Computer-Aided Dosage Form Design. III. Feasibility Assessment for an Oral Prolonged-Release Phenytoin Product

Joy R. Irvin[1] and Robert E. Notari[1,2]

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Previous publications described computer-aided methodology for assessing the feasibility of designing prolonged release oral dosage forms containing linear-disposition drugs. Those methods determined all useful release rates and examined those rates to decide whether product development was warranted. The present study developed software to obtain similar information for phenytoin, which exhibits Michaelis–Menten disposition. The values for V_{max}, K_m, and V_d in 27 patients were employed to assess the ability of prolonged absorption to maintain steady-state plasma concentrations between 10 and 20 mg/liter following oral administration at 8-, 12-, and 24-hr intervals. Phenytoin steady-state plasma concentrations in this range were controlled by elimination and were not extended by prolonged absorption. Furthermore, single i.v. bolus doses resulting in an initial plasma level of 20 mg/liter provided concentrations above 10 mg/liter for ~1 to 3 days. When an oral multiple-dose regimen was found to maintain steady-state concentrations between 10 and 20 mg/liter, that dose and interval produced concentrations within that range regardless of the absorption *rate*. While absorption rate was not important, each patient's dose ranges were extremely narrow, emphasizing that dose size was the dominant factor in the control of phenytoin levels.

KEY WORDS: phenytoin dosage; prolonged release dosage forms; computer simulation; pharmacokinetics; sustained release.

INTRODUCTION

The development of prolonged-release oral dosage forms entails altering the release rate and dose in an attempt to maintain selected plasma concentrations using a desired dosing interval (tau). However, the pharmacokinetic properties of the drug may prevent any combination of rate and dose from achieving that goal. Since formulation and its evaluation are difficult, it is prudent to assess the pharmacokinetic limitations before beginning product development.

Previous publications (1,2) described methods to determine which combinations of release rates and doses maintained concentrations within a therapeutic window. Those methods involved (a) selecting a drug, a tau, and a window; (b) obtaining pharmacokinetic values for the drug in representative subjects; (c) using computer simulations to find every dose and release rate which maintained selected concentrations in each individual subject; (d) discerning the range of rates which accommodated the entire group; and (e) using that range to decide whether formulation was merited. These methods (1,2) were designed for linear disposition drugs.

The current goal was to develop and use analogous computer-aided methodology to determine whether phenytoin steady-state therapeutic plasma levels could be extended by prolonging oral absorption. If prolonged absorption cannot extend this duration, there is no reason to examine the influence of prolonged-release dosage forms.

Phenytoin dosing has been complicated by Michaelis–Menten disposition kinetics combined with a narrow therapeutic window of 10 to 20 mg/liter, making individualized dosing a necessity. Methodology was developed to accommodate phenytoin nonlinear clinical pharmacokinetic data (3–7). Sodium phenytoin capsules are available as both extended and prompt release (8). Only the extended-release formulation is indicated for once-daily dosing, thus implying that absorption rate is an important factor.

METHODS

k_a *Versus Dose Profiles.* The method of Lee and Notari (1,2) determined all combinations of absorption rate constants and dose sizes that maintained desired steady-state plasma concentrations using linear disposition drugs. This approach has been adapted to study drugs described by nonlinear disposition. The phenytoin model employed (4–6) involves first-order oral absorption followed by Michaelis–Menten disposition (Scheme I).

$$[\text{PHENYTOIN}]_{g.i.} \xrightarrow{k_a} [\text{PHENYTOIN}]_{body} \xrightarrow{V_{max},\ K_m}$$

Scheme I

Phenytoin steady-state plasma concentrations [Conc] were simulated as a function of time using an IBM 4361 main-frame computer by applying the Runge–Kutta algorithm (9) for numerical integration to Eq. (1),

$$d[\text{Conc}]/dt = [k_a F(\text{Amount})_{g.i.}/V_d] - V_{max}[\text{Conc}]/[K_m + \text{Conc}] \quad (1)$$

where k_a is the apparent first-order absorption rate constant (hr^{-1}), V_d is the apparent volume of distribution (liters), V_{max} is the maximum elimination rate (mg/hr-liter), and K_m is the plasma concentration (mg/liter) at which the elimination rate is one-half of its maximum. The bioavailable fraction, F, was assigned a value of one as reported by Jusko *et al.* (5). All doses are reported as bioavailable doses of phenytoin acid. These doses can be adjusted to represent the administered doses of sodium phenytoin for any desired F value by the reader.

