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# Implementation of a transit compartment model for describing drug absorption in pharmacokinetic studies

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**Abstract** *Purpose*: To compare the performance of the standard lag time model (LAG model) with the performance of an analytical solution of the transit compartment model (TRANSIT model) in the evaluation of four pharmacokinetic studies with four different compounds. *Methods*: The population pharmacokinetic analyses were performed using NONMEM on concentration–time data of glibenclamide, furosemide, amiloride, and moxonidine. In the TRANSIT model, the optimal number of transit compartments was estimated from the data. This was based on an analytical solution for the change in drug concentration arising from a series of transit compartments with the same first-order transfer rate between each compartment. Goodness-of-fit was assessed by the decrease in objective function value (OFV) and by inspection of diagnostic graphs. *Results*: With the TRANSIT model, the OFV was significantly lower and the goodness-of-fit was markedly improved in the absorption phase compared with the LAG model for all drugs. The parameter estimates related to the absorption differed between the two models while the estimates of the pharmacokinetic disposition parameters were similar. *Conclusion*: Based on these results, the TRANSIT model is

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an attractive alternative for modeling drug absorption delay, especially when a LAG model poorly describes the drug absorption phase or is numerically unstable.

**Keywords** TRANSIT model · LAG model · Absorption delay · NONMEM · Pharmacokinetics

## Introduction

After drug administration by the oral route, some time passes before drug appears in the systemic circulation. This time reflects the time required for (i) disintegration of the delivery system, (ii) drug dissolution and/or release from the delivery system, (iii) transit to absorption site(s), (iv) migration of drug molecules to the absorption surface and/or (v) transfer of drug through the absorbing site tissue. Due to these processes, the appearance of drug in the circulation is delayed and this phenomenon is known as an *absorption delay* [1].

Although the drug absorption delay is a complex phenomenon, the standard approach for describing absorption delays in the pharmacokinetic analysis is rather simple, by introducing a lag time parameter. The lag time shifts the time of dosing as if the drug was in fact administered at a later time. This usually helps to describe the delayed absorption profiles more accurately. The importance of the lag time parameter has been stressed in work of Nerella et al., who showed that failure to specify this parameter can lead to incorrect estimates of pharmacokinetic parameters [2]. Nevertheless, lag time models often describe the absorption phase in the concentration–time profile poorly. The introduction of drug into the system at the lag time point signifies an abrupt increase of the absorption rate from a value of zero, which is a rather non-physiological approach. In addition, the discontinuous nature of the resulting concentration–time profile may cause difficulties in finding the optimal parameter values of the model using search algorithms. This type of discontinuous model is also known as a change-point model. A better description of the underlying physiology, as well as the impact of the drug formulation and physicochemical properties of the drug itself on the absorption process, can be assessed by modeling drug absorption as a multiple step process. Physiology-based absorption pharmacokinetic (PK) models have been developed that account for physicochemical properties of the drug, such as dissolution rate or the pH dependence of drug solubility, as well as for the complex physiological processes involved in the drug absorption, such as the metabolism in gut or liver and drug transit to the absorptive surface. These mechanistic models require extensive prior knowledge, such as information about the absorptive surface area, the rate of gastric emptying, drug concentration in the lumen, enzyme abundance in the gastrointestinal wall and liver, and liver blood flow [3,4]. This information is not usually available, preventing the routine application of physiologic models in drug absorption estimation. In a typical PK study, two plasma samples at most are collected during the absorption phase, and this is not enough from which to derive a fully mechanistic model.

Therefore, there is a need for developing models, which accurately describe concentration–time profiles in the absorption phase, without requiring extensive

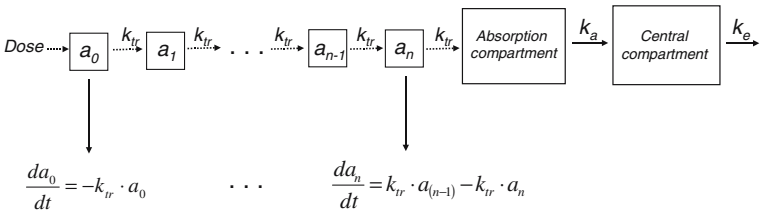


**Fig. 1** Schematic view and mathematical description of the drug flow through the chain of transit compartments

knowledge of the underlying processes. Transit compartment absorption models meet this requirement by describing drug absorption as a multiple step process represented by a chain of presystemic compartments, without assigning a physical correlate to each transit compartment (Fig. 1). In transit compartment models that have been published so far, the optimal number of transit compartments is assessed by stepwise addition of one compartment at the time. One of the drawbacks of stepwise addition is that it is a time consuming process, especially when the optimum number of transit compartments is high. Furthermore, estimation of inter-individual variability (IIV) in the number of transit compartments is not possible with step wise addition, where this number is fixed in the study population. Numerical estimation of the optimal number of transit compartments would address both of these problems, but has not been performed before.

The aims of this work were (i) to develop a transit compartment model in which the number of transit compartments is estimated and (ii) to evaluate the performance of this model in comparison to the standard lag-time model using PK data from four different compounds administered orally to man.

