

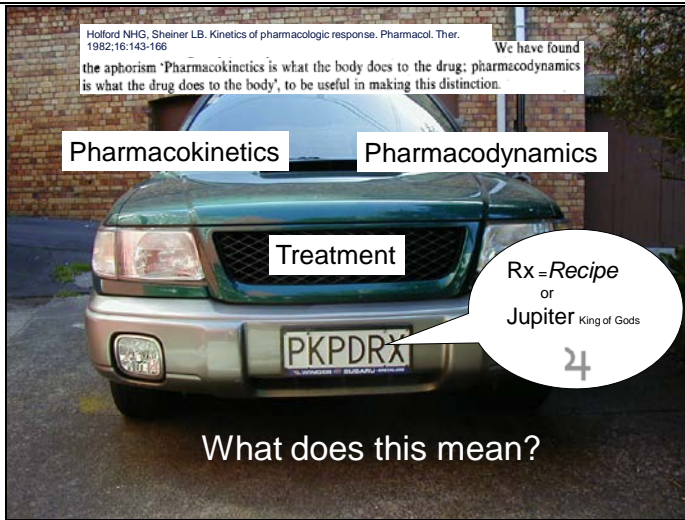
Slide 1

# PKPD

## Workshop

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PK = Pharmacokinetics: What the body does to the drug  
PD=Pharmacodynamics: What the drug does to the body  
Rx=Treatment: What the prescribed and patient need to know.

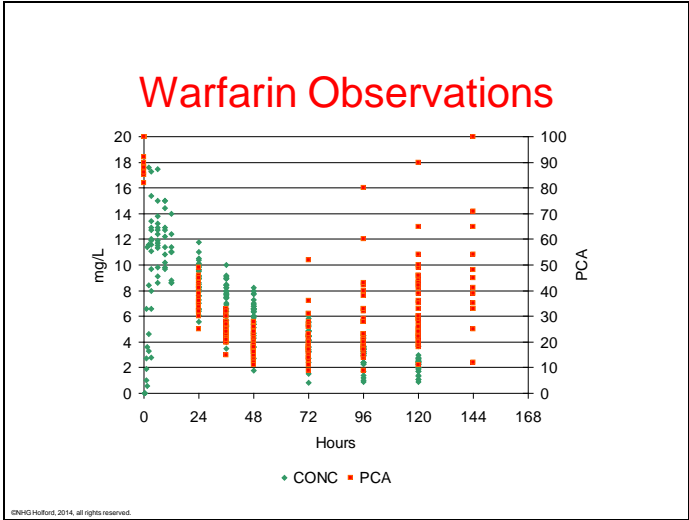
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## Warfarin Data

- PKPD Studies in Healthy Subjects
  - 1.5 mg/kg single oral dose
  - Total racemic warfarin plasma concentration
  - Prothrombin complex activity (PCA)
- 32 subjects, 250 concentrations, 232 PCA
- O'Reilly RA, Aggeler PM, Leong LS. Studies of the coumarin anticoagulant drugs: The pharmacodynamics of warfarin in man. Journal of Clinical Investigation 1963;42(10):1542-1551
- O'Reilly RA, Aggeler PM. Studies on coumarin anticoagulant drugs Initiation of warfarin therapy without a loading dose. Circulation 1968;38:169-177

A classical clinical pharmacology study from 40 years ago.  
Prothrombin complex activity is inversely proportional to the International Normalized Ratio (INR)

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Two features to notice about the time course of warfarin concentration and effect on PCA:

- Peak concentration is about 6 h while greatest effect is at 72 h
- Most marked between subject variability in PCA occurs when PK variability is least