A Fortran program was designed to simulate a multiple-dose regimen at fixed dose and tau by introducing a new dose in Eq. (1) at the end of each tau. Since $F = 1$ (5), the bioavailable amount, $F(\text{Amount})_{g.i.}$, after the first dose was equal to the dose and the [Conc] was zero. Following each tau, the new value for $F(\text{Amount})_{g.i.}$ was set equal to the sum of the dose and the $F(\text{Amount})_{g.i.}$ remaining from the previous dose, while the [Conc] was that remaining from the previous dose.

[1] Department of Pharmaceutical Sciences, College of Pharmacy, Medical University of South Carolina, 171 Ashley Avenue, Charleston, South Carolina 29425.

[2] To whom correspondence should be addressed.

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Each steady-state onset time, T_{ss}, was the time to achieve 98% of the average steady-state concentration, C_{ss}, calculated from known equations for C_{ss} and T_{ss} (10). The boundary values for combinations of k_a and bioavailable dose which provided steady-state plasma concentrations between 10 and 20 mg/liter were stored in 81 data files representing the V_d, V_{max}, and K_m values for 27 subjects (Table I) at τ = 8, 12, and 24 hr. The minimum acceptable k_a value was chosen to provide 90% absorption during tau (1). Therefore, $(k_a)_{min} = -\ln 0.1/\tau = 0.29\ hr^{-1}$ for 8 hr, $0.19\ hr^{-1}$ for 12 hr, and $0.096\ hr^{-1}$ for 24 hr. The user of this method may select any $(k_a)_{min}$ value.

The procedure for developing a k_a-versus-dose profile for a single individual was initiated using that subject's V_d, V_{max}, and K_m values together with a chosen tau, a k_a value less than $(k_a)_{min}$, and a dose found empirically to be too small. The steady-state plasma time course was compared to the 10- to 20-mg/liter window and initially rejected as too low. The dose was increased and the procedure repeated until the steady-state concentration was within the window. This represented the smallest acceptable dose for that k_a value. The dose was continually increased until the steady-state concentration exceeded the window. The dose previous to that was the largest acceptable dose for that k_a value. The k_a was then increased and the procedure was repeated. The final profiles, which showed the smallest and largest acceptable dose for each k_a value, appeared as a continuum owing to the small increments employed as illustrated in Fig. 1.

Plasma Concentrations Following Single Rapid i.v. Doses. A Fortran program was also written to simulate phenytoin plasma concentrations, [Conc], as a function of time following any single rapid i.v. dose. The Runge–Kutta (9) algorithm was applied to the disposition equation,

$$-d[\text{Conc}]/dt = V_{max}[\text{Conc}]/[K_m + \text{Conc}] \qquad (2)$$

and results were examined following several initial concentrations, $[\text{Conc}]_o$ (mg/liter). These simulations were carried out using the V_d, V_{max}, and K_m values for all 27 patients. Parameter values were also selected from the Vozeh *et al.* nomogram (11) representing the limiting combinations of V_{max} and K_m in 97.5% of epileptic patients. A V_d value of 0.65 liter/kg was employed for these hypothetical subjects (7).

RESULTS

Absorption Rate Constant-Versus-Dose Profiles. Figure 2 shows typical tree-trunk-shaped k_a-versus-dose profiles for 11 subjects chosen to avoid overlap. Any combina-

Table I. The Values Used for the Phenytoin Pharmacokinetic Disposition Parameters in 27 Subjects and the Resulting Dose Ranges Which Provided Steady-State Plasma Concentrations Between 10 and 20 mg/L at 24-Hr Dosing Intervals

