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Steady-state Equation for the Bicompartmental Model with Gamma Absorption. Application to Mycophenolate PK in Renal Transplant Patients

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BACKGROUND

The bicompartmental model with gamma-distributed absorption times is a useful empirical model for drugs whose absorption kinetics is not zero- or first-order. We derived for this model a steady-state equation, involving one parameter less than the previous derivation (1). The equation involves the incomplete gamma function P. An approximation (based on equivalence with a chi-squared distribution) is proposed in order to facilitate its implementation in NONMEM.

OBJECTIVES

To compare the population estimates obtained with NONMEM (approximate equation for P) and MONOLIX (no approximation for P) on real data.

RESULTS AND DISCUSSION

Accuracy of the approximation : See fig 1. The 95th percentile of relative prediction error is ~ 1%.

Comparison of population parameter estimates: See Table I and II. MONOLIX is similar to NONMEM with FOCE INTERACTION and full covariance matrix but NONMEM convergence could not be reached with these settings. Therefore, differences in parameter estimates may be due to differences in the likelihood computation. Nevertheless, PREDs were similar for both approaches (fig 2). Data and typical profile are shown fig 3.

Goodness of fit : See fig 4. Prediction discrepancies did not reveal any lack of fit.

Table I : MONOLIX estimates

Parameter	Median (SE)	Interindividual CV (%)
V_1 (L)	33.7 (1.2)	50
λ_2 (h^{-1})	0.0414 (0.0017)	77
K_{21} (h^{-1})	0.23 (0.01)	7
λ_1 (h^{-1})	2.69 (0.02)	21
Ka (h^{-1})	7.57 (0.91)	296
s	5.39 (0.46)	105
σ	0.40 (0.06)	-

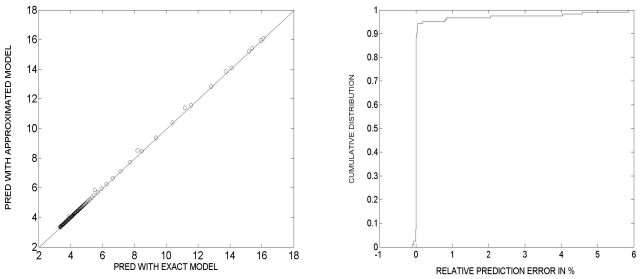
Covariances also estimated (not shown)

Table II: NONMEM estimates

Parameter	Median (SE)	Interindividual CV (%)
V_1 (L)	33.6 (3.8)	40
λ_2 (h-1)	0.0451 (0.0042)	45
K_{21} (h-1)	0.31 (0.03)	7.5
λ_1 (h-1)	3.41 (0.4)	13
Ka (h-1)	7.18 (0.67)	153
s	5.11 (0.55)	30
σ	0.51 (0.04)	-

Covariances fixed to zero, FOCE NO INTERACTION

Fig. 1. Comparison of model output for the exact and the approximated function for P.
Parameters are fixed to the typical value of table 1. Dose = 1000 mg every 12 h.



MATERIALS AND METHODS

Study design : 77 adult renal transplant patients treated with tacrolimus and mycophenolate, 3 to 4 blood samples per occasion (114 occasions, 594 concentrations), median time between transplant and sampling dates 37 d, IQR 12 to 377 d, mycophenolate concentrations measured by HPLC.

Pharmacokinetic analysis : The data were analyzed by a population approach. The final model was a two- compartment model with gamma-distributed absorption times.

Individual parameters:

- V_1 = volume of central compartment
- λ_1, λ_2 = eigenvalues = slopes of phase 1 (rapid) and phase 2 (slow)
- Ka = absorption rate constant
- K_{21} = rate constant peripheral to central
- s = shape parameter of gamma distribution

Parameter Distribution: multivariate lognormal.

Residual error model : Cobs = Cpred + ε.Cpred$^{0.5}$ SD(ε) = σ

Parameters were estimated by using MONOLIX 1.1 and NONMEM VI (FOCE method).

