

PERSPECTIVE

Individualized Absorption Models in Population Pharmacokinetic Analyses

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Absorption processes are complex but rarely have sufficient data to capture parameters of a mechanistic model. Typically, a single absorption model (e.g., first-order, mixed-order, lag, or distributive delay model), is assumed to apply to all individuals with the expectation that random effects will accommodate individual differences. However, distinct absorption profiles may coexist in a given dataset. We propose that individualized absorption models should be considered when multiple absorption profiles are evident in a population analysis.

Absorption models in pharmacokinetic studies are typically empirical. There are multiple steps for a drug product to be absorbed into the body and the granularity of the absorption process that can be determined is a function of the sampling frequency. When sampling is relatively limited, simpler absorption models are preferred because inadequate data are available to support a more complicated model. Upon ingesting a tablet, it disaggregates, disperses, and the drug must go into solution before being absorbed, usually in the duodenum. Even ignoring complicating issues with poor aqueous solubility, the highest rates of absorption are not likely to occur for some time after administration. Nonetheless, the first-order absorption model does dictate that the maximal transfer of drug into the central compartment occurs immediately upon dosing. This model misspecification is largely accepted as ignorable as there are usually little data to suggest a more complicated absorption process is needed. Furthermore, confidence intervals around absorption parameters are usually quite large (often with relative standard errors > 100%) and include zero. That does not mean we do not need an absorption parameter, but does speak to our contention that the absorption model is a mathematical necessity that allows the drug concentration to be zero (or low) at time zero and increase over time.

Given the physical reality of the pre-absorption steps that occur, our models are generally a highly simplified convenience. Looked at this way, the absorption process becomes little more than a nuisance model, at least from a pharmacokinetic perspective. However, one cannot always ignore early exposures and there are examples when the absorption process is associated with clinical outcomes.^{1–3} In such cases, it is necessary to have an appropriate study design to collect samples when they make a difference, have an absorption model that reasonably reflects those observations,

and have an outcome model that links early exposure to outcome. This would be particularly important in simulation projects that are optimizing dosing to outcomes.

Absorption models become more complicated when we move into population pharmacokinetic analyses. One may examine absorption in a population via a concentration-time plot and make a decision to use, for example, a first-order absorption model. This practice, however, can mask a multitude of misspecifications. It might initially seem that a simple absorption model might be sufficient from inspection of the pooled data, but, on closer examination, a more complicated absorption profile may be observed in individual profiles. Some drugs demonstrate an observed delay in absorption or multiple irregular peaks and more complicated models have been described^{4–6} to accommodate these observations. Indeed, mechanism-based absorption models have been described and successfully applied⁷ as have mixture models.⁸ However, they become quite complicated and require considerable data to estimate the parameters.

Beyond our compelling fanaticism to predict all observations as closely as possible, perhaps the reason we invest time in considering the absorption process is that it may influence other estimated parameters in an adverse way. Many long-term survivors of nonlinear mixed-effects model building have examples of absorption misspecification impacting other parameters. Notably, the estimates of volume of distribution (V/F) or perhaps bioavailability may be biased, with upwardly biased estimates of the population variability, while total apparent clearance seems less likely to be sensitive to model misspecification in absorption.

In practice, we typically assume there is a single absorption process whether the model is simple or complex. However, it may not be the case that all subjects exhibit the same absorption profile. Some subjects may seem to have a first-order process, whereas other profiles may be better described using an Erlang process.⁹ In an Erlang model, for example, the *post hoc* absorption transit rate constant for someone with an apparent first-order absorption could be quite large, although it would be estimated to be smaller for another individual with a more distributed delay absorption process. We justify a single absorption process by assuming the random effect will accommodate individual differences, leading to the overall result of a decidedly large population variability.

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The concept of using different absorption processes for different groups is not foreign. It is what we often do when we create a FAST/FED covariate in our data sets. That covariate may be useful to identify differences in the rates (KA) or extents (F) of absorption between two groups, or allow parameters to change within an individual in crossover studies.

It may be the case that no covariate is available to explain a difference in absorption profiles. One may postulate two groups and create a mixture model that allows any individual to be in one group or the other. However, that level of sophistication is perhaps unnecessary, particularly if one considers absorption to be more of a nuisance process. Our contention is that it may be possible to examine data from an individual and make a reasonable assignment to an appropriate group. Although such an approach may be sufficiently arbitrary to make one uncomfortable, it need not. The difference in absorption between two subjects may be immediately obvious on visual inspection. There has been little discussion in the community regarding the selection of different absorption models at the individual level within a single population analysis when absorption data are limited.

In this perspective, we wish to provide an example to illustrate differences seen when prespecifying the absorption model for each individual by visual inspection of the data from a cohort of children with congenital adrenal hyperplasia being treated with hydrocortisone. The study was approved by the University of Minnesota Institutional Review Board. Informed consents and assents were obtained. Concentration-time data consisting of 682 hydrocortisone observations from 53 patients were subject to a population analysis. Samples were obtained at 0, 0.25, 0.5, 0.75, 1, 1.25, 1.5, 2, 2.5, 3, 4, and 6 hours. Upon visual inspection of the data, it became obvious that three distinct absorption profiles existed (see **Figure 1**). It seemed that absorption data from many subjects would conform to a simple first-order absorption process ($n = 20$). Many others demonstrated a delayed absorption process, which would conform to an Erlang model with four transit compartments ($n = 21$).⁹ Finally,

some subjects demonstrated distinct shoulders on the peak indicating a double peak process ($n = 12$).¹⁰ The input process for such a model does become more complicated, but it is tractable. It requires two dosing depot compartments with the fraction of the total dose split between each compartment being estimated. One dose was put into the first transit compartment of the distributed-delay model (delayed fraction), whereas the remaining dose was placed in a depot compartment immediately prior to the central compartment (first-order). The schematic for each of these models is provided in **Figure S1**. We fit the data using NONMEM version 7.4 (ICON Development Solutions) with first-order conditional estimation method with interaction to each of three approaches that differed in terms of absorption assignment: (i) all subjects assigned to first-order absorption; (ii) all subjects assigned to Erlang absorption; and (iii) assignment via visual inspection to first-order, Erlang, or the shoulder model. For the visual assignment, two authors (M.M.J. and R.C.B.) classified and agreed upon the patterns.

