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Double-Blind Randomized Study Comparing Brand-Name and Generic Phenytoin Monotherapy

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Summary: Ten patients with well-controlled seizures receiving chronic phenytoin (PHT) monotherapy for seizure prophylaxis completed a randomized double-blind crossover study comparing brand-name and generic PHT. Each patient received the same dose of each preparation for 3 months during which trough PHT concentrations and adverse effects were monitored. The average predose steady-state total PHT concentration was 11.9 ± 4.9 μg/ml during brand-name therapy and 14.2 ± 8.2 μg/ml during generic therapy. The average predose steady-state free PHT concentrations were 0.93 ± 0.47 μg/ml (brand name) and 1.14 ± 0.64 μg/ml (generic), respectively ($p < 0.005$). The potency (capsule content) values for the lots used in the study were 99.2% for the brand-name and 104.6% for generic. Because of the nonlinear Michaelis-Menten kinetics of PHT, a 5.4% difference in potency could account for the observed differences in plasma concentrations. When compared with brand-name PHT therapy, the generic drug was associated with an increase in serum concentration. This increase was consistent with the reported difference in capsule content between the generic and brand-name lots used in this study. **Key Words:** Anticonvulsants—Phenytoin—Nonlinear pharmacokinetics—Therapeutic equivalency—Capsules—Generic drugs.

Phenytoin (PHT) is a useful first-line antiepileptic drug (AED) for the treatment of partial and generalized seizures. PHT manifests dose-dependent kinetics. At low plasma PHT concentrations, elimination half-life is 16–24 h. At therapeutic concentrations, PHT disappears at a slower rate, with a half-life of up to 42 h. After i.v. infusions of 15–18 mg/kg (which generally produce therapeutic levels), PHT half-life varies from 10 to 160 h. A patient manifesting a half-life of 160 h (~1 week) is not expected to achieve steady-state before five half-lives, or 5 weeks, after onset of therapy (Woodbury, 1989).

There are numerous reports of therapeutically inequivalent PHT products. In many cases these products have resulted in alterations in serum concentrations with or without associated clinical problems (Balla, 1968; Rail, 1968; Tyrer et al., 1970; Melikian et al., 1977; Sawchuk et al., 1982*a*,*b*; Rosenbaum, 1988). To avoid such complications the U.S. Food and Drug Administration has developed criteria that allow for only minimal differences in bioavailability for products that are passed as bioequivalent. In addition, United States Pharmacopeia (USP) criteria allow for some variation (93–107%) in capsule content (potency). Because of the nonlinear kinetics manifested by PHT, small differences in the amount absorbed could theoretically result in larger changes in serum concentrations in patients who have changed from one PHT preparation to another. The role that variation in capsule content may play in generic substitution of PHT during chronic monotherapy for seizures has not been studied.

A double-blind crossover study comparing the serum concentrations and the adverse effects in patients during long-term monotherapy with generic and brand-name PHT has not been performed.

The goal of this study was to investigate these issues in patients receiving chronic PHT monotherapy.

MATERIALS AND METHODS

Study design

This was a 6-month double-blind randomized crossover study comparing two extended-release PHT preparations: a generic one (Phenytex) and the

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brand-name product (Dilantin). Phenytex is a generic PHT preparation that until recently was considered as bioequivalent to Dilantin. Each patient was randomly assigned to one preparation, and after 3 months changed to the same dose of the alternative preparation. The protocol received Institutional Review Board approval.

Test medications

Generic and brand-name 100-mg PHT capsules were used. Each was enclosed in a number-zero identically looking opaque gelatin capsule that completely obscured the preparation. The research pharmacist dispensed a 1-month supply. The number of pills dispensed and returned was verified and recorded at each visit by the research nurse and the pharmacist. A separate sealed bottle with an emergency supply was given at each visit and returned on the subsequent visit.

Patients

Thirteen patients (seven male, six female) were randomized and received at least one PHT preparation. All fulfilled the following criteria: (a) Adults (ages 18–60 years) who were receiving PHT monotherapy for seizure prophylaxis. All had suffered from prior seizures except one, who was receiving PHT prophylaxis after intracranial surgery. All other patients had had either partial or generalized seizures necessitating PHT monotherapy as judged by their referring physicians. All had had an EEG within the 2 years preceding enrollment in the study. None was receiving any other chronic medication except for one postmenopausal woman who was receiving a chronic constant dose of Premarin (1.25 mg/day). This was maintained at the same dose throughout the study. (b) Patients judged to have poor compliance were excluded. None of the patients had significant cardiovascular, gastrointestinal, hematologic, hepatic, renal, or psychiatric disease or alcohol or drug abuse. Patients judged to be unreliable in reporting the necessary information, side effects, or seizures were not enrolled. Patients with significant abnormalities in liver function or blood count were also not enrolled. If a patient developed any potentially interfering condition (like infections requiring antibiotic therapy during the study), enrollment was terminated.