Subject No.	Reference designation[a]	V_{max} (mg/hr-L)	K_m (mg/L)	V_d (L)	Dose range[b] (mg/day)
1	Child 1	0.259	2.22	37.7	200–208
2	Child 2	0.605	4.74	12.2	127–142[c]
3	Child 3	0.386	2.21	10.3	82–84
4	Child 4	0.176	1.45	43.6	165–171
5	Child 5	0.563	10.7	13.1	100–111
6	1	0.197	4.98	56.2	188–209
7	JS	0.317	3.62	57.0	339–358
8	WLW	0.245	6.48	51.4	197–223
9	GH	0.234	6.56	53.7	195–222
10	WFW	0.286	5.64	53.0	251–275
11	K.K.	0.302	2.92	44.5	263–276
12	E.E.	0.346	6.67	44.4	244–264
13	S.A.	0.375	6.91	44.4	261–284
14	R.E.	0.258	3.75	68.2	328–348
15	N.K.	0.396	6.27	43.4	282–299
16	A	0.338	10.8	41.3	178–207
17	B	0.531	7.73	53.2	436–457
18	C	0.795	16.2	59.1	533–542
19	D	0.476	3.97	46.7	419–425
20	E	0.654	11.4	51.4	452–465
21	F	0.624	14.3	41.3	311–331
22	G	0.654	11.6	41.7	364–374
23	H	0.592	4.98	48.0	482–540[c]
24	I	0.449	3.73	46.4	398–403
25	J	0.432	1.03	43.4	421–422
26	K	0.537	7.11	28.7	249–254
27	L	0.483	8.13	39.9	289–307

[a] Subjects 1–10 from Ref 4; subjects 11–15 from Ref 5; for subjects 16–27 V_d = 0.65 L/kg, V_{max}, K_m, and body weights from Ref 6.

[b] Observed in k_a-independent regions at τ = 24 hr (see Results). Ranges were slightly larger at low k_a values (Fig. 3) and τ = 8 or 12 hr (Fig. 4).

[c] Doses observed at $(k_a)_{min} \sim 0.1\ hr^{-1}$ since no k_a-independent regions were observed at τ = 24 hr for subjects 2 and 23 (Fig. 6).

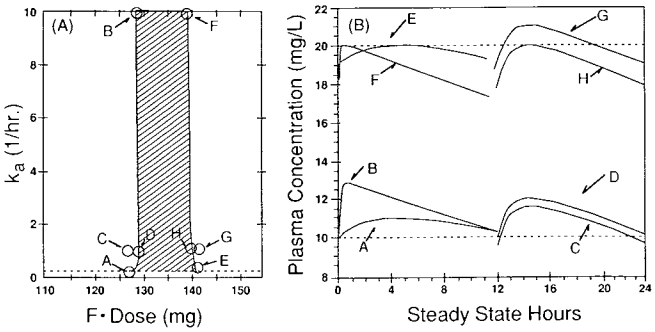

Fig. 1. (A) Absorption rate constant (k_a as hr^{-1}) versus bioavailable dose for subject 11 using τ = 12 hr. Any combination of dose and rate constant within this profile (shaded area) maintained phenytoin steady-state concentrations between 10 and 20 mg/liter as demonstrated in B, where each curve represents one 12-hr steady-state period for the corresponding k_a and dose combination in A. In A, the dashed line at k_a = 0.19 hr^{-1} is the suggested minimum k_a which provided 90% absorption during tau.

tion of k_a and dose within one profile (shaded areas) maintained that subject's steady-state phenytoin plasma concentration between 10 and 20 mg/liter using a 12-hr dosing interval. These profiles were shaped like tree trunks, with roots for all 27 subjects at 8-, 12-, and 24-hr dosing intervals with the notable exception of subjects 2 and 23 when dosed at 24-hr intervals. These two exceptions are examined in the Discussion as part of the explanation for the tree trunk patterns.

Relative Independence of the Maintenance Dose to the Absorption Rate. The k_a values in Fig. 2 have been purposefully extended to include unrealistically high values to emphasize the insensitivity of the dose ranges to the absorption rate. A slight expansion of the dose ranges occurred at low k_a values and produced the root-like appearance. These wider ranges were clinically unimportant for two reasons. The increases were too small to be of practical value as illustrated in Fig. 3, where the k_a-independent region was superimposed on the k_a-dependent region for two typical subjects. In addition, the increases were most pronounced at extremely small k_a values.

