Phenytoin II: *In Vitro–In Vivo* Bioequivalence Standard for 100-mg Phenytoin Sodium Capsules

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Abstract □ A bioequivalence study was undertaken using an oral solution, a fast-dissolving capsule and a slow-dissolving phenytoin sodium capsule. The *AUC*, t_{max} and C_{max} correlated with *in vitro* dissolution data. The results of the present studies substantiate the presence of two types of phenytoin sodium products on the market. On the basis of these studies, *in vitro* specifications for fast- and slow-dissolving phenytoin sodium capsules as well as the *in vivo* bioequivalence requirements for these two types of products are recommended.

Keyphrases □ Phenytoin—*in vitro–in vivo* bioequivalence standard for phenytoin sodium capsules, dissolution □ Dissolution—*in vitro–in vivo* bioequivalence standard for phenytoin sodium capsules □ Bioequivalence—*in vitro–in vivo* standard for phenytoin sodium, capsules, dissolution

A good correlation between *in vitro* dissolution and *in vivo* parameters for phenytoin sodium (sodium salt of 5,5-diphenylhydantoin) capsules has been established (1). Previous work indicated that there are two types of phenytoin sodium products on the market, *i.e.*, fast and slow dissolving (1). It was shown that some of the marketed products including the innovator's phenytoin sodium capsules[1] dissolved slowly. Furthermore, the slow-dissolving innovator's product achieved significantly lower peak concentration at a later time (t_{max}) compared with other faster-dissolving products used in the study. Since there are differences between products, bioavailability studies using a solution as a reference standard were initiated. Two studies (single and multiple dose) were carried out using a slow-dissolving product, a fast-dissolving product, and a phenytoin sodium solution. The multiple-dose study was reported previously (2).

EXPERIMENTAL

***In-Vitro* Dissolution Studies**—The dissolution studies were carried out with distilled water using USP method I (rotating basket method) as described in USP XX with an agitation speed of 50 rpm (3).

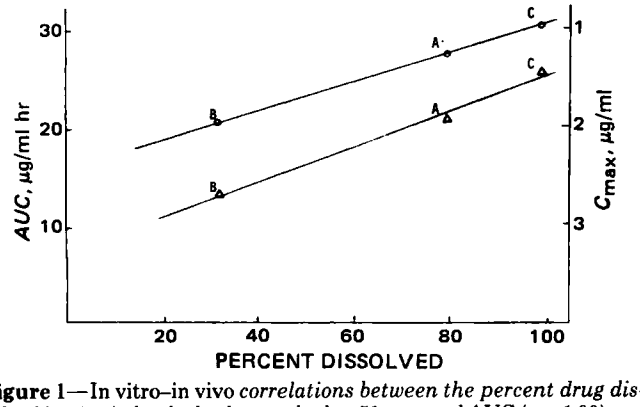

Figure 1—In vitro–in vivo *correlations between the percent drug dissolved in 30 min by the basket method at 50 rpm and* AUC (r = *1.00) and* C_{max} (r = *0.98) for products A, B, and C. Key:* (○) AUC; (△) C_{max}.

[1] Parke-Davis.

Using a randomized Latin-square design, the single-dose study was carried out in 15 healthy volunteers employing the following phenytoin sodium products: a fast-dissolving 100-mg phenytoin sodium capsule (product A); a slow-dissolving 100-mg phenytoin sodium capsule (product B); and a 100-mg phenytoin sodium solution (product C)[2,3]. Blood and saliva samples were collected over a period of 32 hr and analyzed by the published GC method with minor modifications (4).

The multiple-dose study was carried out in 24 epileptic patients using a fast-dissolving 100-mg phenytoin sodium capsule (product D), a slow-dissolving 100-mg phenytoin sodium capsule (product E), and a 100-mg phenytoin sodium solution (product F)[4,5] on a regimen of three doses per day for a 2-week period (2). Blood samples were collected and analyzed by a previous high-performance liquid chromatographic method (5).

RESULTS AND DISCUSSION

The evaluation of the data from the earlier single-dose study suggested that the reference phenytoin sodium product commonly used was slow dissolving and gave lower peak plasma concentrations (4). The C_{max} for this product was 0.93 μg/ml compared to C_{max} values of 1.06–1.44 μg/ml for other products (4).

Table I summarizes the various pharmacokinetic parameters obtained in this single-dose study. Statistical analysis of the data indicates a significant difference in *AUC*, C_{max}, and t_{max} for the three products tested. The use of a phenytoin sodium solution resulted in a higher C_{max}, higher *AUC*, and shorter t_{max} than the fast-dissolving capsule which, in turn, was higher and faster than the slow-dissolving capsule. The relative bioavailability of the slow-dissolving product was 73% compared with the solution and 80% compared with fast-dissolving product. As expected, these data correlate very well (r = 1.00 for *AUC*, and r = 0.98 for C_{max}) with the dissolution data (Fig. 1, Table I). The correlation between values of C_{max}, t_{max}, and the percent dissolved in 30 min by the basket method is shown in Fig. 1.

