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Intermittent Drug Dosing Intervals Guided by the Operational Multiple Dosing Half Lives for Predictable Plasma Accumulation and Fluctuation

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Abstract

Intermittent drug dosing intervals are usually initially guided by the terminal pharmacokinetic half life and are dependent on drug formulation. For chronic multiple dosing and for extended release dosage forms, the terminal half life often does not predict the plasma drug accumulation or fluctuation observed. We define and advance applications for the operational multiple dosing half lives for drug accumulation and fluctuation after multiple oral dosing at steady-state. Using Monte Carlo simulation, our results predict a way to maximize the operational multiple dosing half lives relative to the terminal half life by using a first-order absorption rate constant close to the terminal elimination rate constant in the design of extended release dosage forms. In this way, drugs that may be eliminated early in the development pipeline due to a relatively short half life can be formulated to be dosed at intervals three times the terminal half life, maximizing compliance, while maintaining tight plasma concentration accumulation and fluctuation ranges. We also present situations in which the operational multiple dosing half lives will be especially relevant in the determination of dosing intervals, including for drugs that follow a direct PKPD model and have a narrow therapeutic index, as the rate of concentration decrease after chronic multiple dosing (that is not the terminal half life) can be determined via simulation. These principles are illustrated with case studies on valproic acid, diazepam, and anti-hypertensives.

Keywords

dosing interval; half life; pharmacokinetics; pharmacodynamics; drug accumulation; fluctuation

Introduction

Current initial dosing recommendations are often guided by the terminal pharmacokinetic half life under the assumption that this slowest phase in drug elimination will predict drug behavior in the body. Following linear kinetics, in the rare case of a drug that exhibits a single phase in its elimination and is dosed via intravenous bolus, there is only one half life. If the drug is dosed at an intermittent dosing interval equal to this single half life, a predictable pattern of fluctuation and accumulation at chronic multiple dosing occurs, where the plasma concentration can be expected to fall in half during each dosing interval (fluctuation), and the multiple dosing steady-state levels of drug at any time during the dosing interval will be twice the levels of drug at that same time following the first dose (accumulation). Similarly, the total exposure to the drug (area under the plasma

concentration-time curve, AUC) at steady-state will be twice the single dose AUC over the dosing interval. Dosing more frequently than the half life will lead to less fluctuation and more accumulation; dosing less frequently than the half life will lead to more fluctuation and less accumulation.

This predictability in fluctuation and accumulation led to the association between dosing interval and half life. The overwhelming majority of drugs, however, follow multi-exponential kinetics and are dosed orally, leading to multiple half lives that describe the behavior of the drug. It has been shown that the dosing interval that leads to a two-fold accumulation in the maximum concentration following a dose, $C_{\max}$, for multi-compartment drugs and/or drugs that are dosed orally can be very different from the terminal half life. This dosing interval was defined by Sahin and Benet [1] as the operational multiple dosing half life (here denoted $t_{1/2, \text{op } C_{\max}}$). For example, diazepam has a terminal half life of ~30 hours that accounts for 95% of the intravenous AUC, yet $t_{1/2, \text{op } C_{\max}}$ determined via simulation is around 5 hours for an intravenous dose and about 15 hours for an oral formulation [1].

Here, we consider two additional pharmacokinetic dosing interval measures: the dosing interval to two-fold accumulation in $\text{AUC}_{0 \rightarrow \tau}$ (operational multiple dosing half life for $\text{AUC}_{0 \rightarrow \tau}$, where τ is the dosing interval; $t_{1/2, \text{op AUC}}$), and the dosing interval to two-fold fluctuation in plasma concentrations at multiple dosing steady-state (operational multiple dosing half life for fluctuation; $t_{1/2, \text{op fluct}}$). The dosing interval to two-fold accumulation in $\text{AUC}_{0 \rightarrow \tau}$ can also be considered a measure of accumulation in average concentration (C_{ave}), as $C_{\text{ave}} = \text{AUC}_{0 \rightarrow \tau} / \tau$, and it is similar to the effective half life proposed by Boxenbaum and Battle [2]. Again, dosing at a dosing interval shorter than these dosing interval predictors will lead to more accumulation and less fluctuation, and dosing at a longer interval will lead to less accumulation and more fluctuation in plasma concentrations.

