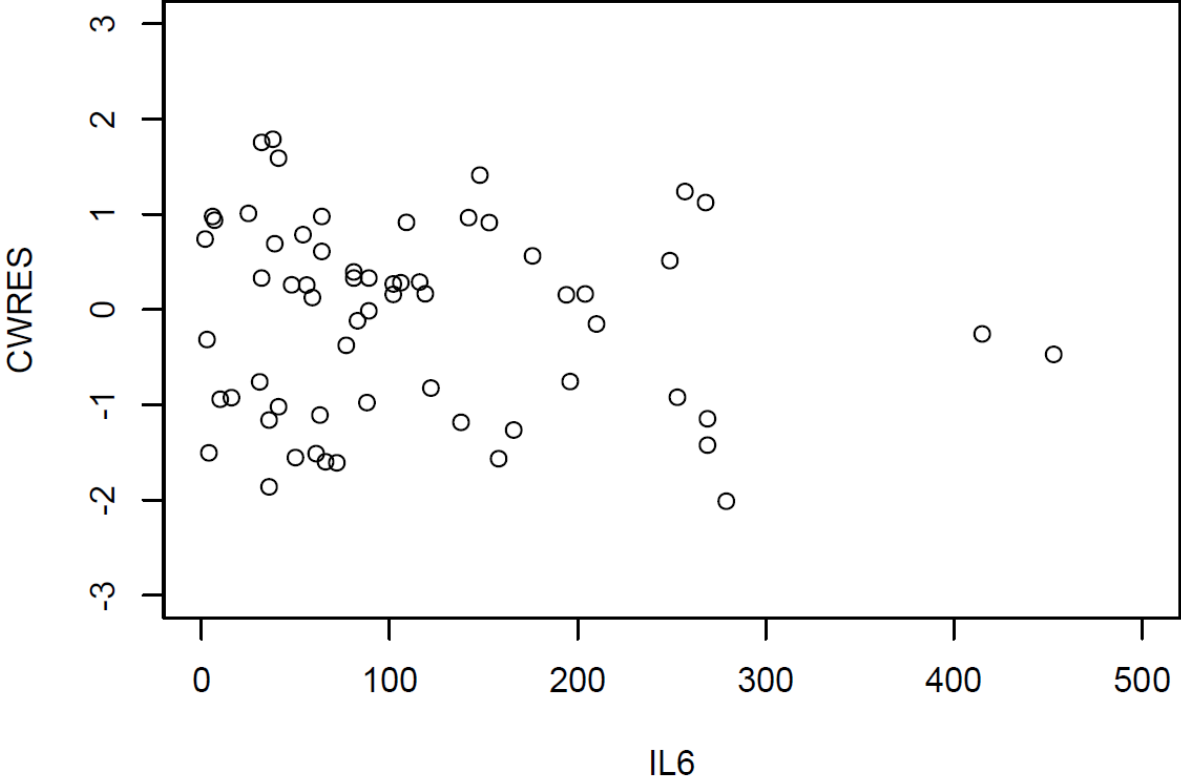


Figure S4: Goodness-of-fit plots of the final model. Conditional weighted residuals of 1-OH-midazolam-glucuronide versus creatinine concentrations