## Material and methods

### Data sets

The analysis was performed using data from pharmacokinetic studies with four different compounds: glibenclamide, moxonidine, furosemide, and amiloride. The main characteristics of the analyzed data are summarized in Table 1. A PK analysis of the glibenclamide data set and the moxonidine data set has been published before [5,6], while the manuscript reporting a PK analysis of Furosemide and Amiloride is in preparation (Frick et al., in preparation). Here, only a brief summary of the analyzed data will be given.

#### *Glibenclamide*

Eight healthy Caucasian subjects (four of each sex) participated in a placebo-controlled, randomized, single-blind crossover study, using intravenous and oral administration of glibenclamide. Multiple venous blood samples for analysis of serum drug concentration were drawn between 0 and 10 h after oral dose administration (0.33, 0.50, 0.67,

**Table 1** Summary of analyzed data

| | Glibenclamide | Furosemide | Moxonidine | Amiloride |
|---|---|---|---|---|
| No. of subjects | 8 | 43 | 74 | 43 |
| No. of samples/subject | 18 | 4 | 6–8 | 3 |
| Dose (mg) | 2.24, 3.5 | 20–250 | 0.2–0.6 | 5 |
| Administration route[a] | IV, PO | PO | PO | PO |
| Sex | Male, Female | Male, Female | Male, Female | Male, Female |
| Age (yrs) | 25 (21–33) | 69.5 (44–85) | 66 (43–78) | 69.5 (44–85) |
| Weight (kg) | –[b] | 77 (53–125) | 78 (41–125) | 77 (53–125) |

[a] PO, oral route; IV, intravenous route
[b] No data available

0.83, 1.0, 1.25, 1.5, 1.75, 2.0, 2.25, 2.5, 2.75, 3.0, 3.5, 4.0, 5.0, 6.0, 8.0, and 10.0 h). Sampling scheme following intravenous administration included additional sampling times at 0.083 and 0.017 h.

Serum concentrations of glibenclamide were measured by HPLC with a detection limit of 1 ng $ml^{-1}$. The details of this study can be found in previous reports [6–8].

*Moxonidine*

The study was conducted as a phase II, multicenter, dose-finding study of oral moxonidine tablets versus placebo in patients with congestive heart failure. Active treatment started at 0.1 mg twice daily and was escalated to a predefined dose; 0.1, 0.2 or 0.3 mg twice daily. Pharmacokinetic samples were collected at two occasions in each subject, after the first dose and after 12 weeks of therapy of which the last 8 weeks had been on the same dose. The sampling times were 0.5, 1, 1.5, 2, 4, 6, and 8 h after the morning dose. Plasma moxonidine concentrations were measured by the GC/MS method, validated at a range from 0.025 to 5.0 ng $ml^{-1}$. The details of this study have been reported previously [5].

*Furosemide and amiloride*

A total of 43 patients with clinically stable congestive heart failure participated in this study. All patients were treated with an amiloride dose of 5 mg once daily and with 30–250 mg furosemide once daily on different study occasions. At study day 21, 3–4 venous blood samples were collected at various time points between 30 and 395 min after dose administration. Serum concentrations of both drugs were measured by ion-pair reversed phase liquid chromatography with a detection limit of 1 ng $ml^{-1}$ and 5 ng $ml^{-1}$ for amiloride and furosemide, respectively (Frick et al., in preparation).

## Model structure

Initially, the structural model building was redone for all studies using the final model from the previous analysis [5,6]. One- and two-compartment disposition models were

evaluated for all drugs using non-linear mixed effect modeling software, NONMEM (version VI $\beta$) [9].

Initially, the delay was modeled using a traditional lag time model (LAG model), i.e., including the estimation of a lag time parameter, $t_{\text{lag}}$. Improvement of the model by addition of IIV in $t_{\text{lag}}$ was examined.

The next step was to analyze the absorption delay with the transit compartment model (TRANSIT model) shown schematically in Fig. 1. This model described the absorption delay by the passage of drug through a series of transit compartments with a single transfer rate constant, $k_{\text{tr}}$ (Eq. 1). The rate of change of the amount of drug in the $n$th compartment is given by:

$$\frac{da_n}{dt} = k_{\text{tr}} \cdot a_{(n-1)} - k_{\text{tr}} \cdot a_n \tag{1}$$

In Eq. 1, $da_n/dt$ stands for the rate of change of substance $a$ in compartment $n$ at time $t$, $a_n$ is the drug amount in the $n$th compartment at time $t$, $k_{\text{tr}}$ stands for a transit rate constant from $n\text{th}-1$ compartment to the $n$th compartment and $n$ is the number of transit compartments.

For estimating the optimal number of transit compartments, the analytical solution for $a_n$ is given by the function:

$$a_n(t) = F \cdot \text{Dose} \cdot \frac{(k_{\text{tr}} \cdot t)^n}{n!} \cdot e^{-k_{\text{tr}} \cdot t} \tag{2}$$

In Eq. 2, $F$ stands for drug bioavailability and $n!$ for the $n$ factorial function with argument $n$. To compute this function numerically, the approximation of Stirling to $n!$ was used (Eq. 3):

$$n! \approx \sqrt{2\pi} \cdot n^{n+0.5} \cdot e^{-n} \tag{3}$$

An approximation error of the Stirling formula is less then 1% for $n > 2$. If $n$ is approaching a small value ($< 2$), an improved version of the approximation has been proposed [10].