Here, we aim to develop an understanding of the relevance of the terminal pharmacokinetic half life in the prediction of drug accumulation and fluctuation during the clinically relevant chronic multiple dosing scenario. Using Monte Carlo simulation, we determine theoretical relationships between the operational multiple dosing half lives introduced above and the terminal pharmacokinetic half life. As the dosing interval is tied to drug formulation, we also aim to elucidate trends between the operational multiple dosing and terminal half lives and dosage form. We propose that one or more of the operational multiple dosing half lives will remain predictive of the dosing interval with formulation changes. Finally, we present pharmacodynamic considerations and validate our results with case studies.

Methods

Monte Carlo Simulation—Plasma concentration-time curves for one- and two-compartment pharmacokinetic models with first-order absorption were simulated 10,000 times to represent 10,000 hypothetical drugs with randomized input values from a uniform distribution, with disposition (k_{10} , k_{12} , k_{21}) and absorption (k_a), parameters ranging from 0.01 to 5 hours⁻¹. It is important to note we use a uniform distribution to represent a range of possible drugs, where k_{10} , k_{12} , k_{21} , and k_a are independent. This is in contrast to typical population pharmacokinetic simulations where concentration-time curves are simulated for a single drug with inter-subject variability around the disposition and absorption parameters. From our approximations, the range [0.01, 5] hours⁻¹ covers the typical span of disposition and absorption rate constant parameters for current drugs. Additionally, we found in our early simulations that changes in the operational multiple dosing half lives were negligible for parameter values above this range; the most drastic changes were within the [0.01, 1] hours⁻¹ range. We also ran into computational difficulties below this range, but believe that rate constants reflecting half lives longer than 70 hours (lowest end of this range) will not

represent many drugs although our simulations included 75 cases where the β -phase half life is greater than 70 hours.

Assuming linear kinetics, we set the two scaling factors $F \cdot \text{Dose}$ and V_1 to 1. The maximum concentrations after a single dose and at steady-state were calculated via numerical iteration to determine $t_{\max}$ at the time when the derivative of the concentration-time equation is 0, for both dosing situations. The minimum concentration at time τ at steady-state and $AUC_{0 \rightarrow \tau}$ after a single dose and at steady-state were calculated according to standard pharmacokinetic equations. The operational multiple dosing half lives yielding two-fold accumulation in $C_{\max}$ ($C_{\max,ss}/C_{\max,sd} = 2$), two-fold accumulation in $AUC_{0 \rightarrow \tau}$ ($AUC_{0 \rightarrow \tau,ss}/AUC_{0 \rightarrow \tau,sd} = 2$), and two-fold fluctuation ($C_{\max,ss}/C_{\min,ss} = 2$) were calculated for each set of input values via numerical iteration. All numerical iterations were performed with the Solver optimization function in Microsoft Excel 2002. For ease in understanding the following sections, we use the terminology α -phase to reflect the fast disposition constant (λ_1) and β -phase to reflect the slow disposition constant (λ_2) in the two-compartment model. Commonly used abbreviations and their definitions are included in Table 1.

Sensitivity Analysis—Sensitivity of each operational multiple dosing half life to each disposition or absorption input parameter from the Monte Carlo simulation was calculated using nonparametric rank-based methods, where the sensitivity of an output to each input is the weighted square of the Spearman correlation coefficient (r^2) between the independently rank-ordered operational multiple dosing half lives and inputs [3]. Input values that were randomly selected were verified to be uncorrelated.

Case Studies—Operational multiple dosing half lives for drugs in the case studies were determined through numerical integration, as described above.

Results

Each of the three operational multiple dosing half lives can be longer or shorter than the terminal pharmacokinetic half life in the multi-compartment model. We define the terminal pharmacokinetic half life ($t_{1/2,term}$) as the slowest phase of drug elimination, either $t_{1/2,\beta}$ or $t_{1/2,abs}$ for an absorption rate limited (flip-flop) model as often used for an extended release (ER) formulation. As shown in Fig. 1, the operational multiple dosing half lives are never smaller than the terminal half life for the flip-flop model ($t_{1/2,\beta}/t_{1/2,abs} < 1$) in our simulations.

