Binding of 5,5-Diphenylhydantoin and Its Major Metabolite to Human and Rat Plasma Proteins

GORDON J. CONARD*, CORYCE O. HAAVIK†, and KENNETH F. FINGER‡

Abstract □ Equilibrium dialysis was used to determine the degree of plasma protein binding of both 5,5-diphenylhydantoin and its major metabolite, 5-(*p*-hydroxyphenyl)-5-phenylhydantoin, in man and in the rat. Binding studies show that diphenylhydantoin is extensively bound to human and rat plasma proteins and that the amount of diphenylhydantoin bound per gram protein, at equivalent free diphenylhydantoin concentrations, is greater in human plasma than in rat plasma. Since the rat has higher (≈1.6-fold) free diphenylhydantoin levels at equivalent total plasma drug levels, correlation of free diphenylhydantoin levels in these species with the *in vivo* incidence of drug-induced gingival hyperplasia was not possible. Dialysis studies show that the *para*-hydroxy metabolite is strongly plasma protein bound and that the amount of metabolite bound per gram protein, at equivalent free metabolite concentrations, is greater in rat plasma than in human plasma. Since a given total metabolite plasma concentration results in higher (≈1.4-fold) free levels in human plasma than in rat plasma, differences in plasma protein binding of the metabolite between these species *in vivo* may contribute to an explanation for the species selectivity of diphenylhydantoin-induced gingival hyperplasia.

Key phrases □ 5,5-Diphenylhydantoin, metabolite—plasma protein binding, rats, man □ 5-(*p*-Hydroxyphenyl)-5-phenylhydantoin—plasma protein binding, rats, man □ Plasma protein binding—5,5-diphenylhydantoin and metabolite, rats, man □ Equilibrium dialysis—drug–plasma protein binding □ Gingival hyperplasia—effect of drug–plasma protein binding

The antiepileptic, 5,5-diphenylhydantoin, has been shown by several investigators to be partially bound to plasma proteins (1–12). The possibility exists that species differences in the degree of plasma protein binding of diphenylhydantoin may account for species-specific drug responses.

Chronic administration of diphenylhydantoin can produce a high incidence (mean approximately 35%) of gingival hyperplasia in man (10, 13, 14). However, it has not yet been possible to produce this effect experimentally in the rat and most other laboratory species (10, 15–17). Consequently, it has been difficult to study the etiology of the adverse reaction to diphenylhydantoin, and the mechanism involved remains obscure. Differences in free plasma levels of diphenylhydantoin or of its major metabolite, 5-(*p*-hydroxyphenyl)-5-phenylhydantoin, that result from species differences in plasma protein binding may help to explain the species selectivity of this adverse drug reaction.

The equilibrium dialysis studies reported here determined the degree of plasma protein binding of both diphenylhydantoin and its *para*-hydroxy metabolite in the human and the rat. The results of these studies provide a comparison of free plasma drug and of free drug–metabolite concentrations between these species. The possible influence of drug binding on the development of gingival hyperplasia in these species is discussed.

Table I—Total Plasma Protein Values for Diphenylhydantoin Binding Studies

Plasma Source		Total Protein[a,b], mg./ml.
Species	Sex	
Human GC	Male	84.6 ± 1.0
Human JW	Male	94.0 ± 1.1
Human JO	Female	83.2 ± 1.5
Human KS	Female	85.2 ± 0.8
Rat	Male	79.5 ± 1.4
Rat	Female	85.0 ± 1.2

[a] Mean of eight determinations with standard deviation of the mean. [b] Two-tailed Student *t* test shows significant difference ($p < 0.05$) for: human *versus* rat, male rat *versus* female rat, and human JW *versus* other human samples.

EXPERIMENTAL

Materials—*Chemicals*—ACS reagent grade chemicals or the equivalent obtained from standard sources were employed in these studies. The following hydantoin derivatives were used: 5,5-diphenylhydantoin[1], 5-(*p*-hydroxyphenyl)-5-phenylhydantoin[2], 5-(*m*-hydroxyphenyl)-5-phenylhydantoin[2], and 5,5-diphenylhydantoin-4-^{14}C (10.9 mc./mmole)[3].

