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;DATE:      12/06/18
;DRUG/S:    S-KETAMINE + NORKETAMINE + TICLOPIDINE
;MODEL:     KETAMINE + NORKETAMINE + TICLOPIDINE + DRUG-DRUG-INTERACTION MODEL

;-------------------------------------------------------------------------
$PROBLEM    KETAMINE/NORKETAMINE/TICLOPIDINE/INTERACTION MODEL

;-------------------------------------------------------------------------
$INPUT      ID PHASE=DROP TICLO FLAG=DROP TIME DV AMT ADDL II CMT RATE MDV EVID
WTKG SEXF=DROP

;-------------------------------------------------------------------------
$DATA       data.csv IGNORE=@

;-------------------------------------------------------------------------
$SUBROUTINE ADVAN13 TRANS1 TOL=6

;-------------------------------------------------------------------------
; UNITS
;  Time - hours
;  Dose - mg
;  Cp     - ng/ml = mcg/L
;  Clearances - L/hour
;  Volumes - L

;-------------------------------------------------------------------------
$MODEL
COMP=(KDEPOT)                          ; 1 Ketamine depot
COMP=(CENTRAL)                         ; 2 Ketamine central
COMP=(PERIPH1)                         ; 3 Ketamine peripheral shallow
COMP=(PERIPH2)                         ; 4 Ketamine peripheral deep
COMP=(NKCENT)                          ; 5 Norketamine central
COMP=(PERIM)                           ; 6 Norketamine peripheral
COMP=(TDEPOT)                          ; 7 Ticlopidine depot
COMP=(TGUTWALL)                        ; 8 Ticlopidine gutwall
COMP=(TPV)                             ; 9 Ticlopidine portal vein
COMP=(TLIVER)                          ; 10 Ticlopidine liver
COMP=(TCENT)                           ; 11 Ticlopidine central
COMP=(TPERIPH)                         ; 12 TIclopidine peripheral
COMP=(TT1)                             ; 13 Ticlopidine transit 1
COMP=(TT2)                             ; 14 Ticlopidine transit 2
COMP=(TT3)                             ; 15 Ticlopidine transit 3
COMP=(TT4)                             ; 16 Ticlopidine transit 4

;-------------------------------------------------------------------------
$PK
; Ketamine model

KV1 = THETA(1)                         ; Ketamine: volume of central comp.
KQ = THETA(2)                          ; Ketamine: central to peripheral clearance
KV2 = THETA(3)*EXP(ETA(1))             ; Ketamine: volume of periph comp.
KKA = THETA(4)*EXP(ETA(2))             ; Ketamine: absorption rate constant
KCLINTH1 = THETA(5)*EXP(ETA(3))        ; Ketamine: intrinsic hepatic clearance
KV3 = THETA(6)                         ; Ketamine: volume of peripheral 2
KQ2 = THETA(7)                         ; Ketamine: clearance to peripheral 2
KCLINTG1 = THETA(8)*EXP(ETA(4))        ; Ketamine: intrinsic gutwall clearance
KCLP = THETA(9)                        ; Ketamine: permeability clearance

;-------------------------------------------------------------------------
; Norketamine model

NKV5 = THETA(10)                       ; Norketamine: volume of central
NKQ3 = THETA(11)                       ; Norketamine: central to peripheral cl
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NKV6 = THETA(12)                        ; Norketamine: volume of peripheral
NKCLINTH = THETA(13)*EXP(ETA(5))        ; Norketamine: hepatic cl of metabolite
NKCLINTG = THETA(14)                    ; Norketamine: gutwall cl of metabolite

;-------------------------------------------------------------------------------
; Ticlopidine model

TKA = THETA(15)                         ; Ticlopidine: fast absorption rate constant
TCLINTH = THETA(16)*EXP(ETA(6))         ; Ticlopidine: intrinsic hepatic clearance
TV1  = THETA(17)                        ; Ticlopidine: volume of central
TQ = THETA(18)                          ; Ticlopidine: central to peripheral cl
TV2 = THETA(19)                         ; Ticlopidine: volume of peripheral
TCLINTG = THETA(20)                     ; Ticlopidine: gutwall clearance

