[Chem. Pharm. Bull. 28(8)2443—2449(1980)]

Influence of Dietary Components on the Bioavailability of Phenytoin

Hitoshi Sekikawa,[1a] Masahiro Nakano,[1b] Masahiko Takada,[1a] and Takaichi Arita[1c]

Faculty of Pharmaceutical Sciences, Higashi-Nippon-Gakuen University,[1a] Faculty of Pharmaceutical Sciences, Hokkaido University,[1b] and Department of Pharmacy, Hokkaido University Hospital, School of Medicine, Hokkaido University[1c]

(Received March 15, 1980)

The influence of food on the bioavailability of phenytoin was studied. A balanced meal enhanced the bioavailability significantly. A high lipid meal, however, resulted in larger inter-subject variation in bioavailability. Phenytoin-polyvinylpyrrolidone coprecipitate was administered with and without the balanced meal. The bioavailability of phenytoin administered in this form was enhanced markedly and was not greatly influenced by food intake.

Keywords——phenytoin; dietary effect; bioavailability; balanced meal; high lipid meal; coprecipitate; polyvinylpyrrolidone; urinary excretion; gastrointestinal absorption; anticonvulsant

Dietary effects on drug absorption are important, because they influence the bioavailability of drugs.[2] Various experiments have been reported on the influence of diet on drug absorption. It is generally recognized that oral administration of drugs before or after a meal may affect the absorption of the drugs from the gastrointestinal tract. Wood[3] reported that the absorption half-life of aspirin was more than doubled in the nonfasting state. The absorptions of lincomycin[4] and penicillins[5] were also reduced by intake of food. Serum levels of various tetracycline antibiotics were reduced when patients were under nonfasting conditions[6] or when they ingested milk and dairy products[7] compared to the serum levels obtained in fasting patients. On the other hand, absorption of the orally administered antifungal antibiotic, griseofulvin, was significantly improved when it was administered with a high lipid meal.[8] Effects of food on the bioavailability of poorly water-soluble drugs, such as nitrofurantoin,[9] dicumarol,[10] carbamazepine,[11] digoxin,[12] and riboflavin[13] have also been reported. Generally, food appears to increase the absorption of poorly water-soluble drugs.

1) Location: *a) 1757 banchi, Kanazawa, Ishikari-Tobetsu, 061-02, Japan*; *b) Kita 12-jo, Nishi 6-chome, Kita-ku, Sapporo, 060, Japan*; *c) Kita 14-jo, Nishi 5-chome, Kita-ku, Sapporo, 060, Japan.*
2) *a)* A. Melander, *Clin. Pharmacokinet.*, 3, 337 (1978); *b)* T.R. Bates and M. Gibaldi, "Current Concepts in the Pharmaceutical Sciences: Biopharmaceutics," ed. by J. Swarbrick, Lea and Febiger, Philadelphia, 1970, pp. 57—99.
3) J.H. Wood, *Lancet*, **2**, 212 (1967).
4) J.G. Wagner, in "Determination of Drug Activity," Symposium, Philadelphia College of Pharmacy and Sciences, Nov. 14, 1968.
5) J.O. Klein and M. Finland, *New Engl. J. Med.*, **269**, 1019 (1963).
6) W.M.M. Kirby, C.E. Robert, and R.E. Bardick, *Antimicrob. Agents Chemother.*, **1961**, 286.
7) J. Scheiner and W.A. Altemeiner, *Surg. Gynecol. Obstet.*, **114**, 9 (1962).
8) *a)* J. Kraml, J. Dubuc, and D. Beall, *Canad. J. Biochem. Physiol.*, **40**, 1449 (1962); *b)* R.G. Crounse, *Arch. Dermatol.*, **87**, 176 (1963).
9) T.R. Bates, J.A. Sequeira, and A.U. Tembo, *Clin. Pharmacol. Ther.*, **16**, 63 (1974).
10) D.C. Bloedow and W.L. Hayton, *J. Pharm. Sci.*, **65**, 328 (1976).
11) R.H. Levy, W.H. Pitlick, A.S. Troupin, J.R. Green, and J.M. Neal, *Clin. Pharmacol. Ther.*, **17**, 657 (1975).
12) D.J. Greenblatt, D.W. Duhme, J. Koch-Weser, and T.W. Smith, *Clin. Pharmacol. Ther.*, **16**, 444 (1974).
13) G. Levy and W.J. Jusko, *J. Pharm. Sci.*, **55**, 285 (1966).