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### PK Model

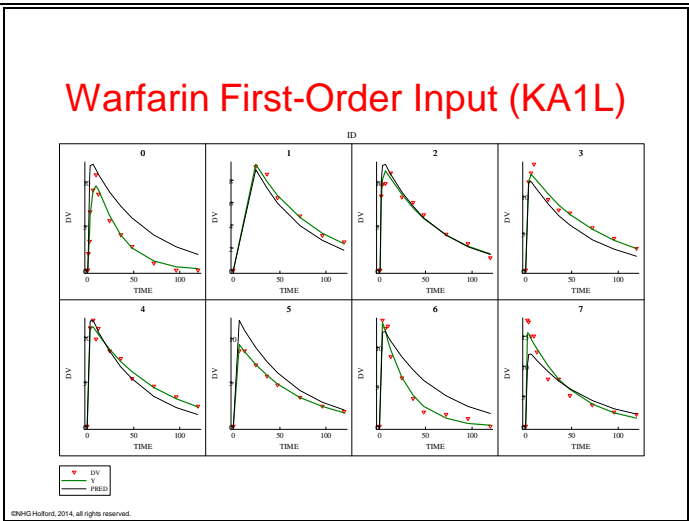
```

$PROB Warfarin PKPD                                $$SUBR ADVAN2 TRAN2
$INPUT ID time wt age sex amt dvid dv mdv          $PK
$DATA warfarin_conc_pca.csv
IGNORE (DVID,EQ,2) ; Don't include PCA
$EST METHOD=COND INTER                               IF (NEWIND.LE.1) LN2=LOG(2)
MAX=9990 NSIG=3 SIGL=9 PRINT=20 NOABORT
$COV
$THETA
(0.01,0.134,1) ; POP_CL L/h/70kg
(0.01,8.11,20) ; POP_V L/70kg
(0.01,0.523,24) ; POP_TABS h
(0.01,0.823,24) ; POP_LAG h
$OMEGA
0.0713 ; PPV_CL
0.0181 ; PPV_V
0.696 ; PPV_TABS
0.156 ; PPV_LAG
$SIGMA
0.00752 ; RUV_CV
0.0661 ; RUV_SD mg/L
    
```

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One compartment model with first-order absorption and lag time. Note the use of IGNORE on the \$DATA record so that only concentration observations are used in the fit (DVID=2 means PCA observation record).

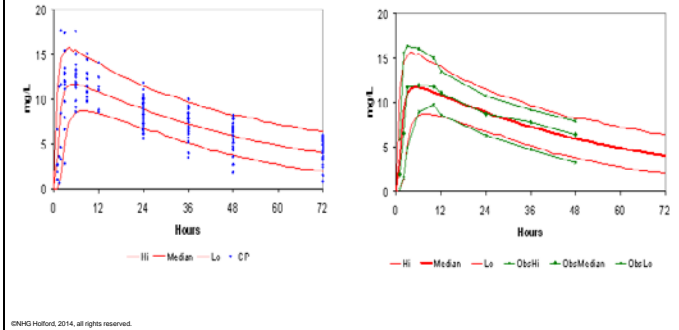
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Individual "post hoc" predictions of concentration fit the time course well and should be adequate for driving the pharmacodynamic model.

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## Warfarin KA1L Predictive Check



The visual predictive check reveals that the model overestimates the early variability in concentration.

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## Immediate Effect Model

- Two Basic Approaches
  - PREDPP
    - ADVAN2
    - ADVAN6 Differential Equations
  - \$PRED
    - Write model for CP

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An immediate effect model uses central compartment concentrations to predict the drug effect. Concentrations can be predicted using \$PRED or one of the PREDPP library ADVAN subroutines. Using ADVAN subroutines is usually easier to code but the model is not so clear.

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## Central Compartment Using ADVAN2

```
$SUB ADVAN2 TRANS2          ; Define parameters
$PK                          KA=LN2/TABS
; Define LN2 for efficiency   ALAG1=TLAG
IF (NEWIND.EQ.0) THEN        S2=V
  LN2=LOG(2)                 $ERROR
ENDIF

CP=A(2)/V ; or CP=F
IF (DVID.LE.1) THEN
  Y=CP*(1+RUV_CV) + RUV_SD
ENDIF

CE=CP
PCA=E0 + EMAX*CE/(C50+CE)
IF (DVID.EQ.2) THEN
  Y=PCA + RUV_FX
ENDIF
```

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TABS is the half-life of absorption. The absorption rate is parameterised in terms of TABS but because ADVAN2 requires a value for KA it must be calculated from TABS in the code. The NEWIND variable is a built in feature of NONMEM. When it is  $\leq 1$  it means this is the first record for this individual. The variable LN2 is calculated from LOG(2) just once for efficiency. Note how the DVID data item is used to distinguish predictions of concentration (DVID=1) from predictions of PCA (DVID=2).

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## Data for Joint PKPD Model

#ID	time	wt	age	sex	amt	dvid	dv	mdv
1	0	66.7	50	1	100	0		1
1	0	66.7	50	1		2		1
1	0.5	66.7	50	1		1	0	0
1	1	66.7	50	1		1	1.9	0
1	2	66.7	50	1		1	3.3	0
1	3	66.7	50	1		1	6.6	0
1	6	66.7	50	1		1	9.1	0
1	9	66.7	50	1		1	10.8	0
1	12	66.7	50	1		1	8.6	0
1	24	66.7	50	1		1	5.6	0
1	24	66.7	50	1		2	44	0
1	36	66.7	50	1		1	4	0
1	36	66.7	50	1		2	27	0
1	48	66.7	50	1		1	2.7	0
1	48	66.7	50	1		2	28	0
1	72	66.7	50	1		1	0.8	0
1	72	66.7	50	1		2	31	0
1	96	66.7	50	1		1		1
1	96	66.7	50	1		2	60	0
1	120	66.7	50	1		1		1
1	120	66.7	50	1		2	65	0
1	144	66.7	50	1		2	71	0

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NONMEM requires that all observations are in a single DV column. In order to distinguish concentrations from effects (PCA) the DVID data item is used to identify the kind of DV. A DVID of 0 is used to indicate a dose record, 1 for a concentration record and 2 for a PCA record. Note that MDV is used to indicate if there are missing observations e.g. this subject does not have a PCA observation at TIME=0.

