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Technical Note

Influence of Absorption Rate, Dosing Frequency, and Intrinsic Pharmacokinetic Profile on Steady-State Drug Concentrations

Michael A. Eldon[1,3] and Wayne A. Colburn[2]

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INTRODUCTION

Chronopharmacokinetic studies of several drugs have led us to evaluate possible factors governing steady-state drug concentrations. Previous chronopharmacokinetic reports have attributed diurnal fluctuations in drug concentration mostly to changes in the extent of drug absorption or changes in clearance, or both (1). Others have considered the effect of clearance changes on bioavailability estimates (2), while possible changes in the rate of absorption were thought to be of little importance.

It is our hypothesis that area under the concentration–time curve (AUC) and the maximum plasma concentration (C_{max}) for a given dosing interval at steady state are sensitive to changes in the rate of absorption as a function of time of day. That is, if the rate of absorption fluctuates during the day, steady-state AUC can differ between dosing intervals, but total AUC for each day should be constant. Although others have alluded to this possibility (3,4), a systematic study has not been reported.

To evaluate this possible mechanism for diurnal fluctuations in drug concentration, we have simulated situations where the extent of absorption and clearance are held constant while the rate of absorption is reduced as a function of time of day. These simulations have been performed to evaluate the influence of intrinsic distribution and elimination profiles, i.e., the extent of polyexponential pharmacokinetic characteristics, and the dosing frequency within a 24-hr period.

MATERIALS AND METHODS

Steady-state concentration–time data were simulated based on the superposition method and an assumption of linear pharmacokinetics using MLTIDOSE, a compiled BASIC computer program which allows the use of an individual parameter set for each dose (5). From a series of simulations, six sets of pharmacokinetic parameter values for a two-compartment intravenous pharmacokinetic model (Table I) were chosen to illustrate the impact of intrinsic pharmacokinetic characteristics on changes in drug concentrations as a function of changing absorption rate. Corresponding two-compartment peroral pharmacokinetic model parameters specific for selected absorption rate constant (k_a) values were calculated as described by Gibaldi and Perrier (6). Parameter values were chosen to yield distinctly biexponential (sets 1, 2, and 3) and minimally biexponential (Sets 4, 5, and 6) pharmacokinetic profiles.

Steady-state concentration–time data corresponding to each of the six parameter sets were simulated at 0.1-hr intervals based on dosing every 12 hr (BID), every 8 hr (TID), and every 6 hr (QID). The fraction of dose absorbed was held constant at 1.0 for all dosing intervals. Values for k_a were assigned to serial dosing intervals within each 24-hr period to represent a procession from fast to slow absorption as a function of time of day, with Dosing Interval 1 representing the 7 AM dose. The k_a values were 7.5 and 0.25 hr^{-1} for BID Dosing Intervals 1 and 2; 7.5, 0.75, and 0.25 hr^{-1} for TID Dosing Intervals 1, 2, and 3; and 7.5, 2.5, 0.75, and 0.25 hr^{-1} for QID Dosing Intervals 1, 2, 3, and 4. These extreme k_a values were selected to test the hypothesis that diurnal fluctuations in drug concentrations could be caused by changes in k_a as a function of time of day. Examples of application of these concepts to clinical pharmacokinetic data are given in the Discussion.

AUC values were calculated using trapezoidal approximation of the simulated concentration–time data from each serial dosing interval. Corresponding C_{max} and t_{max} values were selected by observation. Changes in these values as a function of time of day were expressed as percentage change relative to Dosing Interval 1.

RESULTS AND DISCUSSION

BID, TID, and QID simulation results are given in Tables II, III, and IV, respectively. The results of progressively reducing k_a during a 24-hr period show anticipated changes in C_{max} and t_{max} values as well as reductions in

[1] Clinical Pharmacology Department, Parke-Davis Pharmaceutical Research, 2800 Plymouth Road, Ann Arbor, Michigan 48105.

[2] Pharmacokinetics/Drug Metabolism Department, Parke-Davis Pharmaceutical Research, 2800 Plymouth Road, Ann Arbor, Michigan 48105. Current address: Harris Laboratories, Inc., Clinical Investigation Division, 7432 E. Stetson Dr., Scottsdale, Arizona 85251.