Thus, the influence of food on gastrointestinal drug absorption is complex because of the different dietary components involved[14] and the various physiological conditions of the gastrointestinal tract, *i.e.*, pH and movement of the tract, osmotic pressure, secretion of bile or digestive juice, *etc.* The physico-chemical characteristics, stability, *etc.*, of the drug may further complicate the absorption properties of the drug.

An antiepileptic drug, phenytoin, has been shown to exhibit large variations in bioavailability following oral administration of patients,[15] because of its poor water-solubility. In the present study, influence of dietary components on the bioavailability of phenytoin was examined. Furthermore, as the authors have already reported on the improvement of the dissolution characteristics and bioavailability of phenytoin by coprecipitation with polyvinylpyrrolidone (PVP),[16] the influence of food on the absorption of phenyoin from the coprecipitate was also investigated.

Materials and Methods

Materials——Phenytoin (J.P.IX) was obtained from Dainippon Pharmaceutical Co., Osaka (Aleviatin, lot HL435HN). The mean particle size of a phenytoin sample, as measured by optical microscopy, was 47.1 μm (Green diameter). 5-(*p*-Hydroxyphenyl)-5-phenylhydantoin and 5-(*p*-methylphenyl)-5-phenylhydantoin were obtained from Aldrich Chemical Co., Milwaukee, Wis. Coprecipitate (phenytoin: PVP K-15 = 1: 3 weight ratio) was prepared by the conventional method.[16] All other chemicals were of reagent grade.

Subjects——The subjects participating in this study were 5 healthy male volunteers whose ages ranged from 23 to 27 (average of 25 years) and whose weights ranged from 50 tc 65 kg (average of 58 kg).

Test Meals——The foods given as the test meals were the so-called balanced meal and the high lipid meal.[14] The balanced meal consisted of 115 g of bread, 5.6 g of butter, 37 g of corned beef, and 200 ml of water (17 g of protein, 19 g of lipid, and 50 g of carbohydrate; representing about one-sixth of the normal daily requirement). The high lipid meal consisted of 23 g of bread, 61 g of butter, and 200 ml of water (3 g of protein, 56 g of lipid, and 11 g of carbohydrate; representing about one-half of the normal daily requirement of lipid).

Urinary Excretion of the Metabolites of Phenytoin——Phenytoin (250 mg) or 1000 mg of the coprecipitate (containing 250 mg of phenytoin) was orally administered to the subjects. The subjects were fasted after the evening meal prior to the morning during which the test meal and the drug were to be administered. However, they were permitted to have drinks other than alcoholic ones. They were also asked to get a normal night's sleep. At about 9 o'clock in the morning, the subjects ingested the test meal. The time required for consuming the meal was approximately 10 min. Subsequently each subject took the phenytoin or the coprecipitate sample powder in a wafer. No food or beverage was given to the subjects for 4 hours postadministration. Urine was collected at hourly intervals for the first 9 hours and thereafter at convenient times up to 120 hours after administration. At least 2 weeks were allowed between experiments. The volume and pH of each urine sample were recorded, and a portion of the urine was stored in a refrigerator for subsequent analysis. The same dosage schedule was used for subjects without a meal. The total amount of 5-(*p*-hydroxyphenyl)-5-phenylhydantoin and its glucuronide conjugate, the main metabolites in humans,[17] in urine was assayed after acid hydrolysis by the GC method[18] using 5-(*p*-methylphenyl)-5-phenylhydantoin as an internal standard.