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## Central Compartment Using ADVAN6

```

$SUBR ADVAN6 TOL=9          $DES
$MODEL                      GUT=A(1)
  COMP (GUT)                DCP=A(2)/V
  COMP (CENTRAL)            RATEIN=KA*GUT
$PK                          DADT(1)= -RATEIN
; Define LN2                 DADT(2)= RATEIN - DCP*CL
  IF (NEWIND.LE.1) THEN     $ERROR
  LN2=LOG(2)
  ENDIF
; Define parameters         CP=A(2)/V
  KA=LN2/TABS               IF (DVID.LE.1) THEN
  ALAG1=TLAG                Y=CP*(1+RUV_CV) + RUV_SD
  S2=V                      ENDIF
                           CE=CP
                           PCA=E0 + EMAX*CE/(C50+CE)
                           IF (DVID.EQ.2) THEN
                           Y=PCA + RUV_FX
                           ENDIF

```

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Note the variables defined in \$DES cannot have the same name as variables in other blocks e.g. you cannot define CP=A(2)/V in \$DES and also in \$ERROR. In this example the variable name DCP is used in \$DES and the variable name CP is used in \$ERROR.

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## Central Compartment Using \$PRED

```

$PRED                        ; Plasma concentration
; Get DOSE from AMT         EXPKA=EXP(-KA*TAD)
  IF (NEWIND.LE.1) THEN    EXPKE=EXP(-KE*TAD)
  LN2=LOG(2)               CP=DOSE*KA/(V*(KA-KE))*(EXPKE-EXPKA)
  DOSE=0
  ENDIF
  IF (AMT.GT.0) DOSE=AMT   IF (DVID.LE.1) THEN
                           Y=CP*(1+RUV_CV) + RUV_SD
                           ENDIF
; Define parameters        CE=CP
  KA=LN2/TABS              PCA=E0 + EMAX*CE/(C50+CE)
  KE=CL/V                  IF (DVID.EQ.2) THEN
                           Y=PCA + RUV_FX
                           ENDIF
; Adjust time for lagtime
  IF (TIME.LE.TLAG) THEN
  TAD=0
  ELSE
  TAD=TIME-TLAG
  ENDIF

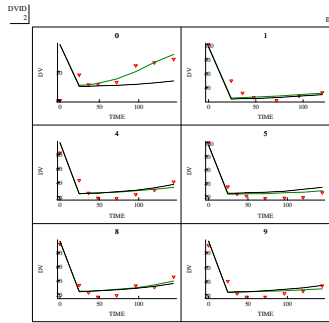
```

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Note that DOSE must be defined on every record so it is obtained 'on the fly' from the AMT value. The AMT value is only >0 at TIME=0.

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## Warfarin Immediate

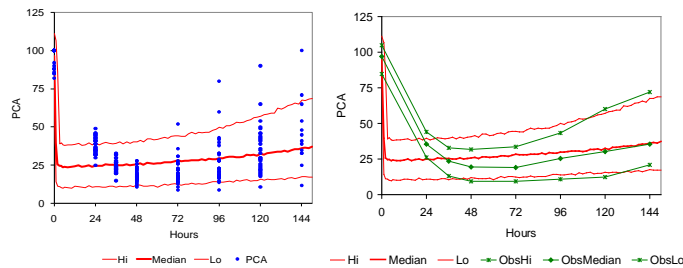


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Individual 'post hoc' predictions from the immediate effect model describe most of the time course of PCA but in general the time of the predicted greatest effect is earlier than the observed effect.

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## Warfarin Immediate



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Individual 'post hoc' predictions from the immediate effect model describe most of the time course of PCA but in general the time of the predicted greatest effect is earlier than the observed effect.