The results from the multiple-dose study summarized in Table II support the results of the single-dose study. The analysis of the steady-state blood level data from the multiple-dose study showed a significant difference in C_{max} and *AUC* values achieved with fast- and slow-dissolving products. The fast-dissolving phenytoin sodium product (D) and the phenytoin sodium solution resulted in significantly higher steady-state plasma levels when compared with the slow-dissolving phenytoin sodium product (E). The fast-dissolving product (D) was equivalent to the solution in C_{max} and *AUC*. Comparison of the C_{min} values revealed little, if any, difference in the three products tested. However, in 40% of the patients, therapeutically significant differences in plasma levels (> ±25%) were observed. In some instances plasma level differences of >5 μg/ml were observed (2, 6). These data substantiate the premise that the rate of dissolution is an important contributing factor in determining the rate of absorption and bioavailability of the product. The details of this study will be published elsewhere.

***In Vitro* Dissolution Studies**—The dissolution studies for products[6]

[2] Product A, Zenith capsules, lot no. 2057-35; product B, Parke-Davis capsule, lot no. RL288; and product C, Phenytoin sodium solution, Parke-Davis, lot no. RxX42884. The 100-mg phenytoin sodium solution was specially formulated and supplied by Parke-Davis Co., Dept. of Clinical Investigation, Detroit, Mich.

[3] Appropriate clearances and approvals from the Risk Involving Human Subjects Committee of the Agency and the University of Maryland were obtained before initiating the studies.

[4] Product D, Zenith capsules, lot no. 2057-40; product E, Parke-Davis capsules, lot no. TB479-RS; and product F, Phenytoin sodium solution, Parke-Davis, lot no. RxX43093.

[5] Appropriate clearances and approvals from the Risk Involving Human Subjects Committee of the Agency and the equivalent committee of University of Minnesota were obtained before initiating the studies.

[6] The dissolution of product E used in the multiple-dose study was 35% in 30 min, 62% in 60 min, and 88% in 120 min.

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Table I—Pharmacokinetic Parameters After Administering a Single Dose of 100-mg Phenytoin Sodium and Dissolution Characteristics of the Products

Product	*In Vivo* Parameters[a]			*In Vitro* Parameters	
	AUC_{0-32}, μg/ml hr	C_{max}, μg/ml	t_{max}, hr	% Dissolved[c] 30 min	60 min
A	28.77 ± 6.93	2.08 ± 0.56	3.00 ± 1.12	80	97
B	22.91 ± 6.76	1.42 ± 0.53	4.67 ± 2.0	33	61
C	31.44 ± 7.04	2.68 ± 0.84	1.20 ± 0.63	100[b]	100
Statistics	C > B A > B	C > B A > B	B > A B > C A > C		

[a] Data represents mean ± *SD*. [b] Assumed as 100%. [c] Basket method, 50 rpm.

used in these bioavailability studies were carried out by the basket method in water at 50 rpm (1). The fast-dissolving product showed a dissolution of ~80% in 30 min. The slow-dissolving product showed a dissolution of ~35% in 30 min, 60% in 60 min and 85% in 120 min.

***In Vitro–In Vivo* Correlations**—A number of researchers have attempted to study the correlation between *in vitro* dissolution and *in vivo* performance of phenytoin sodium products. A good correlation has been reported (7) for a variety of phenytoin products (including free acid, sodium salt, and calcium salt in tablet or capsule dosage forms) and the percent drug dissolved in 30 min when the dissolution is carried out by the USP basket method at 150 rpm in pH 9 borate buffer. Correlations of 0.920 and 0.950 were observed between percent dissolved in 30 min and C_{max} and *AUC* values, respectively (7). In this report, correlations of 0.98, 0.97, and 1.00 were observed between percent drug dissolved in 30 min and C_{max}, t_{max}, and *AUC* values, respectively (Table I, Fig. 1).

Poor correlation between *in vivo* and *in vitro* data, in spite of observed significant differences in *AUC*, C_{max}, and t_{max} has also been reported (8). Dissolution studies were carried out by the basket method in pH 9 borate buffer at 120 rpm (9). The lack of correlation found by these researchers can be attributed to the dissolution conditions employed. However, the phenytoin products were found to be acceptable, but were not considered to be interchangeable. The *in vivo* studies described here substantiate these findings. However, because of the differences in the dissolution methodologies employed, it is possible to correlate the *in vitro* results with *in vivo*, thus substantiating previous work (7).