Animals—Male and female Holtzman rats, weighing between 200 and 270 g., were employed. Rats were maintained on a complete diet[4] and water *ad libitum* for at least 1 week prior to use.

Human Volunteers—Adult Caucasian male and female humans[5], between the ages of 21 and 29 years, volunteered for these studies. The participants abstained from alcohol, coffee, tea, nicotine, and all drugs for 24 hr. preceding the blood sampling.

Methods—*Diphenylhydantoin Colorimetric Assay*—Diphenylhydantoin was determined in aliquots of plasma and of diffusate obtained from equilibrium dialysis experiments by means of the colorimetric method of Dill *et al.* (18). The sodium diphenylhydantoin concentration was calculated using the extinction coefficient determined from diphenylhydantoin standards carried through the procedure simultaneously with unknown samples.

Diphenylhydantoin Radioisotope Measurement—Aqueous diphenylhydantoin-4-^{14}C aliquots (1.0–3.0 ml.) from dialysis studies were adjusted to 3.0 ml. with distilled water and mixed with 10.0 ml. of scintillator solution[6] to form an emulsion gel stable at 5°. ^{14}Carbon was counted by liquid scintillation spectrometry. The diphenylhydantoin sodium concentration was calculated using the specific activity of ^{14}carbon determined by counting diphenylhydantoin-4-^{14}C samples of known drug concentration.

para-*Hydroxy Metabolite GLC Assay*—The *p*-hydroxy metabolite was quantitated in plasma and diffusate aliquots by means of the GLC method of Chang and Glazko (19) as modified by Conard *et al.* (10, 20). The modification permits extraction of 5-(*p*-hydroxyphenyl)-5-phenylhydantoin and its internal standard, 5-(*m*-hydroxyphenyl)-5-phenylhydantoin, without extraction of plasma constituents which cause interference peaks. Metabolite quantitation was carried out using an internal standard, digital integrator area count of peaks, and predetermined relative weight responses (metabolite/internal standard) from standard samples carried through the extraction and assay procedure.

[1] Dilantin, Parke, Davis and Co., Ann Arbor, Mich.
[2] Parke, Davis and Co., Ann Arbor, Mich.
[3] Schwarz BioResearch, Inc., Orangeburg, N. Y.
[4] Rockland Teklad Mouse-Rat Pellet Complete Diet.
[5] Employees of the American Dental Association, Research Institute.
[6] Insta-Gel, Packard Instrument Co., Inc., Downers Grove, Ill.