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## Delayed Effect Effect Compartment Model

- Two Basic Approaches
  - PREDPP
    - ADVAN4 Very small peripheral compartment
    - ADVAN6 Differential Equations
  - \$PRED
    - Write model for CP and CE

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The visual predictive check points to using a model with a delayed effect. The simplest form of delayed effect model uses an effect compartment. This is usually considered an empirical model but if the delay in effect is only a few minutes then it might be a reasonable way to described the time course of drug distribution from plasma to the site of action in an organ. \$PRED and ADVAN6 can be used to write exact solutions to the effect compartment model. Because ADVAN6 has to solve differential equations it is slower. ADVAN4 can be used by making the peripheral compartment have a negligible volume. This is helpful for complex dosing histories that would be hard to code in \$PRED.

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## Effect Compartment Using ADVAN4

```

; Define parameters
KA=LN2/TABS
ALAG1=TLAG
S2=V
V2=V

$SUB ADVAN4 TRANS4
$PK
; Define LN2
IF (NEWIND.EQ.0) THEN
  LN2=LOG(2)
ENDIF

KEQ=LN2/TEQ
V3=V2*0.0001 ; negligible volume
Q=V3*KEQ

$ERROR
CP=A(2)/V2
IF (DVID.LE.1) THEN
  Y=CP*(1+RUV_CV) + RUV_SD
ENDIF

CE=A(3)/V3
PCA=E0 + EMAX*CE/(C50+CE)
IF (DVID.EQ.2) THEN
  Y=PCA + RUV_FX
ENDIF

```

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Note how the peripheral compartment volume is scaled to be a very small fraction (0.0001) of the central compartment volume. This ensures it will have a negligible influence on the model predictions for the central compartment concentrations.

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## Effect Compartment Using ADVAN6

```

$SUBR ADVAN6 TOL=9
$MODEL
COMP (GUT)
COMP (CENTRAL)
COMP (EFFECT)

$PK
; Define LN2
IF (NEWIND.LE.1) THEN
  LN2=LOG(2)
ENDIF
; Define parameters
KA=LN2/TABS
ALAG1=TLAG
S2=V
KEQ=LN2/TEQ

$DES
GUT=A(1)
DCP=A(2)/V
DCE=A(3)

RATEIN=KA*GUT
DADT(1)= -RATEIN
DADT(2)= RATEIN - DCP*CL
DADT(3)= KEQ*(DCP - DCE)

$ERROR
CP=A(2)/V
IF (DVID.LE.1) THEN
  Y=CP*(1+RUV_CV) + RUV_SD
ENDIF

CE=A(3)
PCA=E0 + EMAX*CE/(C50+CE)
IF (DVID.EQ.2) THEN
  Y=PCA + RUV_FX
ENDIF

```

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The solution to differential equation 3 is scaled in terms of concentration. There is no need to define a volume of this compartment. It has no meaning for this model.

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## Effect Compartment Using \$PRED

```

$PRED
; Get DOSE from AMT
IF (NEWIND.LE.1) THEN
  LN2=LOG(2)
  DOSE=0
ENDIF
IF (AMT.GT.0) DOSE=AMT

; Define parameters
KA=LN2/TABS
KE=CL/V
KEQ=LN2/TEQ

; Adjust time for lagtime
IF (TIME.LE.TLAG) THEN
  TAD=0
ELSE
  TAD=TIME-TLAG
ENDIF

; Plasma concentration
EXPKA=EXP(-KA*TAD)
EXPKE=EXP(-KE*TAD)
EXPKE=EXPKE/(V*(KA-KE))*(EXPKE-EXPKA)
IF (DVID.LE.1) THEN
  Y=CP*(1+RUV_CV) + RUV_SD
ENDIF

; Effect compartment model concentration
EXPKQ=EXP(-KEQ*TAD)
CEEXKE=EXPKE/(KA-KE)/(KEQ-KE)
CEEXKA=EXPKA/(KE-KA)/(KEQ-KA)
CEEXKQ=EXPKQ/(KA-KEQ)/(KE-KEQ)
CE=DOSE*KA*KEQ/V*(CEEXKE+CEEXKA+CEEXKQ)
PCA=E0 + EMAX*CE/(C50+CE)
IF (DVID.EQ.2) THEN
  Y=PCA + RUV_FX
ENDIF

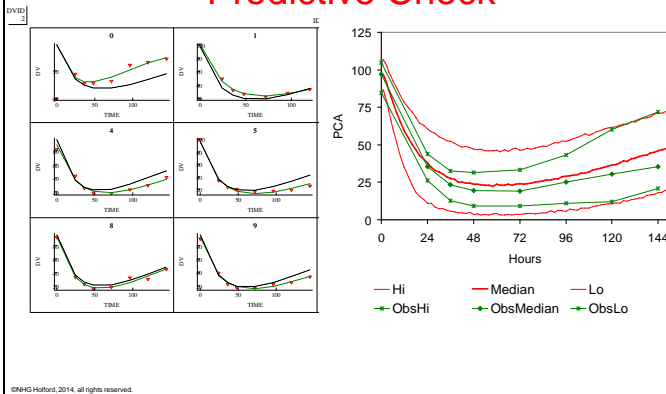
```

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The effect compartment model for a first-order input one compartment model requires an additional exponential term.