[3] To whom correspondence should be addressed.

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Table I. Intravenous Pharmacokinetic Parameter Values Used as the Basis for Simulations[a]

Set	A[b] (μg/ml)	α (hr^{-1})	B (μg/ml)	β (hr^{-1})	Comments
1	80	0.693	20	0.029	Distinctly biexponential, $t_{1/2\alpha}$ = 1 hr, $t_{1/2\beta}$ = 24 hr
2	80	0.693	20	0.116	Distinctly biexponential, $t_{1/2\alpha}$ = 1 hr, $t_{1/2\beta}$ = 6 hr
3	80	2.772	20	0.116	Distinctly biexponential, $t_{1/2\alpha}$ = 0.25 hr, $t_{1/2\beta}$ = 6 hr
4	20	0.693	80	0.029	Minimally biexponential, $t_{1/2\alpha}$ = 1 hr, $t_{1/2\beta}$ = 24 hr
5	20	0.693	80	0.116	Minimally biexponential, $t_{1/2\alpha}$ = 1 hr, $t_{1/2\beta}$ = 6 hr
6	20	2.772	80	0.116	Minimally biexponential, $t_{1/2\alpha}$ = 0.25 hr, $t_{1/2\beta}$ = 6 hr

[a] Corresponding peroral pharmacokinetic parameters were calculated using these parameters and k_a values given in the text with dose = 1000 mg and volume of central compartment = 10 liters.
[b] Pharmacokinetic symbolism and nomenclature taken from Ref. 2.

AUC for all parameter sets and all dosing regimens. The magnitude of AUC reduction for the last dosing interval relative to the first dosing interval ranges from 10 to 30%, and it increases as the dosing frequency is increased within each parameter set. The effect is most pronounced for parameter Sets 3 and 6, which have total clearance values approximately four times that of Sets 1 and 4, respectively. It is least pronounced for Set 4, having the lowest clearance and the least biexponential intrinsic character, which actually shows a slight reduction of the effect with increasing frequency of dosing. These findings suggest that reductions in AUC would be most pronounced for high-clearance drugs having distinctly multiphasic pharmacokinetic characteristics.

We have reported reductions in steady-state C_{max} and AUC values as a function of time of day for oral verapamil (7), a high-clearance drug which has been described using a three-compartment pharmacokinetic model after intravenous dosing (8). Statistically significant successive decreases in verapamil C_{max} and AUC values were observed corresponding to dosing at 8 AM, 4 PM, and 12 AM, with mean C_{max} and AUC from the 12 AM dose reduced 36 and 30%, respectively, relative to those from the 8 AM dose. The methods described herein were used to estimate k_a values of 2.5, 1.25, and 0.75 hr^{-1}, corresponding to the doses administered at the times given above.

We have also observed this effect for a variety of drugs, including diphenhydramine as shown in Fig. 1 (9). The mean percentage reduction in diphenhydramine AUC during the second and third dosing intervals compared to the first interval are 10 and 21%, respectively, as depicted in Fig. 1. These values are in the range of those from the TID simulations presented in Table III. As observed for verapamil, the reductions in diphenhydramine steady-state plasma concentrations as a function of time of day were modeled using k_a values of 1.1, 0.70, and 0.30 hr^{-1} while holding all other pharmacokinetic parameters constant (9) (Fig. 1). A decrease in the absorption rate without changes in extent of absorption or clearance can result in erroneous estimates of steady-state plasma concentrations and corresponding pharmacokinetic parameter values if assessed during just one dosing interval. This phenomena could occur as a greater portion of the dose is shifted into one or more subsequent

Table II. Simulated Steady-State Pharmacokinetic Parameters Based on Administering Drug Every 12 Hours (BID)