Results and Discussion

Figure 1 shows the indivisual excretion rates of the metabolites following the oral administration of phenytoin with each type of meal and without a meal. Major metabolites of phenytoin in humans were 5-(*p*-hydroxyphenyl)-5-phenylhydantoin (HPPH) and its glucuronic

14) *a*) J.M. Jaffe, J.L. Colaizzi, and H. Barry, III, *J. Pharm. Sci.*, **60**, 1646 (1971); *b*) E. Owada, S. Suzuki, and T. Arita, *Chemotherapy*, **22**, 1430 (1974).
15) *a*) P.J. Pentikäin, P.J. Neuvonen, and S.M. Elfving, *Europ. J. Clin. Pharmacol.*, **9**, 213 (1975); *b*) K. Arnold, N. Gerber, and G. Levy, *Can. J. Pharm. Sci.*, **5**, 89 (1970).
16) H. Sekikawa, J. Fujiwara, T. Naganuma, M. Nakano, and T. Arita, *Chem. Pharm. Bull.*, **26**, 3033 (1978).
17) T.C. Butler, *J. Pharmacol. Exp. Ther.*, **119**, 1 (1957).
18) K. Yamamoto, M. Nakano, T. Arita, Y. Takayama, and Y. Nakai, *J. Pharm. Sci.*, **65**, 1484 (1976).

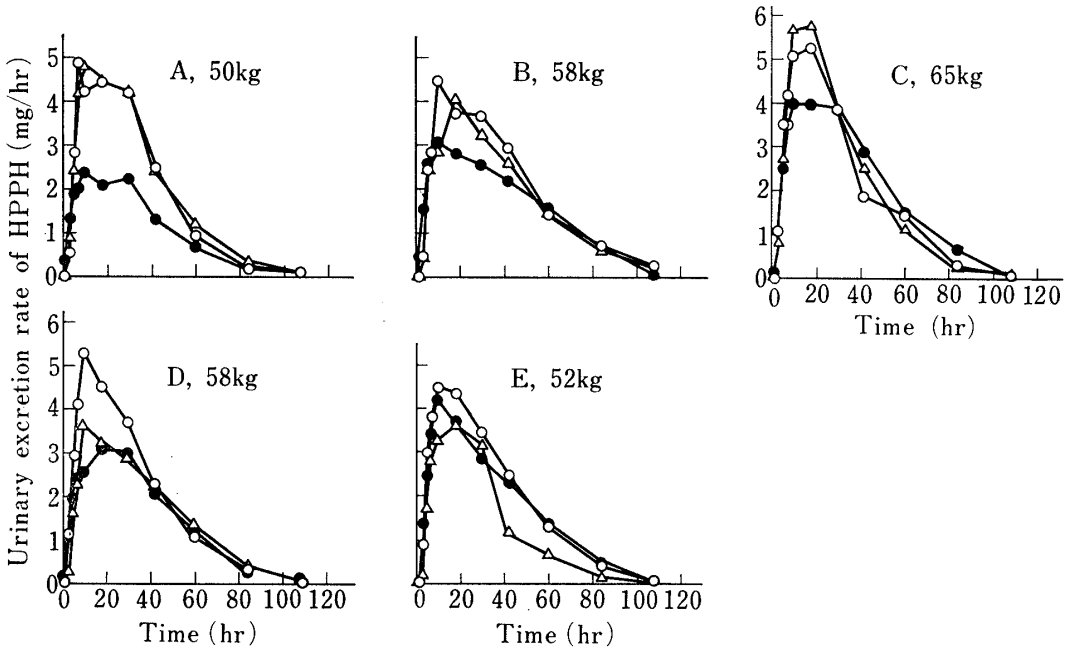

Fig. 1. Urinary Excretion Patterns of Metabolites following Oral Administration of 250 mg of Phenytoin