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## Warfarin Ce ADVAN4 Predictive Check



The individual 'post hoc' predictions are much better than using the immediate model. This model looks fine. But are we missing something?  
The visual predictive check confirms that the average prediction matches the observed effect time course but the variability is clearly overestimated.

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## Turnover Using ADVAN6 NONMEM VI or NONMEM 7

```

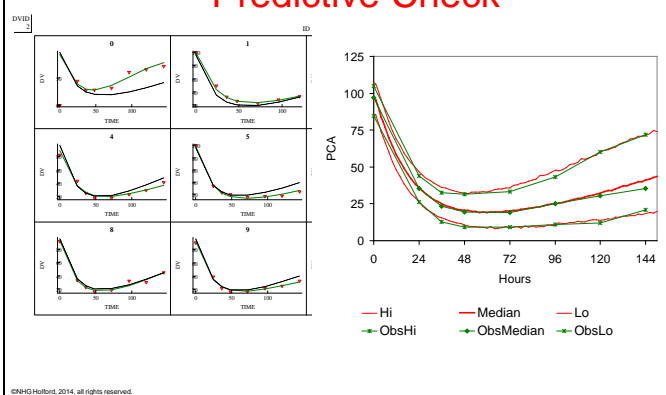
$SUBR ADVAN6 TOL=9
$MODEL
  COMP (GUT)
  COMP (CENTRAL)
  COMP (TRNOVR)
$PK
  A_0(3)=E0
  ;TOVER is turnover half-life
  KOUT=LN2/TOVER
  RIN=E0*KOUT
$DES
  RATEIN=KA*A(1)
  DCP=A(2)/V
  DPCA=A(3)
  PD=1+EMAX*DCP/(C50+DCP)
  DADT(1)=-RATEIN
  DADT(2)=RATEIN - CL*DCP
  DADT(3)=RIN*PD - KOUT*DPCA
$ERROR
  CP=A(2)/V
  IF (DVID.LE.1) THEN
    Y=CP*(1+RUV_CV) + RUV_SD
  ENDIF
  PCA=A(3)
  IF (DVID.EQ.2) THEN
    Y=PCA + RUV_FX
  ENDIF

```

The turnover family of models describe delayed drug effects where the delay is due to the turnover of a physiological mediator. This is well understood as the mechanism of the delay for warfarin. NONMEM VI allows initialization of the turnover compartment directly using the special variable A\_0().

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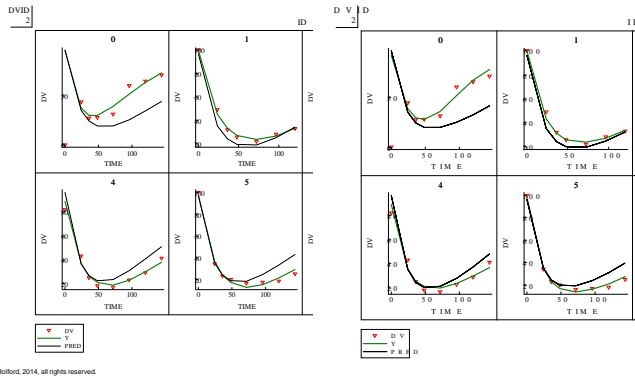
## Warfarin Turnover Predictive Check



The visual predictive check shows that the turnover model describes the variability of the observations much better than the effect compartment model.

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## Effect Cpt vs Turnover



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The individual “post hoc” predictions from the turnover model do not look any better than the predictions from the effect compartment model.

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## Comparison of Models NONMEM 730 ivf11

Run	Obj	Min	Covariance	Eval	Sig	Ttot (mins)
ka1_to_emax1_ADVAN6	1202.815	SUCCESSFUL	ABORTED	409	4.3	3.66
ka1_to_emax_ADVAN6	1203.002	SUCCESSFUL	NONE	638	3.5	1.59
ka1_ce_emax_ADVAN4	1271.932	SUCCESSFUL	NONE	598	3.1	0.26
ka1_ce_emax_ADVAN6	1271.938	TERMINATED	NONE	914	NA	1.35
ka1_ce_emax_PRED	1271.938	SUCCESSFUL	NONE	899	3.1	0.15
ka1_im_emax_ADVAN2	1449.094	SUCCESSFUL	NONE	590	4.1	0.19
ka1_im_emax_ADVAN6	1449.094	SUCCESSFUL	NONE	565	3.2	2.66
ka1_im_emax_PRED	1449.094	SUCCESSFUL	NONE	575	4.1	0.13