Also shown in Fig. 1, the operational multiple dosing half life to terminal half life ratio is greatest as $t_{1/2,abs}$ and $t_{1/2,\beta}$ approach each other ($t_{1/2,\beta}/t_{1/2,abs} \approx 1$). For these cases when $t_{1/2,abs}$ and $t_{1/2,\beta}$ are similar, the concentration-time curves were verified to show the same fluctuation and accumulation using the concentration-time equation for when the absorption rate constant and terminal elimination rate constant are the same, generated from the Laplace transform for the two-compartment model with first-order absorption again assuming $F \cdot \text{Dose} = 1$ and $V_1 = 1$, as shown in Eq. 1, where $\lambda_2 = k_a$.

$$C(t) = \frac{k_a(k_{21} - \lambda_1)}{(k_a - \lambda_1)^2} e^{-\lambda_1 t} + \frac{k_a(\lambda_1 - k_{21})}{(k_a - \lambda_1)^2} e^{-k_{at}} + t \cdot \frac{k_a(k_a - k_{21})}{(k_a - \lambda_1)} e^{-k_{at}} \quad (1)$$

In contrast, there appears to be no relationship with $t_{1/2,\alpha}$ (λ_1 , not shown).

Figure 2 shows the line of unity for comparisons within the operational multiple dosing half lives. There is a strong correlation between $t_{1/2,op} C_{\max}$ and $t_{1/2,op} \text{fluct}$ as noted by Sahin and Benet [1], $r^2 = 99.1\%$, and $t_{1/2,op} \text{fluct}$ is never less than $t_{1/2,op} C_{\max}$ in our simulations. The

average $t_{1/2,op\ fluct}$ to $t_{1/2,op\ C_{max}}$ ratio is 1.34 [25% percentile/median/75% percentile: 1.23/1.36/1.46]. There is less of a correlation between $t_{1/2,op\ AUC}$ and $t_{1/2,op\ C_{max}}$, and between $t_{1/2,op\ AUC}$ and $t_{1/2,op\ fluct}$, $r^2 = 30.1\%$ and $r^2 = 28.4\%$, respectively. In our simulations, $t_{1/2,op\ AUC}$ is almost exclusively greater than $t_{1/2,op\ C_{max}}$. Similarly, $t_{1/2,op\ fluct}$ is generally, but not exclusively, greater than $t_{1/2,op\ AUC}$, and tends to be less than $t_{1/2,op\ AUC}$ when the beta phase is more than 50% of the intravenous AUC. The average $t_{1/2,op\ AUC}$ to $t_{1/2,op\ C_{max}}$ ratio is 1.25 [25% percentile/median/75% percentile: 1.03/1.07/1.11], and the average $t_{1/2,op\ fluct}$ to $t_{1/2,op\ AUC}$ ratio is 1.22 [25% percentile/median/75% percentile: 1.15/1.30/1.38]. The spread around the line of unity is greatest in the $t_{1/2,op\ fluct}$ vs. $t_{1/2,op\ AUC}$ comparison as shown in the third panel of Fig. 2.

We also simulated the one-compartment model with first-order absorption for comparison under the same conditions and distributions described above. For this model, all three operational multiple dosing half lives are always longer than the terminal half life.

$t_{1/2,op\ C_{max}}$ can be approximated by $(t_{1/2,abs} + t_{1/2})$, especially when the absorption rate constant and elimination rate constant are different; when they are similar $t_{1/2,op\ C_{max}}$ is at most 1.07 times $(t_{1/2,abs} + t_{1/2})$ in our simulations. $t_{1/2,op\ fluct}$ is always greater than $t_{1/2,op\ C_{max}}$ and $t_{1/2,op\ AUC}$, and $t_{1/2,op\ AUC}$ is always greater than $t_{1/2,op\ C_{max}}$. The average $t_{1/2,op\ fluct}$ to $t_{1/2,op\ C_{max}}$ ratio is 1.54, the average $t_{1/2,op\ fluct}$ to $t_{1/2,op\ AUC}$ ratio is 1.39, and the average $t_{1/2,op\ AUC}$ to $t_{1/2,op\ C_{max}}$ ratio is 1.10. Shown in Fig. 3 are the corresponding $t_{1/2,op}/t_{1/2,term}$ vs. $t_{1/2}/t_{1/2,abs}$ graphs for the one-compartment model. Each graph is symmetric about the y-axis as the absorption and elimination rate constants are indistinguishable in the oral one-compartment model. In contrast to Fig. 1, these graphs show a clean relationship between the axes, signifying the importance of the alpha phase in the two-compartment model. Again, the operational multiple dosing half lives are maximized as the absorption and elimination half lives approach each other.