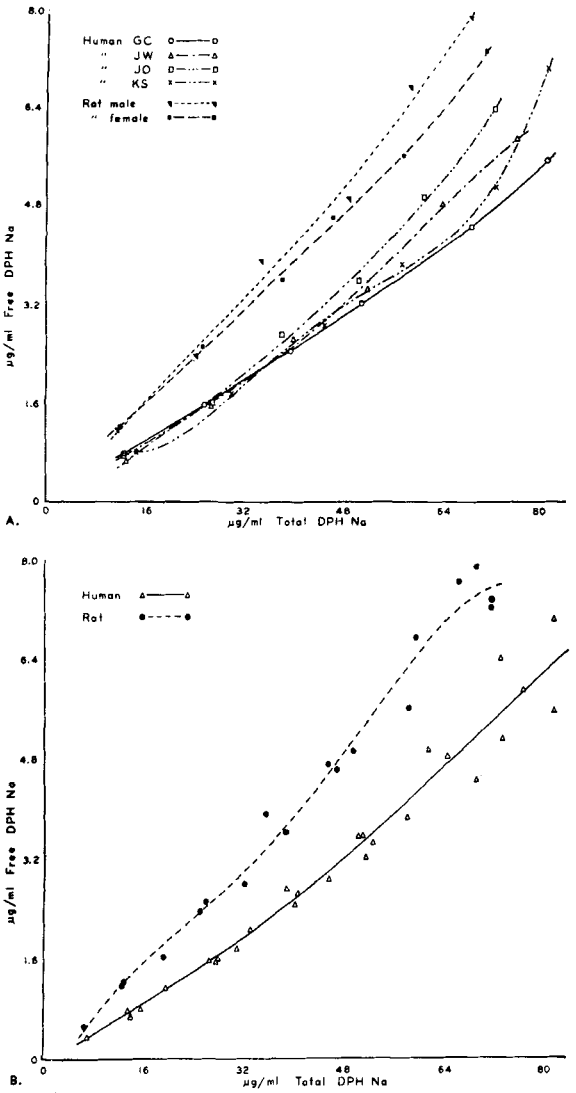

Figure 1—*Sodium 5,5-diphenylhydantoin (DPH Na) binding to six plasma sources as determined by the colorimetric assay. Key: A, data from individual plasma samples; and B, data grouped according to species of plasma. Each point represents the mean binding values from one dialysis experiment; each line drawn is a least-squares curve, computer fitted using a fourth-order polynomial.*

Protein Determination—The colorimetric protein assay of Lowry *et al.* (21) was utilized to determine total plasma protein concentration. Protein was quantitated using a standard curve prepared daily with known amounts of crystalline bovine plasma albumin[7]. The percent albumin in plasma preparations was determined by cellulose acetate electrophoresis and zone measurement by densitometry. Electrophoresis of plasma was run in barbital buffer, μ = 0.075, pH 8.6, at 250 constant volts. Densitometry was performed on the cellulose acetate membrane after trichloroacetic acid fixation and staining[8].

Equilibrium Dialysis Method—Binding of diphenylhydantoin and of the *p*-hydroxy metabolite to plasma proteins was determined *in vitro* by equilibrium dialysis. Studies utilized undiluted human and rat plasma freshly prepared daily from heparinized blood. Human plasma studies employed plasma from individuals, while the rat plasma studies utilized pooled plasma from 8–12 animals of one sex. The amounts of diphenylhydantoin added to the dialysis system were chosen to result in plasma diphenylhydantoin concentrations after equilibrium equivalent to *in vivo* levels ranging from low to very toxic. A similar concentration range was employed for the metabolite of diphenylhydantoin. Plasma samples of either 5 or 10 ml. were placed in size 20 dialysis tubing[9] and dialyzed against either 25 or 50 ml. of diffusate, respectively. The diffusate consisted of modified Locke's physiological salt solution buffered to pH 7.4 with 0.04 *M* phosphate, as described by Eik-Nes *et al.* (22), and 1.0 ml. drug solution. The dialysis system was maintained at 4° with continuous stirring. After 24 hr., sufficient time for equilibration, duplicate aliquots of each fraction were removed for drug extraction and assay or for radiodrug assay. The concentration of drug (diphenylhydantoin or metabolite) determined in the diffusate fraction represents the free drug level, while the concentration of drug (diphenylhydantoin or metabolite) measured in the plasma fraction represents the total drug level, a sum of free and bound drug. The change in pH observed during equilibration was nominal (<0.2 unit) and constant between dialysis experiments.

RESULTS AND DISCUSSION

Diphenylhydantoin Binding to Plasma—Figure 1A permits a comparison of free diphenylhydantoin levels between the various plasma sources; the bottom four lines represent data from individual human plasma samples of both sexes and the top two lines represent data from rat plasma of each sex. These data indicate