●, fasting.
○, with balanced meal.
△, with high lipid meal.
HPPH: 5-(*p*-hydroxyphenyl)-5-phenylhydantoin

acid conjugate.[17] Sulfate conjugate and unmetabolized phenytoin were not detected in the urine samples. Smith and Kinkel[19] reported that following oral administration of a single dose of 250 mg of phenytoin as a tablet, the peak plasma level of phenytoin was observed over 4 to 12 hours postadministration. On the other hand, the maximum rate of urinary excretion of the metabolites was observed over 24 to 48 hours. Yamamoto *et al.*[18] shows that the peak urinary excretion rates of the metabolites appeared a few hours after the peak plasma concentration of the intact drug. They also showed that the higher urinary excretion rates of the metabolites for the first 10 hours after administration of a rapidly dissolving form of the drug (compared to the rate for phenytoin alone) reflected the higher plasma levels of the drug. The authors[16] also showed that the plasma levels of phenytoin following the administration of the coprecipitate, a rapidly dissolving form, were higher than those of phenytoin alone, in the rabbit. The excretion rate and cumulative amount of the metabolites excreted following administration of the coprecipitate were also greater than those for phenytoin alone.

The peak times of the excretion rate (Fig. 1) varied from 10 to 18 hours postadministration among the fasted subjects. The peak values of the excretion rate varied from 2.36 to 4.20 mg/hr among the subjects. When phenytoin was administered with the two types of the meal, the excretion rates of the metabolites were lower than in the subjects not given a meal, for the first 3 (subject B, C, and E) to 5 hours (A and D). Food might retard the gastric emptying and intestinal transit of the drug in the early period.[20] Under non-fasting conditions a reduced rate of absorption of the drug in the early period may be due to a number of factors, including poor gastrointestinal mixing and possible complex formation with components of the food. The excretion rates of the metabolites tended to be higher when the drug was administered with meals than in the case of the fasted subjects.

19) T.C. Smith and A. Kinkel, *Clin. Pharmacol. Ther.*, **20**, 738 (1976).
20) *a*) I.J. McGilverray and G.L. Mattok, *J. Pharm. Pharmacol.*, **24**, 615 (1972); *b*) G. Levy and W.L. Jusko, *J. Pharm. Sci.*, **54**, 219 (1965).

Figure 2 shows the mean urinary excretion rates of the metabolites for five subjects. Table I compares the data on the basis of the paired *t*-test.

It is clear that the urinary excretion rate of the metabolites following the administration of phenytoin with the balanced meal was larger than that in the fasted case, from 5 to 42 hours. It was significantly different at 5, 10, 18 and 30 hours postadministration. After 60 hours, the mean excretion rate in the fasted case was somewhat larger, but the difference was not significant. Food-induced enhancement of the absorption may be explained by assuming that the dispersion and dissolution characteristics of poorly water-soluble phenytoin were improved in the presence of food, or that its retention in the upper region of the intestinal tract was prolonged in the presence of food. In addition, food-induced secretion of bile might enhance the dissolution of lipophilic phenytoin. Similar effects of food on the absorption of poorly water-soluble drugs have been reported.[9–13]

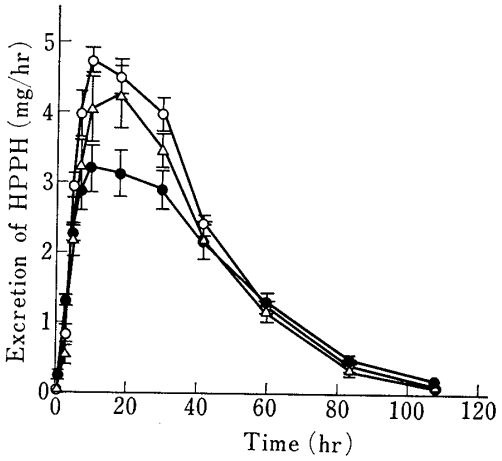

Fig. 2. Urinary Excretion Rate of Metabolites following the Oral Administration of 250 mg of Phenytoin

●, fasting; ○, with balanced meal; △, with high lipid meal
Each point represents the mean±S.E.M. of five subjects.