Steady-state equations for the two- compartment model with gamma-distributed absorption times:

$$C(t) = Co(t) + C_1(t).\exp(-\lambda_1 t) + C_2(t).\exp(-\lambda_2 t)$$

where $$Co(t) = C_1(Tau).\frac{\exp(-\lambda_1.t)}{\exp(\lambda_1.Tau)-1} + C_2(Tau).\frac{\exp(-\lambda_2.t)}{\exp(\lambda_2.Tau)-1}$$

and $$C_1(t) = \frac{D}{V_1}\left(\frac{K_{21}-\lambda_1}{\lambda_2-\lambda_1}\right)\left(\frac{Ka}{Ka-\lambda_1}\right)^s.P[s,(Ka-\lambda_1).t]$$

$$C_2(t) = \frac{D}{V_1}\left(\frac{K_{21}-\lambda_2}{\lambda_1-\lambda_2}\right)\left(\frac{Ka}{Ka-\lambda_2}\right)^s.P[s,(Ka-\lambda_2).t]$$

Computation of the incomplete gamma function P(nu,x) in NONMEM: the hard way

Use a Fortran subroutine for P( ). Call this subroutine from $PRED via verbatim code.

Inconvenient: the derivatives of the model have to be written in the PRED routine generated by NMTRAN.

Computation of the incomplete gamma function P(nu,x) in NONMEM: the tricky way

(Step 1) Use the equivalence:

$P(nu,x) = p(\chi^2(2.nu) < 2.x)$ *i.e.* the probability that χ^2 with 2nu d.f. is less than 2x

(Step 2) Use the approximation:

$p(\chi^2(nu) < x) = f(A / B)$ where $A = (x / nu)^{1/3} + (2 / 9nu) - 1$ and $B = (2 / 9nu)^{1/2}$

$f(A / B) = 1 / [1 + \exp(- h(A / B))]$

$$h\left(\frac{A}{B}\right) = \frac{A}{B}\left(1.59145 + 0.01095\frac{A}{B} + 0.06651\left(\frac{A}{B}\right)^2\right)$$

In NONMEM, these equation are coded in $PRED: no verbatim code.

In MONOLIX, a very accurate built-in function is used for P( ).

Fig. 2. Comparison of PREDs for the final model

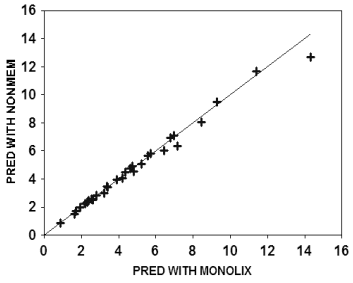


Fig. 3. Data, model output for typical parameters (MONOLIX)

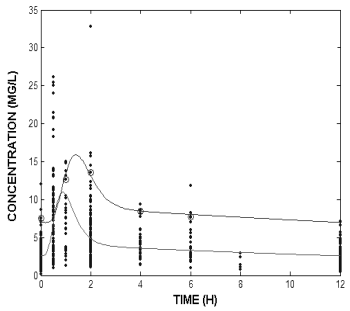
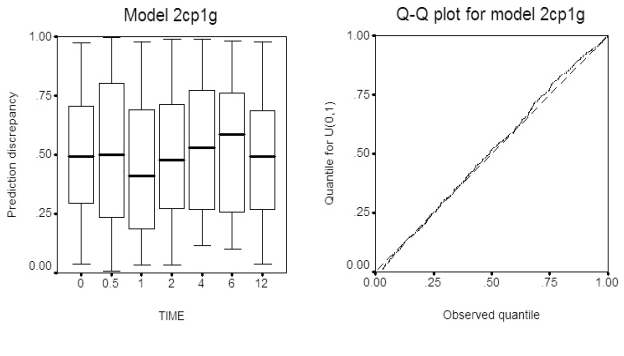


Fig. 4. Prediction discrepancies with MONOLIX



CONCLUSIONS

The proposed approximation for the incomplete gamma function is reasonably accurate and allows a simple implementation in NONMEM, avoiding the code of model derivatives.

A new formulation of the steady-state equation for the two-compartment model with gamma-distributed absorption times has been derived.

This model may be useful when absorption kinetics is not simply zero or first order.

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