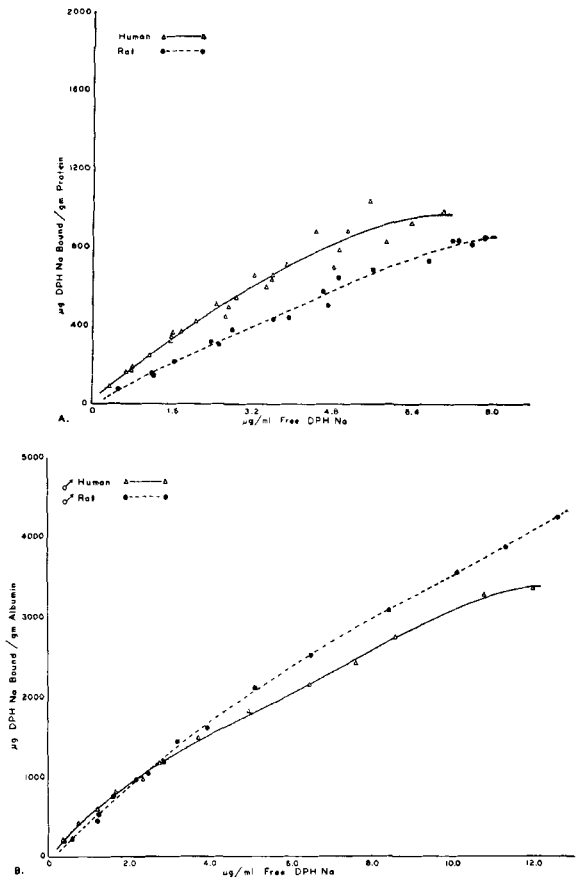

Figure 2—*Sodium 5,5-diphenylhydantoin (DPH Na) binding to human and rat plasma. Key: A, binding per gram total protein as determined by the colorimetric assay; and B, binding per gram albumin as determined by the radiodrug assay. Each point represents the mean binding values from one dialysis experiment; each line drawn is a least-squares curve, computer fitted using a fourth-order polynomial.*

[7] Armour Pharmaceutical Co., Chicago, Ill.
[8] With Ponceau S.
[9] Visking, Food Products Division, Union Carbide Corp., Chicago, Ill.

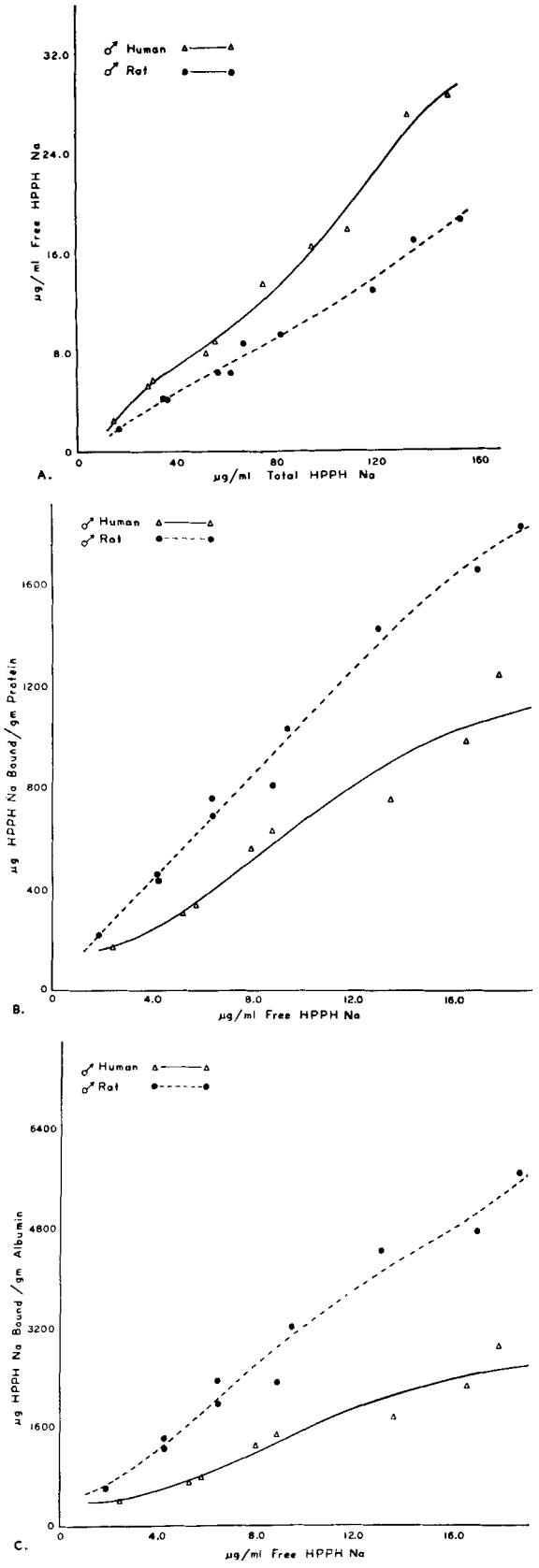

Figure 3—*Sodium 5-(p-hydroxyphenyl)-5-phenylhydantoin (HPPH Na) binding to human and rat plasma as determined by the GLC assay. Key: A, data from each species of plasma; B, binding per gram total protein; and C, binding per gram albumin. Each point represents the mean binding values from one dialysis experiment; each line drawn is a least-squares curve, computer fitted using a fourth-order polynomial.*