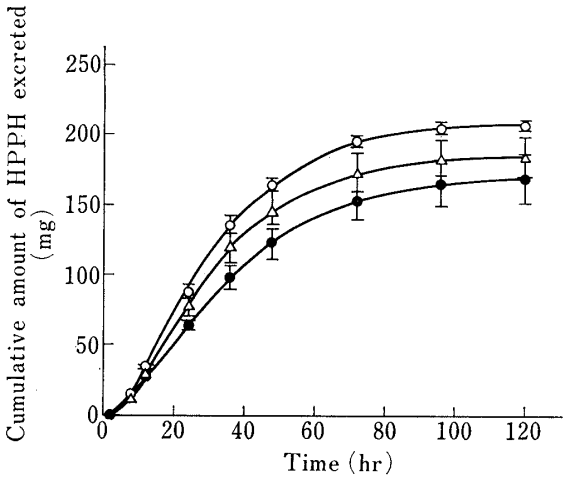

Fig. 3. Effect of Food on the Urinary Excretion of Metabolites following the Oral Administration of 250 mg of Phenytoin

○, with balanced meal; △, with high lipid meal; ●, fasting
Each point represents the mean±S.E.M. of five subjects.

Table I. Urinary Excretion Rates of Total *p*-Hydroxylated Phenytoin compared by the Paired *t*-Test

Time interval, hr	Urinary excretion rate,[a] mg/hr			Fasting *versus* balanced meal	Fasting *versus* high lipid meal	Balanced meal *versus* high lipid meal
	Fasting	With balanced meal	With high lipid meal			
0— 2	0.24±0.08	0.02±0.01	0.02±0.01	N.S.[b]	$p<0.05$	N.S.
2— 4	1.29±0.10	0.83±0.14	0.53±0.14	N.S.	$p<0.01$	N.S.
4— 6	2.25±0.14	2.96±0.18	2.17±0.24	$p<0.025$	N.S.	$p<0.05$
6— 8	2.88±0.29	3.97±0.33	3.23±0.38	N.S.	N.S.	N.S.
8— 12	3.21±0.36	4.72±0.20	4.04±0.53	$p<0.025$	N.S.	N.S.
12— 24	3.12±0.33	4.51±0.25	4.22±0.44	$p<0.05$	N.S.	N.S.
24— 36	2.90±0.27	3.97±0.33	3.45±0.24	$p<0.01$	N.S.	$p<0.05$
36— 48	2.16±0.26	2.41±0.17	2.18±0.26	N.S.	N.S.	N.S.
48— 72	1.27±0.15	1.23±0.10	1.16±0.14	N.S.	N.S.	N.S.
72— 96	0.45±0.09	0.39±0.09	0.33±0.08	N.S.	N.S.	N.S.
96—120	0.15±0.04	0.11±0.03	0.09±0.03	N.S.	N.S.	N.S.

a) Mean±S.E.M.
b) Not significant.

On the other hand, ingestion of the high lipid food resulted in a lower excretion rate during the first 3 hours. The mean excretion rate of the metabolites tended to be higher than in the fasting case from 3 to 42 hours. However, it tended to be lower than that following ingestion of the balanced meal from 3 to 118 hours. The inter-subject variation was the largest among the three cases. Significant differences were observed at 5 and 30 hours versus the balanced meal and at 1 and 3 hours versus fasting.

Figure 3 shows the cumulative amounts of metabolites following the administration of phenytoin with and without meals. Table II shows the results of analysis by the paired *t*-test.

TABLE II. Cumulative Amounts of Total *p*-Hydroxylated Phenytoin Excreted compared by the *t*-Test

Time interval, hr	Cumulative amount excreted,[a] mg			Fasting *versus* balanced meal	Fasting *versus* high lipid meal	Balanced meal *versus* high lipid meal
	Fasting	With balanced meal	With high lipid meal			
0— 2	0.5± 0.2	0.04±0.02	0.04± 0.02	N.S.[b]	N.S.	N.S.
0— 4	3.1± 0.3	1.7 ±0.3	1.1 ± 0.3	N.S.	$p<0.01$	N.S.
0— 6	7.5± 0.6	7.6 ±0.6	5.4 ± 0.8	N.S.	$p<0.05$	N.S.
0— 8	13.3± 0.8	15.5 ±1.0	11.9 ± 1.4	N.S.	N.S.	N.S.
0— 12	26.1± 2.1	34.4 ±1.5	28.0 ± 3.4	$p<0.05$	N.S.	N.S.
0— 24	63.6± 5.9	88.6 ±4.4	78.7 ± 8.5	$p<0.01$	N.S.	N.S.
0— 36	98.4± 8.7	136.3 ±6.8	120.1 ±11.0	$p<0.01$	N.S.	N.S.
0— 48	124.3±11.7	165.3 ±4.8	146.2 ±12.7	$p<0.025$	N.S.	N.S.
0— 72	154.9±14.8	195.3 ±5.3	173.9 ±13.8	$p<0.025$	N.S.	N.S.
0— 96	165.6±16.8	204.6 ±5.2	182.1 ±14.3	$p<0.05$	N.S.	N.S.
0—120	169.3±17.4	207.2 ±5.3	184.2 ±14.6	$p<0.05$	N.S.	N.S.