Results from the sensitivity analyses are shown in Table 2. Positive sensitivities indicate a positive correlation between the parameter and the half life (e.g. as k_{12} increases, $t_{1/2,op\ C_{max}}$ will also increase), and negative sensitivities indicate a negative correlation between the parameter and the half life (e.g. as k_{10} increases, $t_{1/2,op\ C_{max}}$ decreases). Each of the operational multiple dosing half lives are extremely sensitive to k_{10} , and will thereby be sensitive to changes in clearance. None of the operational multiple dosing half lives are notably sensitive to k_{12} and k_{21} , the distribution parameters, and thus distribution changes are unlikely to affect the values of the half lives. As noted by Sahin and Benet [1], $t_{1/2,op\ C_{max}}$ is sensitive to the absorption rate constant. Similarly, $t_{1/2,op\ fluct}$ is the most sensitive to absorption rate constant, and $t_{1/2,op\ AUC}$ is the least sensitive to the absorption rate constant.

As would be expected, all three operational multiple dosing half lives from the one-compartment model are equally sensitive to the absorption and elimination rate constants (data not shown).

Discussion

Drug Formulation

The dosing interval is closely tied to the drug formulation and can be easily modified with extended or sustained release formulations. It has been shown that the accumulation in C_{max} is sensitive to the oral first-order absorption rate constant that is commonly modified in formulation changes [1]. Given our sensitivity analyses, $t_{1/2,op\ fluct}$ and $t_{1/2,op\ AUC}$ will also be relevant in predicting dosing interval changes with formulation changes. As discussed below, we remark that many extended release (ER) dosage forms that are engineered to have a zero-order absorption rate constant actually behave first-order.

As noted, the operational multiple dosing half lives are greater than $t_{1/2,term}$ as $t_{1/2,abs}$ and $t_{1/2,\beta}$ approach each other. This has implications for the design of ER dosage forms: surprisingly, when a dosage form is designed with an absorption half life close to beta half life, the dosing interval for predictable pharmacokinetic fluctuation and accumulation will be (possibly much) longer than either half life. As the absorption half life increases beyond the beta half life, all three operational multiple dosing half lives will be similar and approximately equal to the absorption half life. In this way, drugs that may be cut early in the drug development pipeline due only to a relatively short half life (at least 5-6 hours) could actually easily remain once- or twice-daily dosed drugs through modification of the absorption rate constant. For example one of the highest $t_{1/2,op}$ to $t_{1/2,term}$ ratios in our two-compartment Monte Carlo simulations is 3.29, for $t_{1/2,op\ fluct}$. This hypothetical drug with a 0.11 hour alpha half life and a 5.2 hour ($\lambda_2 = 0.133\text{ hour}^{-1}$) beta half life can be dosed for two-fold fluctuation at $\tau = 17.2$ hours, approximately once-daily, simply with an absorption rate constant of 0.145 hour^{-1} . We want to emphasize the relevance of this finding. A drug with a relatively short 5 hour terminal half life can be formulated as a once-a-day dosage form by slowing the first-order absorption half life, rather than formulating a zero-order release. We recognize that it may not be possible to slow the absorption half life to 4.8 hours ($\ln(2)/0.145\text{ hour}^{-1}$), however, it is obvious that any change in the absorption half life can markedly effect the clinically acceptable dosing interval. We focus here on the time course and dosing interval; the actual dose may be adjusted to ensure efficacious concentrations.

As shown in Fig. 4 for this hypothetical drug, dosing at the 5 hour dosing interval predicted by the terminal half life gives a 4-fold accumulation in C_{max} and only a 1.2 C_{max}/C_{min} ratio at steady-state. Dosing at an interval in the range of the terminal half life does not lead to two-fold accumulation or fluctuation. In contrast, dosing at the 17 hour dosing interval predicted by $t_{1/2,op\ fluct}$ leads to 2-fold fluctuation and 1.4-fold accumulation in C_{max} . In comparison, $t_{1/2,op\ Cmax}$ and $t_{1/2,op\ AUC}$ are 10.7 and 11.7 hours, respectively, for this hypothetical drug. Understanding the relationships between these three operational multiple dosing half lives affords further prediction of drug accumulation and fluctuation. As discussed, $t_{1/2,op\ fluct}$ is never smaller than and on average 1.34 times greater than $t_{1/2,op\ Cmax}$, so we expect accumulation in C_{max} to be less than two-fold by dosing according to $t_{1/2,op\ fluct}$. It is also important to note that in our simulations, $t_{1/2,op\ fluct}$ can be up to 1.65 times greater than $t_{1/2,op\ Cmax}$, but this is independent of the relationship between the absorption rate constant and the terminal elimination rate constant. As exemplified below with valproic acid, a two- or three-fold increase in the dosing interval predicted by the terminal half life may then be suitable for once-daily dosing, optimizing patient compliance.

