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Interaction between phenytoin and enteral nutrients and its influence on gastrointestinal absorption

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The gastrointestinal absorption of phenytoin (PHT), an antiepileptic drug, is often affected by its interaction with co-administered enteral nutrients through a nasogastric (NG) tube, resulting in decreased plasma PHT concentration. In this study, we measured the recovery rate (%) of PHT (Aleviatin® powder) passed through an NG tube when co-administered with distilled water or enteral nutrients (F2α®, Racol® NF, Ensure Liquid® and Renalen® LP). We also measured plasma PHT levels in rats, after oral co-administration of PHT with enteral nutrients. We demonstrate that PHT recovery rate was close to 100 % in all cases after passage through the NG tube. In the rat study, the $AUC_{0\rightarrow\infty}$ of PHT concentration after oral administration significantly decreased when it was co-administered with F2α® and Racol® NF compared to distilled water. However, the $AUC_{0\rightarrow\infty}$ of PHT was unchanged when co-administered with F2α® 2 h after initial PHT administration. We therefore conclude that the co-administration of PHT with F2α® and Racol® NF caused a reduction in the absorption of PHT from the gastrointestinal tract to the blood, without adsorption to the NG tube. The administration of enteral nutrients 2 h after PHT is one clear way to prevent a decrease in plasma PHT concentration.

1. Introduction

Interactions between drugs and enteral nutrients, usually co-administered through a NG tube, have been reported to affect the absorption and resultant plasma concentration of anti-epileptic drugs, leading to reduced therapeutic effects and an increased number of epileptic seizures. In particular, many reports describe an interaction between phenytoin (PHT) and enteral nutrients, where co-administration using a nasogastric (NG) tube results in decreased plasma PHT concentration (Bauer 1982; Saklad et al. 1986; Sneed and Morgan 1988; O'Hagan and Wallace 1994). From Japan, a decrease in plasma PHT concentration caused by F2®, an enteral nutrient containing fiber, was reported (Kitada et al. 2002). Recently F2α®, a new formulation with similar composition to F2®, was also reported to decrease plasma PHT concentration, an effect that was ameliorated by including an interval of 2 h between the administration of PHT and enteral nutrients (unpublished data). PHT is a drug for which strict control of plasma concentration is essential, and the reduction of plasma concentration causes the onset of seizures. Therefore, detailed information on the effects of enteral nutrients on plasma levels of PHT is needed.

Regarding the mechanism of plasma PHT concentration reduction, previous reports have indicated decreases in the amount of gastrointestinal transition by binding of the PHT suspension to the plastic of the NG tube (Bader 1993; Rodman et al. 1995), as well as absorption inhibition due to binding to enteral nutrient components (Guidry et al. 1989; Weinryb and Cogen 1989). Detailed information about the nature of the these interactions is needed more than ever in order to ensure the safety of the combined use of PHT with various enteral nutrients used routinely in clinical practice.

In this study, we investigated the adsorption of PHT to an NG tube when co-administered with four enteral nutrients frequently used in Japan, namely F2α® (reported to interact with PHT), Racol® NF, Ensure Liquid® and Renalen® LP (Table 1). We quantified the data by evaluating the recovery rate (%) of PHT passed through the NG tube using a common clinical method. Subsequently, we measured changes in plasma PHT levels in normal rats after PHT was co-administered with these enteral nutrients.

2. Investigations and results

2.1. Recovery rate of PHT passed through NG tubes with enteral nutrients

We prepared a closed enteral administration system consisting of an enteral container and infusion route with an NG tube, simulating hospital-ward conditions for the administration of enteral nutrients (Fig. 1). PHT (1000 mg) in the form of Aleviatin® 10-fold diluted powder, widely used in Japan, was used for these experiments. We

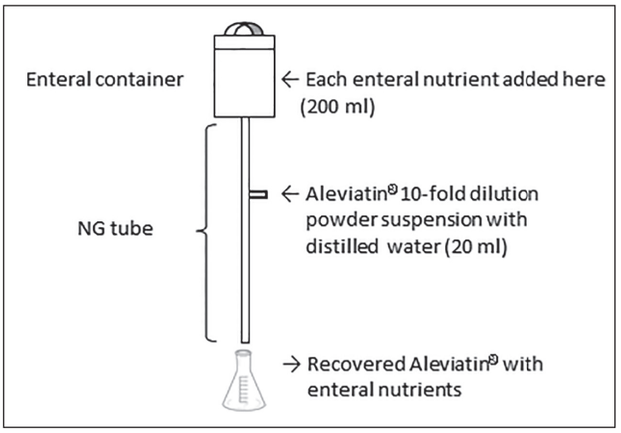

Fig. 1: Nasogastric (NG) infusion system for Aleviatin® powder with enteral nutrients.