Procedures

At the screening visit the patient's inclusion and exclusion criteria were reviewed, and the patient was informed about the study. In many cases several screening visits were conducted to establish the reliability and compliance of the patient. At the first study visit, the patient signed an informed consent, the history was reviewed, and full physical and neurological examinations were done. At that time the patient was randomized to treatment with either brand-name or generic PHT therapy. The randomization code was kept by the research pharmacist (with 24-h coverage), and was not available to the investigators or to the patients. During this first visit seizure frequency and adverse effects were reviewed and recorded. Blood studies, including hematology, liver function, and free and total PHT concentrations were obtained. The patient was dispensed a month's supply of the study medication in a double-blind fashion. Patients were instructed to take the medication always at exactly the specified time throughout the study (every 12 h for some patients and every 24 h for others). Patients also always recorded the exact time (hour and minute) of their intake of the last PHT dose received before a scheduled visit. All visits were scheduled at the same time of the day. PHT concentrations were always drawn within 1 h of intake of the next dose.

Patients were seen monthly and were telephoned frequently in between (as needed) to ensure compliance. At each visit compliance was verified by pill count, careful interviews, and reviewing seizure frequency and adverse effect diaries. During the study patients kept daily records of seizure frequency and of any potential adverse effects they may have developed. The number, severity, duration, and type of seizures and adverse effects were reviewed and verified during each monthly visit, and evidence for neurotoxicity was examined by the following tests: finger–nose–finger, heel–knee–shin, gait, tandem gait, Romberg, and nystagmus. Free and total plasma PHT levels were obtained at each visit, and PHT was dispensed in the same fashion as at the initial visit. On the fourth visit (end of month 3), the patient was changed to the same dose of the alternative preparation. Blood studies were repeated during the fourth visit and during the last visit at the conclusion of the study. Complete physical and neurological examinations were also repeated during the last visit.

Total PHT assay methodology (enzyme-multiplied immunoassay technique) coefficient of variation was $\leq 10\%$, while that of free PHT [high-performance liquid chromatography (HPLC) ultrafiltration] was $\leq 8\%$.

RESULTS

Serum concentrations

The average daily PHT dose was 4.58 mg/kg (range, 2.86–5.35 mg/kg). Ten of our patients com-

pleted both arms of the study (generic and brand-name). The other three could not complete the study because of adverse experiences necessitating introduction of new AEDs and/or change in therapy (Table 1). None of these adverse experiences could be attributed to changes in PHT concentrations (see Table 1 for details).

Because the mean total and free PHT levels are not normally distributed and because the *t* test assumes normal distribution, we also performed the Wilcoxon signed rank test. This test is based on the ordinal scale of measurement and does not assume normal distribution of the data. The results showed agreement between analyses performed by the *t* test and the Wilcoxon signed rank test.

Because serum concentrations can be altered by changes in body weight, the level/dose ratio was used as our primary parameter of analysis (Table 2). Only very minimal changes in weight were observed during this study.

$$\text{level/dose ratio} = \frac{\text{average predose steady-state concentration}}{\text{dose}}$$

The dose was the total daily dose (in mg/kg/day). The average predose steady-state concentration (μg/ml) was the average trough concentration of months 2 and 3 (for one preparation) and of months 5 and 6 (for the other preparation). Months 1 and 4 concentrations were excluded because steady-state levels may not have been achieved at that time (see introductory statement). The only exception was patient 10, who could not receive the same dose of generic PHT because of development of symptoms of toxicity with high serum concentrations 2 weeks after being changed to generic therapy. Thus this patient's PHT concentration, obtained after 2 weeks of generic therapy, was used as an approximation of steady-state concentration. This concentration probably underestimated steady-state concentration and biased the analysis toward not finding a difference between the two preparations.