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## Comparison of Models NONMEM 730 gfortran

Run	Obj	Min	Covariance	Eval	Sig	Ttot (mins)
ka1_to_emax1_ADVAN6	1202.815	SUCCESSFUL	ABORTED	409	4.3	4.08
ka1_to_emax_ADVAN6	1203.002	TERMINATED	NONE	636	NA	2.24
ka1_ce_emax_ADVAN4	1271.932	SUCCESSFUL	NONE	595	3.9	0.23
ka1_ce_emax_ADVAN6	1271.938	TERMINATED	NONE	1005	NA	2.89
ka1_ce_emax_PRED	1271.938	SUCCESSFUL	NONE	689	3.4	0.21
ka1_im_emax_ADVAN2	1449.094	SUCCESSFUL	NONE	576	4.3	0.22
ka1_im_emax_ADVAN6	1449.094	TERMINATED	NONE	680	NA	4.13
ka1_im_emax_PRED	1449.094	SUCCESSFUL	NONE	576	4.5	0.17

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Run times are longer than ivf11.



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## Comparison of Models NONMEM 7 ivf11

Run	Obj	Min	Covariance	Eval	Sig	Ttot (mins)
ka1_to_emax1_ADVAN6	1202.815	SUCCESSFUL	OK	512	3.2	3.38
ka1_to_emax_ADVAN6	1203.002	SUCCESSFUL	NONE	616	3.4	1.53
ka1_ce_emax_ADVAN4	1271.932	SUCCESSFUL	NONE	582	4	0.14
ka1_ce_emax_ADVAN6	1271.938	SUCCESSFUL	NONE	573	3.4	1.16
ka1_ce_emax_PRED	1271.938	SUCCESSFUL	NONE	568	4	0.10
ka1_im_emax_ADVAN2	1442.873	SUCCESSFUL	NONE	583	3.3	0.12
ka1_im_emax_ADVAN6	1442.873	SUCCESSFUL	NONE	603	4.2	2.48
ka1_im_emax_PRED	1442.873	SUCCESSFUL	NONE	614	3.9	0.10

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## Comparison of Models NONMEM 7 gfortran

Run	Obj	Min	Covariance	Eval	Sig	Ttot (mins)
ka1_to_emax1_ADVAN6	1202.815	SUCCESSFUL	OK	409	4.3	3.76
ka1_to_emax_ADVAN6	1203.002	TERMINATED	NONE	635	N/A	2.11
ka1_ce_emax_ADVAN4	1271.932	SUCCESSFUL	NONE	600	3.5	0.20
ka1_ce_emax_ADVAN6	1271.938	SUCCESSFUL	NONE	594	3.1	1.28
ka1_ce_emax_PRED	1271.938	SUCCESSFUL	NONE	595	3.1	0.16
ka1_im_emax_ADVAN2	1449.094	SUCCESSFUL	NONE	589	3.7	0.18
ka1_im_emax_ADVAN6	1449.094	SUCCESSFUL	NONE	567	3.1	3.00
ka1_im_emax_PRED	1449.094	SUCCESSFUL	NONE	602	3.8	0.15

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Gfortran objective function is higher for immediate models compared with ivf11. Run times are longer than ivf11.

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## Comparison of Models NONMEM VI

Run	Obj	Min	Covariance	Eval	Sig
ka1_to_emax_ADVAN6	1202.815	Terminated Inf Obj Func	NONE	657	.
ka1_to_emax1_ADVAN6	1202.816	Successful	OK	367	3.1
ka1_ce_emax_ADVAN4	1271.931	Successful	ABORTED	597	3.3
ka1_ce_emax_ADVAN6	1271.936	Successful	ABORTED	539	3.2
ka1_ce_emax_PRED	1271.939	Successful	OK	608	3.2
ka1_im_emax_ADVAN2	1442.809	Successful	ABORTED	1225	3.0
ka1_im_emax_ADVAN6	1442.809	Successful	OK	929	3.0
ka1_im_emax_PRED	1442.809	Successful	ABORTED	1384	3.5

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Fixing Emax to 1 allowed the turnover model to finish successfully. Whether the covariance step runs is not a helpful criterion of model suitability.