a) Mean±S.E.M.
b) Not significant.

The bioavailability of the drug preparation can be estimated by comparing the total amounts excreted in urine after administration. Taking the amount of the metabolites excreted up to 120 hours following the administration of phenytoin in the fasting case as 100, the percentages with the balanced meal were A, 177.2; B, 122.0; C, 104.1; D, 125.5; E, 108.7, and those with the high lipid meal were A, 185.8; B, 111.2; C, 100.7; D, 104.8; E, 73.5. The mean values were 122.4 for the balanced meal and 108.8 for the high lipid meal, respectively. A dose of 250 mg of phenytoin corresponds to 265.9 mg of HPPH. The mean recoveries of the metabolites in the fasting case, with the balanced meal and with the high lipid meal were 63.7%, 77.9% and 69.3%, respectively. The inter-subject variations were larger in the fasting case and with the high lipid meal. With the balanced meal, bioavailability was increased in all the subjects, and the inter-subject variations were rather small. Melander *et al.*[21] have recently reported on the influence of food on the absorption of phenytoin in man, and showed that ingestion of a standardized breakfast enhanced the bioavailability of phenytoin. They found significant increases in the peak plasma level and AUC up to 48 hours (18.5% increase). Two subjects among 8, however, showed smaller AUC following intake of the food than in the preprandial case. Though the components of the food and the phenytoin preparation differed from those used in our study, it appears that food tends to increase the absorption of phenytoin.

On the other hand, administration of phenytoin with the high lipid meal resulted in larger variation of the bioavailability than with the balanced meal. For subject A, the bioavailability was considerably increased. Subject E, however, showed a lower bioavaila-

21) A. Melander, G. Brante, Ö. Johansson, T. Lindberg, and E. Wåhlin-Boll, *Europ. J. Clin. Pharmacol.*, **15**, 269 (1979).

bility than in the fasting case. Some physiological abnormality of the gastrointestinal tract on intake of the high lipid meal might result in larger variation in the absorption characteristics of phenytoin in indivisual subjects. Alternatively, the food-induced secretion of bile might be not sufficient to emulsify both lipid and phenytoin crystals. Diarrhea did not occur in the subjects within the experimental period. A similar effect of the high lipid meal on bioavailability has been found in an absorption study of thiamphenicol.[14b]

The authors have already reported on the improved bioavailability of phenytoin with a rapidly dissolving preparation of phenytoin-PVP coprecipitate.[16] Following the administration of the coprecipitate to the fasted subjects, the bioavailability of the drug was markedly increased with reduced inter-subject variation. As phenytoin in the coprecipitate did not show crystalline properties,[16] it might dissolve more rapidly in the gastrointestinal tract. Whether the coprecipitate is administered with or without food, phenytoin should be well absorbed from the gastrointestinal tract, because the rate of absorption of phenytoin was considered to be determined by the dissolution rate. The influence of the balanced meal on the bioavailability of phenytoin using the coprecipitate was studied. Figure 4 shows the excretion rate of the metabolites following the administration of the coprecipitate with and without a meal. The excretion rate of the metabolites following the administration of phenytoin crystal powder without a meal is also plotted in the figure.