Case Study: Valproic Acid and an Extended Release Formulation

Valproic acid exhibits two-compartment kinetics with an α -phase half life of 0.60 hours and a β -phase half life of 13.1 hours [patient 'FG' in reference [4]], so twice-daily dosing is usually recommended for patients without induced hepatic enzymes. The immediate release (IR) formulation has an absorption rate constant (k_a) of 3.5 hour^{-1} [5; we assume that once the enteric coating has worn off, the release rate for the delayed release formulation is the same as for an IR formulation). An extended release formulation has been developed to allow for once-daily dosing with the aim of maximizing patient convenience and compliance. Although this ER formulation is engineered to have a zero-order release rate, when k_a is calculated as $1/MAT$, it can be modeled as having a first-order absorption rate constant of 0.0942 hour^{-1} [5]. Following numerical deconvolution, Dutta et al. [6] note that the absorption rate for the ER formulation is higher during the initial hours following the dose and then tails off, possibly due to increased intestinal surface area and water content in the early phases of absorption. The authors also note this is not unexpected, and we conclude that a first-order absorption model is appropriate even for dosage forms that are designed to

be zero-order. That is, the human pharmacokinetic data often show first-order absorption rates even for formulations engineered to be zero-order release, signaling the utility of the operational multiple dosing half lives in the design of extended release dosage forms.

The operational multiple dosing and terminal half lives for valproic acid are shown in Table 3. The absorption half life for the extended release formulation ($t_{1/2,abs} = 7.36$ hours) is faster than the β -phase half life, so the terminal half life does not change with the formulation change. For the IR formulation, all four half lives in Table 3 predict the twice-daily dosing interval. In contrast, the operational multiple dosing half lives are approximately twice the terminal half life for the extended release formulation. Only the operational multiple dosing half lives predict the once-daily dosing interval for the ER formulation of valproic acid.

Also included for reference in Table 3 are the operational multiple dosing and terminal half lives for an intravenous bolus of valproic acid. As also shown by Sahin and Benet [1], $t_{1/2,op\ C_{max}}$ and $t_{1/2,op\ fluct}$ are the same for intravenous dosing. $t_{1/2,op\ AUC}$ will predict a marginally longer dosing interval.

Therapeutic Index

Our results thus far have not considered the duration of drug response as an empirically determined dosing interval. For example, towards the determination of dosing intervals for analgesics, the 2001 EMEA guidance recommends duration of analgesia and time to rescue as endpoints in clinical trials [7, 8]. In contrast to these empirical measures, the operational multiple dosing half lives provide a simulation- and model-based tool to determine a dosing interval. We assume no active or toxic metabolites. In that light, the time above a therapeutic minimum concentration, constrained below a toxic concentration, and the pharmacokinetic-pharmacodynamic (PKPD) model will be useful in predicting a dosing interval based on drug effect. For example, diazepam has been featured as an example of a drug whose dosing interval is significantly less than the terminal half life, and $t_{1/2,op\ C_{max}}$ predicts the dosing interval more accurately for both intravenous and oral formulations than does the terminal half life [1]. That is, $t_{1/2,op\ C_{max}}$, and by extension $t_{1/2,op\ fluct}$, predict the fall off in drug concentrations during multiple dosing steady-state when the terminal half life does not. We propose that this is because of the therapeutic index of the drug, as discussed below.