TABLE 1. *Patients who could not complete 6 months of the study because of an adverse experience*

Patient	Month	Preparation	Adverse experience
11	1	Brand name[a,b]	Worse seizures
11	1	Generic[a,c]	Worse seizures
12	4	Generic[a,d]	Worse seizures
13	4.5	Brand name	Allergic rash

[a] Worsening of seizure control could not be attributed to a change in phenytoin (PHT) levels (see below).

[b] The trough PHT concentration was 6 μg/ml in baseline. It was 8.3 μg/ml during month 1 when the patient suddenly developed poor (complex partial) seizure control.

[c] Patient 11 was reenrolled after the dose was increased and after stabilizing with excellent seizure control for 2.5 months. Trough PHT level was 9 μg/ml at the time of worsening of seizures.

[d] Trough PHT concentrations were remarkably stable at 6, 6, 6, 6, 6, μg/ml at baseline, months 1, 2, 3, and 4, respectively. The increased seizure frequency was thus thought to be independent of the PHT preparation.

The average predose free PHT concentration during brand-name therapy was 0.93 ± 0.48 μg/ml, and during generic therapy 1.14 ± 0.64 μg/ml. Each of the nine patients showed a higher average free PHT concentration during generic therapy (Table 2). The difference was statistically significant (two-sided paired *t* test, $p < 0.01$; Wilcoxon rank sum test, $p < 0.005$).

The average predose total PHT concentration during brand-name therapy was 11.9 ± 4.9 μg/ml, and during generic 14.2 ± 8.2 μg/ml. The difference approached but did not achieve statistical significance ($0.05 < p < 0.1$ for two-sided paired *t* test and Wilcoxon rank sum test).

Adverse experiences

The most common adverse experiences observed in the 10 patients completing both arms of the study included headaches, gastrointestinal upset, fatigue, dizziness, and lethargy. With one exception, these experiences were mild, transient, tolerable, and in most cases the relationship to PHT therapy was not definite. The incidence of each of these adverse experiences was not statistically different between the two preparations (McNemar test, $p > 0.25$). One patient (10), a 27-year-old woman, developed intolerable adverse effects after changing from brand-name to generic therapy. During the first phase of the study this patient received 300 mg of brand-name PHT per day, which she tolerated very well despite an average predose steady-state concentration of 20.5 μg/ml. Twelve days after changing to the generic preparation (same daily dose), she noted the gradual onset of difficulty in concentration, headaches, ataxia, diplopia, and progressive somnolence. Thirty-six hours later, her symptoms were more severe and her serum PHT concentration was 30.2 μg/ml. PHT was stopped. Two days later PHT concentration dropped to 25.9 μg/ml and symptoms gradually subsided. Three days later 200 mg/day generic preparation was started. Subsequent PHT serum concentrations were 8.0, 7.0, and 7.0 μg/ml at months 4, 5, and 6 of the study.

The results of the laboratory tests during therapy with each preparation are summarized in Table 3. There were no statistically significant differences

TABLE 2. *Phenytoin (PHT) serum concentration to dose ratios*[a]

	Total			Free		
	Dilantin	Generic	Change	Dilantin	Generic	Change
1	1.45	1.84	0.39	0.127	0.151	0.024
2	4.22	4.82	0.60	0.343	0.408	0.065
3	1.69	1.91	0.22	0.125	0.139	0.014
4	3.43	4.36	0.93	0.284	0.388	0.104
5	1.53	2.01	0.48	0.117	0.139	0.022
6	3.56	4.98	1.42	0.465	0.572	0.107
7	2.56	2.08	−0.48	0.185	0.244	0.059
8	1.99	1.65	−0.34	0.140	0.158	0.018
9	1.41	1.24	−0.17	0.102	0.116	0.014
10300[b]	3.79	5.75	1.96	(0.370)	NA	—
10200[b]	—	(1.96)	—	—	(0.122)	—
Mean	2.56	3.06	0.501	0.210	0.257	0.0474
SD	1.09	1.70	0.773	0.127	0.161	0.0379

The numbers in parentheses were not used in calculating the mean and SD values.
NA, not available.
[a] Concentration to dose ratio = Concentration (μg/ml)/Dose (mg/kg/day).
[b] Patient 10 was initially started with 300 mg/day of brand-name PHT (300). Upon being changed to generic PHT the patient developed toxic concentrations and the dose had to be decreased to 200 mg/day (200).

between the laboratory values with either preparation (paired t test, $p > 0.05$).

Seizure frequency

Daily seizure records were kept by all patients. Most of the patients were very well controlled, and eight of ten completing both arms of the study were seizure-free. Thus, the number of patients and their low seizure frequency do not allow for any meaningful comparison of efficacy.