The Influence of the Dosing Interval. With two exceptions (see Discussion), the rate constant-versus-dose profiles resembled those in Fig. 2 for τ = 8, 12 and 24 hr. For any subject eliciting the trunk-shaped profile, the *total* daily acceptable dosage range increased when the tau value was reduced as illustrated for subject 11 in Fig. 4, where the center profile is the 24-hr tau and the larger profiles are tau values of 12 and 8 hr. As the daily intake was divided from once to twice to three times a day, fluctuations about the mean steady-state plasma concentrations were reduced. Consequently, the concentrations from τ = 8 hr remained within the therapeutic window over total daily dosage ranges that were slightly larger than those observed with a single daily dose in the same subject. However, the magnitude of the changes, as typified in Fig. 4, were too small to be of practical importance. The k_a-independent dose ranges at τ = 24 hr are listed in Table I.

DISCUSSION

Comparison of k_a*-Versus-Dose Profiles to Those Previously Reported.* A computer-aided approach was previously applied to theophylline, where rate-limiting first-order release ($k_{release}$) from the dosage form was followed by rapid first-order oral absorption and biexponential disposition (1). Since release was rate limiting, theophylline $k_{release}$ values represented the effective k_a values. Profiles for the useful combinations of $k_{release}$ and dose sizes were therefore analogous to the phenytoin profiles employing absorption rate constants per se. When the method was applied to theophylline, using pharmacokinetic data for 17 subjects, all $k_{release}$-versus-dose profiles were tent-shaped as illustrated in Fig. 5A. These were in sharp contrast to the tree-trunk-shaped profiles observed for phenytoin (Fig. 5B).

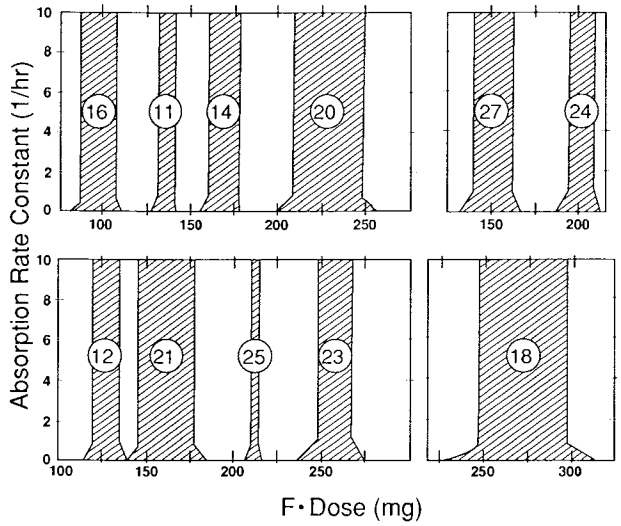

Fig. 2. Absorption rate constant (k_a as hr^{-1}) versus bioavailable dose profiles for 11 subjects (as labeled) using τ = 12 hr. Any combination of dose and rate constant within these profiles (shaded area) maintained phenytoin steady-state concentrations between 10 and 20 mg/liter. These tree-trunk-shaped profiles were typical of 79 of 81 profiles generated for 27 subjects (Table I) at τ = 8, 12, and 24 hr.

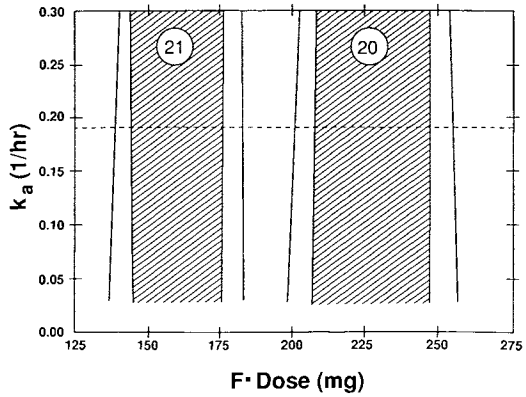

Fig. 3. Absorption rate constant (k_a as hr^{-1})-versus-bioavailable dose profiles for subjects 21 and 20 at τ = 12 hr. The shaded regions show the dosage ranges that were independent of k_a (see Fig. 2) superimposed within the k_a-dependent regions. The dashed line at k_a = 0.19 hr^{-1} is the suggested minimum k_a which provided 90% absorption during tau.