Table 1: List of main components in each enteral nutrient per 200 ml

		F2α®	Racol® NF	Ensure liquid®	Renalen® LP
Protein	Total amount (g)	10	8.8	7	3.2
	Composition (g)	Milk protein (8.0)	Milk casein (7.8)	Casein sodium (6.8)	Milk protein (UNK)
		Soy protein (2.0)	Soy protein isolate (3.4)	Soy protein isolate (1.0)	
	Animal protein: Plant protein	4:1	2:1	7:1	Animal protein only
Carbohydrate	Total amount (g)	30.2	31.2	27.4	59.2
	Composition (g)	Dextrin (UNK)	Maltodextrin (29.8)	Dextrin (19.6)	Dextrin (UNK)
		Sucrose (UNK)	Sucrose (2.6)	Sucrose (8)	Sucrose (UNK)
Lipid	Total amount (g)	4.4	4.4	7	9
	Composition (g)	Medium-chain triglyceride (UNK)			Medium-chain triglyceride (UNK)
		Soybean oil (UNK)	Soybean oil (1.4)	Soy Lecithin (0.32)	
		Canola oil (UNK)			Canola oil (UNK)
			Tricaprylin (1.5)		
			Perilla oil (0.36)		
			Palm oil (0.66)		Palm oil (UNK)
				Corn oil (6.6)	
					Fish oil (UNK)
	Medium-chain : Long-chain triglyceride	1:1	Long-chain triglyceride only	Long-chain triglyceride only	1:4
Fiber (g)		4.0	–	–	3.2
Osmotic pressure (mOsm/l)		370	300-360	330	720
pH		7.0	6.0-7.2	6.6	6.2
Calorie (kcal)		400	200	200	320
Viscosity (mPa's at)		10.0	5.5-6.5	9.0	15.0
Specific gravity (g/cm^3)		1.08	1.08	1.10	1.12

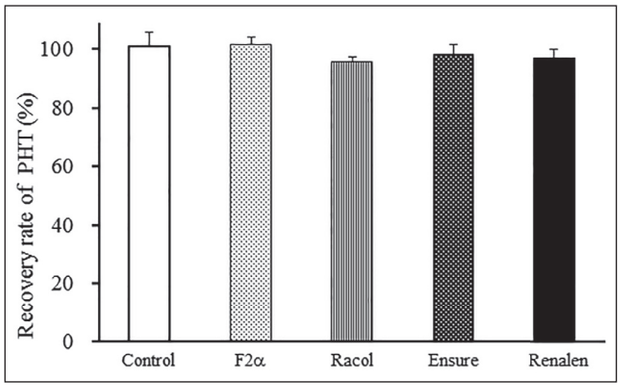

Fig. 2: PHT passage rate through NG tubes with distilled water (control), F2α® (F2α), Racol® NF (Racol), Ensure liquid® (Ensure), and Renalen® LP (Renalen). Each PHT passage rate (%) was calculated by dividing the mass of recovered PHT (mg) from the outlet of the NG tube by the injected mass of PHT (mg). Data are shown as the mean ±S.D. (n = 6).

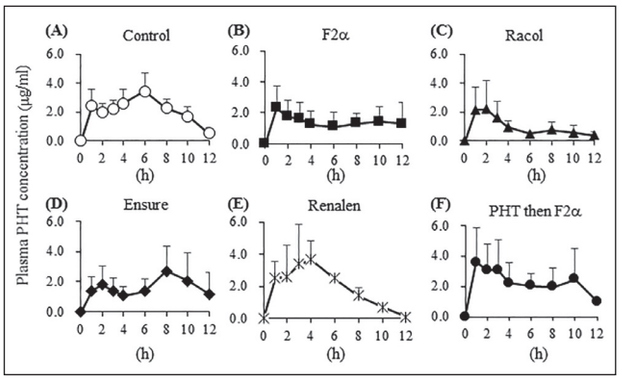

Fig. 3: PHT (30 mg/kg) was orally administered with distilled water or each enteral formulation; open-circle, distilled water (control); closed square, F2α® (F2α) group ; closed circle, Racol® NF (Racol) group; closed-rhombus, Ensure liquid® (Ensure) group; asterisk, Renalen® LP (Renalen) group; closed-circle, and F2α® 2 h after initial PHT administration (PHT then F2α) group. Data are shown as the mean ±S.D. (n = 4-6).

measured the amount of PHT recovered after 2 h from the outlet of the NG tube co-administered with either 200 ml of distilled water (control) or 200 ml of each enteral nutrient; F2α®, Racol® NF, Ensure liquid® and Renalen® LP. PHT recovery rate (%) was then calculated (detailed in the experimental section). PHT recovery rates in distilled water and in the presence of each enteral nutrient were approximately 100 % (Fig. 2).