DISCUSSION

Interpretation of the data

We observed a statistically significant difference in the free PHT concentration between the two preparations. The average predose free steady-state PHT concentration was 22.6% higher during generic than during brand-name therapy (0.93 vs. 1.14 μg/ml). The difference between the total PHT concentrations approached but did not achieve statistical significance. The average predose steady-state PHT total concentration was 19.3% higher during generic than during brand-name therapy (11.9 vs. 14.2 μg/ml).

There are four possible explanations for our findings: (a) There is increased bioavailability and/or capsule content of generic as compared to brand-name PHT and the number of patients studied was large enough to detect differences in the free levels but not in the total levels. (b) There is less protein binding of PHT during generic therapy. (c) There is a decrease in PHT clearance during generic therapy. (d) There is a systematic confounding variable affecting PHT levels obtained under each preparation (e.g., more intake of medication during the generic phase of the study).

We favor the first explanation because: (a) there were no differences between albumin and protein levels with either preparation; (b) it is biologically impossible for a change in clearance or protein binding to result from a change in preparation; (c) our study was double-blind and randomized; and (d) there are multiple factors biasing our data toward not detecting differences that may actually exist. These factors appear to have affected the total concentration more than the free concentration (see below).

Factors in our study that make it more difficult to detect real differences between the two preparations include: (a) Interindividual variability in drug clearance. (b) Day-to-day variability in PHT assays. This variability was higher for the total PHT assay than for the free fraction assay (≤10 vs. ≤8%). (c) Interpatient variability of protein binding and albumin concentrations. (d) Steady-state concentrations

TABLE 3. *Blood studies*

	Dilantin	Generic
Hgb (gm/dl)	14.3 ± 1.5	14.2 ± 1.2
WBC (10^3/mm^3)	7.9 ± 3.0	7.2 ± 2.5
Bilirubin (mg/dl)	0.2 ± 0.08	0.24 ± 0.05
SGOT (U/L)	21 ± 14	25 ± 9
SGPT (U/L)	34 ± 22	34 ± 21
Alkaline phosphatase (U/L)	100 ± 87	115 ± 80
GGT (U/L)	88 ± 71	112 ± 73

Hgb, hemoglobin; WBC, white blood cells; SGOT, serum glutamic oxaloacetic transaminase; SGPT, serum glutamic pyruvic transaminase; GGT, gamma-glutamyl transpeptidase.

were probably not achieved by the one patient (10) who manifested the largest increase in concentration upon changing from brand-name to generic PHT. Thus in this patient the concentration used for generic PHT was an underestimate of the real steady-state concentration. (e) A relatively small number of patients.

These factors result in underestimating the magnitude of the observed concentration increases during generic PHT therapy and/or in increasing the standard deviation of the data. This is particularly true for the total PHT concentrations, where the standard deviation/mean ratio is 0.773/0.501 = 1.54 (Table 2). This ratio for free PHT concentrations was 0.0379/0.0474 or 0.80 (Table 2). Power calculations (Zar, 1984) show that, given the standard deviation of our data, ~20 patients are needed to detect a mean increase of 20% in total PHT concentration ($\alpha = 0.05$, $\beta = 0.1$). To detect a 20% increase in free PHT concentration ($\alpha = 0.05$, $\beta = 0.1$) only nine patients are needed. Having studied 10 patients, we were thus able to detect statistically significant differences in the free levels, but the number of our patients was not sufficient to detect differences that probably also existed in the total concentrations.

Potency (capsule content) analyses were performed using an HPLC technique with ultraviolet light detection based on the USP XXII procedures. The potency of the brand-name lot was 99.21% ± 1.47, and that of the generic preparation was 104.63% ± 3.72. Because of the nonlinear Michaelis-Menten PHT pharmacokinetics, a difference of 5.4% in the amount absorbed can account for a 20% difference in serum concentrations (see calculations below).

By using the published adult mean K_m and V_m values (Browne et al., 1985) and the mean steady-state concentrations achieved on each preparation in the group of patients we studied, the observed relative generic/brand-name dosing rate ratio can be calculated using the following formula (Shargel and Yu, 1985):

$$\frac{R_2}{R_1} = \frac{\dfrac{V_m \cdot C_2}{K_m + C_2}}{\dfrac{V_m \cdot C_2}{K_m + C_1}}$$

where R_2 is the dosing rate with generic PHT; C_2 is the steady-state concentration with generic PHT (14.2 μg/ml); V_m (the maximum rate of metabolism of PHT) = 487 mg/day (Browne et al., 1985); K_m (the plasma concentrations at which the metabolic rate is one-half the maximum) = 4.3 μg/ml (Browne et al., 1985); R_1 is the dosing rate with brand-name PHT; and C_1 is the steady-state concentration with brand-name PHT (11.9 μg/ml).