We posit that drugs with a “direct” PKPD model, including those for which the site of action is the central circulation, those governed by rapid distribution to their site of action, and those with rapid receptor binding, turnover, and transduction mechanisms, are likely to have a narrow therapeutic window for toxicities resulting from increased drug effect because of the immediate drug effects. This is in contrast to “indirect” drugs for which turnover and transduction processes are slow, requiring application of indirect or irreversible response models (for more detail, see references [9-11]). We do not argue the inverse or converse of this position, as warfarin and many chemotherapeutics, for example, have indirect mechanisms of action but narrow therapeutic indices; we only argue that direct PKPD model drugs are likely to have a narrow therapeutic index. The inherent check for a narrow therapeutic window due to the built in two-fold criteria make the operational multiple dosing half lives especially pertinent for narrow therapeutic index drugs. Moreover, we also recognize that pharmacokinetic measures will in general be more relevant for direct PKPD model drugs, and the dosing interval for indirect acting drugs will be less correlated with pharmacokinetics due to the time course differences. Finally, we propose that it is these direct drugs, because of the immediate drug effects (in contrast to indirect PKPD model drugs), that are more likely to have or require formulation changes, where the operational multiple dosing half lives will be useful.

Case Study: Valproic Acid and its Narrow Therapeutic Index

Prediction of accumulation and fluctuation measures at multiple dosing steady-state is important particularly for a drug with a narrow therapeutic index, where there is a small range of plasma concentrations above a therapeutic concentration and below a toxic ceiling. Valproic acid is one such drug; the plasma concentration targets in seizure control are within the range of 50 – 100 $\mu\text{g/ml}$ [12].

The operational multiple dosing half lives will be especially applicable to predicting the dosing interval for such narrow therapeutic drugs because of the two-fold definition. For example, because $t_{1/2, \text{op fluct}}$ is longer than $t_{1/2, \text{op Cmax}}$, we can predict a patient's valproic acid concentrations to remain within the narrow therapeutic window, less than two-fold fluctuation at steady-state, by dosing at $t_{1/2, \text{op Cmax}}$. Similarly, given a patient's drug levels at approximately t_{max} following the first dose, we can predict that drug levels will be twice this value at t_{max} following a steady-state dose by dosing at $t_{1/2, \text{op Cmax}}$. For a 1000 mg dose of the ER formulation (as used in [5] and listed as the recommended target dose in [12]), dosing at a dosing interval equal to the $t_{1/2, \text{op Cmax}}$ of 21.8 hours, as in Table 3, C_{max} after each dose at steady-state will be 106 $\mu\text{g/ml}$ and C_{min} after each dose at steady-state will be 78.6 $\mu\text{g/ml}$. Once-daily dosing will lead to approximately similar levels: $C_{\text{max}} = 98.1 \mu\text{g/ml}$ and $C_{\text{min}} = 53.1 \mu\text{g/ml}$. Similarly, dosing 400 mg (recommended twice-daily dose [12]) of the IR formulation at $t_{1/2, \text{op Cmax}}$ of 11.2 hours will lead to $C_{\text{max}} = 104 \mu\text{g/ml}$ and $C_{\text{min}} = 54.4 \mu\text{g/ml}$. All of these concentration values are approximately within the narrow therapeutic window because of the two-fold criteria in the operational multiple dosing half lives.

Case Study: Diazepam and its Therapeutic Index

An exact therapeutic window is not available for diazepam because active metabolites and the development of tolerance to the drug upon multiple dosing complicate plasma concentration-effect relationships. Although considered to have a large therapeutic index from a safety perspective (before coma or death [13]), as noted, the dosing interval is more frequent than the terminal half life and patient convenience predict. This is likely because the undesired side effects for diazepam, such as dizziness, occur at much lower concentrations than coma or death, and, therefore, the clinical therapeutic index is narrower. For the oral formulation highlighted by Sahin and Benet [1], $t_{1/2, \text{op Cmax}}$ is 14.9 hours, $t_{1/2, \text{op AUC}}$ is 28.2 hours, and $t_{1/2, \text{op fluct}}$ is 15.2 hours. The recommended starting dosing interval for oral diazepam is 12 hours for management of anxiety disorders. Again, by dosing at a slightly shorter interval than $t_{1/2, \text{op fluct}}$ predicts, we can ensure diazepam concentrations are within a narrow concentration window throughout the dosing interval. $t_{1/2, \text{op AUC}}$ does not predict the dosing interval. Of note, an ER formulation for diazepam was once developed [14] but, to our knowledge, is not marketed because of the potential for abuse.