that diphenylhydantoin is extensively bound to plasma proteins of both man and rat, but the degree of binding differs between the rat and individual humans. Since the concentration of free diphenylhydantoin in human plasma is lower than that in rat plasma at all equivalent total diphenylhydantoin levels studied (5–80 mcg./ml.), grouping of the dialysis data according to species appears justified. Grouping of the data in this manner (Fig. 1B) permits a direct comparison of diphenylhydantoin binding between species. It can be seen that at an intermediate total plasma diphenylhydantoin level, such as 40.0 mcg./ml., which has been encountered during therapeutic use of diphenylhydantoin, the free drug level in rat plasma is 3.9 mcg./ml., while that in human plasma is 2.5 mcg./ml. At this total drug level, the rat/human free drug ratio is 1.6; this value shows that a species difference exists in the binding of diphenylhydantoin to plasma proteins.

When these data are expressed as fraction sodium diphenylhydantoin bound *versus* total plasma drug level, it becomes apparent that the bound drug fraction decreases with increasing total diphenylhydantoin level. The fraction bound in human plasma throughout the total plasma drug concentration range employed is 0.95–0.92, while in rat plasma the fraction bound is 0.91–0.89.

The species difference in diphenylhydantoin binding in plasma shown here results in higher free drug levels in rat plasma than in human plasma at any given total diphenylhydantoin plasma level. These results, obtained by equilibrium dialysis, should be indicative of the degree of *in vivo* drug binding to plasma proteins in man and in the rat. Therefore, differences in drug binding between these two species apparently do exist and may contribute to species differences in pharmacological and toxicological responses. However, this species difference observed in free plasma diphenylhydantoin levels *in vitro* does not appear to contribute to the *in vivo* failure of diphenylhydantoin to induce gingival hyperplasia in the rat (10).

Diphenylhydantoin–Plasma Protein Binding—Total protein concentration values for the six sources of plasma utilized are summarized in Table I. Statistical analysis shows that significant differences exist between species of plasma and between sexes of rat plasma (*Footnote b*, Table I). Human total protein values are within the normal range (23); rat total protein values are consistent for the strain. These total protein values were utilized in subsequent calculations of the amount of diphenylhydantoin bound per gram total protein. Data expressed in this manner are corrected for drug binding differences which result from differences in plasma protein concentration between plasma sources. In Fig. 2A, it can be seen that human plasma proteins adsorb more drug per gram protein over the free diphenylhydantoin levels studied than do the rat plasma proteins. This difference between species in diphenylhydantoin binding is similar to that observed in Fig. 1A.

Diphenylhydantoin-^{14}C–Plasma Protein Binding—Since species differences in total protein do not account for differences in diphenylhydantoin binding to plasma proteins, the influence of species differences in albumin levels on binding was evaluated in additional studies. Diphenylhydantoin-^{14}C was employed in these studies to improve analytical sensitivity and precision. A significant difference exists in the albumin fraction between the two species of plasma (*Footnote c*, Table II). The albumin values shown in Table IIA are means of the values used to calculate the amount of diphenylhydantoin bound per gram albumin in these studies. The diphenylhydantoin-^{14}C dialysis binding data, when plotted similarly to Fig. 2A, are in good agreement and substantiate the species difference in diphenylhydantoin binding to human and rat plasma proteins.

However, when the ^{14}carbon binding data are plotted as micrograms of sodium diphenylhydantoin adsorbed per gram albumin *versus* free sodium diphenylhydantoin concentration to correct for species differences in albumin concentration (Fig. 2B), the species difference in diphenylhydantoin binding observed previously (Fig. 2A) is diminished at low free drug levels. In addition, the species difference in diphenylhydantoin binding is reversed at high free drug levels. A comparison of these data with the data presented in Fig. 2A shows that the observed species difference in diphenylhydantoin binding to human and rat plasma proteins can be accounted for in part by the differences in plasma albumin concentration.