Drug was transferred from the last of the presystemic transit compartments to the central compartment via an absorption compartment in which the disappearance of drug was described with the rate constant $k_a$. The rate of change of drug amount in the absorption compartment ($dAa/dt$) is given by:

$$\frac{dAa}{dt} = \text{Dose} \cdot F \cdot k_{\text{tr}} \cdot \frac{(k_{\text{tr}} \cdot t)^n \cdot e^{-k_{\text{tr}} \cdot t}}{\sqrt{2\pi} \cdot n^{n+0.5} \cdot e^{-n}} - k_a \cdot A_a \tag{4}$$

Stirling's approximation to $n!$ is a continuous function of $n$, which allowed implementation of Eq. 4 in NONMEM using subroutines for general non-linear models, i.e., ADVAN6 or ADVAN 8, and to estimate a non-integer number of transit compartments $n$. To prevent numerical difficulties when $n$ was large, the transformation shown in Eq. 5 was needed.

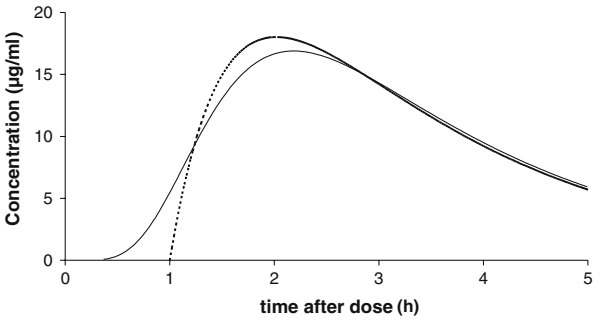


**Fig. 2** Simulated concentration–time profiles with the LAG (dotted line) and TRANSIT model (solid line) when $k$=0.5 1/h, $k_a$ = 1.7 1/h, Dose = 30 mg, $n$=5, and $MTT$ (or $t_{\text{lag}}$) = 1 h

$$\frac{dAa}{dt} = e^{\ln(\text{Dose}\cdot F\cdot k_{\text{tr}}\cdot \frac{(k_{\text{tr}}\cdot t)^n\cdot e^{-k_{\text{tr}}\cdot t}}{\sqrt{2\pi}\cdot n^{n+0.5}\cdot e^{-n}})} - k_a \cdot A_a \tag{5}$$

A useful parameter in the TRANSIT model is the mean transit time (*MTT*), which represents the average time spent by drug molecules traveling from the first transit compartment to the absorption compartment. The relationship between *MTT*, $n$ and $k_{\text{tr}}$ is shown in Eq. 6:

$$k_{\text{tr}} = \frac{n+1}{MTT} \tag{6}$$

Within NONMEM, two parameters are estimated while the third parameter is derived through Eq. 6. In this work we have chosen to estimate $n$ and *MTT*. An example of implementation of the TRANSIT model in NONMEM is shown in the appendix. A comparison of the concentration–time profiles obtained with the LAG model and the TRANSIT model is shown in Fig. 2. The concentration–time profile obtained with the TRANSIT model has a smoother initial increase in the concentration-time curve as a consequence of the gradually increasing absorption rate. This is in contrast to the abrupt on/off absorption modeled by means of the LAG model, assuming an abrupt switch in the absorption rate from 0 to a constant value at $t_{\text{lag}}$. With increasing number of transit compartments, the absorption rate profile becomes more delayed, asymmetric and skewed to the right. The reason for this is that for a given value of *MTT*, $k_{\text{tr}}$ will simultaneously increase with increasing $n$ according to Eq. 6 and the time for drug to reach the absorption compartment will increase leading to a delayed absorption. Figure 3 shows that with a large number of transit compartments, i.e., if $n$ would be increased to infinity, the TRANSIT model becomes equivalent to the LAG model, although it will never become a discontinuous change-point model.

Compared to the standard analysis with the LAG model, the TRANSIT model differed by the presence of one additional parameter, the number of transit compartments $n$. All other model features, i.e., the structural PK disposition model, the covariate model and the residual error model were kept the same as assessed previously with the LAG model.

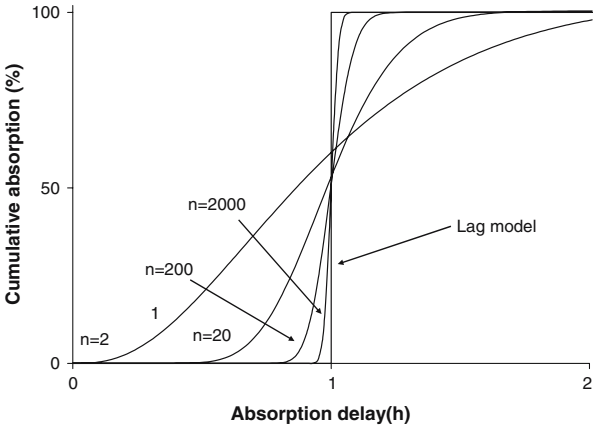


**Fig. 3** Simulated profiles of the cumulative amount of drug reaching the absorption compartment by the LAG model ($t_{lag} = 1$ h) and several TRANSIT models, which differ in the number of transit compartments (2, 20, 200, 2000) when Dose = 100 mg and $MTT = 1$ h

## Model development

Each of the four studies was analyzed separately with both models, TRANSIT and LAG. The analyses were performed using NONMEM with the first order conditional estimation method with interaction (FOCE INTER). If estimation of the certain random effect parameters was associated with numerical difficulties, the estimation method that is a hybrid of the first order (FO) and first order conditional estimation method (FOCE HYBRID) was tried so that parameter in question was set to be estimated with the FO method.