Set	Dosing interval	AUC	% reduction[a]	C_{max}	% reduction[a]	t_{max}	% delay
1	1	845.0	—	133.5	—	0.4	—
	2	764.4	9.5	72.4	45.8	2.7	575
2	1	317.8	—	91.9	—	0.4	—
	2	257.2	19.1	30.1	67.3	2.7	575
3	1	224.2	—	69.5	—	0.2	—
	2	177.6	20.8	18.0	74.1	2.6	1200
4	1	2917.2	—	293.2	—	0.5	—
	2	2657.1	8.9	231.5	21.0	4.1	720
5	1	808.4	—	126.1	—	0.5	—
	2	627.9	22.4	62.0	50.9	4.0	700
6	1	785.0	—	118.6	—	0.4	—
	2	608.1	22.5	59.3	50.0	4.2	950

[a] Percentage reduction relative to parameter value for Dosing Interval 1.
[b] Percentage delay in t_{max} relative to t_{max} for Dosing Interval 1.

Table III. Simulated Steady-State Pharmacokinetic Parameters Based on Administering Drug Every 8 Hours (TID)

Set	Dosing interval	AUC	% reduction[a]	C_{max}	% reduction[a]	t_{max}	% delay[b]
1	1	849.5	—	164.8	—	0.4	—
	2	812.6	4.3	121.4	26.3	1.5	275
	3	752.3	11.4	100.4	39.1	2.3	475
2	1	330.4	—	101.7	—	0.4	—
	2	290.9	12.0	56.6	44.3	1.5	275
	3	241.5	26.9	36.3	64.3	2.4	500
3	1	227.0	—	76.6	—	0.2	—
	2	203.8	10.2	36.2	52.7	0.9	350
	3	172.2	24.2	24.3	68.3	1.7	750
4	1	2890.6	—	405.4	—	0.5	—
	2	2814.6	2.6	371.3	8.4	2.1	320
	3	2656.7	8.1	339.6	16.2	2.8	460
5	1	814.0	—	152.6	—	0.5	—
	2	727.6	10.6	111.3	27.0	2.0	300
	3	613.3	24.6	83.3	45.4	3.0	500
6	1	788.1	—	114.5	—	0.4	—
	2	705.8	10.4	105.7	26.9	2.0	400
	3	596.0	24.4	80.3	44.5	3.0	650

[a] Percentage reduction relative to parameter value for Dosing Interval 1.
[b] Percentage delay in t_{max} relative to t_{max} for Dosing Interval 1.

dosing intervals when the absorption rate is reduced, as shown in Fig. 2.

The limited number of extreme k_a changes presented here was selected to demonstrate that reductions in the absorption rate as a function of time of day could be responsible for diurnal variation in plasma concentration. Examples of clinical trial results were used to support the simulations. These results support our concept that if only k_a varies, AUC will vary between dosing intervals during a 24-hr period, while the overall 24-hr concentration–time profile will remain constant from day to day. Therefore, it will be necessary to compare test and reference formulations

Table IV. Simulated Steady-State Pharmacokinetic Parameters Based on Administering Drug Every 6 Hours (QID)

Set	Dosing interval	AUC	% reduction[a]	C_{max}	% reduction[a]	t_{max}	% delay
1	1	847.4	—	195.2	—	0.4	—
	2	828.5	2.2	175.0	10.3	0.8	100
	3	801.3	5.4	149.4	23.5	1.5	275
	4	741.8	12.5	128.6	34.1	2.0	400
2	1	333.1	—	110.8	—	0.4	—
	2	307.0	7.8	89.0	19.7	0.7	75
	3	280.5	15.8	62.7	43.4	1.4	250
	4	229.8	31.0	43.0	61.2	2.1	425
3	1	223.5	—	83.1	—	0.2	—
	2	215.2	3.7	63.0	24.2	0.5	150
	3	197.9	11.4	42.4	49.0	0.9	350
	4	167.5	24.0	30.6	63.2	1.2	500
4	1	2851.8	—	514.7	—	0.5	—
	2	2858.1	−0.2	509.0	1.1	1.0	100
	3	2788.4	2.2	480.6	6.6	1.8	260
	4	2650.9	7.0	448.7	12.9	1.9	280
5	1	794.3	—	176.5	—	0.5	—
	2	771.7	2.8	164.1	7.0	0.9	80
	3	704.9	11.3	133.5	24.4	1.8	260
	4	602.3	24.2	105.6	40.2	2.2	340
6	1	766.9	—	167.9	—	0.4	—
	2	748.8	2.4	155.8	7.2	0.9	125
	3	684.2	10.8	127.8	23.9	1.8	350
	4	586.7	23.5	102.4	39.0	2.1	425

[a] Percentage reduction relative to parameter value for Dosing Interval 1.
[b] Percentage delay in t_{max} relative to t_{max} for Dosing Interval 1.

