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PERSPECTIVE

The influence of flip-flop in population pharmacokinetic analyses

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Flip-flop is a term used to describe the scenario where the rate constants for multiexponential models appear to be switched. However, in reality, it is a permutation of the rank order of the parameter values. In this perspective, we revisit flip-flop pharmacokinetics and discuss its influence in population pharmacokinetic analyses.

INTRODUCTION

The term flip-flop is used somewhat incorrectly in pharmacokinetics to describe the scenario where the rate constants for multiexponential models appear to be switched. A common flip-flop scenario is a drug or dosage formulation that displays absorption limited elimination (i.e., where it is observed that the elimination rate constant [k] > absorption rate constant [k_a]). The use of the term "flip-flop" is somewhat misleading because, in reality, there is usually only "flip" (where a particular rank order of rate constants is observed, for example $k > k_a$) or "flop" (where a different rank order of rate constants occurs, for example, $k < k_a$) but not both. True examples of both flip and flop occurring (alternate switching between solutions) are not common but may manifest if the drug has slow absorption from the gastrointestinal tract and if clearance is sufficiently different between patients to change the relationship between k and k_a. This scenario has been hypothesized for metformin, where patients with normal renal function will display $k > k_a$ whereas those with impaired renal function may exhibit $k < k_a$.[1] Flip-flop can also occur during the estimation process within a subject, where the estimated parameter values may switch between the corollary parameterization with identical prediction characteristics. Both between-subject and within-subject flip-flop is of interest in data analysis settings.

Flip-flop pharmacokinetics is in reality a permutation of the rank order of the parameter values. It is therefore an issue of local identifiability in that there exists a finite set of parameter values (rather than a single set) that solves the problem. Essentially, all mammillary pharmacokinetic models that are constructed from multiple exponential functions will also only be locally identifiable. The simplest pharmacokinetic example is a one-compartment model with first-order input and output which has two sets of permutations of parameter values that provide the same input–output relationship. Note the sets of permutation of parameter values are not simply a function of swapping the rate constants. The two permutations using a CL, V, k_a and k, V, k_a parameterization are shown in Table 1, where CL is clearance and V is volume of distribution and k and k_a the "elimination" and "absorption" rate constants, respectively. Here, it can be seen that, when parameterizing a pharmacokinetic model using the k, V, k_a parameterization, it is a complete permutation of the parameters but this is not so for the CL, V, k_a parameterization. In the latter, V and k_a are a function of CL/k_a and CL/V respectively, whereas CL remains unchanged in

TABLE 1 Possible permutations for a one- and two-compartment model

	Parameterization	
One compartment model	CL, V, k_a	k, V, k_a
Permutation 1	$CL' = CL$ $V' = V$ $k_a' = k_a$	$k' = k$ $V' = V$ $k_a' = k_a$
Permutation 2	$CL' = CL$ $V' = \frac{CL}{k_a}$ $k_a' = CL / V$	$k' = k_a$ $V' = (V \bullet k) / k_a$ $k_a' = k$
Two-compartment model	$\alpha, \beta, k_a, k_{21}, V_c$	
Permutation 1	$\alpha' = \alpha$ $\beta' = \beta$ $k_a' = k_a$ $k_{21}' = k_{21}$ $V_c' = V_c$	
Permutation 2	$\alpha' = k_a$ $\beta' = \beta$ $k_a' = \alpha$ $k_{21}' = k_{21}$ $V_c' = \frac{V_c \bullet \alpha}{k_a}$	
Permutation 3	$\alpha' = \alpha$ $\beta' = k_a$ $k_a' = \beta$ $k_{21}' = k_{21}$ $V_c' = \frac{V_c \bullet \beta}{k_a}$	

Abbreviations: CL, clearance; k_a, absorption rate constant; k, elimination rate constant; k_{21}, rate of transfer from peripheral to central compartments; V, volume of distribution; V_c, central volume of distribution.

both permutations and is therefore invariant to flip-flop. A figure showing the overlap of profiles with the different permutations is presented in Appendix S1. An important implication is that the standard exposure relationship $AUC = Dose / CL$ remains true irrespective of whether the system is in a state of "flip" or "flop" (i.e., $k > k_a$ or $k < k_a$). In addition, the mathematical relationship $CL = V \bullet k$ holds as a mathematical principle (but not necssarily a biological principle) as follows; $k = \frac{CL}{V} = \frac{CL}{\frac{CL}{k_a}} = k_a$. It is therefore important to note that noncompartmental analyses are unaffected by a model being in either a "flip" or a "flop" state, where area under the concentration-time curve from zero to infinity ($AUC_{0-\infty}$) is determined from AUC_{0-data} and the terminal *phase* half-life. However, for parameter estimation (single subject or population analysis) the nature of the flip or flop or flip-flop is important and under one set of permutations V is a function of itself and other parameters irrespective of parameterization.