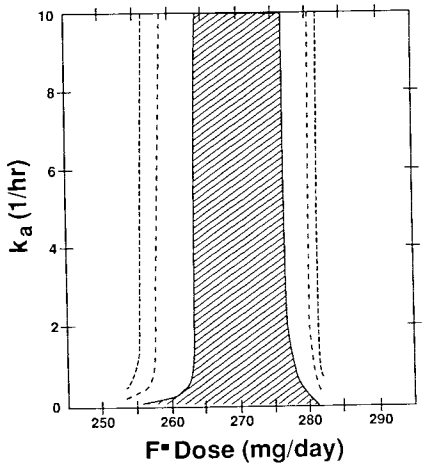

Fig. 4. Absorption rate constant (k_a as hr^{-1}) versus total bioavailable dose per day for subject 11. Innermost boundaries (solid lines) represent τ = 24 hr, the widest boundaries (dotted lines) represent τ = 8 hr, and the intermediate boundaries (dashed lines) represent τ = 12 hr.

The dosage ranges which maintained theophylline concentrations within its therapeutic window (coincidentally 10 to 20 mg/liter) were dependent on the absorption rate, which was controlled by $k_{release}$. The acceptable dose ranges decreased as $k_{release}$ increased, culminating at an apex where only one dose maintained desired steady-state concentrations (Fig. 5A). At rates that were higher than this apex, there were no doses which maintained steady-state theophylline concentrations within the window.

Conversely, the dosage ranges within the trunk of a phenytoin profile (Fig. 5B) were effective regardless of the absorption rate constant. An observable, though clinically unimportant, increase in dosage range occurred at k_a values which were less than $(k_a)_{min}$. Figures 2 and 3 illustrate that the overall ranges of phenytoin doses were largely independent of k_a.

There are two key comparisons shown in Fig. 5. At any given dose within the theophylline profile, an orally administered product was successful if the $k_{release}$ value was below the profile limit but unsuccessful if the $k_{release}$ value was too

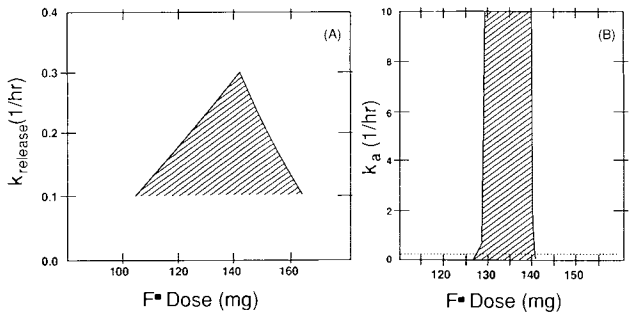

Fig. 5. (A) Previously published (1) $k_{release}$ (hr^{-1}) versus bioavailable dose of theophylline, where $k_{release}$ is the rate-limiting rate constant for oral absorption. (B) Absorption rate constant (k_a as hr^{-1}) versus bioavailable dose of phenytoin for subject 11. In both cases any combination of dose and rate constant within the boundaries (shaded areas) maintained steady-state concentrations between 10 and 20 mg/liter when τ = 12 hr.

high. The slow rate of absorption extended the theophylline plasma levels. Conversely, the rate of phenytoin absorption had no significant influence on the duration of the successful doses. This implied that slow release from a dosage form cannot extend the phenytoin durations. Also, the lack of any maximum limit for the phenytoin k_a inferred that steady-state levels were controlled by disposition and that multiple-dose rapid i.v. injections would be effective within the same dosage ranges.

Why Phenytoin Is Not a Candidate for an Oral Prolonged-Release Product. Table II summarizes the dependency of the "apparent $t_{0.5}$" values for 27 subjects based on their elimination as described by Eq. (2). When $K_m \gg$ [Conc], the mean value for the time to reduce any initial $[Conc]_0$ in half was 11 hr. As the $[Conc]_0$ was increased, the mean value increased from 12 hr at 1 mg/liter to 38 hr at 20 mg/liter, where the total range for 27 subjects was 22 to 68 hr. These data illustrate how the apparent $t_{0.5}$ is a function of [Conc], K_m, and V_{max} for each subject. Single-dose studies at low concentrations where the mean apparent $t_{0.5}$ value was only 12 hr would erroneously suggest that a once-a-day slow-release formulation might prove beneficial. However, once in the therapeutic range, phenytoin concentrations were self-sustaining for 1 to 3 days in these 27 subjects.

