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Influence of concurrent and staggered dosing of semi-solid nutrients on the pharmacokinetics of orally administered carbamazepine in rats

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Received July 22, 2021, accepted January 9, 2022

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Pharmazie 77: 118-120 (2022) *doi: 10.1691/ph.2022.1756*

In the present study, we examined the effects of concurrent and staggered dosing of PG-soft ace-MP™ (PG), novel semi-solid enteral nutrients, on the pharmacokinetics of orally administered carbamazepine (CBZ) in rats due to the high possibility of drug interaction during the absorption process. The pharmacokinetic behavior of CBZ was considerably altered when administered concurrently with PG. The maximum serum CBZ concentration (C_{max}) significantly decreased and the mean residence time (MRT) significantly increased. The elimination constant (k_e) also significantly increased, but there were no significant changes in the area under the serum CBZ concentration *versus* time curve (AUC) and the time to reach C_{max} (T_{max}). However, these changes in the pharmacokinetic parameters were eliminated by waiting 20 min, the time interval equivalent to the T_{max} described above, between CBZ administration and PG dosing. This study suggested that PG interferes with CBZ absorption from the digestive tract, although staggered administration of CBZ and PG prevented their interaction.

1. Introduction

Enteral tube feeding (ETF) is widely used for adequate nutritional management. Liquid and semi-solid enteral nutrients are accepted as the preferred medical products for ETFs in patients who cannot be fed orally. However, gastrointestinal complications often occur in patients taking liquid enteral nutrients (Blumenstein et al. 2014; McClave et al. 2016). In addition, application of liquid enteral nutrients carries a risk at leakage from insertion site of the tube after ingestion (Lin et al. 2001). Semi-solidification of enteral nutrients has been reported as a useful strategy to solve the problems during ETF (Kanie et al. 2004).

In contrast to the benefits, there are concerns about possible interactions between semi-solid enteral nutrients and other chemical medications. Our previous study demonstrated that carbamazepine (CBZ), an anticonvulsant, is adsorbed on guar gum and xanthan gum used for the semi-solidification of enteral nutrients, which may be responsible for the decrease in the serum concentration of CBZ after oral administration to rats (Nagai et al. 2018). In addition, we clarified using rats that the serum concentration of CBZ after oral administration was significantly reduced by concurrent administration of semi-solid RACOL™, which resulted in a decrease in the value of the area under the serum CBZ concentration *versus* time curve from 0 hr to 5 hr after administration ($AUC_{0\rightarrow5hr}$) (Nagai et al. 2019). This revealed that the pharmacokinetic behavior of CBZ is affected by concurrent dosing of semi-solid enteral nutrients through the absorption process. The clinical effects of CBZ correlate better with serum levels than administered doses (Neels et al. 2004), and thus clinically significant alterations in the serum CBZ concentration increase the risk of treatment failure due to a relatively narrow therapeutic index. In this regard, we considered it necessary to investigate the effects of other semi-solid enteral nutrients on the pharmacokinetics of CBZ.

Secretion of gastrointestinal hormone and gastric peristalsis caused by sufficient gastric development are considered to be required for smooth absorption of semi-solid enteric nutrients. The semi-solid enteral nutrients require sufficient viscosity to stretch the stomach and the standard of viscosity is considered to be 20,000 mPa·s. PG-soft ace-MP™ (PG) has a viscosity of 20,000 mPa·s, which is higher than that of semi-solid RACOL™, and causes more sufficient gastric extension; therefore, it is widely used in clinical practice. As such, CBZ and PG are likely to be used together in the medical field.

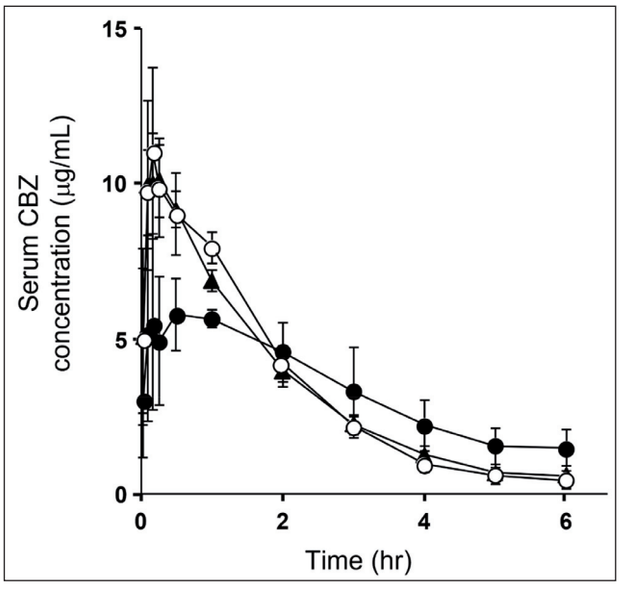

Fig.: Serum concentration-time courses of CBZ after oral administration to rats. Serum concentrations of CBZ were measured after oral administration (50 mg/kg). Results are shown as the means±SD of four rats per group. Open circle: control group; Closed circle: concurrent dosing group; Closed triangle: staggered dosing group.