As anticipated, the issue of local identifiability becomes more complicated when the number of mammillary-compartments (n) increases. The possible number of permutations of parameter values that provide the same input–output relationship for a given n-compartmental model is $n + 1$ for drug administered into a depot site. For instance, for a two-compartment model with oral absorption there are three possible permutations of parameter values that can give the same input–output relationship. The three permutations of sets of parameter values are presented in Table 1. Here, permutations 2 and 3 can be substituted into the two-compartment pharmacokinetic model and provide the same answer as permutation 1 (see Appendix S2).

Flip-flop may result in spurious covariate relationships being found in population analyses. In the absence of intravenous data, it is theoretically possible for covariates describing elimination, such as creatinine clearance, to be significant on absorption parameters (e.g., k_a) if not already accounted for on elimination parameters (e.g., CL). This is an issue of local identifiability (i.e., flip-flop behavior) and could be addressed by incorporating a mechanistic model for the absorption and elimination processes. This is, however, generally not possible in a standard data-focused estimation setting. A simpler alternative is to consider that there is a level of functioning of the elimination organ at which the absorption and elimination rate constants switch around and that this can be estimated as a transition cutoff value. The model could then be stabilized into either its flip or flop state for any given individual and hence avoid population level flip-flop to yield a globally identifiable model.

We explored the influence of flip-flop in population pharmacokinetic models using metformin as a motivating example. Metformin pharmacokinetic data after oral administration were available from three published studies, which included study participants with varying degrees of renal function.[2–4] There were a total of 55 patients whose creatinine clearance ($CLcr_{CG}$, creatinine clearance calculated using the Cockcroft and Gault equation[5]) ranged from 9.5 to 167.0 ml/min. Modeling was performed using NONMEM version 7.3 (ICON Development Solutions, Ellicott City, MD) with the first-order conditional estimation method with interaction. A one-compartment with first-order input and output model was fit to the data. $CLcr_{CG}$ was considered as a covariate on (i) CL, (ii) k_a, and (iii) both CL and k_a. The univariate addition of $CLcr_{CG}$ to either CL or k_a resulted in a statistically significant improvement in model fit. A detailed description of the methodological details is provided in Appendix S3. The greatest reduction in objective function value followed

the univariate addition of $CLcr_{CG}$ as a covariate on CL. It is important to note that the order in which $CLcr_{CG}$ was added as a covariate on CL or k_a was found to influence model findings. When $CLcr_{CG}$ was first added as a covariate on CL, the further addition of $CLcr_{CG}$ on k_a did not result in any further improvement in global fit. However, when $CLcr_{CG}$ was first added as a covariate on k_a, the further addition of $CLcr_{CG}$ on *CL* improved the global fit. The preference for $CLcr_{CG}$ on k_a was in part dependent on the rank order of the initial estimates of k_a and k (i.e., whether the patient was initially determined to be in the "flip" or "flop" state). In the setting where k was smaller than k_a, $CLcr_{CG}$ was found to be a significant covariate on k_a, whereas, when the initial estimates for k were larger than k_a $CLcr_{CG}$ was not found to be a significant covariate on k_a.

There are few published compartmental population pharmacokinetic models where flip-flop pharmacokinetics were observed that also explain how the data were analyzed. The methodology used to solve the issues of local identifiability due to flip-flop pharmacokinetics in population pharmacokinetic modeling ranged from methods that simply ignored flip-flop to studies that had applied constraints in the structural model.[6–8] In addition, only one study was identified that explicitly stated how constraints were applied to maintain a certain rank order among model parameters.[6]

In conclusion, flip-flop can be considered a mathematical abstraction and a special case of a local identifiability problem in that it is not just a finite set of parameter values but a partial permutation of the set. In addition, it is important to note that spurious covariate relationships may be found if mechanistic relationships are ignored.

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CONFLICT OF INTEREST

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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