The hypothetical cases from Vozeh *et al.* (11) showed that predicted ranges for epileptic patients agreed with those observed for the 27 subjects. The values representing a 10-mg/liter decrease in concentration under capacity-limited conditions ([Conc] $\gg K_m$), where the time required is (10 mg/liter)/V_{max}, showed that elimination was not "saturated" at 20 mg/liter.

In order for oral absorption to prolong plasma concentrations, the absorption process must extend the intrinsic phenytoin duration. Since the therapeutic durations were 1 to 3 days, oral absorption would have to be prolonged over several days to increase these values. Consequently, dosage forms which traverse the gastrointestinal tract would tend to be expelled before the release of phenytoin was complete.

Subjects 2 and 23 at τ = 24 hr produced the only two exceptions to the tree trunk patterns. In doing so, they provided evidence that disposition is rate limiting in the remaining 79 tree-shaped profiles. These two subjects showed the shortest apparent $t_{0.5}$ values following single rapid i.v. injections resulting in initial plasma levels of 20 mg/liter. At that concentration, their 22- and 23-hr values were the only ones less than 25 hr. Since the intrinsic phenytoin durations in these two subjects were less than the 24-hr tau value, these two profiles reflected the influence of k_a on the phenytoin plasma durations. Although their profiles at tau values of 8 and 12 hr were trunk shaped, at τ = 24 hr, they resembled profiles for theophylline (Fig. 6).

Although elimination kinetics were not "saturated" at initial concentrations of 20 mg/liter, phenytoin concentration-versus-time plots were nearly linear following single i.v. injections. The portion of the window which was transversed during multiple dosing was approximately proportional to tau. Therefore, tent-shaped profiles would be expected if the window was restricted. A 12- to 15-mg/liter window, which represents 0.3 of the original value, reduced the apparent $t_{0.5}$ range from 22 to 68 hr at 20 mg/liter to approximately 7 to 20 hr. Simulations carried out at tau values of 12 and 24 hr using

Table II. The Time (Hours) to (1) Reduce Phenytoin Plasma Concentration by 10 mg/L When the Rate is Equal to V_{max} [Time = (10 mg/L)/(V_{max})]; (2) Reduce the Concentration in Half Starting at Concentrations of 20, 10, 2, and 1 mg/L Based on Eq. (2); (3) Reduce the Concentration in Half When $K_m \gg [Conc]_o$ ["Apparent $t_{0.5}$" = (0.693 K_m)/V_{max}]

Subject No.	10 mg/L / V_{max}	Initial concentration (mg/L) [20]	[10]	[2]	[1]	0.693 K_m / V_{max}
1	39	45	25	9.9	7.9	5.9
2	17	22	14	7.1	6.3	5.4
3	26	30	17	6.6	5.3	4.0
4	57	63	34	11	8.6	5.7
5	18	31	22	15	14	13
6	51	68	43	23	20	18
7	31	40	30	11	9.5	7.9
8	41	59	39	22	20	18
9	43	62	41	24	22	19
10	35	49	24	17	15	14
11	33	40	23	10	8.4	6.7
12	29	42	28	16	15	13
13	27	39	26	15	14	13
14	39	49	29	14	12	10
15	25	36	24	14	12	11
16	30	52	37	25	24	22
17	19	29	20	12	11	10
18	13	27	20	15	15	14
19	21	27	16	7.9	6.8	5.8
20	15	27	20	14	13	12
21	16	32	24	18	17	16
22	15	28	20	14	13	12
23	17	23	14	7.6	6.7	5.8
24	22	28	17	8.0	6.9	5.8
25	23	25	13	4.0	2.8	1.6
26	19	28	19	11	10	9.2
27	21	32	22	14	13	12
Mean (SD)	25 (12)	38 (13)	24 (8)	14 (5)	12 (5)	11 (1)
A[a]	31	55	39	27	25	24
B	14	15	8.5	3.1	2.4	1.7
C	39	51	32	16	14	12
D	12	16	9.7	4.9	4.3	3.7