2.2. PHT pharmacokinetics after oral administration in combination with enteral nutrients in rats

PHT (30 mg/kg) was orally administered in combination with 3 ml/kg of distilled water (control group) or each enteral nutrient; F2α® (F2α group), Racol® NF (Racol group), Ensure liquid® (Ensure group), Renalen® LP (Renalen group) in normal rats. In addition, we included a condition in which F2α® was administered 2 h after an initial dose of PHT in 3 ml/kg of distilled water (PHT then F2α group). Plasma PHT concentration was measured at 1 or 2 h timepoints up to a maximum of 12 h after oral administration of each group, as shown in Fig. 3. The pharmacokinetic parameters of PHT are described in Table 2. Plasma PHT concentration was differentially modulated among the five enteral nutrient combination groups, compared to the control group (Fig. 3).

As shown in Table 2, the area under the PHT concentration-time curve from time zero to ∞ ($AUC_{0\to\infty}$) was significantly decreased in the F2α and Racol groups compared to the control group (both, $P < 0.01$). There were no significant changes in the Ensure group, Renalen group or F2α separate group. Total clearance per bioavailability (CL_{tot}/F) was significantly increased in the F2α group ($P < 0.05$) and Racol group ($P < 0.01$) compared to the control. There was no significant difference in the maximum plasma

Table 2: Pharmacokinetic parameters of phenytoin after oral administration with each enteral formulations in rats

	Control	F2α	Racol	Ensure	Renalen	PHT then F2α
$AUC_{0\to\infty}$ (mg/h/ml)	27.5 ± 3.20	18.1 ± 5.34**	13.0 ± 2.02**	23.3 ± 8.30	23.5 ± 5.64	26.7 ± 5.82
C_{max} (mg/h)	3.89 ± 1.04	2.78 ± 1.11	2.81 ± 1.47	3.78 ± 0.97	3.97 ± 1.48	3.78 ± 0.82
T_{max} (h)	4.33 ± 2.69	3.17 ± 2.64	3.00 ± 2.92	5.83 ± 2.71	4.00 ± 1.73	1.50 ± 1.00
$t_{1/2}$ (h)	1.89 ± 0.66	1.83 ± 0.49	3.49 ± 1.21	3.99 ± 4.24	1.47 ± 0.25	3.89 ± 1.78
ka (h^{-1})	0.29 ± 0.05	0.46 ± 0.35	0.76 ± 0.82	0.76 ± 1.29	0.40 ± 0.14	0.47 ± 0.28
CLtot/F (ml/min)	1.10 ± 0.11	1.86 ± 0.60*	2.34 ± 0.49**	1.22 ± 0.58	1.33 ± 0.37	1.32 ± 0.16
Vdss/F (l/kg)	6.91 ± 1.01	10.99 ± 6.55	13.17 ± 8.14	9.05 ± 2.18	6.78 ± 3.31	8.89 ± 2.44

concentration (C_{max}), the time to reach C_{max} (T_{max}), the elimination half-life in blood plasma ($t_{1/2}$), the absorption rate constant (ka) or distribution volume at steady state per bioavailability (Vdss/F) among all groups.

3. Discussion

Previous clinical reports have frequently discussed the possibility of PHT adsorption to the NG tube due to their combined administration with enteral nutrients (Bader 1993; Rodman et al. 1995). In this study, almost 100 % of the PHT was delivered through an NG tube in the presence of four enteral nutrients, using a routine clinical administration method (Fig. 2). Differences between previous studies and our work may explain this. For example, in the study conducted by Bader (1993), the PHT suspension was administered in an undiluted form without tube irrigation, and in the Roadman et al. (1995) study a longer jejunostomy tube was used. Our results suggest, because almost all of the PHT passed through the NG tube in the presence of nutrients, almost the full dosage would at this point enter the gastrointestinal tract.