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## Comparison of Parameters NONMEM 730 ivf11

Run	POP S0	POP EMAX	POP C50	POP TEQ/TOVER
ka1_to_emax1_ADVAN6	96.6	-1	1.18	13
ka1_to_emax_ADVAN6	96.6	-0.999	1.18	13
ka1_ce_emax_ADVAN4	96.7	-256	11.1	39.5
ka1_ce_emax_ADVAN6	96.7	-256	11.1	39.5
ka1_ce_emax_PRED	96.7	-256	11.1	39.5
ka1_im_emax_ADVAN2	96.7	-72.7	0.0875	.
ka1_im_emax_ADVAN6	96.7	-72.7	0.0875	.
ka1_im_emax_PRED	96.7	-72.7	0.0875	.

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The half-life of PCA is reported in the literature to be about 14 hours. This is very close to the TOVER estimate of 13 hours from this data set. Notice also the more physiological meaning of an Emax of -1 i.e. 100% inhibition of PCA formation.

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## Comparison of Parameters NONMEM 7 ivf11

Run	POP S0	POP EMAX	POP C50	POP TEQ/TOVER
ka1_to_emax1_ADVAN6	96.6	-1	1.18	13
ka1_to_emax_ADVAN6	96.6	-0.999	1.18	13
ka1_ce_emax_ADVAN4	96.7	-256	11.1	39.5
ka1_ce_emax_ADVAN6	96.7	-256	11.1	39.5
ka1_ce_emax_PRED	96.7	-256	11.1	39.5
ka1_im_emax_ADVAN2	96.5	-74.3	0.221	.
ka1_im_emax_ADVAN6	96.5	-74.3	0.221	.
ka1_im_emax_PRED	96.5	-74.3	0.221	.

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The half-life of PCA is reported in the literature to be about 14 hours. This is very close to the TOVER estimate of 13 hours from this data set. Notice also the more physiological meaning of an Emax of -1 i.e. 100% inhibition of PCA formation.

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## Comparison of Parameters NONMEM 730 gfortran

Run	POP S0	POP EMAX	POP C50	POP TEQ/TOVER
ka1_to_emax1_ADVAN6	96.6	-1	1.18	13
ka1_to_emax_ADVAN6	96.6	-0.999	1.18	13
ka1_ce_emax_ADVAN4	96.7	-256	11.1	39.5
ka1_ce_emax_ADVAN6	96.7	-256	11.1	39.5
ka1_ce_emax_PRED	96.7	-256	11.1	39.5
ka1_im_emax_ADVAN2	96.7	-72.7	0.0875	.
ka1_im_emax_ADVAN6	96.7	-72.7	0.0875	.
ka1_im_emax_PRED	96.7	-72.7	0.0875	.

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Gfortran estimate of Emax is higher (less negative) and EC50 are lower than with ivf11

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## Comparison of Parameters NONMEM 7 gfortran

Run	POP S0	POP EMAX	POP C50	POP TEQ/TOVER
ka1 to emax1 ADVAN6	96.6	-1	1.18	13
ka1 to emax ADVAN6	96.6	-0.999	1.18	13
ka1 ce emax ADVAN4	96.7	-256	11.1	39.5
ka1 ce emax ADVAN6	96.7	-256	11.1	39.5
ka1 ce emax PRED	96.7	-256	11.1	39.5
ka1 im emax ADVAN2	96.7	-72.7	0.0875	.
ka1 im emax ADVAN6	96.7	-72.7	0.0875	.
ka1 im emax PRED	96.7	-72.7	0.0875	.

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Gfortran estimate of Emax is higher (less negative) and EC50 are lower than with ivf11

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## Comparison of Parameters NONMEM VI

Run	POP S0	POP EMAX	POP C50	POP TEQ/TOVER
ka1 to emax1 ADVAN6	96.6	-1	1.18	13
ka1 to emax ADVAN6	96.6	-1	1.18	13
ka1 ce emax ADVAN4	96.7	-256	11.1	39.5
ka1 ce emax ADVAN6	96.7	-256	11.1	39.5
ka1 ce emax PRED	96.7	-257	11.1	39.5
ka1 im emax ADVAN2	96.5	-74.3	0.22	.
ka1 im emax ADVAN6	96.5	-74.3	0.22	.
ka1 im emax PRED	96.5	-74.3	0.22	.

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The half-life of PCA is reported in the literature to be about 14 hours. This is very close to the TOVER estimate of 13 hours from this data set. Notice also the more physiological meaning of an Emax of -1 i.e. 100% inhibition of PCA formation.