The studies described here and in a previous report (1) have demonstrated a wide variance in the dissolution performance of marketed phenytoin sodium products which has been correlated with significant differences in *in vivo* performance. Because of the critical nature of this drug and documented bioinequivalence of phenytoin, an approved New Drug Application is required before marketing a phenytoin or phenytoin sodium drug product. Based on dissolution data, bioavailability data from single-dose and multiple-dose studies, and *in vitro–in vivo* correlation, it appears that there are two distinct types of phenytoin sodium products on the market, a slow-dissolving phenytoin sodium capsule (or extended phenytoin sodium capsule) and a fast-dissolving phenytoin sodium capsule (or prompt phenytoin sodium capsule). Phenytoin often is administered on a long-term basis. Due to its dose-dependent metabolism and narrow therapeutic range, even small changes in bioavailability profile can cause major changes in serum phenytoin concentration and can have serious clinical implications. Because of the differences in rate of drug delivery and absorption, it is possible that a patient accustomed to the slow-dissolving product and changed over to the fast-dissolving product may achieve higher, possibly toxic, blood levels. If the patient is accustomed to the fast-dissolving product, he or she may not achieve therapeutic levels when changed over to the slow-dissolving product. These products are not interchangeable and are therefore, not therapeutically equivalent.

Based on the information available, two separate *in vitro* and *in vivo* bioequivalence requirements for the two types of phenytoin sodium products, fast- and slow-dissolving, can be established. The *in vitro* dissolution specifications have already been accepted by the USP.

For fast-dissolving or prompt phenytoin sodium products, the bioequivalence requirements are:

Table II—Steady-State Pharmacokinetic Parameters During Administration of 100-mg Phenytoin Sodium Three Times a Day

Product	C_{min}, μg/ml	C_{max}, μg/ml	*AUC*, μg/ml hr
D	12.2	14.0	100
E	10.8	11.8	86
F	12.4	14.3	103
ANOVA	No difference	D ≠ E E ≠ F D = F	D ≠ E E ≠ F D = F

1. The test product shall be deemed to meet the *in vitro* bioequivalence requirement if it dissolves ≥80% in 30 min, and 95% in 60 min when the dissolution is carried out in water using the rotating basket method at 50 rpm.
2. The test product shall be deemed to meet the *in vivo* requirement when a satisfactory single-dose bioavailability study in humans is carried out comparing the test product with phenytoin sodium solution and the reference product.

For slow-dissolving or extended phenytoin sodium products, the *in vivo* bioequivalence testing will involve satisfactory human single-dose and multiple-dose study data. The single-dose bioavailability study should compare the test product with the reference product and a phenytoin sodium solution. The multiple-dose study should compare equivalent doses of the test and reference product administered once a day in patients. The USP labeling requirement for rapidly dissolving phenytoin sodium products contains the statement "not for once a day dosing" (10). The extended-release (slow-dissolving) phenytoin sodium products can be given once a day, and the prompt-release (fast-dissolving phenytoin sodium products are for two or three times a day dosing and not for once a day.

A good correlation has been observed with *in vitro* dissolution and *in vivo* bioavailability data. Based on *in vitro* and *in vivo* data, specifications for fast- and slow-dissolving phenytoin sodium capsules have been established. These products are not interchangeable because they are not therapeutically equivalent.

REFERENCES

(1) V. P. Shah, V. K. Prasad, T. Alston, B. E. Cabana, R. Gural, and M. C. Meyer, *J. Pharm. Sci.*, **72**, 306 (1982).

(2) FDA Contract No. 223-76-3019, University of Minnesota, Minneapolis, MN.

(3) "United States Pharmacopeia" 20th rev., U.S. Pharmacopeial Convention, Rockville, Md., 1980, p. 959.

(4) A. P. Melikan, A. B. Straughn, G. W. A. Slywka, P. L. Whyatt, and M. C. Meyer, *J. Pharmacokinet. Biopharm.*, **5**, 133 (1977).

(5) R. J. Sawchuk and L. L. Carter, *Clin. Chem.*, **26**, 835 (1980).

(6) B. E. Cabana, E. Purich, J. Hunt, R. Gummit, I. Leppick, and R. Sawchuk, "Abstracts," First European Congress of Biopharmaceutics and Pharmacokinetics Imprimerie Jouve 17, rue du Louvre, 75001 Paris (1981).

(7) V. R. Brandau and H. V. Wehnert, *Arzneim-Forsch/Drug Res.*, **29(I)**, 552 (1979).

(8) S. Sved, R. D. Hossie, I. J. McGilvery, N. Beaudoin, and R. Brien, *Can. J. Pharm. Sci.*, **14**, 67 (1979).

(9) P. J. Neuvonen, P. J. Pentikainen, and S. M. Elfving, *Int. J. Clin. Pharmacol.*, **15**, 84 (1977).

(10) "United States Pharmacopeia" XX, Addendum 'a' to supplement 1, U.S. Pharmacopeial Convention, Rockville, Md., 1980, p. 144.

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