***para*-Hydroxy Metabolite Binding to Plasma**—In view of the conclusion that species differences in diphenylhydantoin–plasma protein binding do not appear to correlate with the species-specific

Table II—Total Protein and Albumin Values for Plasma Preparations

Plasma Source: Species	Plasma Source: Sex	Number of Preparations[a]	Total Protein[b,c], mg./ml.	Percent Albumin[b,c]	Albumin[b,c], mg./ml.
A. Values from Diphenylhydantoin-^{14}C Binding Studies					
Human GC	Male	7	87.2 ± 0.6	42.9 ± 0.3	37.4 ± 0.3
Rat	Male	3	77.7 ± 1.6	32.0 ± 1.0	24.8 ± 0.2
B. Values from *para*-Hydroxy Metabolite Binding Studies					
Human GC	Male	3	86.9 ± 0.3	42.9 ± 0.2	37.2 ± 0.3
Rat	Male	2	79.0 ± 2.2	33.5 ± 1.4	26.4 ± 0.4

[a] Eight determinations per plasma preparation. [b] Mean value with standard deviation of the mean. [c] Two-tailed Student *t* test shows significant difference ($p < 0.01$) between species.

induction of gingival hyperplasia, the binding of the major diphenylhydantoin metabolite, 5-(*p*-hydroxyphenyl)-5-phenylhydantoin, to plasma proteins was studied by equilibrium dialysis. Figure 3A permits a comparison of free metabolite levels between species of plasma. These data indicate that the metabolite is strongly bound to proteins of both species of plasma. Free metabolite levels in the human plasma are higher than those in the rat plasma throughout the total plasma metabolite range employed (10–160 mcg./ml.). At an intermediate total plasma metabolite level, such as 80 mcg./ml., the free metabolite level in human plasma is 13.0 mcg./ml., while that in rat plasma is 9.0 mcg./ml. At this total metabolite level, the human/rat free drug ratio is 1.4; this value indicates that the binding of the metabolite also differs in these two species and that this binding difference varies markedly from that found to exist for the parent drug.

When these data are expressed as fraction metabolite bound *versus* total plasma metabolite level, it becomes apparent that the bound fraction decreases with increasing total metabolite level. The fraction bound throughout the total plasma metabolite concentration range employed is 0.89–0.88 in rat plasma, while in human plasma the fraction bound is 0.84–0.81. A comparison of these data with those obtained for diphenylhydantoin indicates that in rat plasma the fraction bound is decreased slightly for the metabolite, which is a more polar molecule than is the parent drug, while in human plasma the fraction bound is greatly decreased for the metabolite relative to the parent drug.

This species difference in the metabolite binding to plasma proteins results in higher free *para*-hydroxy metabolite levels in human plasma than in rat plasma at any given total metabolite level. Consequently, this difference observed in free plasma metabolite concentrations between species *in vitro* may contribute to an explanation for the *in vivo* species selectivity of diphenylhydantoin-induced gingival hyperplasia.

***para*-Hydroxy Metabolite–Plasma Protein Binding**—Total protein, percent albumin, and albumin concentration values for the plasma utilized in diphenylhydantoin metabolite dialysis binding studies are summarized in Table IIB. These values are means of the values used to calculate the amount of metabolite bound per gram total protein and the amount of metabolite bound per gram albumin. In Fig. 3B, it can be seen that rat plasma proteins adsorb more metabolite per gram total protein at free metabolite levels, ranging from 1.0 to 20.0 mcg./ml., than do the human plasma proteins. This difference in metabolite binding between species is similar to that observed in Fig. 3A. When these binding data are corrected for differences in albumin levels (Fig. 3C), the species difference previously observed in the binding of the metabolite is increased.

CONCLUSION

The interaction of drugs with plasma proteins is of both theoretical and practical importance; drug–plasma protein binding modifies drug distribution in the body and, therefore, can influence the dose–response relationship, the rate of drug elimination, and the pharmacological and toxicological actions of a drug (24–27). Species differences in plasma protein binding consequently could account for species-specific adverse drug reactions.

Plasma protein binding of diphenylhydantoin and of its major metabolite, 5-(*p*-hydroxyphenyl)-5-phenylhydantoin, was determined using equilibrium dialysis of undiluted human and rat plasma samples to compare the degree of *in vitro* protein binding between these species. This comparison was made to determine whether species differences in free plasma drug or drug–metabolite levels correlate with *in vivo* species differences in pharmacological and toxicological responses.