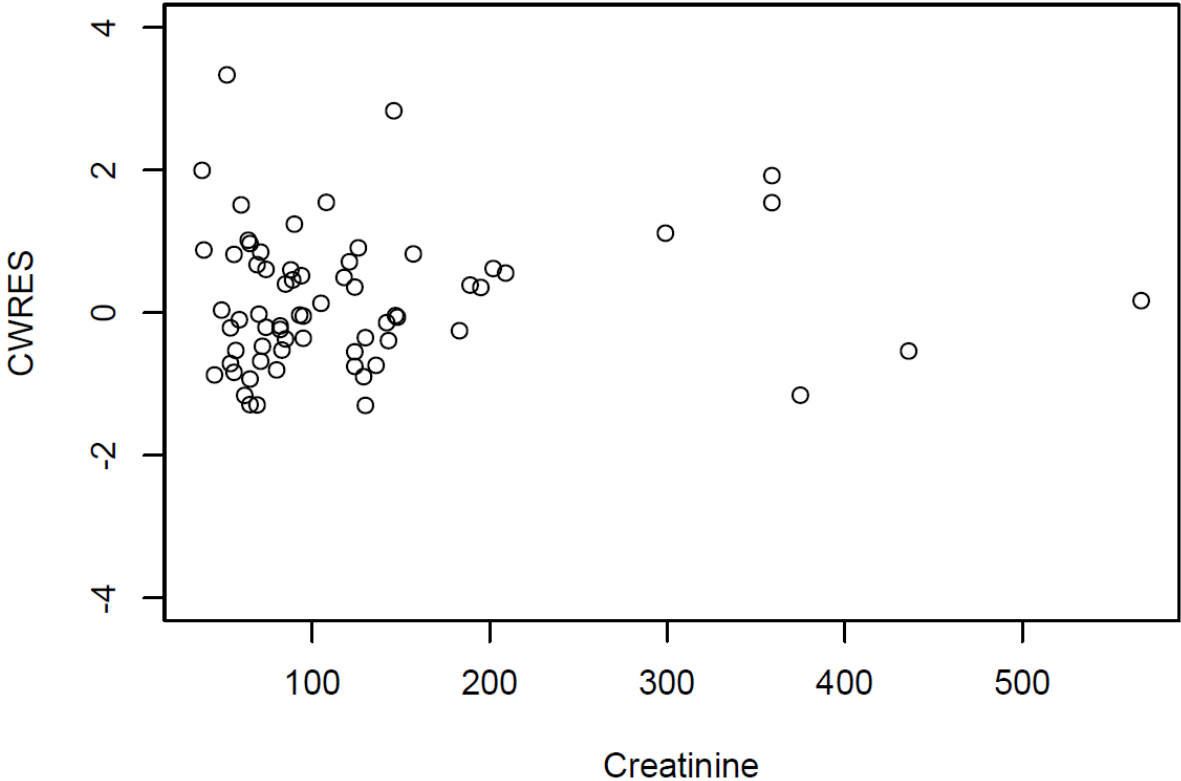


Figure S5: Individual midazolam clearance versus IL-6 concentrations. This figure is plotted with only IL-6 values were also a midazolam observation has been measured, excluding one outlier of IL-6 2500 pg/mL.

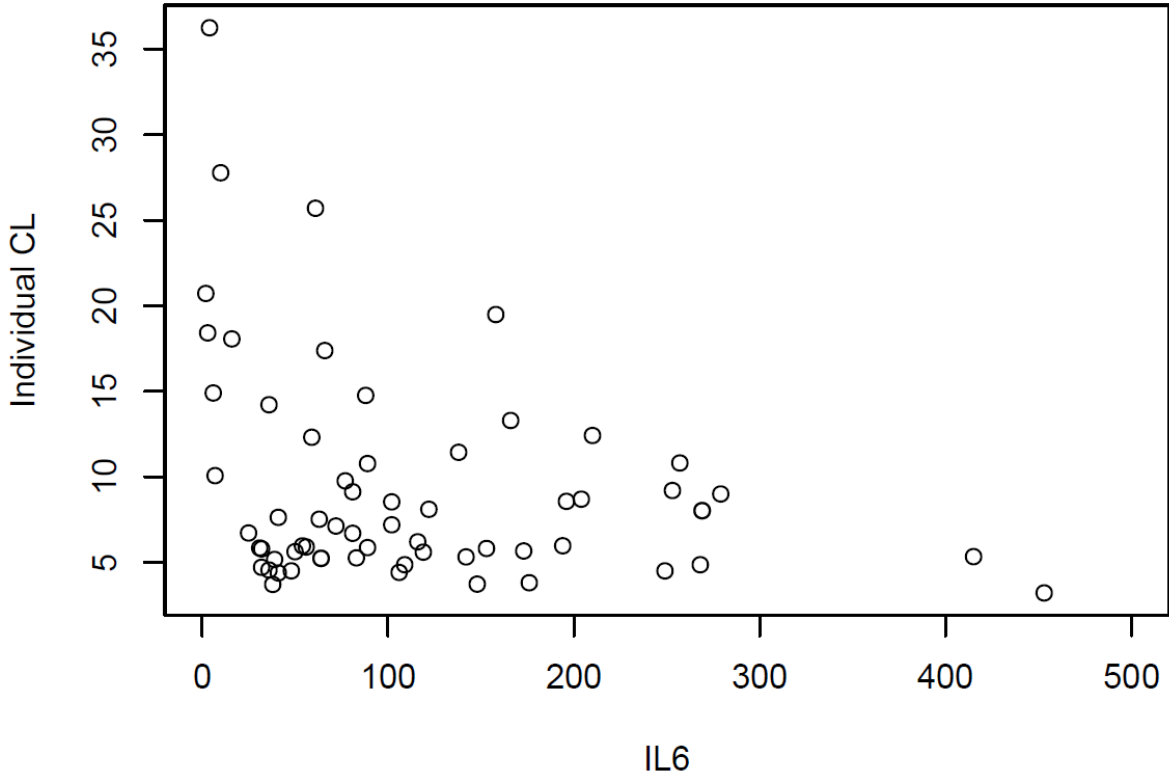


Figure S6: Individual 1-OH-midazolam-glucuronide clearance versus creatinine concentrations