We also focused on the dissolution process of PHT as a factor affecting its pharmacokinetics. In this study we orally administered PHT in a powdered state, suspended in an enteral nutrient, to normal rats. We then analyzed the pharmacokinetics of plasma PHT, taking into account the process in which the PHT powder dissolves, in the presence of each enteral nutrient. A significantly decreased $AUC_{0\to\infty}$ of PHT was observed when it was co-administered with F2α® and Racol NF®, compared to distilled water, Ensure Liquid® and Renalen® LP. In addition, there was no difference in the $AUC_{0\to\infty}$ of PHT when F2α® was administered 2 h after PHT administration with distilled water. These results confirm that the co-administration of PHT with F2α® and Racol® NF caused a reduction in the total absorption of PHT from the gastrointestinal tract, and that the administration of F2α® 2 h after PHT is an effective approach for preventing any decrease in plasma PHT concentration.

A decrease in PHT absorption was observed only in the case of co-administration with F2α® and Racol® NF. We surmise that this is likely to be caused by differences in the composition of these nutrients as compared to Ensure Liquid® and Renalen® LP (Table 1). It has been pointed out in the literature that PHT may bind to magnesium, fibers, and calcium casein present in some enteral nutrient mixes (Smith et al. 1988; Guidry et al. 1989; Weinryb and Cogen 1989). However, the magnesium content of F2α® is significantly lower than that of Racol® NF, Ensure Liquid® and Renalen® LP. In addition, fiber is contained in both F2α® and Renalen® LP. As these factors do not match with the results of our study, we reason that magnesium and fiber contents are less likely to influence the gastrointestinal absorption of PHT. In contrast, milk casein content is higher in F2α® and Racol® NF than Ensure Liquid® and Renalen® LP and has the potential to prevent PHT from being absorbed in gastrointestinal tract by forming a casein complex with PHT. F2α® and Racol® NF contained 10.0 g and 8.8 g total protein per 200 ml respectively; much higher than Ensure Liquid® (7.0 g) and Renalen® LP (3.2 g). Typically, ~90 % of PHT in the blood is bound to plasma proteins, thus binding to these proteins in enteral nutrient mixes could reduce the amount of free PHT. There is a possibility that the decreased absorption of PHT co-administered with F2α® and Racol® NF may be caused by a decreased amount of free PHT in the gastrointestinal tract, due to the high total protein content in F2α® and Racol® NF. Further studies are needed to clarify the mechanism by which PHT absorption in the GI tract occurs, by analyzing the dissolution process of PHT in the presence of enteral nutrients as well as the permeation process into the digestive tract membrane.

In summary, we demonstrated that PHT co-administered with F2α®, Racol® NF, Ensure Liquid®, Renalen® LP passed entirely through an NG tube, at which point it would have reached the gastrointestinal tract. Furthermore, F2α® and Racol® NF decreased the gastric absorption of PHT, and this interaction could be avoided by first administering PHT, waiting 2 h and then administering enteral nutrients.

4. Experimental

4.1. Chemicals

PHT (5-5-diphenylhydantoin) and 5-methylphenyl-5-phenylhydantoin as the internal standard were purchased from Sigma-Aldrich (Tokyo, Japan). For pretreatment, PHT powder was milled to a fine particle size (< 25 mm) in an agate mortar. Aleviatin® powder (at 10-fold dilution in the presence of a vehicle, Dainippon Pharmaceutical Co. Ltd., Osaka, Japan), F2α® (TERUMO Co. Ltd., Tokyo, Japan), Racol® NF (Otsuka Pharmaceutical Factory, Inc., Tokyo, Japan), Ensure Liquid® (Abbott Japan Co. Ltd., Tokyo, Japan) and Renalen® LP (Meiji Seika Pharma Co. Ltd., Tokyo, Japan) were purchased from commercial sources. For animal anesthesia, diethyl ether was purchased from FUJIFILM Wako Pure Chemical Co. Ltd (Tokyo, Japan). Acetonitrile (Nacalai Tesque, Inc., Kyoto, Japan) was of chromatographic-reagent grade, and other chemicals were of analytical-reagent grade.

4.2. Passage study of PHT with enteral nutrients products through NG tubes

First, 200 ml of each enteral nutrient (F2α®, Racol® NF, Ensure Liquid® or Renalen® LP), or distilled water was added to the enteral administration system. This consisted of an enteral container (Cardinal Health Japan Inc., Tokyo, Japan) and polyvinyl chloride NG tube (inner diameter; 8 Fr, length; 122 cm, NIPRO Co. Ltd., Osaka, Japan)(Fig. 1). Aleviatin® powder as a 1000 mg suspension in 20 ml distilled water was drawn into a plastic syringe (NIPRO Co. Ltd., Osaka, Japan), and then administered through the side injection port of a catheter. Immediately after administration of Aleviatin® powder suspension, enteral nutrient was introduced dropwise at a rate of 1-2 ml/min. The mixture of distilled water or enteral nutrient and Aleviatin® powder suspension was recovered over a time period of 2 h from the NG tube outlet into a clean glass flask.