Maximum excretion rate of the metabolites was observed at 10 hours postadministration in both cases. The excretion rates in the fasting case were significantly higher than in the case of the balanced meal, at 1, 3 and 5 hours postadministration. This may indicate a retarding effect of food on the gastric emptying of the drug. No significant differences were observed after 7 hours.

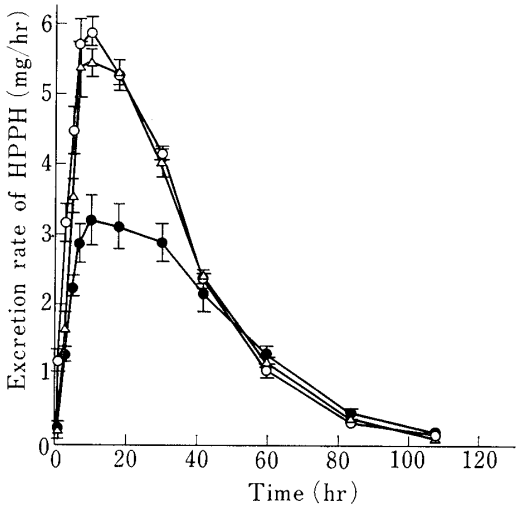

Fig. 4. Urinary Excretion Rate of Metabolites following the Oral Administration of 1000 mg of Coprecipitate or 250 mg of Phenytoin

○, coprecipitate without meal;
△, coprecipitate with balanced meal;
●, phenytoin without meal.
Each point represents the mean±S.E.M. of five subjects.

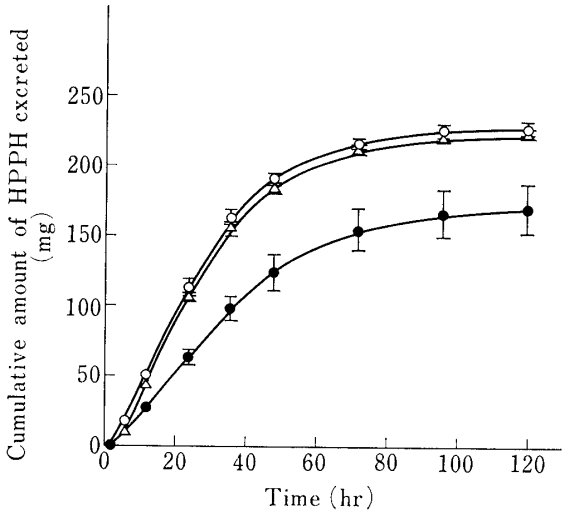

Fig. 5. Effect of Food on the Urinary Excretion of Metabolites following the Oral Administration of 1000 mg of Coprecipitate or 250 mg of Phenytoin

○, coprecipitate without meal;
△, coprecipitate with balanced meal;
●, phenytoin without meal.
Each point represents the mean±S.E.M. of five subjects.

Figure 5 shows the cumulative amount of the metabolites up to 120 hours following the administration of the coprecipitate with and without the meal. The cumulative amount of metabolites following the administration of phenytoin crystal powder without a meal is also plotted in the figure.

The mean cumulative amounts of the metabolites uo to 120 hours following the administration of the coprecipitate with and without the balanced meal were 222.9 mg and 227.4 mg, respectively. These values are not significantly different. Significant differences existed between the cases of coprecipitate without food ($p<1\%$) and between the cases of coprecipitate with food and phenytoin powder without food ($p<1\%$). The coprecipitate exhibited good bioavailability irrespective of food intake. These results suggest that the rate-determining step of phenytoin absorption may be dissolution of the drug, and that the preparation with improved dissolution properties is not influenced by food intake.

From these results, it is apparent that the food may influence the absorption of phenytoin. The major factor may be the effects of physiological conditions of the gastrointestinal tract and the food-induced bile secretion on drug dissolution. However, the ability of food to enhance the dissolution characteristics of phenytoin is limited. It was ascertained that the phenytoin-PVP coprecipitate showed enhanced bioavailability irrespective of food intake, presumably because the coprecipitated phenytoin exists in an amorphous state.[16]

Acknowledgement The authors are grateful to Mr. Koji Tanimoto for his assistance in the experimental work.