Goodness-of-fit was assessed using the Objective Function Value (OFV), the precision of parameter estimates and graphical analysis of the predictions and residuals, which was performed within the program Xpose, version 3.1 [11]. The 95% confidence intervals for parameter estimates were estimated using the log-likelihood profiling method. The confidence intervals (CI) that can be calculated from the standard error (SE) estimates that is output by NONMEM, rely on the assumption that the parameter estimates are normally distributed, whereas the log-likelihood profiling is a method which does not make any assumptions regarding the parameter symmetry distribution [12,13].

The assessment of statistical significance between two hierarchical models was based on the difference between OFV values, OFV being proportional to minus twice the log likelihood. The difference in OFV between two hierarchical models ($\Delta$OFV) is assumed to follow a $\chi^2$ distribution with degrees of freedom equal to the number of differing parameters. On this basis, the improvement in the model fit from the inclusion of a model parameter can be assigned a significance level. A $\Delta$OFV of 3.84 corresponds to a $p$ value of 0.05. Models were expanded with a parameter if the addition of that parameter resulted in a decrease in the OFV of 3.84 or more [9]. As the TRANSIT model collapses into the LAG model when $n$ is approaching infinity, these models may be considered as hierarchical; otherwise other tests for model selection can be performed using OFV (e.g., Akaike Information Criterion) [12].

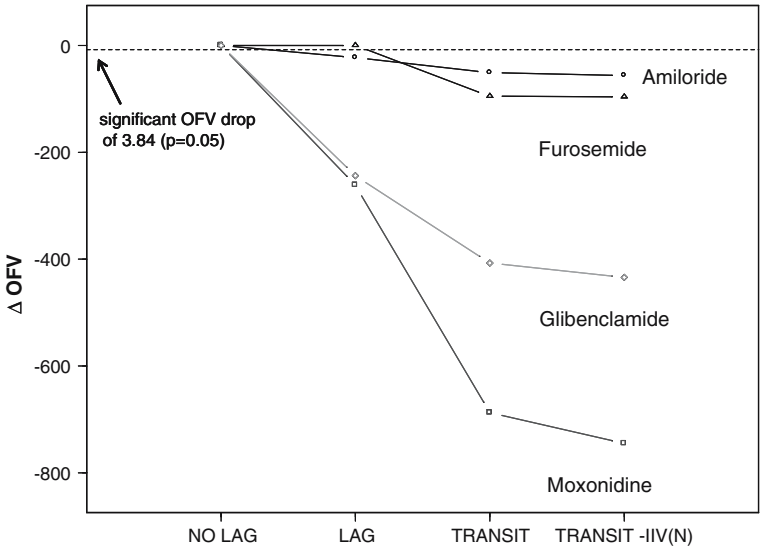


**Fig. 4** Improvement in the goodness-of-fit with the TRANSIT model for all investigated compounds. NO LAG—model without a lag time, LAG—model with a lag time, TRANSIT—transit compartment model with estimated IIV in *MTT* if possible, TRANSIT-IIV (N)—transit compartment model with estimated IIV in number of transit compartments

## Results

The LAG and the TRANSIT model described all data sets adequately. For all investigated drugs, a significant absorption delay was estimated with the TRANSIT model, while absorption delay was not estimable for furosemide when the LAG model was applied. With the TRANSIT model, a statistically significant improvement in the fit, up to ΔOFV of −483 units, was visible with all data sets (Fig. 4). Visually, this model described the concentration–time profile more accurately, especially in the absorption phase and around the concentration peak (Fig. 5). The differences in population parameter estimates obtained with the LAG and the TRANSIT model were in general more pronounced for absorption pharmacokinetic parameters ($k_a$ and $t_{lag}/MTT$) than for disposition PK parameters, e.g., clearance (CL) and central volume of distribution ($V$) (Fig. 6). The estimated number of transit compartments for glibenclamide, furosemide, amiloride, and moxonidine were 22.9, 20.1, 8.15, and 7.17, respectively.

In the following section, results obtained from analysis of the four different data sets are reported with focus on the modeling of the absorption delay. Parameter estimates from the LAG and TRANSIT final runs are given in Tables 2–5.

