Absorption Models
Using NM-TRAN

Nick Holford
Dept Pharmacology & Clinical Pharmacology
University of Auckland, New Zealand

Absorption

• Extent of Absorption
• Rate of Absorption

Extent (F)

• Fraction Absorbed (f)
  – into portal vein from gut
  – physicochemistry
    • theophylline (100%) (small, unionized)
    • gentamicin (< 5%) (large, ionized)
  – metabolism/transport
    • simvastatin (50%?) (CYP3A4)
    • digoxin (65%) (PGP transporter)

The extent of oral absorption can be considered in 2 parts. The first part is the fraction of drug absorbed across the gut wall (f). This describes how much drug gets from the gut into the portal venous system. It is determined in part by physicochemical properties. Small, unionized molecules e.g. theophylline, are almost completely absorbed across the gut wall. Large, ionized molecules like gentamicin cross membranes with difficulty and only a small fraction is absorbed across the gut wall. Many drugs are cross the luminal cell membrane but are then metabolized in the gut wall (typically by CYP3A4 e.g. simvastatin) and/or transported out of the cell back into the gut lumen (typically by P-glycoprotein e.g. digoxin).
### Extent (F)

- **First Pass Extraction (ER)**
  - drug removed while passing through liver
  - organ clearance and blood flow
  - morphine (60%)  
  - ethanol (10-70%)

### Input Processes

- **Bolus**
  - e.g. Intra-venous injection

- **Zero-Order**
  - e.g. Constant rate IV infusion

- **First-Order**
  - e.g. Intra-muscular injection
Rate

- Zero-Order
  - Stomach emptying (Tmax)
    - physiological control
  - Slow Release Formulation (Tk0)
    - pharmaceutical control

$$C(t) = \frac{\text{Rate}}{CL} \left(1 - e^{-\frac{CL}{Vd}t}\right)$$

Rate

- First Order
  - Intestinal Absorption (KA)
    - Diffusion limited
    - Absorption Thalf = 0.7/KA
    - Complete after 4 x absorption Thalf

$$C(t) = \frac{\text{Dose} \times Ka}{V \left(Ka - \frac{CL}{Vd}\right)} \left(e^{-\frac{CL}{Vd}t} - e^{-Kaat}\right)$$

Extent of Absorption
Dose or Rate Dependence?

- Empirical Models use Dose
- Mechanistic Models use Rate
Finding the Dose

```plaintext
$PK
; Make sure dose is 0 for each subject
IF (NEWIND.LE.1) DOSE=0

; Remember dose using AMT
IF (AMT.GT.0) DOSE=AMT
```

Finding the Time After Dose

```plaintext
$PK
; Make sure values are 0 for each subject
IF (NEWIND.LE.1) THEN
  DOSE=0
  TDOS=0
ENDIF

; Remember dose and time of dose
IF (AMT.GT.0) THEN
  DOSE=AMT
  TDOS=TIME
ENDIF

; Time after dose for every record
TAD=TIME-TDOS
```

Empirical Dose and Extent Models

```plaintext
$THETA -.01 ; KFDOSE
$PK
FDOSE=EXP(KFDOSE*DOSE)
F1=FDOSE

$THETA (-1,-.5,0) ; DMAX
$THETA (0,100,) ; D50
$PK
FDOSE=1+DMAX*DOSE/(D50+DOSE)
F1=FDOSE
```

Two empirical models are illustrated showing how dose might be used to predict changes in extent of absorption. The model on the right is approximately linear if the effect on bioavailability is small. The model on the left requires an additional parameter to describe a saturable increase in extent of absorption with dose. The maximum extent is \( 1 + DMAX \) with \( 1 + DMAX/2 \) extent at a dose D50.

NONMEM data files require that the amount of each dose is recorded in the AMT data item only at the time the dose is administered. It is often useful to know the value of the last DOSE. This code shows how to save the DOSE by looking at the AMT data item.
Mechanistic Rate and Extent
Well Stirred Model

Dose is 100

Two Part Rate Models
Parallel/Sequential K0KA

Two Part Rate Models
Sequential Linked K0KA

Hepatic extraction can change with concentration delivered to the liver if intrinsic clearance is mixed order in the range of concentrations achieved in the liver during absorption. Under the well stirred model of liver extraction the time changing extraction ratio (ER) can be predicted from the absorption rate and an assume value for hepatic blood flow.