Case Study: Anti-hypertensive Mechanism of Action, Drug Formulation, and Therapeutic Index

We analyzed two classes of anti-hypertensives: the direct-acting calcium channel blockers [15, 16] and the indirect-acting angiotensin-II antagonists [17]. We focused on drugs approved between 1980 and 2007 with IR drug or active metabolite terminal half lives in the range of 6-15 hours. Of these, all four of the calcium channel blockers: felodipine, isradipine, nifedipine, and nisoldipine have extended release formulations listed on the drugs@FDA database to allow for once-daily dosing [18]. Only ER formulations are on the market for felodipine and nisoldipine. In contrast, none of the angiotensin-II antagonists have ER formulations listed on the drugs@FDA database [18], but are dosed once-daily despite the relatively short terminal half lives. That is, within this comparison of two (albeit

only two) classes of drugs with similar therapeutic targets in blood pressure reduction, the direct-acting drugs “require” an extended release formulation for once-daily dosing that is not necessary for the indirect-acting drugs.

This is further evidenced as we begin to analyze the hypothesis that drugs with a direct PKPD model are likely to have a narrow therapeutic window through the comparison of blood pressure control between valsartan and felodipine ER. Valsartan, an angiotensin-II antagonist, follows an indirect PKPD model [19], and felodipine, a calcium channel blocker, follows a direct PKPD model [20]. Valsartan has a 6 hour terminal half life [21], and felodipine has a 15 hour terminal half life [19]. As mentioned above, the IR formulation of valsartan and the ER formulation of felodipine are both dosed once-daily.

Once-daily dosing with 80 mg valsartan leads to approximately 2-fold fluctuation in systolic blood pressure (SBP) and diastolic blood pressure (DBP) at 8 weeks, steady-state [22]. At day 8, also steady-state, accumulation in plasma $C_{\max}$ is 1.1-fold and peak-to-trough concentration fluctuation is around 8-fold [21]. Following the standard 80 mg dose of valsartan (as used to calculate SBP and DBP fluctuation in [22]), the trough concentration is only ~50% of the EC_{50} for DBP control [19], and concentrations are in the range of the EC_{50} at around 12 hours. Blood pressure control is maintained with once-daily valsartan despite minimal concentrations during the second half of the dosing interval. Once-daily dosing with 20 mg of felodipine ER also leads to approximately 2-fold fluctuation in SBP and DBP at 2 weeks, steady-state [20]. In contrast to valsartan, however, at 2 weeks, the $C_{\max}$ accumulation is 1.3-fold, pharmacokinetic fluctuation is 3.3-fold, and plasma concentrations are above the EC_{50} for the duration of the dosing interval [20]. The direct-acting drug necessitates a narrower concentration range than the indirect-acting drug for the same 2-fold fluctuation in pharmacodynamic effect, signaling a narrower therapeutic index.

This case study suggests the angiotensin-II antagonists do not only have an IR formulation due to a wide therapeutic window because concentrations are below the EC_{50} for a large part of the dosing interval. In contrast, while the direct-acting drug requires concentrations above the EC_{50} for the entire dosing interval to maintain pharmacodynamic effect, the indirect nature of valsartan provides for a drug effect even when plasma concentrations are low, making an ER dosage form unnecessary for indirect PKPD model drugs. We also highlight that while effect fluctuation is in the range of pharmacokinetic fluctuation for the direct-acting felodipine, effect fluctuation for the indirect-acting valsartan is considerably less than the pharmacokinetic fluctuation.

Conclusions

The operational multiple dosing half lives, in contrast to the terminal pharmacokinetic half life, are applicable to the prediction of drug concentration fluctuation, and thereby dosing intervals, and in the design of extended release dosage forms. Our results predict a way to maximize the operational multiple dosing half lives relative to the terminal half life by using a first-order absorption rate constant close to the terminal elimination rate constant in the design of an ER dosage form. In this way, drugs that may be eliminated early in the development pipeline due to a relatively short half life can be formulated to be dosed once-daily, maximizing patient convenience and compliance, while maintaining tight plasma concentration accumulation and fluctuation ranges. As exemplified with valproic acid and as also acknowledged by Brocks and Mehvar [23], because therapeutic minimums and toxic ceilings are often more accurately determined than a single average target concentration, $t_{1/2,op} C_{\max}$ and $t_{1/2,op} \text{fluct}$ will be easily integrated into drug and formulation development. Because the relationship between $t_{1/2,op} C_{\max}$ and $t_{1/2,op} \text{fluct}$ is more easily defined than are the relationships between the other two sets of operational multiple dosing half lives, and

because $t_{1/2,op}$ AUC does not seem to predict the diazepam oral dosing interval, we propose that $t_{1/2,op}$ C_{max} and $t_{1/2,op}$ fluct be used in the prediction of dosing intervals. As prediction of accumulation and fluctuation at multiple dosing steady-state is important particularly for a drug with a narrow therapeutic index, we propose the operational multiple dosing half lives will be especially useful for drugs that follow a direct PKPD model, where drug effect is more sensitive to the pharmacokinetics, and for drugs that have a narrow therapeutic index.