### Glibenclamide

The glibenclamide data set was initially described with a two-compartment model and first order absorption with a lag time. With FOCE INTER, estimation of IIV in $t_{lag}$ was associated with numerical difficulties which could not be resolved by using FOCE

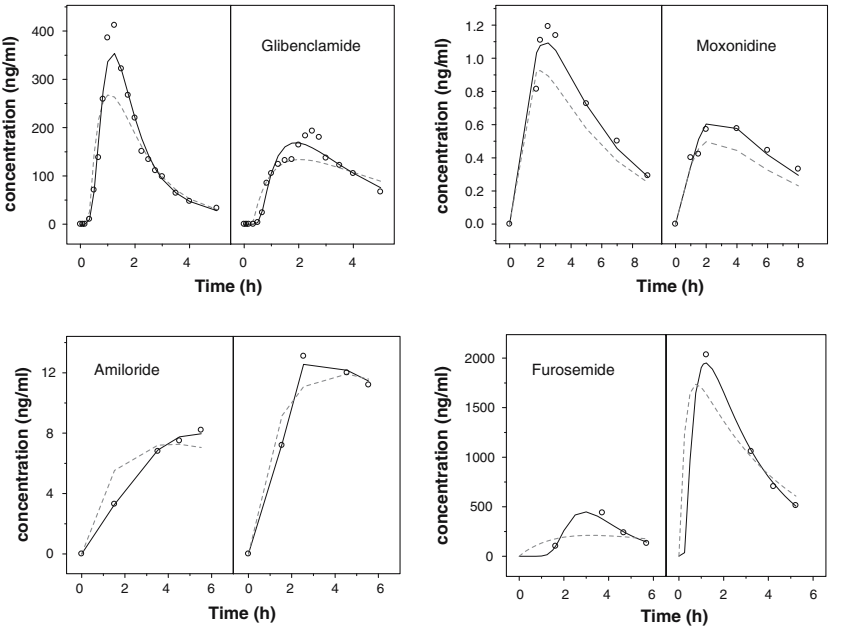


**Fig. 5** A comparison of individual predictions obtained with the LAG (thin grey line) and the TRANSIT (thick black line) models, for two representative profiles of each drug. Observations are represented with an open circle

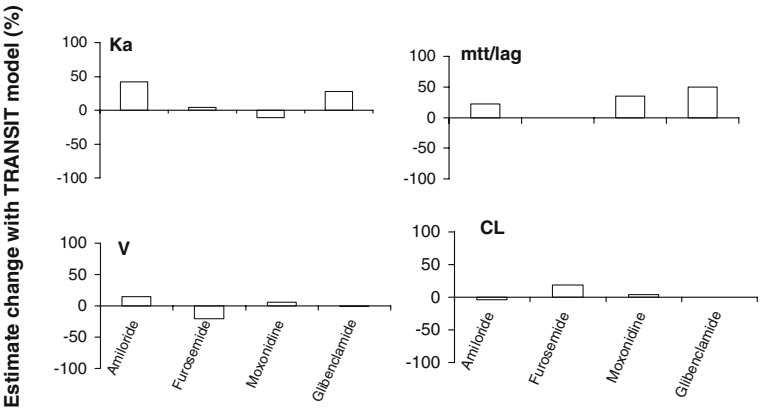


**Fig. 6** The relative change in population PK parameter estimates obtained with the TRANSIT model compared with the LAG model for all investigated compounds

HYBRID method with IIV in $t_{lag}$ set to be estimated with FO method. Accordingly, the final LAG model could be estimated with FOCE INTER without IIV in $t_{lag}$.

The analysis of the data with the TRANSIT model resulted in a statistically significant improvement in the model fit compared to the final LAG model, with an OFV decrease of 163 and successful estimate of IIV in MTT. Addition of IIV in *n* improved the fit with a further decrease in OFV of 27 in the final FOCE INTER run. In addition,

**Table 2** Final population parameter estimates for analysis of glibenclamide

| Parameter | LAG | | TRANSIT | |
|---|---|---|---|---|
| | Estimate | Confidence interval limits (95%) | Estimate | Confidence interval limits (95%) |
| OFV | 1840 | | 1649 | |
| $k$ (1/h) | 1.13 | 1.02–1.24 | 1.14 | 1.03–1.26 |
| $V$ (l) | 3.84 | 3.39–4.34 | 3.79 | 3.35–4.28 |
| k23 | 0.34 | 0.30–0.39 | 0.363 | 0.317–0.419 |
| k32 | 0.66 | 0.53–0.80 | 0.69 | 0.56–0.83 |
| IIV in $k$ (%) | 12 | 7–21 | 12 | 7–21 |
| IIV in $V$ (%) | 15 | 9–27 | 15 | 9–27 |
| IIV in k32 (%) | 18 | 7–39 | 17 | 7–37 |
| Residual variability (%) | 8.1 | 7.1–9.3 | 8.2 | 7.2–9.6 |
| *Absorption* | | | | |
| $k_a$ (1/h) | 0.51 | 0.27–0.92 | 0.65 | 0.35–1.20 |
| $t_{\text{lag}}$ (h) | 0.306 | 0.295–0.313 | –[b] | – |
| $MTT$ (h) | –[b] | – | 0.458 | 0.359–0.584 |
| $n$ | –[b] | – | 22.9 | 10.8–64.8 |
| Bioavailbility ($F$) | 0.94 | 0.75–1.23 | 0.96 | 0.78–1.19 |
| IIV in $k_a$ (%) | 74 | 45–140 | 76 | 47–140 |
| IIV in $t_{\text{lag}}$ (%) | 0 [a] | – | –[b] | – |
| IIV in $MTT$ (%) | –[b] | – | 30 | 19–55 |
| IIV in $n$ (%) | –[b] | – | 89 | 48–193 |
| IIV in $F$ (%) | 25 | 13–52 | 25 | 16–48 |

[a] Fixed to zero as estimation of this parameter resulted in numerical difficulties
[b] Parameter is not used

it was observed that the TRANSIT model made an improvement in the goodness of fit of disposition phase in some instances compared to the LAG model (Fig. 5). Table 2 shows the parameter estimates obtained with the two models.