CLFO is a parameter describing a first-order elimination clearance process.

http://pkpdx.com/holford/docs/rate-dependent-extraction.pdf

Two part models require the data file to have two dosing records at the time of each actual dose. The first record has a CMT of 1 (the default absorption compartment for a first-order process when using ADVAN2 or ADVAN4) and a RATE of 0. The second record has a CMT of 2 (the default central compartment when using ADVAN2 or ADVAN4) and a RATE of -2. The duration of input (TK0) by the zero-order process into compartment 2 is defined in $PK by assigning TK0 to the special variable D2. The fraction of the dose absorbed by each process is determined by FK0 (the fraction absorbed by the zero-order process). ALAG1 and ALAG2 are used to estimate the lagtime (if any) for each process. If it is assumed that the zero-order process starts only when the first-order process has started (sequential input) then ALAG2 must be set to the sum of ALAG1 and ALAG2.

The sequential linked zero-order then first-order model can be interpreted in a mechanistic way if the concentration in the gut is initially at the solubility limit for the drug. As drug is absorbed and the concentration falls below the solubility limit then the process converts from a zero-order input to a first-order input. Note that ALAG1 (lag time of the first order process) must be equal to TK0 (the duration of the zero-order process) plus any lagtime for the zero-order process. This ensures that the first-order process will take over at the end of the zero-order input.

The use of transit compartment models to describe delays in onset of absorption was developed by Radojka Savic at Uppsala. The following set of slides is taken from her work.
Transit Models

Estimating the number of transit compartments

\[ a_i(t) = \text{Dose} \cdot \frac{(k_{w} \cdot t)^i}{n!} \cdot e^{-k_{w} \cdot t}, \quad \text{amount of drug in the } n^\text{th}-\text{compartment at time } t \]

Transit Models

Stirling approximation

\[ \frac{dA(1)}{dt} = \text{Dose} \cdot \left( \frac{(k_w \cdot t)^n}{n!} \cdot e^{-k_w \cdot t} \right) \cdot k_w - k_{x_w} \cdot A(1) \]

\[ n! \approx \sqrt{2\pi} \cdot n^{n+0.5} \cdot e^{-n} \]

Transit Models

Improvement in GOF for all compounds

Delta OFV vs FOCE with interaction

Rich data

- Moxonidine: n=7.2
- Gilbenclamide: n=23.3
- Furosemide: n=8.2
- Amlodipine: n=12.4
Transit Models

Slide 22

$THETA$
3 : pop_cl L/h 
10 : pop_v L 
1 : pop_ka h-1 
5 : pop_nt

$SUBR ADVAN6 TOL=3

$MODEL

PK
CL=pop_cl
V =pop_v
KA=pop_ka
NT=pop_nt
KTR=(NT+1)/pop_mtt
NFAC= SQRT(2*3.1415)*NT**(NT+0.5)*EXP(-NT)
F1=0 ; Very important!

DES
DCP=A(2)/V
RATEIN=KA*A(1)
GUT=DOS*EXP(-KTR*(T-TLAST))
DADT(1)=GUT*KTR*(KTR*(T-TLAST))**NT/NFAC - RATEIN
DADT(2)=RATEIN - CL*DCP

Slide 23

$THETA$
3 : pop_cl L/h 
10 : pop_v L 
1 : pop_ka h-1 
5 : pop_nt

$SUBR ADVAN6 TOL=3

$MODEL

PK
CL=pop_cl
V =pop_v
KA=pop_ka
NT=pop_nt
KTR=(NT+1)/pop_mtt
LNFAC= SQRT(2*3.1415)*(NT+0.5)*EXP(-NT)
LNDK=LOG(DOSE+.00001)+LOG(KTR)
F1=1 ; Very important!

IF (AMT.GT.0) TDOSE=TIME

DES
DCP=A(2)/V
RATEIN=KA*A(1)
GUT=NT/LNFAC
DADT(1)=GUT^KTR*(KTR*(T-TLAST))**NT/NFAC - RATEIN
DADT(2)=RATEIN - CL*DCP

Slide 24

$THETA$
3 : pop_cl L/h 
10 : pop_v L 
1 : pop_ka h-1 
5 : pop_nt

$SUBR ADVAN9 TOL=3

$MODEL

IF (AMT.GT.0) TDOSE=TIME

DES
DCP=A(3)/V
RATEIN=KA*A(2)
GUT=NT/LNFAC
DADT(1)=GUT^KTR
DADT(2)=GUT*KTR*(KTR*(T-TLAST))**NT/NFAC - RATEIN
DADT(3)=RATEIN - CL*DCP

ERROR
TLAST=TDOSE

The code for a single dose transit model involves the use of differential equations and closed form solution to transit through NT transit compartments. It is important that the extent of absorption for the dosing compartment 1 is set to 0 because the actual drug input rate from this compartment is modelled explicitly in DADT(1).

If it can be assumed that absorption is complete within the dosing interval then it is possible to model concentrations arising from multiple doses with a transit time delay after each dose. In this case the first compartment is used to model input from the most recent dose and its extent of bioavailability must be set to 1.