[a] V_{max} (mg/hr-L) and K_m (mg/L) values—A, 0.321 and 11.0; B, 0.731 and 1.8; C, 0.256 and 4.5; D, 0.840 and 4.5—from 97.5% limits for expected values reported by Vozeh *et al.* (11).

a 12- to 15-mg/liter window produced triangular k_a-versus-dose profiles resembling those in Fig. 6 for subjects who previously showed trunk shaped profiles.

Conclusions. Although the USPXXII/NFXVII (8) contains separate monographs for extended and prompt sodium phenytoin capsules, the current study indicated that phenytoin was not an acceptable candidate for a prolonged release dosage form intended to increase duration. Instead, the dosage size was critical (see ranges in Table I), rather than the rate of presentation to the systemic circulation. When the required dosage range was used by a given patient, steady-state plasma concentrations were acceptable regardless of the absorption rate.

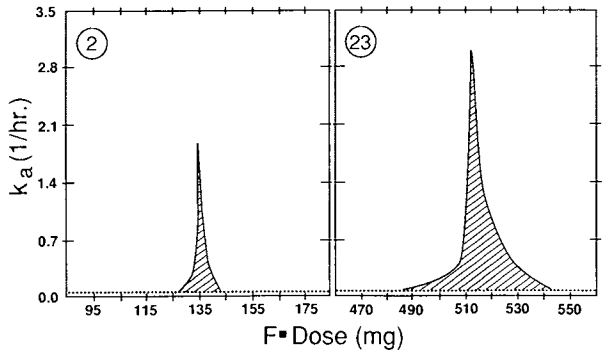

Fig. 6. Absorption rate constant (k_a as hr^{-1}) versus bioavailable dose for subjects 2 and 23 when τ = 24 hr. These were the two exceptions of 81 profiles representing 27 subjects (Table I) using τ = 8, 12, and 24 hr, where the remaining 79 profiles were similar in shape to those in Fig. 2.

Two exceptions were noted of the 81 profiles calculated for 27 patients. When τ = 24 hr, these two k_a-versus-dose profiles exhibited maximum allowable absorption rate constants above which plasma levels were unacceptable (Fig. 6). Although these maxima may rule out the use of daily i.v. injections in these patients, they were not relevant to oral administration since these observed k_a maxima were higher than k_a values for phenytoin absorption (6,7,12).

Previous investigations have also concluded that repetitively dosing instantly absorbed phenytoin (i.v. bolus injections) can maintain steady-state plasma levels within the 10- to 20-mg/liter range. Sawchuk and Rector (13) examined steady-state phenytoin plasma concentrations by simulating

constant-rate infusions and multiple-dose i.v. bolus injections using 12 combinations of V_{max} and K_m values based on ranges observed in 30 patients. Average steady-state levels for i.v. bolus doses at tau values of 6, 8, 12, and 24 hr were similar to those for constant-rate infusion when the total daily dose was the same. When steady-state concentrations remained within the window, the degree of fluctuation was small. Those i.v. bolus doses which produced average steady-state concentrations of 15 mg/liter resulted in fluctuations which were therapeutically unimportant even at τ = 24 hr. Although the rate of absorption and tau values minimally influenced the degree of fluctuation, small differences in dose size were significant.

Phenytoin plasma concentrations were clinically compared in a three-way crossover study in 18 patients given the equivalent of 100 mg of phenytoin sodium every 8 hr in (A) an extended-release capsule, (B) a prompt-release capsule, and (C) an oral solution (14). Differences between the C_{max} and the C_{min} values averaged only 1 to 2 mg/liter throughout the study. Statistically significant rank order was reported for AUC values (A < B ~ C) and C_{max} values (A < B ~ C), while no significant differences could be assigned to t_{max}. Since V_{max} and K_m values were not available, the relative bioavailable doses could not be quantitatively assessed. However, it was suggested that bio-inequivalent fractions were responsible for the observed differences since the absorption rate was previously shown to be of little consequence (13).

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