## Furosemide

The furosemide data set was initially described with a one-compartment model and first order absorption. It was not possible to estimate $t_{\text{lag}}$, as the estimate of this parameter approached the time of the first observation in the data set (0.5 h) giving unreliable disposition parameter estimates associated with large IIVs and large final gradients during the minimization procedure. The latter is an indication of an unsuccessful minimization. Applying the TRANSIT model to the data resulted in successful minimization with satisfactory (low) final gradients, estimable *MTT* with associated IIV and an OFV reduction of 95 units. However, it was not possible to obtain the standard errors calculated by NONMEM. Addition of IIV in $n$ did not significantly improve the model. The final parameter estimates are given in Table 3.

**Table 3** Final population parameter estimates for analysis of furosemide

| Parameter | LAG | | TRANSIT | |
|---|---|---|---|---|
| | Estimate | Confidence interval limits (95%) | Estimate | Confidence interval limits (95%) |
| OFV | 59 | | −36 | |
| CL(l/h) | 14.5 | 10.2–20.1 | 17.2 | 12.3–24.2 |
| $V$ (l) | 56.8 | 33.7–77.7 | 45.1 | 31.3–70.1 |
| Residual variability (%) | 20.5 | 15.9–30.1 | 20 | 17–24 |
| *Absorption* | | | | |
| $k_a$ (1/h) | 0.365 | 0.02–1.92 | 0.38 | 0.18–0.91 |
| $t_{\text{lag}}$ (h) | –[a] | – | –[b] | – |
| $MTT$ (h) | –[b] | – | 0.37 | 0.12–0.72 |
| $n$ | –[b] | – | 20.1 | 8.6–145.7 |
| IIV in $k_a$ (%) | 190 | 100–324 | 105 | 73–169 |
| IIV in $t_{\text{lag}}$ (%) | –[a] | – | –[b] | – |
| IIV in $MTT$ (%) | –[b] | – | 120 | 62–235 |

[a] Fixed to zero as estimation of this parameter resulted in numerical difficulties
[b] Parameter is not used

**Table 4** Final population parameter estimates for analysis of moxonidine

| Parameter | LAG | | TRANSIT | |
|---|---|---|---|---|
| | Estimate | Confidence interval limits (95%) | Estimate | Confidence interval limits (95%) |
| OFV | −754 | | −1237 | |
| CL(l/h) | 26.6 | 25.1–28.2 | 27.7 | 27.6–28.3 |
| $V$ (l/kg) | 1.43 | 1.35–1.51 | 1.51 | 1.44–1.59 |
| IIV in CL (%) | 21 | 17–24 | 19 | 16–21 |
| IIV in $V$ (%) | 16 | 14–20 | 17 | 14–22 |
| IOV in CL (%) | 13 | 9–18 | 12 | 9–15 |
| Residual variability (%) | 33 | 31–35 | 22 | 21–23 |
| *Absorption* | | | | |
| $k_a$ (1/h) | 4.34 | 2.76–6.91 | 3.88 | 3.54–4.50 |
| $t_{\text{lag}}$ (h) | 0.24 | 0.23–0.25 | –[b] | |
| $MTT$ (h) | –[b] | | 0.324 | 0.255–0.369 |
| $n$ | – | | 8.17 | 4.66–8.88 |
| IIV in $k_a$ (%) | 165 | 128–212 | 107 | 89–148 |
| IIV in $t_{lag}$ (%) | –[a] | | –[b] | |
| IIV in $MTT$ (%) | –[b] | | –[a] | |
| IIV in $n$ (%) | –[b] | | 47 | 0–152 |
| IOV in $k_a$ (%) | 70 | 50.3–99.3 | 43 | 0–52 |
| IOV in $MTT$ (%) | –[b] | | 232 | 157–271 |
| IOV in $n$ (%) | –[b] | | 280 | 255–348 |

[a] Fixed to zero as estimation of this parameter resulted in numerical difficulties
[b] Parameter is not used