This formula gives an observed R_2/R_1 ratio of 1.046. This is remarkably similar to the predicted R_2/R_1 value of 1.046/0.992 = 1.054. Thus, the most likely explanation for our findings is the presence of differences in capsule content between the two preparations studied.

We must point out the limitations of our methodology. There was variability in the assays of free and total PHT concentrations. Although we took extra care to achieve and check for compliance with repeated pill counts and careful records, these outpatient methods do not ensure complete compliance (Pullar et al., 1989; Rudd et al., 1989). Hence, in any one of our patients, including the one who developed toxic concentrations, we cannot absolutely rule out an undetected confounding variable, for example, an unrecognized change in compliance. Confounding variables, however, would not account for statistically significant differences unless those variables were systematically associated with one preparation (Osorio and Reed, 1988). This possibility can be eliminated because our study was double-blind and randomized.

Review of the literature and significance of the study

Differences in serum concentrations and/or patient response upon nonequivalent preparation substitution have been reported for carbamazepine (Koch and Allen, 1987; Sachdeo, 1987), valproate (MacDonald, 1987), and PHT (Balla, 1968; Eadie et al., 1968; Tyrer et al., 1970). The FDA criteria for bioequivalence (Federal Register 1977) allow for a ±20% difference in bioavailability between generic and brand-name products. In addition, USP criteria specify that capsule content should be within ±7% (93–107%) of the stated content (100 mg in the case of the studied PHT capsules). Thus, certain differences (albeit small) are allowable in products that are considered bioequivalent. Such differences may be particularly important in medications that manifest nonlinear kinetics, particularly in patients who happen to be on the nonlinear portions of their dose–concentration curves.

Studies to establish bioequivalence are performed on healthy volunteers, and thus may not account for the full pharmacologic and therapeutic impact of generic substitution. Physicians considering generic substitution should consider several factors: (a) the risk that such a substitution could result

in a change in serum concentration; (b) the risk that such a change, if it occurs, may lead to significant adverse effects or loss of efficacy; (c) the cost of generic versus brand-name therapy; (d) the cost of blood tests necessary to ensure that the new concentrations are adequate; (e) the cost of time and effort spent in adjusting the dose (if needed); (f) the risk that patients may receive different generics each time they refill the prescription; (g) the effect generic substitution may have on patient compliance; and (h) patient motivation and interest in receiving a generic preparation.

Our study was designed to address several of these issues. Its advantages were as follows: (a) The protocol was double-blind and randomized. (b) We took extra care to control potential confounding variables. We believe that the fact we were able to demonstrate statistically significant differences while studying a relatively small number of patients is due, at least in part, to a favorable degree of control of confounding variables. (c) Our findings have direct relevance to daily clinical practice because we studied patients receiving chronic monotherapy. (d) When adverse effects or changes in seizure frequency occurred they were managed according to guidelines based on standard clinical practice. (e) We followed patients for 3 months with each preparation and excluded the concentrations from months one and four to exclude a sequence effect.

We conclude that generic substitution of PHT can be associated with increases in PHT serum concentrations. In our experience, these increases were asymptomatic in nine of ten patients, but were associated with intolerable dose-dependent adverse effects in the tenth. Such increases may be even more important if there is increased interlot variability in capsule content of generic preparations or if there is increased intergeneric variability as compared to the interlot variability of the brand-name product. Prior studies have emphasized the role of differences in bioavailability in producing differences in serum concentrations between brand-name and generic preparations. The potential role of capsule content (potency) has been largely ignored. Out study indicates that variability in capsule content may be an important factor to be considered during generic substitution of medications that, like PHT, manifest nonlinear pharmacokinetics.