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Figure 1.

Operational multiple dosing half life to terminal half life (the longer of $t_{1/2,\beta}$ and $t_{1/2,abs}$) ratio vs. $t_{1/2,\beta}$ to $t_{1/2,abs}$ ratio for the two-compartment pharmacokinetic model, from top to bottom: $t_{1/2,op} C_{max}$, $t_{1/2,op} AUC$, $t_{1/2,op} fluct$.

Figure 2.

From top to bottom: $t_{1/2,op\ fluct}$ vs. $t_{1/2,op\ Cmax}$, $t_{1/2,op\ AUC}$ vs. $t_{1/2,op\ Cmax}$, $t_{1/2,op\ fluct}$ vs. $t_{1/2,op\ AUC}$. Solid line is the line of unity.

Figure 3. Operational multiple dosing half life to terminal half life (the longer of $t_{1/2,\beta}$ and $t_{1/2,abs}$) ratio vs. $t_{1/2,\beta}$ to $t_{1/2,abs}$ ratio for the one-compartment pharmacokinetic model, from top to bottom: $t_{1/2,op} C_{max}$, $t_{1/2,op} AUC$, $t_{1/2,op} fluct$.

Figure 4.

Concentration-time curves for a hypothetical drug with approximately the same 5 hour beta and absorption half lives. The solid line shows the simulated curve for dosing at a 5 hour interval, and the dashed line shows the simulated curve for dosing at a 17 hour interval predicted by $t_{1/2,op}$ fluct.

Table 1

Commonly Used Abbreviations and Definitions

$t_{1/2,abs}$	Absorption half life
$t_{1/2,\beta}$	Beta pharmacokinetic half life
$t_{1/2,term}$	Terminal half life; the longer half life between the absorption and beta half lives
$t_{1/2,op\ C_{max}}$	Operational multiple dosing half life to two-fold accumulation in C_{max} ; calculated as the dosing interval to two-fold accumulation in C_{max}
$t_{1/2,op\ AUC}$	Operational multiple dosing half life to two-fold accumulation in $AUC_{0 \rightarrow \tau}$; calculated as the dosing interval to two-fold accumulation in $AUC_{0 \rightarrow \tau}$
$t_{1/2,op\ fluct}$	Operational multiple dosing half life to two-fold fluctuation at chronic multiple dosing; calculated as the dosing interval to a C_{max}/C_{min} ratio of 2 during chronic multiple dosing

Table 2

Sensitivity of Operational Multiple Dosing Half Lives to Disposition and Absorption Rate Parameters

	$t_{1/2,op} \text{ Cmax}$	$t_{1/2,op} \text{ AUC}$	$t_{1/2,op} \text{ fluct}$
k_{10}	-52.6%	-55.0%	-50.9%
k_{12}	5.94%	6.98%	2.60%
k_{21}	-1.00%	-3.71%	-0.102%
k_a	-40.5%	-34.3%	-46.4%

Sensitivity of each operational multiple dosing half life to each disposition or absorption input parameter from the Monte Carlo simulation, where each input is selected from a uniform distribution $[0.01, 5] \text{ hours}^{-1}$, was calculated using nonparametric rank-based methods. Sensitivities calculated following 10,000 simulations.

Table 3

Operational Multiple Dosing and Terminal Half Lives for Immediate Release, Extended Release, and Intravenous Valproic Acid

	$t_{1/2,op} C_{max}$ (hours)	$t_{1/2,op} AUC$ (hours)	$t_{1/2,op} fluct$ (hours)	$t_{1/2,term}$ (hours)
Immediate Release	11.2	13.0	11.9	13.1
Extended Release	21.8	23.9	34.5	13.1
Intravenous Bolus	9.22	12.7	9.22	13.1