**Table 5** Final population parameter estimates for analysis of amiloride

| Parameter | LAG | | TRANSIT | |
|---|---|---|---|---|
| | Estimate | Confidence interval limits (95%) | Estimate | Confidence interval limits (95%) |
| OFV | 450 | | 422 | |
| CL(l/h) | 0.368 | 0.328–0.413 | 0.354 | 0.321–0.391 |
| $V$ (l) | 426 | 342–549 | 487 | 394–607 |
| IIV in CL (%) | 22 | 13–30 | 19 | 12–28 |
| IIV in $V$ (%) | 32 | 19–49 | 40 | 22–57 |
| Residual variability (%) | 11 | 9–14 | 7.5 | 6.3–9.4 |
| *Absorption* | | | | |
| $k_a$ (1/h) | 1.25 | 0.84–1.86 | 1.77 | 1.06–9.12 |
| $t_{lag}$ (h) | 0.841 | 0.612–0.977 | –[b] | – |
| $MTT$ (h) | –[b] | – | 1.03 | 0.65–1.53 |
| $n$ | –[b] | | 8.15 | 2.42–21.21 |
| IIV in $K_a$ (%) | 69 | 46–100 | –[a] | |
| IIV in $t_{lag}$ (%) | –[a] | – | –[b] | – |
| IIV in $MTT$ (%) | –[b] | – | 52 | 36–61 |

[a] Fixed to zero as estimation of this parameter resulted in numerical difficulties
[b] Parameter is not used

## Moxonidine

Moxonidine concentrations were initially described by a one-compartment model with first order absorption and a lag time. IIV in $t_{lag}$ could not be estimated with the LAG model. Similarly, the variability in absorption delay (IIV in *MTT*) could not be estimated when the TRANSIT model was used. However, the variability in the absorption profile could be captured by IIV and inter-occasion variability in $n$. This resulted in an OFV decrease of 483 compared with the final LAG model. For both models, NONMEM failed to estimate standard errors. Table 4 shows the parameter estimates obtained with the two final models.

## Amiloride

The concentration of amiloride was initially described with a one compartment model and first order absorption with a lag time. An attempt to estimate IIV in $t_{lag}$ resulted in large final gradients, numerical difficulties and failure in obtaining the standard error within NONMEM. By applying the TRANSIT model successful minimization, estimable IIV in *MTT*, successful estimation of standard errors and an OFV drop of 28 units were achieved. IIV in $n$ was possible to estimate and resulted in a further OFV decrease of 5, but standard errors could not be obtained and this variance term was omitted. The parameter estimates are shown in Table 5.

## Discussion

An adequate model for the delay in the initial appearance of drug in plasma is essential for studying drug absorption properties and may be of importance in the development of pharmacodynamic models on the basis of predicted concentration–time profiles. In this study, the performance of a transit compartment model for describing absorption delays was evaluated by estimating the optimal number of transit compartments. Conventional PK models describe a delay in the absorption of drug by introducing a lag time. These models often give a poor description of the absorption phase, which may result in bias in other PK parameter estimates included in the model.

The LAG model predicts a sudden increase in concentration, which can result in numerical difficulties during estimation and is not likely to be a realistic physiological description of the drug absorption. In contrast, the TRANSIT model describes the concentration–time profile as a gradually increasing continuous function. Hence, the nature of the TRANSIT model is more descriptive of the physiological conditions, although the number of estimated transit compartments is not related to physical compartments. The modeling of PK data from four different compounds favored the TRANSIT model for all compounds according to OFV and graphical diagnostics.

Parameter estimates for the absorption phase, $k_a$ and $t_{\text{lag}}$ (*MTT*) significantly differed between the LAG and TRANSIT models. For two drugs studied (furosemide and glibenclamide) the estimated $t_{\text{lag}}$ value was 0.5 h and 0.3 h, respectively. These values are very close to the time of the first observation after dosing (0.5 h for furosemide and 0.333 for glibenclamide), suggesting that these parameter estimates are biased by the observation times.

The TRANSIT model yielded estimates of the IIV in *MTT* in all four drugs except moxonidine, while the LAG model did not allow estimation of IIV in $t_{\text{lag}}$ for any of the example drugs. This is most likely due to numerical problems that might arise when the differential equation solver (Runge–Kutta algorithm in NONMEM) attempts to integrate over a discontinuity at the lag time point. In our experience, also including an IIV parameter on $t_{\text{lag}}$ frequently gives rise to this estimation problem. In contrast, extension of the TRANSIT model with IIV in $n$ resulted in a statistically significant improvement in the model fit for both glibenclamide and moxonidine.

The TRANSIT model offers greater flexibility for modeling the drug absorption phase and was with our data numerically more stable compared to the LAG model. These are important advantages in population analysis because an accurate description of drug absorption is in practice difficult to achieve when little information about the absorption phase is available. Misspecification of the rate of absorption is an issue since it can lead to biased disposition parameter values, in particular to bias in the volume of distribution [14]. A hint of such bias was observed in our analysis of amiloride and furosemide in which the estimate for the volume of distribution obtained with the LAG model differ approximately 20% from the estimate obtained with the TRANSIT model.