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## Comparison of Random Effects NONMEM 730 ivf11

Run	PPV S0	PPV EMAX	PPV C50	PPV TEQ	RUV FX
ka1 to emax1 ADVAN6	0.053	0	0.445	0.104	3.82
ka1 to emax ADVAN6	0.053	0	0.446	0.104	3.83
ka1 ce emax ADVAN4	0.051	0.002	0.224	0.269	3.81
ka1 ce emax ADVAN6	0.051	0.002	0.224	0.269	3.81
ka1 ce emax PRED	0.051	0.002	0.224	0.269	3.81
ka1 im emax ADVAN2	0.008	0.025	1.308	.	8.37
ka1 im emax ADVAN6	0.008	0.025	1.308	.	8.37
ka1 im emax PRED	0.008	0.025	1.308	.	8.37

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The residual error is very similar for the effect compartment and turnover models. The turnover model suggests that between subject differences in C50 are more important than the value predicted using the effect compartment model. Gfortran estimates for immediate models have larger PPV compared with ivf11

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## Comparison of Random Effects NONMEM 7 ivf11

Run	PPV S0	PPV EMAX	PPV C50	PPV TEQ	RUV FX
ka1_to_emax1_ADVAN6	0.053	0	0.445	0.104	3.82
ka1_to_emax_ADVAN6	0.053	0	0.446	0.104	3.83
ka1_ce_emax_ADVAN4	0.051	0.002	0.224	0.269	3.81
ka1_ce_emax_ADVAN6	0.051	0.002	0.224	0.269	3.81
ka1_ce_emax_PRED	0.051	0.002	0.224	0.269	3.81
ka1_im_emax_ADVAN2	0.008	0.010	0.880	.	8.37
ka1_im_emax_ADVAN6	0.008	0.010	0.880	.	8.37
ka1_im_emax_PRED	0.008	0.010	0.880	.	8.37

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The residual error is very similar for the effect compartment and turnover models. The turnover model suggests that between subject differences in C50 are more important than the value predicted using the effect compartment model. Gfortran estimates for immediate models have larger PPV compared with ivf11

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## Comparison of Random Effects NONMEM 730 gfortran

Run	PPV S0	PPV EMAX	PPV C50	PPV TEQ	RUV FX
ka1_to_emax1_ADVAN6	0.053	0	0.445	0.104	3.82
ka1_to_emax_ADVAN6	0.053	0	0.446	0.104	3.83
ka1_ce_emax_ADVAN4	0.051	0.002	0.224	0.269	3.81
ka1_ce_emax_ADVAN6	0.051	0.002	0.224	0.269	3.81
ka1_ce_emax_PRED	0.051	0.002	0.224	0.269	3.81
ka1_im_emax_ADVAN2	0.008	0.025	1.308	.	8.37
ka1_im_emax_ADVAN6	0.008	0.025	1.308	.	8.37
ka1_im_emax_PRED	0.008	0.025	1.308	.	8.37

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The residual error is very similar for the effect compartment and turnover models. The turnover model suggests that between subject differences in C50 are more important than the value predicted using the effect compartment model.

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## Comparison of Random Effects NONMEM 7 gfortran

Run	PPV S0	PPV EMAX	PPV C50	PPV TEQ	RUV FX
ka1_to_emax1_ADVAN6	0.053	0	0.445	0.104	3.82
ka1_to_emax_ADVAN6	0.053	0	0.446	0.104	3.83
ka1_ce_emax_ADVAN4	0.051	0.002	0.224	0.269	3.81
ka1_ce_emax_ADVAN6	0.051	0.002	0.224	0.269	3.81
ka1_ce_emax_PRED	0.051	0.002	0.224	0.269	3.81
ka1_im_emax_ADVAN2	0.008	0.025	1.308	.	8.37
ka1_im_emax_ADVAN6	0.008	0.025	1.308	.	8.37
ka1_im_emax_PRED	0.008	0.025	1.308	.	8.37

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The residual error is very similar for the effect compartment and turnover models. The turnover model suggests that between subject differences in C50 are more important than the value predicted using the effect compartment model.

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## Comparison of Random Effects NONMEM VI

Run	PPV E0	PPV EMAX	PPV C50	PPV TEQ	RUV FX
ka1_to_emax_ADVAN6	0.0533	6.54E-07	0.445	0.104	3.82
ka1_to_emax1_ADVAN6	0.0533	0	0.445	0.104	3.82
ka1_ce_emax_ADVAN4	0.0510	1.77E-05	0.224	0.269	3.81
ka1_ce_emax_ADVAN6	0.0510	2.93E-06	0.224	0.269	3.81
ka1_ce_emax_PRED	0.0510	1.78E-04	0.224	0.269	3.81
ka1_im_emax_ADVAN2	0.0000	1.73E-02	0.879	.	8.37
ka1_im_emax_ADVAN6	0.0000	1.72E-02	0.878	.	8.37
ka1_im_emax_PRED	0.0000	1.72E-02	0.878	.	8.37

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The residual error is very similar for the effect compartment and turnover models. The turnover model suggests that between subject differences in EC50 are more important than the value predicted using the effect compartment model.

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Way to go!