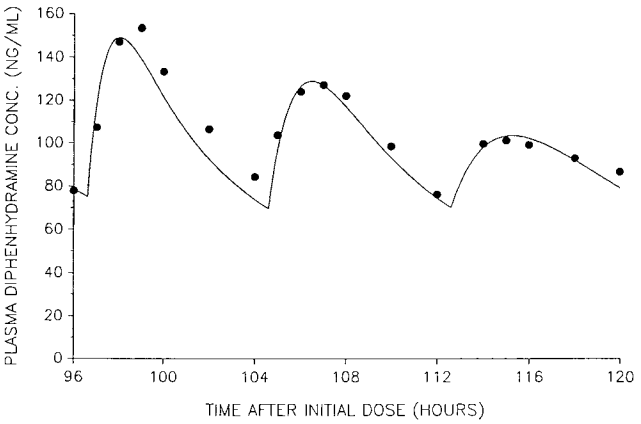

Fig. 1. Mean observed (●) and predicted (——) plasma diphenhydramine concentrations after administration of 50-mg Benadryl capsules every 8 hr for 15 doses to 25 healthy subjects. Predicted data were calculated as described in the text using intravenous diphenhydramine pharmacokinetic parameter values as the basis for the simulation and k_a values of 1.1, 0.70, and 0.30 hr^{-1}, corresponding to the doses administered at 96, 104, and 112 hr respectively (see Ref. 9).

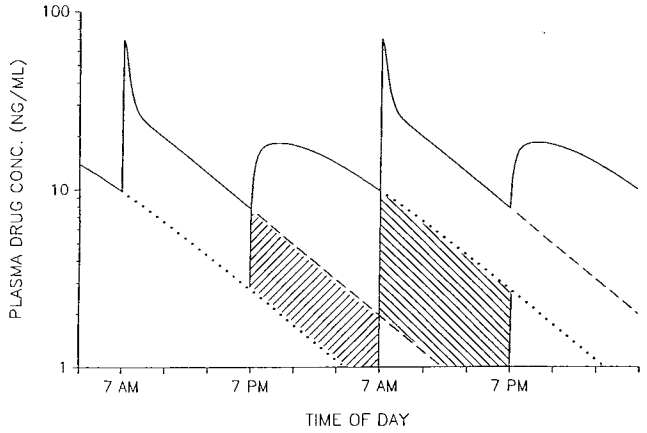

Fig. 2. Contribution of drug from one dosing interval to steady-state concentrations during the subsequent dosing interval when the rate of absorption varies as a function of time of day. Note that through concentrations before 7 AM doses are higher than those before 7 PM doses due to the greater contribution of slowly absorbed drug (\ \ \) to the subsequent interval as compared to the quickly absorbed drug (/ / /). Data from BID simulation of parameter Set 3.

over a 24-hr period to ensure a valid comparison when conducting bioavailability studies of controlled release formulations of drugs subject to diurnal variation. This recommendation holds even if a smaller common interval exists; i.e., if a common 12-hr interval for a controlled-release formulation dosed every 12 hr is compared to an instant-release reference formulation dosed every 6 hr.

In conclusion, we have shown that changes in absorption rate while all other parameters are constant can lead to diurnal rhythms in drug concentrations. This observation indicates that factors other than decreases in the extent of absorption or increases in clearance can account for these rhythms. Prediction of steady-state concentrations based on results from single oral doses of drugs which are administered more frequently than once a day may be inappropriate if the drug is subject to diurnal rhythms. Hence sampling during only one steady-state dosing interval during the day may not give an accurate estimate of true steady-state pharmacokinetics.

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