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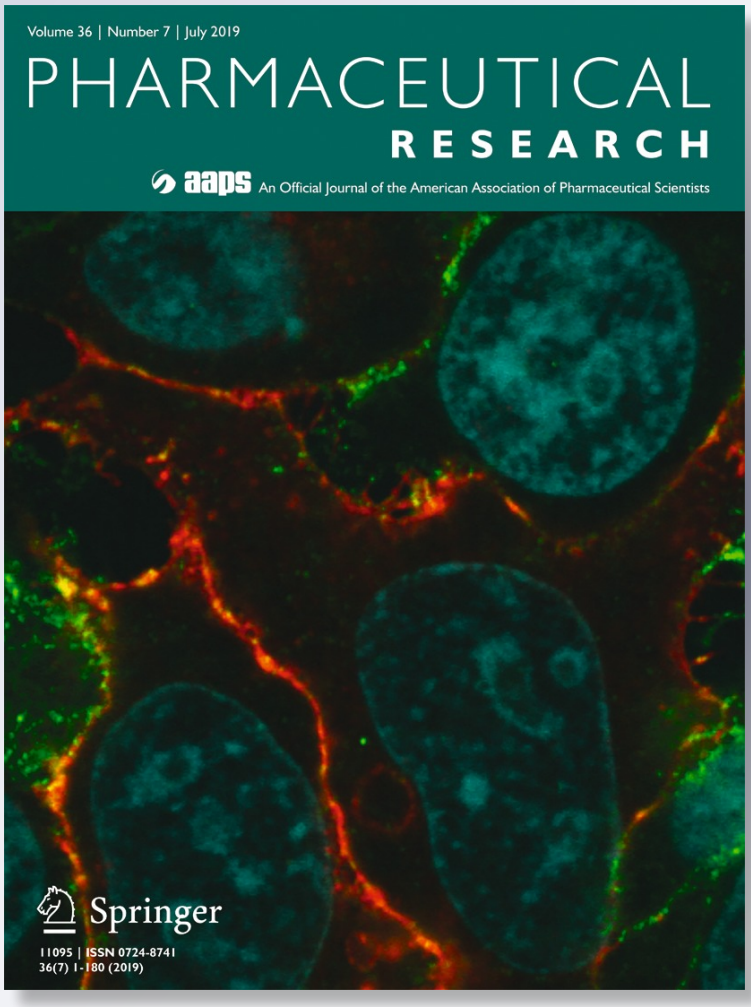

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COMMENTARY

On an Unphysical Hypothesis of Bateman Equation and its Implications for Pharmacokinetics

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The classical pharmacokinetic analysis of oral drug-absorption data relies on Bateman equation (Eq. 1) assuming a one compartment model disposition with first-order absorption and elimination rate (1):

$$C = \frac{F \cdot D \cdot ka}{V \cdot (ka - kel)} \cdot \left(e^{-k_{el} \cdot t} - e^{-k_a \cdot t}\right) \quad (1)$$

where C is the drug concentration in the body (compartment) at time t, F is the bioavailable fraction of dose (D), V is the volume of distribution and k_a, k_{el} are the absorption and elimination rate constants, respectively. Depending on the relative magnitude of the rate constants, classical ($k_a > k_{el}$) and flip-flop ($k_a < k_{el}$) cases are encountered (1). In the extreme case of equality of rate constants ($k_a = k_{el} = k$), the C, t curve is as follows (Eq. 2) (1):

$$C = \frac{F \cdot D}{V} \cdot k \cdot t \cdot exp(-k \cdot t) \quad (2)$$

The history of Eq. 1 goes back to 1908 when the British physicist Henry Bateman (2) described the abundances and activities in a decay chain of three isotopes as a function of time. In fact, Eq. 1 describes the time profile of the daughter isotope of the parent-daughter-granddaughter chain. Almost half a century later the German Professor of paediatrics *Friedrich* Hartmut Dost (3) adopted this equation for the pharmacokinetic analysis of blood data following a one compartment model disposition with first-order absorption and elimination rate. The similarity of drug processes is obvious with the isotopes chain, namely, drug in the gastrointestinal tract-drug in the blood-drug eliminated via the renal and hepatic routes. Dost was the first to coin the term "pharmacokinetics" in his 1953 monograph 'Der Blutspiegel" (Blood levels) (3) wherein Eq. 1 was quoted. Although Eq. 1 has been used in thousands of oral drug absorption research articles, the unrecognized assumption of infinite absorption time associated with Eqs. 1 and 2 is not physiologically sound. Current commercially available software *e.g.* Simcyp, Gastroplus as well as relevant research papers allow the user to assign specific values for the transit (absorption) of drug from the gastrointestinal tract (GI) *e.g.* the mean intestinal transit time is set equal to 199 min (4,5).