2. Investigations, results and discussion

The aim of the present study was to investigate the effects of concurrent dosing of PG on the pharmacokinetic profile of CBZ after oral administration in rats. We also examined whether the pharmacokinetic interaction between CBZ and PG disappeared by extending the dosing interval of these drugs. The pharmacokinetic behavior of orally administered CBZ was considerably altered by the concurrent dosing of PG (Fig.). The C_{max} of CBZ significantly decreased without a significant change in T_{max}, reflecting the reduced intestinal absorbability of CBZ at an early phase after administration (Table). On the other hand, it is of pharmacokinetic interest that the k_e decreased and MRT correspondingly increased despite little possibility of impaired metabolic function (Table). This strongly suggests that the delayed disappearance of CBZ is a phenomenon caused by an intra-intestinal event prior to entry of CBZ into the body.

Table: Pharmacokinetic parameters of CBZ after oral administration

	Control	Concurrent	Staggered
C_{max} (mμ/mL)	11.7 ± 2.5	6.7 ± 1.1 *	11.1 ± 2.2
T_{max} (min)	16.3 ± 8.2	22.5 ± 21.7	16.3 ± 8.9
AUC (mg·h/L)	21.9 ± 3.1	26.0 ± 6.4	21.8 ± 1.6
k_e (1/h)	0.615 ± 0.153	0.278 ± 0.039 *	0.502 ± 0.075
MRT (h)	1.76 ± 0.30	3.69 ± 0.52 *	2.30 ± 0.15

Results are shown as the means±SD of four rats per group. * $p<0.05$ *vs* the control group (Dunnett's test).

We previously demonstrated that CBZ was adsorbed to a high degree on guar gum, a botanical fiber used for semi-solidification of PG, independent of pH values measured in digestive tract fluids (Nagai et al. 2018). Therefore, CBZ adsorption onto fibers may be the mechanism of interaction between CBZ and PG, and is responsible for the alteration of absorptive behavior of CBZ. The marked decrease in the C_{max} is attributable to the reduction in concentration of un-adsorbed free CBZ available for rapid intestinal absorption. According to a previous report, adsorption of chemical drugs on fibers is reversible (Lara-Espinoza et al. 2018). Thus, it is likely that CBZ adsorbed on fiber is continuously dissociated while being moved to enterocytes in order to maintain the physicochemical equilibrium of the intraluminal ratio of free and absorbed fraction. A likely explanation for the slow decline in serum CBZ is that free CBZ dissociated from fiber was gradually incorporated into the body while the drug in systemic circulation was metabolically eliminated by hepatic CYP3A. This suggests that CBZ in serum is supplied by continuous absorption even after reaching the elimination phase, suggesting that CBZ possesses immediate- and sustained-release properties in the presence of PG. On the other hand, the concurrent dosing of PG resulted in no decrease in CBZ bioavailability based on the AUC, probably due to its biphasic absorptive performance. This may be pharmacokinetically desirable because of the reduced fluctuation of the CBZ concentration-time curve with the degree of exposure to CBZ remaining unchanged. However, drug bioavailability is highly dependent on many factors, including the gastric emptying rate, dietary conditions, intestinal environment, and bowel mobility. In addition, it is generally believed that the amount of drug trapped to fiber is governed by its affinity to fiber, kinds and quantity of fibrous components in nutrient products, and duration of contact to fibers. The bioavailability of CBZ administered in combination with PG may be susceptible to change depending upon the residence time of PG at absorption sites. Adsorbed CBZ may be readily excreted into stool along with fiber before being absorbed if PG passes though the intestinal tract in a relatively short time, leading to loss of the dosage subject to absorption. Assuming reduction in the absorbed amount makes it difficult to assess the therapeutic oral dosage. In the previous report describing the interaction between CBZ and semi-solid RACOL™, the bioavailability and C_{max} of CBZ were significantly reduced by concurrent dosing (Nagai et al. 2019). The reduced C_{max} is consistent with the observation in the present study, but not the bioavailability. The reason for the disagreement is unclear, but this demonstrates that constant bioavailability is not necessarily assured in all cases because the involvement of complicated conditions may affect absolute bioavailability.

The T_{max} in the control group was approximately 16 min (Table), indicating that the orally administered dose of CBZ was almost absorbed in the absence of PG within this time frame. Indeed, the pharmacokinetic change in CBZ disappeared by spacing the dosing of CBZ and PG by 20 min, thereby prevents PG interference by the staggered dosing schedule. Based on our study, extension of the time interval between CBZ and PG dosing may be a promising strategy to avoid their interaction. Staggered dosing should be generally applicable to the combined use of oral drugs with semi-solid enteral nutrients in clinical practice by understanding the absorption rate of the drugs.