4.3. Pharmacokinetic study in rats

4.3.1. Animals

Healthy male Sprague-Dawley rats (Japan SLC Inc., Shizuoka, Japan) weighing about 200 g (7-8 weeks of age) were used for the oral studies. They were housed in rooms with a controlled environment (temperature: 22±2 °C, humidity 55±5 % on a 12-h light/dark cycle, diurnal time; 0800-2000 h) with food and water *ad libitum* for a week. All experimental procedures were conducted in accordance with Osaka Ohtani University Guidelines for the Care and Use of Laboratory Animals (approval No. 1401). All experiments were carried out in accordance with ARRIVE guidelines.

4.3.2. Oral administration of PHT combined with enteral nutrients

Rats were cannulated *via* the right jugular vein under diethyl ether anesthesia 24 h before the drug absorption experiment. Rats were divided into 6 groups; 1 to 4) co-administration group with PHT and 1 of 4 enteral nutrients, 5) PHT only group (in distilled water, control group), and 6) PHT (in distilled water) administered 2 h before F2α® (PHT then F2α group). PHT 30 mg/kg was mixed with 3 ml/kg enteral nutrients; F2α®, Racol® NF, Ensure Liquid® or Renalen® LP (F2α group, Racol group,

Ensure group and Renalen group, respectively) or distilled water, and administrated orally using a metallic gastric delivery device. Plasma samples (0.3 ml) were collected through the jugular vein cannula at 1, 2, 3, 4, 6, 8, 10 and 12 h after administration of the PHT suspension. We sacrificed the rats by deep anesthesia using diethyl ether after the final plasma sample was taken. Plasma was obtained by centrifuging at 1000 rpm, 4 °C for 10 min. Samples were stored at -30 °C prior to analysis.

4.4. Determination of PHT content by high performance liquid chromatography (HPLC)

To dissolve Aleviatin® powder for facilitating passage through tubes, 200 ml distilled water and 20 ml 0.6 M sodium hydrate were added and the solution was mixed. Ten milliliters of this solution was transferred into a 15-ml tube, which was then centrifuged at 3000 rpm for 10 min. One milliliter of the supernatant was added to 1 ml of 0.2 M hydrochloric acid and 48 ml distilled water in a new tube, for neutralization and dilution, and stored at -30°C prior to analysis.

PHT concentration in enteral nutrient or plasma samples was determined by HPLC. Three-hundred nanograms of the internal standard (5-methylphenyl-5-phenylhydantoin), 100 ml distilled water and 100 µl ethyl acetate were added to 100 µl of sample mix. Samples were vortexed for 1 min and then centrifuged at 3000 rpm and 4 C for 10 min. 200 µl of the supernatant was transferred to a clean tube and evaporated under vacuum at 40 °C to desiccate the sample. The residue was then reconstituted into a 50-µl mobile phase (8 mM phosphate buffer (pH 7.0): acetonitrile (65:35 (v/v)), and 40 µl was injected into the HPLC system.

The HPLC system used belonged to the Shimadzu VP-series consisting of an LC-20AD pump, DGU-20A deaeration unit, CTO-20Avp column oven, SPD-20ADvp UV detector, and SIL-20ADvp auto-injector, controlled by an SCL-10 Avp controller (Shimadzu Co., Kyoto, Japan). Separations were performed on a Cosmosil® $5C_{18}$-MS II column (4.6 mm I.D. × 150 mm, Nacalai Tesque, Inc., Kyoto, Japan), preceded by a run through the Cosmosil® $5C_{18}$-MS-II guard column (4.6 mm I.D. × 10 mm). The flow rate was 0.8 ml/min. The column temperature was maintained at 40°C and eluting peaks were monitored by UV absorbance at 250 nm.

4.5. Analysis

PHT recovery rate (%) after passage through the NG tube was calculated by dividing the mass of PHT (µg) recovered from outlet of NG tube by the mass of injected PHT (µg). Pharmacokinetic parameters were calculated using Moment. xls ver. 1.0 (Tabata et al. 1999).

Statistical analysis was performed using BellCurve for Excel (version 2.00, Social Survey Research Information Co., Ltd., Tokyo, Japan). The results are given as means ± standard deviation. One-way ANOVA with the Dunnett's post hoc test was performed for each group. The threshold for significance was $P < 0.05$.

Conflict of interests: none declared

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