Oral drug absorption takes place in a certain period of time *e.g.* 0.5, 2, 10 h and not infinite time as it happens to be the case for the decay of nuclei. For example, today's regulatory guidelines (6,7) for Class I drugs rely on dissolution criteria ensuring rapid and complete absorption (fraction of dose absorbed >0.90). Consequently, one should expect the termination of the absorption phase for a Class I drug just after t_{max} (time which corresponds to the maximum concentration, C_{max}) because of complete drug absorption. On the contrary, the heterogeneous drugs (Class II, III and IV) which travel throughout the entire GI tract, exhibit usually slow and incomplete absorption (fraction of dose absorbed <0.90) (8). Intuitively, the termination of the finite absorption phase for Class II, III and IV drugs corresponds to much longer times than t_{max} since it coincides with the passage of the unabsorbed amount of drug beyond the region of the absorptive sites of the GI. Figure 1 shows simulated curves for a rapidly (Fig. 1a) and a slowly (Fig. 1b) absorbed drug. The curves have been generated from Eq. 1 using absorption duration time, 3 and 10 h

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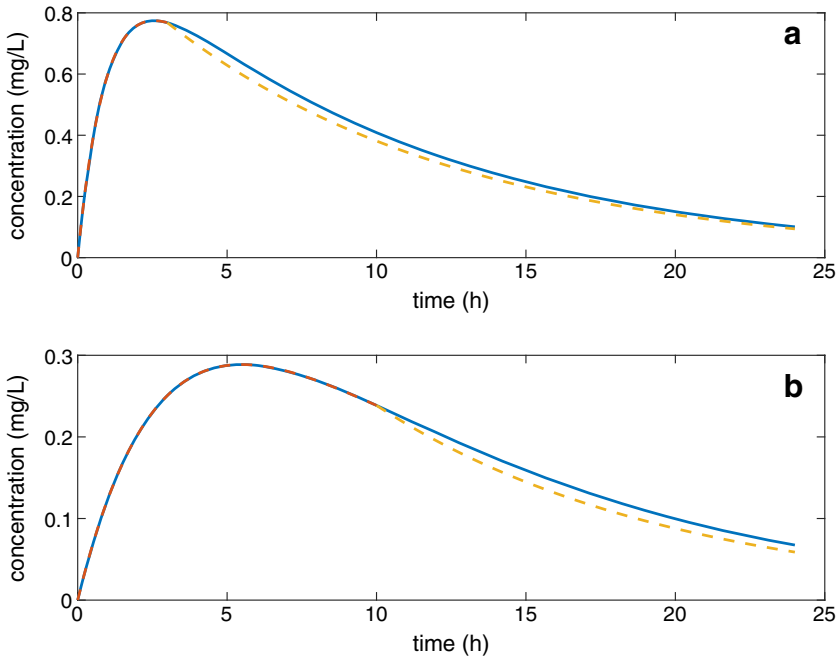

Fig. 1 Simulated curves generated from Eq. 1. Key: (**a**), continuous line, F = 1, D = 100 mg, V = 100 L, $k_a = 1\ h^{-1}$, $k_{el} = 0.1\ h^{-1}$; (**a**), dotted line, F = 1, D = 100 mg, V = 100 L, $k_a = 1\ h^{-1}$, $k_{el} = 0.1\ h^{-1}$, $\tau = 3$ h followed by mono-exponential disposition with $k_{el} = 0.1\ h^{-1}$; (**b**), continuous line, F = 0.5, D = 100 mg, V = 100 L, $k_a = 0.3\ h^{-1}$, $k_{el} = 0.1\ h^{-1}$; (**b**), dotted line, F = 0.5, D = 100 mg, V = 100 L, $k_a = 0.3\ h^{-1}$, $k_{el} = 0.1\ h^{-1}$, $\tau = 10$ h followed by mono-exponential disposition with $k_{el} = 0.1\ h^{-1}$.

for the rapidly and slowly absorbed drug, respectively. This is followed, by a mono-exponential elimination phase which starts at 3 and 10 h, respectively (Fig. 1, dotted lines). The corresponding curves generated from the Bateman equation (Eq. 1) using the same parameter values without the discontinuation of absorption phase are co-plotted in Fig. 1 (continuous curves). Visual inspection of Fig. 1 reveals that the descending limbs of the curves (continuous *versus* dotted lines) in a pair-wise comparison are quite similar. Obviously, when experimental data points are available and analyzed the discontinuation of the absorption phase followed by the elimination phase cannot be justified. In other words, the physiologically sound finite drug absorption duration has been misinterpreted since the introduction in 1953 and use of Eq. 1 in pharmacokinetics for the analysis of oral data. Relying on the above syllogisms and the simple example of Fig. 1, one can conclude that the wrong adoption by Dost (3) of Eq. 1 for the analysis of oral data seriously affected fundamental aspects of biopharmaceutics and pharmacokinetics.