Data reported here show that diphenylhydantoin is extensively bound to proteins in human and rat plasma and that human plasma proteins bind a greater amount of diphenylhydantoin *in vitro* at all total plasma drug concentrations studied than do rat plasma proteins. This difference in drug binding between species results in lower free diphenylhydantoin levels in the human than in the rat at equivalent total drug plasma levels. Therefore, it appears that plasma protein binding differences between these species do not contribute to the *in vivo* failure of diphenylhydantoin to induce gingival hyperplasia in the rat.

Species differences in plasma albumin concentration suggest that this species difference in diphenylhydantoin binding may be explained in part by species differences in albumin levels.

It also has been shown that the major diphenylhydantoin metabolite is strongly protein bound in human and rat plasma and that rat plasma proteins bind the metabolite to a greater extent *in vitro* at all total plasma concentrations studied than do human plasma proteins. This binding difference results in higher free metabolite levels in the human than in the rat at equivalent total plasma levels; this situation is the opposite of that found for diphenylhydantoin. These free metabolite levels observed *in vitro* correlate with the *in vivo* incidence of diphenylhydantoin-induced gingival hyperplasia in man and rat. In the event that *in vivo* differences in the binding of the metabolite to proteins parallel *in vitro* binding differences between these species, plasma protein binding of the metabolite may contribute to an explanation for the species selectivity of the drug-induced pathology.

REFERENCES

(1) H. M. Triedman, R. A. Fishman, and M. D. Yahr, *Trans. Amer. Neurol. Ass.*, **85**, 166(1960).

(2) J. H. Oppenheimer, L. V. Fisher, K. M. Nelson, and J. W. Jailer, *J. Clin. Endocrinol. Metab.*, **21**, 252(1961).

(3) E. W. Loeser, *Neurology*, **11**, 424(1961).

(4) J. Wolff, M. E. Standaert, and J. E. Rall, *J. Clin. Invest.*, **40**, 1373(1961).

(5) J. H. Oppenheimer and R. R. Tavernetti, *Endocrinology*, **71**, 496(1962).

(6) J. H. Oppenheimer and R. R. Tavernetti, *J. Clin. Invest.*, **41**, 2213(1962).

(7) H. Firemark, C. F. Barlow, and L. J. Roth, *Int. J. Neuropharmacol.*, **2**, 25(1963).

(8) R. W. Lightfoot and C. L. Christian, *J. Clin. Endocrinol. Metab.*, **26**, 305(1966).

(9) N. M. A. Viukari and P. Tammisto, *J. Ment. Def. Res.*, **13**, 235(1969).

(10) G. J. Conard, Ph.D. thesis, University of Wisconsin, Madison, Wis., 1970, pp. 34–39, 58–65, 123–134.

(11) G. J. Conard, C. O. Haavik, and K. F. Finger, *Pharmacologist*, **12**, 244(1970).

(12) P. K. M. Lunde, A. Rane, S. J. Yaffe, L. Lund, and F. Sjoqvist, *Clin. Pharmacol. Ther.*, **11**, 846(1970).

(13) E. Aas, "Hyperplasia Gingivae Diphenylhydantoinea," Scandinavian University Books, Boston, Mass., 1963, pp. 19–23.

(14) A. F. Gardner, S. G. Gross, and L. E. Wynne, *Exp. Med. Surg.*, **20**, 133(1962).