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RÉSUMÉ

Dix patients présentant des crises bien contrôlées sous monothérapie chronique par phénytoine (PHT) ont été inclus dans une étude croisée rendomizée en double-aveugle, comparant une PHT de marque et une PHT générique. Chaque patient a reçu la même dose de chaque préparation pendant 3 mois, avec surveillance des taux sanguins de PHT et relevé des effets collatéraux. La concentration totale de PHT à l'état d'équilibre avant la prise du médicament était de 11.9 ± 4.9 mg/ml pendant le traitement par PHT de marque, contre 14.2 ± 8.2 mg/ml par traitement générique. La concentration moyenne à l'état d'équilibre de PHT libre avant prise du médicament, était de 0.93 ± 0.47 mg/ml (PHT de marque) contre 1.14 ± 0.64 mg/ml (générique) ($p < 0.005$). La puissance (contenu de la capsule) pour les les lots utilisés dans les études, était de 99.2% pour le médicament de

marque contre 104.6% pour le générique. En raison de la cinétique non linéaire de la PHT, une différence 5.4% pourrait expliquer les différences observées dans les concentrations plasmatiques. Par comparaison au produit de marque, la PHT générique a été associé à une augmentation des taux sanguins. Cette augmentation a été cohérente avec la différence des contenus des comprimés constatée entre le médicament de marque et le générique utilisés dans cette étude.

(P. Genton, *Marseille*)

RESUMEN

Diez enfermos con ataques bien controlados con Fenitoína (PHT) crónica en forma de monoterapia, para la profilaxis de ataques, completaron un estudio cruzado, randomizado y doble ciego comparando la marca comercial y el nombre genérico de la PHT. Cada paciente recibió la misma dosis de cada preparación durante 3 meses en los cuales se monotorizaron las concentraciones de PHT y los efectos adversos. Las concentraciones promedio pre-dosis, en estado estable, de fenitoína fueron de 11.9 ± 4.9 microgramos/ml durante la terapia con el nombre comercial (marca) y 14.2 ± 8.2 microgramos/ml durante el tratamiento con el preparado genérico. El promedio pre-dosis de las concentraciones de PHT en estado estable libre fueron de 0.93 ± 0.47 microgramos/ml (nombre comercial o marca) y 1.14 ± 0.64 microgramos/ml (preparado genérico) respectivamente ($P < 0.005$). Los valores de potencia (contenido de la cápsula) para los lotes usados en este estudio fueron 99.2% para el preparado con marca y 104.6% para el genérico. Según la cinética no linear de Michaelis-Menten de la PHT, se piensa que un 5.4% de diferencia en la potencia podría ser la causa de las diferencias observadas en las concentraciones plasmáticas. Cuando se compara con el nombre comercial, la terapia con fenitoína genérica se asocia a un incremento en las concentraciones séricas. Este incremento estaba de acuerdo con la diferencia del contenido en la cápsula entre los lotes de preparado genérico y de marca, usados en este estudio.

(A. Portera-Sánchez, *Madrid*)

ZUSAMMENFASSUNG

Bei 10 Patienten mit gut eingestellten Anfällen unter chronischer Phenytoin (PHT) Monotherapie wurde eine randomisierte Doppelblind crossover Studie zum Vergleich einer Reinsubstanz und einse Firmenpräparates gemacht. Jeder Patient erhielt die gleiche Dosis jeder Präparation für die Dauer von 3 Monaten, wobei PHT-Konzentrationen und Nebenwirkungen registriert wurden. Die mittlere gesamte Gleichgewichtskonzentration von PHT vor Einnahme betrug 11.9 ± 4.9 µg/ml bei dem Firmenpräparat und 14.2 ± 8.2 µg/ml bei der reinen Substanz. Die mittlere freie Gleichgewichts-PHT-Konzentration betrug 0.93 ± 0.47 µg/ml (Firmenpräparat) und 1.14 ± 0.64 µg/ml (Reinsubstanz) jeweils vor Gabe ($p < 0.005$). Die Potenzwerte (Kapselinhalt) für die Einheiten bei der Studie betrugen 99.2% für das Fabrikat und 104.6% für die Reinsubstanz. Wegen der nicht-linearen Michaelis-Menten Kinetik von Phenytoin kann eine 5.4% Differenz der Potenz für die beobachteten Unterschihede in den Plasmakonzentrationen verantwortlich sein. Im Vergleich zu der Firmenzubereitung war die Reinsubstanz-Therapie mit einem Anstieg der Serumkonzentrationen assoziiert. Dieser Anstieg war konsistent mit den berichteten Unterschieden im Kapselinhalt zwischen Reinsubstanz und Firmenpräparat bei dieser Untersuchung.

(C. K. Benninger, *Heidelberg*)