The TRANSIT model describes *absorption delay* as drug transit through a chain of identical compartments that are linked to the central compartment by a first-order absorption process. The same principle has been applied in the population PK model developed by Rousseau et al. for orally administered cyclosporine, where

the absorption is described by a linear chain of five compartments connected by a single exiting rate constant and placed upstream of the central compartment [15]. The concept of transit compartments has also been used in population pharmacokinetic/pharmacodynamic (PK/PD) analysis for modeling delayed PD responses [16]. An example is the semi-physiological model for myelosuppression developed by Friberg et al., which successfully uses a chain of transit compartments to mimic the different cell stages within the bone marrow to model the time course of leukocytes after varying schedules of anticancer drug [17]. In transit compartment models that have been published so far, the optimal number of transit compartments is assessed by stepwise addition of one compartment at a time. The analytical solution derived for the TRANSIT model describes the absorption delay and is given by the gamma distribution function. Thus, the absorption profile obtained by the TRANSIT model should be distinguished from the absorption profile modeled by means of the Erlang distribution function, which is a special case of the gamma distribution function when $n$ is constrained to an integer number. The Erlang function used by Rousseau et al. is equivalent to the step-wise addition approach [15]. The usage of the Erlang distribution function, as a discrete function, requires manual optimization of number of transit compartments whereas the TRANSIT model is able to determine the optimum number of the pre-systemic compartments by computation. This offers three advantages. Firstly, the manual optimization of transit compartments is a time-requiring procedure especially when the optimal number of transit compartments is high. With numerical estimation the time required for the analysis is shortened. Secondly, the TRANSIT model allows estimation of a high number of transit compartments, which is not possible with the manual optimization, since NONMEM allows maximally up to 20 compartments to be coded within the control stream. Lastly, the TRANSIT model allows extension for additional parameters, like the IIV and covariance terms for $n$. However, a disadvantage of the TRANSIT model lies in the assumption that the total amount of the drug is administered at time 0 (i.e., initial condition of the differential equation system equals the dose given corrected for its bioavailability) and cannot be changed over time. This assumption prevents from the application of the TRANSIT model to the systems in which input into the first transit compartments occurs continually and it has been discussed previously [16]. For example, when modeling entero-hepatic recirculation, a drug or metabolite is continually secreted into the bile, into the gut and then re-absorbed. A time delay from the drug appearance in the gut to the re-absorption process cannot be modeled using the analytical solution of the TRANSIT model, but it could be very well described by manually implemented transit compartments with their own differential equations.

A considerable improvement in goodness of fit was observed with rich data sets. However, when sparse data were analyzed, the improvement in the fit was not as pronounced in terms of OFV drop, but still statistically significant and visible in GOF plots. In addition to that, the TRANSIT model was more stable and allowed estimation of the lag phase length and IIV in MTT, the latter being not possible with the LAG model. This suggests that the TRANSIT model may perform better in comparison to the LAG model also when analyzing sparse data.

In conclusion, for all four drugs studied, the TRANSIT model described the absorption delay better than the LAG model. There are four advantages of the proposed model.

First, the continuous nature of the model reflected in a gradual (and not abrupt) increase in the absorption rate approximates physiological processes better. Second, the model is able to estimate the optimal number of transit compartments numerically and thereby removes the need for a time-consuming manual determination of this parameter by manual coding of transit compartments. Third, the model has from a computational point of view favorable properties for likelihood optimization due to the absence of a change-point. Last, the stability and flexibility of the TRANSIT model allows further elaboration of the absorption modeling such as IIV on *MTT* and *n*. Therefore, the TRANSIT model is an attractive alternative for characterizing delayed absorption profiles, especially when interindividual variability in the rate and extent of absorption is high.

## Appendix

Example of the implementation of the TRANSIT model for combination of intravenous and single dose oral data in NONMEM

```
$PROB Implementation of the TRANSIT model
$INPUT ID AMT TIME DV CMT EVID
$DATA data.csv IGNORE=@
$SUBROUTINES ADVAN6 TOL5
$MODEL COMP = (ABS)   ; absorption compartment
       COMP = (CEN)   ; central compartment
$PK
IF(AMT.GT.0.AND.CMT.EQ.1)PODO=AMT      ; oral dose
IF(AMT.GT.0.AND.CMT.EQ.2)PODO=0        ; iv dose
CL = THETA(1)*EXP(ETA(1))
V2 = THETA(2)*EXP(ETA(2))
K = CL/V2
; absorption
F1 = 0
F2 = 1
KA = THETA(3)*EXP(ETA(3))                    ; absorption rate constant
BIO = THETA(4)*EXP(ETA(4))                   ; bioavailability
MTT = THETA(5)*EXP(ETA(5))                   ; mean transit time to the absorption comp.
N = THETA(6)*EXP(ETA(6))                     ; number of transit compartments
KTR = (N+1)/MTT                              ; transit rate constant
; NFAC = SQRT(2*3.1415)*N**(N+0.5)*EXP(-N)   ; Stirling approximation to n!
                                               included for completeness
LNFAC = LOG(2.5066)+(N+0.5)*LOG(N)-N         ; logarithmic transformation of Stirling
                                               approximation
S2 = V2
$DES
; untransformed equation, included for completeness
; DADT(1) = BIO*PODO*KTR*(KTR*T)**N*EXP(-KTR*T)/NFAC-KA*A(1)
; transformed equation used to prevent numerical difficulties when n is large
DADT(1) = EXP(LOG(BIO*PODO)+LOG(KTR)+N*LOG(KTR*T)-KTR*T-LNFAC)-KA*A(1)
DADT(2) = KA*A(1)-K*A(2)
$ERROR
$THETA
```

$OMEGA
$SIGMA
$ESTIMATION
$COVARIANCE

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