For example, the integral of Eq. 1 from zero to infinity, which corresponds to area under the curve, $(AUC)_0^\infty$, has been established as a measure of drug exposure; it is also used extensively in pharmacokinetics as a metric of drug's extent of absorption because of the proportionality $(AUC)_0^\infty = F \cdot D/(k_{el} \cdot V)$. Obviously, this simple relationship is inherently linked with the infinite time for the duration of both first-order processes, namely, drug absorption and elimination. However, the present considerations indicate that the $(AUC)_0^\tau$ (where τ denotes the finite duration of the absorption phase) is the proper indicator for the bioavailable fraction of drug. Mathematically, $(AUC)_0^\tau$ can be calculated from Eq. 3 (1):

$$\int_0^\tau C dt = (AUC)_0^\tau = \frac{FDka}{V(k_a - k_{el})}\left[\frac{(1 - e^{-k_{el}\cdot\tau})}{k_{el}} - \frac{(1 - e^{-k \cdot \tau})}{k_a}\right] \quad (3)$$

Eq. 3 reveals that the proportionality between $(AUC)_0^\tau$ and the bioavailable fraction $(F \cdot D)$ is maintained. However, both rate constants, k_a, k_{el} are important too. Although the integral of Eq. 3 is directly proportional to biovailability, one would not use it to estimate F. It is advisable to rely on the familiar relationship F = CL*$(AUC)_0^\infty$ /D to estimate F since it is uninfluenced by when absorption stopped or if indeed it varies, even erratically, during the absorption process, so long as CL is constant.

In BA/BE data analysis, the estimation of $(AUC)_0^\tau$ and $(AUC)_0^\infty$ and their relative magnitude are associated with the biopharmaceutical properties of drug. Thus, for BCS Class I compounds this should not be a practical problem if actual data beyond t_{max} (when absorption is virtually complete) are used to extrapolate the full AUC. This is more of an issue with BCS Classes II, III and IV when it is absolutely essential to measure plasma concentrations beyond the termination of absorption to define terminal elimination accurately. Roughly, for Class I drugs the duration of absorption is terminated either prior or shortly after the t_{max} of Eq. 1 *i.e.* $t_{max} = \ln(k_a/k_{el})/(k_a - k_{el})$. In the former case, the

experimentally observed C_{max}, t_{max} of the study coincides with the end of the absorption phase. For Class II, III and IV drugs the duration of the absorption phase, τ lasts longer. In this case, the value of τ can be even higher than $2t_{max}$, which corresponds to the point of inflexion of Eq. 1 (derived from equating the second derivative of Eq. 1 with zero).

The analysis of *C, t* data based on the concept of the finite duration of the absorption process, requires the development of software for the estimation of τ. The corresponding datum point (C_τ,τ) is a discontinuity point of a piecewise function defined by two sub-functions *i.e.* Eq. 1 holds for $t \leq \tau$ and the one-or two-compartment model disposition function holds for $t > \tau$. In this context, one has to explore through simulation the issue as to under what circumstances *e.g.* experimental error, k_a/k_{el} ratios, would it possible to observe or identify τ from the experimental data.

Besides, other concepts associated with Eqs. 1 and 2 require re-consideration. In this vein, the concept of flip-flop kinetics (Eq. 1, $(k_a < k_{el})$) and the equality of rate constants (Eq. 2) become questionable since drug absorption for infinite time is associated with Eqs. 1 and 2. Similarly, other aspects of GI absorption analysis *e.g.* the percent amount absorbed as a function of time plots, frequently used in *in vitro-in vivo* correlations, require a different treatment under the premises of the finite duration of oral drug absorption. It is hoped that this commentary, after 66 years of use of Eqs. 1 and 2, will trigger the interest of pharmaceutical scientists to initiate studies associated with the scientific and regulatory implications for oral drug absorption. Needless to say that these considerations can be also applied to all extravascularly administered drugs regardless their mono- or multi-exponential disposition. However, caution should be exercised when a long absorption phase is encountered *e.g.* long acting injectables; in these cases, time dependent kinetics (fractal kinetics) and the use of the Weibull function are more appropriate for the analysis of data (9,10).

In conclusion, this commentary shows that the finite absorption duration concept will permit a re-analysis of oral drug absorption data. As a matter of fact, the estimation of τ, it's relative magnitude in relation to GI transit time and the biopharmaceutical classification of drugs studied are crucial for the proper treatment of data. For example, this work shows the inappropriate use of the Bateman function to extrapolate AUC beyond GI transit time for other than Class I drugs. In parallel, the estimation of τ in oral drug absorption studies using various species can help or even improve the well-known poor interspecies bioavailability correlations. One of the reasons can be the remarkable difference in GI transit time. Hopefully, this commentary will initiate studies towards this end.

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Dedicated to the memory of Dr. Arnold Rosen, Chelsea College (now King's College), University of London who taught me pharmacokinetics during my PhD studies (1978–1980) in London. This manuscript, if published, will be used in a plea for the minister of education of Greece to allow professors Emeriti supervise undergraduates, MSc and PhD students after the obligatory retirement.

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