(15) K. Nakamura and Y. Masuda, *Arch. Int. Pharmacodyn.*, **162,** 255(1966).
(16) H. M. Swenson, *J. Dent. Res.*, **33,** 468(1954).
(17) W. G. Shafer, *ibid.*, **27,** 768(1948).
(18) W. A. Dill, A. Kazenko, L. M. Wolf, and A. J. Glazko, *J. Pharmacol. Exp. Ther.*, **118,** 270(1956).
(19) T. Chang and A. J. Glazko, *J. Lab. Clin. Med.*, **75,** 145 (1970).
(20) G. J. Conard, C. O. Haavik, and K. F. Finger, *Pharmacologist*, **11,** 273(1969).
(21) O. H. Lowry, N. J. Rosebrough, A. L. Farr, and R. J. Randall, *J. Biol. Chem.*, **193,** 265(1951).
(22) K. Eik-Nes, J. A. Schellman, R. Lumry, and L. T. Samuels, *J. Biol. Chem.*, **206,** 411(1954).
(23) P. L. Altman and D. S. Dittmer, "Blood and Other Body Fluids," Biological Handbooks, Federation of American Societies for Experimental Biology, Washington, D. C., 1961, p. 307.
(24) A. Goldstein, *Pharmacol. Rev.*, **1,** 102(1949).
(25) J. T. Edsall and J. Wyman, "Biophysical Chemistry," vol. 1, Academic, New York, N. Y., 1958, p. 591.
(26) J. J. Burns, R. K. Rose, T. Chenkin, A. Goldman, A. Schulert, and B. B. Brodie, *J. Pharmacol. Exp. Ther.*, **109,** 346 (1953).
(27) M. C. Meyer and D. E. Guttman, *J. Pharm. Sci.*, **57,** 895 (1968).

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Effects of Dietary Components on GI Absorption of Acetaminophen Tablets in Man

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Abstract □ Various high carbohydrate, high protein, and high lipid test meals were administered concurrently with acetaminophen tablets to human subjects to study the effects of foods on GI absorption of this drug. Balanced test meals and a fasting condition were also employed. An indication of the rate and extent of drug absorption was obtained by measuring urinary excretion at 1.5-hr. intervals over a 9-hr. period. The initial rate of excretion of acetaminophen and its metabolites was significantly reduced with a majority of the carbohydrate test meals. High protein, high lipid, or balanced meals appeared to have no statistically significant effect, while the fasting condition showed only a trend toward initially higher excretion values. The cumulative amounts of total acetaminophen and metabolites excreted in the urine at the end of 9 hr. showed little difference among test meals. The apparent inhibition of acetaminophen absorption by carbohydrate test meals could be partially attributed to an interaction with pectin in some cases.

Keyphrases □ Absorption kinetics, GI—acetaminophen tablets, effect of foods, man □ Acetaminophen tablets—effect of foods on GI absorption, man □ Dietary considerations—GI absorption of acetaminophen tablets in man □ Foods—effect of high carbohydrate, high protein, high lipid test meals on GI absorption of acetaminophen tablets, man

It is generally recognized that administration of drugs by the oral route a short time before or after a meal may alter absorption of the drug from the GI tract. However, few definitive studies have correlated specific dietary components with effects on drug absorption. Generally, meals have been reported to retard absorption. Wood (1) indicated that with five different commercial aspirin preparations tested in humans, half-lives of absorption were more than doubled by the nonfasting condition. Hirsch and Finland (2) demonstrated that similar doses of erythromycin stearate and erythromycin propionate administered orally after breakfast resulted in significantly lowered blood levels when compared with equal doses given before breakfast. In the same study, however, blood levels achieved with orally administered triacetyloleandomycin did not vary significantly when given either before or after breakfast.

Peterson and Finland (3) showed that sulfadiazine administered orally after the morning meal was absorbed more slowly, but more completely, than when administered to fasting subjects. Kirby *et al.* (4) and Rosenblatt *et al.* (5) showed that foods, especially those containing significant amounts of divalent metal ions, can inhibit absorption of tetracyclines, at least partially by a chelation mechanism. Reduction of absorption efficiency by food was also shown for orally administered lincomycin (6) and penicillin (7).

Contrary to these studies, others demonstrated that a meal preceding administration of a drug may enhance its absorption from the GI tract. Levy and Jusko showed that absorption of riboflavin (8) and riboflavin-5′-phosphate (9) was enhanced when administered orally after a standard breakfast of cornflakes and milk, and they attributed these effects to decreased intestinal transit rates. Crounse (10) demonstrated that the absorption of orally administered griseofulvin was doubled when given after a high lipid breakfast (consisting of bacon, eggs, cream, and butter) compared with high protein or high carbohydrate meals or even compared with the fasting state. More recently, Kabasakalian *et al.* (11) indicated that a high fat meal followed by griseofulvin administration at breakfast increased drug absorption,