The differences among the three analyses are summarized in **Table 1**. As expected, prespecifying the absorption process based on visual inspection provided the lowest objective function value, with the longest computational times. Because this is not a formal simulation study, the degree of bias and imprecision that exists in the estimates cannot be commented on. Nonetheless, the total apparent clearance point estimate and variability changed little across the three analyses, whereas the estimates for V/F were more affected. Although the differences are relatively small, it is apparent that the choice of the absorption model does influence V/F. It was also noted that the residual unexplained variability was not highly sensitive to the absorption model, although more of a difference from the visual assignment approach was expected given that approximately half of our data were obtained during the absorption phase.

If one accepts that different individuals may need different absorption models, by extension, different doses for each individual may perhaps require different absorption models. Many intensively sampled population PK studies are single

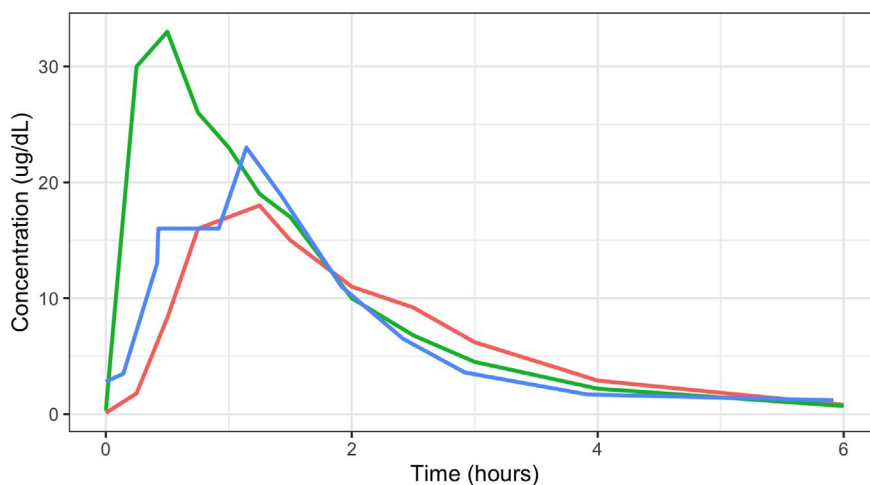


Figure 1 Observed concentration-time profile for three representative subjects, each demonstrating a different absorption shape: first order process (green), an Erlang absorption process (red), and shoulder model for simultaneous distributed-delay and first-order processes (blue).

Table 1 Comparison of key analysis metrics

	First order	Erlang	Visual assignment
Objective function	1,740.16	1,559.57	1,455.61
BIC	1,817.5	1,643.3	1,571.6
CL/F (L/hr) ^a	22.8 (29%)	22.6 (29%)	22.9 (29%)
V/F (L) ^a	35.4 (16%)	41.2 (21%)	39.0 (23%)
KA (hr ⁻¹) ^a	1.96 (49%)	-	3.29 (48%)
KTR (hr ⁻¹) ^a	-	10.5 (40%)	7.7 (29%)
Residual variability (%CV)	23%	18%	17%
Computation time (seconds)	1,136	2,703	3,212

%CV, percentage of coefficient of variation; BIC, Bayes Information (Schwartz) Criterion; CL/F, total apparent clearance; V/F, apparent volume of distribution; KA, absorption rate constant; KTR, absorption transit rate constant for transit compartments.

^aPoint estimate (between-subject variability %CV).

dose and this is a moot point. However, when intensively sampled multiple dose studies involving a drug with variable absorption patterns are being analyzed, it may become important to consider the visual inspection of absorption data to choose the more relevant absorption model for each individual at each dose. This can easily be envisioned with a subject that has a variable lag time for absorption on two different doses. A single realization of the random effect will split the difference and may not fit either profile well. This case might be accommodated by incorporating between-occasion variability into the model but this will not always be useful.

Limitations of visual inspection could arise from personal bias for a particular model; the time commitment required to classify each individual when data sets are large; and the need for a procedure to resolve ambiguous absorption data.

Early exposures may be important in drug therapy and an accurate description of early concentrations is desirable that requires more intensive sampling after the dose. With more intensive sampling, the likelihood of observing different absorption profiles is increased. In conclusion, it may be conventional, but it is not necessary, that one choose a single absorption model to be applied to all individuals in a population analysis. We suggest that the visual inspection of absorption profiles can be used to assign different individuals to different absorption models. Our perspective is that we should embrace those differences and feel comfortable

assigning different models on an individual-by-individual or even dose-by-dose basis.

Supporting Information. Supplementary information accompanies this paper on the *CPT: Pharmacometrics & Systems Pharmacology* website (www.psp-journal.com).

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