There is currently no clinical evidence of the pharmacokinetic interaction between CBZ and semi-solid enteral nutrients. However, in a study of 100 adults weighing approximately 69-81 kg, the basal metabolic rate was approximately 800-1,600 kcal (Abdel-Mageed and Mohamed 2016). Based on this study, we estimated the adult basal metabolic rate to be approximately 10-23 kcal/kg, which is markedly higher than the dose adopted in the present study (2.5 kcal/kg). Thus, the pharmacokinetic behavior of CBZ may be altered by the concurrent dosing of PG in clinical practice. However, individual differences may exist in the degree of alterations in serum CBZ levels during treatments with semi-solid enteral nutrients because the dissolution rate of CBZ in gastrointestinal fluid is slow and the drug possesses anticholinergic properties (Chen et al. 2002). Furthermore, CBZ is administered as tablets and capsules in clinical practice, thus their disintegration and dissolution are highly important factors associated with pharmacokinetic interactions. Therefore, further clinical examination of the interaction between CBZ and semi-solid enteral nutrients is needed.

In conclusion, we demonstrated using rats that concurrent dosing of PG interfered with the absorption of CBZ in the digestive tract, but staggered administration of CBZ and PG prevented their interaction. Our study will help to promote appropriate nutritional management in pharmacotherapy.

3. Experimental

3.1. Chemicals

CBZ was purchased from Fujifilm Wako Pure Chemical Co. (Osaka, Japan). PG was obtained from Terumo Co. (Tokyo, Japan). All other reagents were of commercial or analytical grade, requiring no further purification.

3.2. Animal care and treatment

Male Sprague-Dawley rats, aged 7 weeks, were obtained from Japan SLC, Inc. (Hamamatsu, Japan). Rats were acclimatized for at least 2 days before being assigned to their experimental groups, and were housed in a clean room maintained at 23±2 °C with a relative humidity of 55±10 % and 12-h light/dark cycle. They were allowed free access to a regular animal diet and tap water. The left jugular vein of rats was cannulated with polyethylene tubing (Natsume Seisakusyo Co., Ltd., Tokyo, Japan) under anesthesia and the tube was then externalized to the interscapular area. Rats were fasted overnight following surgery. The next day, the rats were divided into three treatment groups, which were designated as the concurrent dosing group, staggered dosing group, and control group. In the concurrent dosing group and staggered dosing group, PG (2.5 kcal/kg) was orally administered to rats immediately and 20 min, respectively, after CBZ dosing. In the control group, CBZ was administered in a fasted state. CBZ was orally administered at a dosage of 50 mg/kg and volume of 2.5 mL/kg. Serial blood samples were obtained from the left jugular vein at 2, 5, 10, 15, and 30 min, and 1, 2, 3, 4, 5, and 6 h after the oral administration of CBZ, and were replaced with an equal volume of saline. In order to maintain patency, a small volume of heparinized saline was used to fill the cannula after the collection of each blood sample. Heparinized saline was removed just before the collection of the next blood sample. Collected blood was centrifuged at 3,000 *g* for 10 min to obtain serum samples. The experimental protocols and animal care methods used in the present study were approved by the Animal Experiment Committee at Osaka Ohtani University.

3.3. Measurement of serum CBZ concentrations

Fifty microliters of 50 μg/mL phenacetin, an internal standard, 50 μL of 0.1 M sodium hydroxide, and 750 μL of ethyl acetate were added to a 100 μL serum

sample. The mixture was then vortexed and centrifuged at 5,000 *g* for 5 min. The organic layer was decanted into new tubes and evaporated using a centrifugal concentrator to dryness. The residues were resolved in 200 µL of the mobile phase and 50 µL was injected into the HPLC system (Shimadzu, Kyoto, Japan), consisting of an LC-20AD pump and SPD-M20A diode array detector. CBZ and phenacetin were separated on an RP-18GP II column (particle size 5 µm, 150 x 4.6-mm inner diameter; Kanto Chemical Co., Inc., Tokyo, Japan). The mobile phase consisted of 15 mM potassium phosphate buffer (pH 7.0) and acetonitrile (v/v: 66:34), and the flow rate was set at 1.0 mL/min. Absorbance of the eluent was monitored at 230 nm. The concentration of CBZ was calculated using the ratio of the corresponding peak area of CBZ to that of an internal standard.

3.4. Pharmacokinetic analysis

The standard pharmacokinetic parameters of CBZ were calculated based on the non-compartmental method. The maximum concentration (C_{max}) of CBZ in serum and the time to reach the C_{max} (T_{max}) were obtained directly from the measured concentrations. The elimination rate (k_e) was assessed by linear regression of the log-linear portions of plots of serum concentrations against time. The AUC was calculated by a linear trapezoidal approximation from time zero to the last sampling point ($t_{(last)}$), with the addition of a correction term by extrapolation to infinity using the ratio of the last measured concentration ($Cp_{(last)}$) to k_e. The area under the first-moment curve (AUMC) was also calculated by a linear trapezoidal approximation from time zero to $t_{(last)}$ with the addition of a correction term after $t_{(last)}$ to infinity, namely $t_{(last)} * Cp_{(last)}/k_e + Cp_{(last)}/(k_e)^2$. The mean residence time (MRT) was obtained by dividing AUMC by AUC.

3.5. Statistical analysis

Data are expressed as means±SD. Comparisons among groups were made by means of an analysis of variance (ANOVA) followed by Dunnett's test. Differences with a *p*-value of 0.05 or less were considered significant.

Conflicts of interest: None declared.

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