;-------------------------------------------------------------------------------
; Interaction model

TKI = THETA(21)                         ; KI of ticlopidine for CYP2B6
TKINACT = THETA(22)                     ; Inact rate of enzyme CYP2B6 for ticlopidine
KFM2B6 = THETA(23)                      ; Fraction metabolized by CYP2B6
LAMBDA = THETA(24)                      ; Rate of CYP2B6 degradation at ticlo = 1
TKIN = THETA(25)                        ; IC50 of ticlo on CYP2B6

;-------------------------------------------------------------------------------
; Drug constants

KFU = 0.70                              ; Ketamine: fraction unbound in blood
NKFUB = 0.50                            ; Norketamine: fub of norketamine in plasma
TFU = 0.02                              ; Ticlopidine: fraction unbound in blood
KRATIO = 0.50                           ; blood plasma ratio (Launiainen 2014)
KFUB = KFU/KRATIO                       ; fraction unbound in the blood
TRATIO = 1                              ; Ticlopidine ratio assumption = 1
TFUB = TFU/TRATIO                       ; Ticlopidine fraction unbound in blood
KFUG = 1                                ; fixed to 1, acc to Yang et al. 2007
TFUG = 1                                ; fixed to 1 for Ticlopidine
NKFUG = 1                               ; Norketamine: fub of norketamine in gutwall

;-------------------------------------------------------------------------------
; Ticlopidine absorption
F7 = 1
ALAG7 = 0
TKTR = TKA

; Ketamine absorption
F1 = 1
ALAG1 = 0
D2 = 0.03333                           ; duration of ketamine infusion = 2 minutes

;-------------------------------------------------------------------------------
; Physiological parameters

QH = 3.75*WTKG**0.75                    ; in L/HR (according to Brown et al. 1997)
QPV = 0.75*QH                           ; portal vein blood flow. Williams et al. 1989
QHA = 0.25*QH                           ; hepatic art blood flow. Williams et al. 1989
QIN = 0.4*QH                            ; intestial blood flow, Williams et al. 1989
QMU = 0.8*QIN                           ; mucosa blood flow, Yang et al. 2007
QVI = 0.6*QMU                           ; villous blood flow, Yang et al. 2007
QGUT = (QVI*KCLP)/(QVI+KCLP)            ; QGUT model for Ketamine
VGW = 1                                 ; volume of Gut wall fixed to 1 L
VPV = 1                                 ; volume of portal vein fixed to 1 L
VH = 1                                  ; volume of liver fixed to 1 L

;-------------------------------------------------------------------------------
; Gutwall well stirred clearance model Ketamine
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CLINTG = KCLINTG1
FG = QGUT/(QGUT+(CLINTG*KFUG))
EG = 1 - FG
CLG = QGUT*KFUG*CLINTG/(QGUT*KFUG+CLINTG)

;-------------------------------------------------------------------------------
; Gutwall well stirred clearance model Norketamine

CLINTGM = NKCLINTG
FGM = QVI/(QVI+(CLINTGM*NKFUG))
EGM = 1 - FGM
CLGM = QVI*NKFUG*CLINTGM/(QVI*NKFUG+CLINTGM)

;-------------------------------------------------------------------------------
; Hepatic well stirred clearance model Norketamine

FHM = QH/(QH+(NKCLINTH*NKFUB))
EHM = 1 - FHM
CLHM = QH*NKFUB*NKCLINTH/(QH+NKFUB*NKCLINTH)

;-------------------------------------------------------------------------------
; Hepatic well stirred clearance ticlopidine

TFH = QH/(QH+(TCLINTH*TFUB))
TEH = 1 - TFH
TCLH = QH*TCLINTH*TFUB/(QH+TCLINTH*TFUB)

;-------------------------------------------------------------------------------
; Gutwall well stirred clearance model ticlopidine

TEG = (TCLINTG*TFUG)/(QVI+(TCLINTG*TFUG))
TFG = 1 - TEG
TCLG = QVI*TFUG*TCLINTG/(QVI+TFUG*TCLINTG)

;-------------------------------------------------------------------------------
; Three compartmental model Ketamine

K23 = KQ/KV1
K32 = KQ/KV2
K24 = KQ2/KV1
K42 = KQ2/KV3

;-------------------------------------------------------------------------------
; Two compartmental model Norketamine

K56 = NKQ3/NKV5
K65 = NKQ3/NKV6

;-------------------------------------------------------------------------------
; Two compartmental model Ticlopidine

K1112 = TQ/TV1
K1211 = TQ/TV2

;-------------------------------------------------------------------------------
S2 = KV1/1000
S5 = NKV5/1000
S11 = TV1/1000

;-------------------------------------------------------------------------------
$DES

TCE = TFUB*(A(9)+((F7*TKA*AMT)/QH))               ; Inh conc in the portal vein
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TAH = 1/(1 + (TCE/TKIN))                          ; reversible inhibition
TBH = LAMBDA/(LAMBDA + (TKINACT*TCE/(TKI+TCE)))   ; time depend. inhibition
ZETA = (TAH * TBH * KFM2B6) + (1 - KFM2B6)        ; inh param comp and mech models

; Hepatic Clearance Ketamine
; Inhibition model

INHBH = 1
CLINTH = KCLINTH1
IF (TICLO.EQ.1) THEN
INHBH = ZETA                    ; inhib param CLINTH of Ket at ticlo = 1
CLINTH = KCLINTH1 * INHBH       ; reduction in clearance of ketamine at ticlo = 1
ENDIF

; Well stirred clearance model

EH = (CLINTH*KFUB)/(QH+(CLINTH*KFUB))
FH = 1 - EH
CLH = QH*KFUB*CLINTH/(QH+KFUB*CLINTH)

DADT(1) = -(KKA*A(1))

AGUTW = KKA*A(1)/(QVI/VGW)
APV = ((QVI/VGW)*FG*AGUTW + (QPV/KV1)*A(2))/(QPV/VPV)
AH = ((QHA/KV1)*A(2) + (QPV/VPV)*APV)/(QH/VH)

DADT(2) = FH*(QH/VH)*AH - (QHA/KV1)*A(2) - (QPV/KV1)*A(2) - K23*A(2) + K32*A(3) -
K24*A(2) + K42*A(4)
DADT(3) = K23*A(2) - K32*A(3)
DADT(4) = K24*A(2) - K42*A(4)

AGUTWM = (1-FG)*AGUTW
APVM = ((QVI/VGW)*AGUTWM*FGM + (QPV/NKV5)*A(5))/(QPV/VPV)
AHM = ((QHA/NKV5)*A(5) + (QPV/VPV)*APVM + (QH/VH)*EH*AH)/(QH/VH)

DADT(5) = FHM*(QH/VH)*AHM - (QPV/NKV5)*A(5) - (QHA/NKV5)*A(5) - K56*A(5) + K65*A(6)
DADT(6) = K56*A(5) - K65*A(6)

DADT(7) = -(TKA*A(7))

DADT(8) =  TKTR*A(16) - (QVI/VGW)*TEG*A(8) - (QVI/VGW)*TFG*A(8)
DADT(9) =  (QVI/VGW)*TFG*A(8) + (QPV/TV1)*A(11) - (QPV/VPV)*A(9)
DADT(10) = (QPV/VPV)*A(9) + (QHA/TV1)*A(11) - TEH*(QH/VH)*A(10) - TFH*(QH/VH)*A(10)
DADT(11) = TFH*(QH/VH)*A(10) - (QPV/TV1)*A(11) - (QHA/TV1)*A(11) - K1112*A(11) +
K1211*A(12)
DADT(12) = K1112*A(11) - K1211*A(12)

DADT(13) = TKA*A(7) - TKTR*A(13)
DADT(14) =            TKTR*A(13) - TKTR*A(14)
DADT(15) =                         TKTR*A(14) - TKTR*A(15)
DADT(16) =                                      TKTR*A(15) - TKTR*A(16)

;-------------------------------------------------------------------------------
$ERROR

IPRED = 0
IF (TICLO.EQ.0.AND.CMT.EQ.2) THEN
IPRED = F
Y = IPRED*(1+EPS(1))
ENDIF

IF (TICLO.EQ.0.AND.CMT.EQ.5) THEN
IPRED = F
Y = IPRED*(1+EPS(2))
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ENDIF

IF (TICLO.EQ.1.AND.CMT.EQ.2) THEN
IPRED = F
Y = IPRED*(1+EPS(3))
ENDIF

IF (TICLO.EQ.1.AND.CMT.EQ.5) THEN
IPRED = F
Y = IPRED*(1+EPS(4))
ENDIF

IF (TICLO.EQ.1.AND.CMT.EQ.11) THEN
IPRED = F
Y = IPRED*(1+EPS(5))
ENDIF

IRES = DV - IPRED
DEL = 0
IF(IPRED.EQ.0) DEL = 1
IWRES = (1-DEL)*IRES/(IPRED+DEL)

C2 = A(2)/KV1
C3 = A(3)/KV2
C4 = A(4)/KV3
C5 = A(5)/NKV5
C6 = A(6)/NKV6
C8 = A(8)/VGW
C9 = A(9)/VPV
C10 = A(10)/VH
C11 = A(11)/TV1
C12 = A(12)/TV2

;------------------------------------------------------------------------------
$THETA

(0,13.5)                    ; KV1
(0,265.2)                   ; KQ
(0,104.8)                   ; KV2
(0,1.91)                    ; KKA
(0,303.6)                   ; KCLINTH1
(0,174.5)                   ; KV3
(0,21.8)                    ; KQ2
(0,1.16)                    ; KCLINTG1
4.1 FIX                     ; KCLP
(0,87.9)                    ; NKV5
(0,20.9)                    ; NKQ3
(0,85.5)                    ; NKV6
(0,78.1)                    ; NKCLINTH
(0,45.1)                    ; NKCLINTG
3.3 FIX                     ; TKA
(0,1500)                    ; TCLINTH
(0,50)                      ; TV1
(0,25)                      ; TQ
(0,200)                     ; TV2
0 FIX                       ; TCLINTG
0.57 FIX                    ; TKI
18 FIX                      ; TKINACT
0.63 FIX                    ; KFM2B6
0.017 FIX                   ; LAMBDA
0.031 FIX                   ; TKIN

;------------------------------------------------------------------------------
$OMEGA
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0.05                          ; KV2_
0.42                          ; KKA_
0.25                          ; KCLINTH1_
1.99                          ; KCLINTG1_
0.10                          ; NKCLINTH_
0.13                          ; TCLINTH_

;-------------------------------------------------------------------------------
$SIGMA

0.086
0.062
0.065
0.066
0.066

;-------------------------------------------------------------------------------
$ESTIMATION METHOD=COND INTERACTION NSIG=2 SIGL=6 PRINT=5 MAXEVAL=9999 NOABORT
POSTHOC MSFO=msfo.outputfile
; $SIMULATION (123456) ONLYSIM PREDICTION SUBPROBS=1000 TRUE=INITIAL

;-------------------------------------------------------------------------------
$COVARIANCE MATRIX=S PRINT=E

;-------------------------------------------------------------------------------
$TABLE
ID TIME AMT MDV DV IPRED CMT EVID NPD NPDE IWRES CWRES
NOPRINT ONEHEADER
FILE=sdtab1

;-------------------------------------------------------------------------------
$TABLE
ID TIME DV PRED IPRED WTKG KKA KV1 KQ KV2 KCLINTH1 CLINTH
CLH KCLINTG1 CLINTG CLG KV3 KQ2 NKV5 NKQ3 NKV6 NKCLINTH
CLHM NKCLINTG CLINTGM CLGM TKA TCLINTH TV1 TQ TV2 TCLINTG
KCLINTH1 CLINTH TCE LAMBDA TAH
TBH ZETA INHBH
ETA1 ETA2 ETA3 ETA4 ETA5 ETA6
NOPRINT ONEHEADER FILE=patab1

;-------------------------------------------------------------------------------
$TABLE
ID TIME WTKG C2 C3 C4 C5 C6 C8 C9 C10 C11 C12 NOPRINT
ONEHEADER
FILE=mytab1
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