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ORIGINAL ARTICLE

Adsorption of irinotecan onto oral adsorbent AST-120 (Kremezin™) for preventing delayed diarrhea

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Abstract
Purpose One of the significant dose-limiting toxicities of irinotecan hydrochloride (CPT-11) is severe diarrhea due to impairment of the intestinal membrane induced by the excreted CPT-11 and its metabolites. AST-120 (Kremezin) is a prominent oral adsorbent that consists of porous spherical carbonic particles. To evaluate whether Kremezin can prevent the diarrhea induced by CPT-11, we investigated the adsorption characteristics of CPT-11 and its metabolites onto Kremezin in vitro and in vivo.
Methods For in vitro studies, Kremezin was added to each solution containing one of the camptothecin drugs (CPT-11, SN-38, and SN-38-glucuronide), and adsorption activities were determined under various conditions. For in vivo studies, CPT-11 was consecutively administered, and the occurrence of diarrhea was compared between Kremezin-treated and non-treated rats.
Results Kremezin drastically adsorbed the camptothecin drugs in vitro, and the adsorption percentages of the camptothecin drugs for 60 min were more than 85%. In addition, the frequency of diarrhea in Kremezin-treated rats decreased by approximately half of that in the non-treated rats.
Conclusion Kremezin showed potent adsorption capacities for the camptothecin drugs and mitigated the symptoms of diarrhea in rats. These results suggest that Kremezin is useful to prevent the diarrhea in clinical CPT-11 chemotherapy.

Keywords Irinotecan hydrochloride · Diarrhea · Kremezin · Adsorption

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Introduction

Irinotecan hydrochloride [7-ethyl-10-(4-(piperidino)-1-piperidino) carbonyloxycamptothecin] (CPT-11) is a semisynthetic water-soluble analogue of camptothecin that has a potent antineoplastic activity by inhibiting topoisomerase I. The antineoplastic activity of CPT-11 functions after CPT-11 is metabolized to the active form, 7-ethyl-10-hydroxycamptothecin (SN-38), which has 100- to 1,000-fold more potent antineoplastic activity than the parent form, i.e., CPT-11 in vitro [15, 16]. CPT-11 is frequently used in patients with cancers such as non-small-cell lung cancer, gastric cancer, ovarian cancer, and advanced colorectal cancer [18]. One of the significant dose-limiting toxicities of CPT-11 is severe diarrhea, which occurs early secretory diarrhea and subsequently delayed onset diarrhea [11]. The incidence of National Cancer Institute grade 3 or 4 diarrhea is 5–40% [8, 18]. The cause of the delayed diarrhea has been considered to be as follows: CPT-11 is metabolized by carboxylesterase into SN-38 in the liver, which is subsequently conjugated to SN-38-glucuronide (SN-38G) and excreted into the gastrointestinal tract via bile. SN-38G excreted in the gastrointestinal tract is hydrolyzed and is substantially turned to SN-38 by enterobacterial

beta-glucuronidase, in which SN-38 consequently impairs the intestinal membrane [22]. In addition, it has been noted that SN-38 transported into the gastrointestinal tract via the intestinal membrane causes damage of the membrane [3].

Therefore, in order to prevent CPT-11-induced diarrhea, various trials have been conducted. Most of these trials were mainly focused on the reduction of the cytotoxicity caused by SN-38 in the gastrointestinal tract, e.g. the concomitant oral administration of neomycin with CPT-11 [2], the oral alkalization combined with the control of defecation (sodium bicarbonate, magnesium oxide, and ursodeoxycholic acid) [13, 26], the prophylactic administration of Kampo medicine Hangeshashin-to [21], and the pretreatment with activated charcoal [20]. These previous trials partially improved the symptoms of the diarrhea. However, the severe diarrhea in CPT-11 chemotherapy had not been prevented completely. Consequently, the patients were forced to abandon CPT-11 chemotherapy. Therefore, the identification of more effective method preventing the severe diarrhea is important for the success of CPT-11 chemotherapy.

AST-120 (Kremezin) is an oral adsorbent that consists of porous spherical particles composed of carbon [12, 14]. Generally, Kremezin is orally given to patients with advanced chronic renal failure, in order to adsorb harmful endogenous and exogenous substrates, including uremic toxins secreted or produced in the gastrointestinal tract [23, 24], and then to excrete them along with feces. Kremezin also adsorbs various drugs as well as uremic toxins [12, 27, 28]. However, Kremezin is not affected by intestinal bacteria or digestive enzymes, and does not adsorb minerals. Maeda et al. [19] suggest that Kremezin treatment tends to mitigate CPT-11-induced diarrhea in cancer patients. However, to the best of our knowledge, the details of the mechanism for the adsorption of CPT-11, SN-38, and SN-38G onto Kremezin in vitro have not yet been clarified.

Therefore, in the present study, we investigate the adsorption characteristics of CPT-11 and its metabolites onto Kremezin in vitro and in vivo, and to evaluate whether orally administered Kremezin can mitigate CPT-11-induced diarrhea in rats.

Materials and methods

Materials

CPT-11, SN-38, and SN-38G were kindly provided by Yakult Honsha Company (Tokyo, Japan). Kremezin™ was a product of Kurehakagaku Co. (Tokyo, Japan). Ensure Liquid™ was a product of Meiji Dairies Co. (Tokyo, Japan). All other chemicals and solvents were of the highest grade that was commercially available.

Adsorption of CPT-11 and its metabolites onto Kremezin in vitro

Pure CPT-11 and SN-38G were dissolved in distilled water, and SN-38 was dissolved in DMSO. Each camptothecin drug was diluted by 50 mM phosphate buffered saline (PBS) at pH 7.4 to the indicated concentrations. Then, Kremezin (500 mg) was added to 10 ml of each solution. After shaking for the indicated periods under the condition at 37°C, the concentration of each camptothecin drug was measured by HPLC. The influence of pH was investigated using 1 mM HCl (pH 3.0) and 0.01 mM NaOH solution (pH 9.0) instead of PBS. The influence of Ensure Liquid™ was also examined by the same method.

HPLC conditions

The concentrations of CPT-11, SN-38, and SN-38G were determined by HPLC. We used camptothecin as an internal standard. The HPLC system consisted of an LC-10ADvp pump (Shimadzu, Kyoto, Japan), a Shimadzu RF-10Axl fluorescence detector, a Shimadzu SIL-10ADvp auto injector, and a Shimadzu SCL-10Avp system controller. The system was equipped with a Cadenza CD-C18 column (3 μm, 4.6 × 250 mm; Intact, Kyoto, Japan) preceded by a precolumn (5 μm, 2 × 5 mm). The mobile phase consisted of 0.075 M ammonium acetate buffer (pH 6.4)-acetonitrile (7:3, v/v) and was delivered at a flow rate of 0.7 ml/min at 40°C. Detection was monitored with an excitation wavelength at 355 nm and an emission at 515 nm. Under this condition, a coefficient of the intraday and interday variations was below 5%.

Animals

Male Wistar rats (Kyudo Co., Ltd., Kumamoto, Japan) weighing 180–200 g and maintained at the Department of Bio-resources, Division of Biotechnology, Frontier Science Research Center, Miyazaki University, were used throughout the study. The rats were housed in stainless steel cages with three animals per cage in a temperature-controlled (22–24°C) room with a 12-h light/dark cycle. The rats were allowed free access to standard rat food and water for 1 week prior to the experiments. The Ethics Review Committees for Animal Research of Miyazaki University approved the experimental protocol. The experiments were carried

out according to the Guideline for Animal Experiments in Miyazaki University.

Pharmacokinetic experiments

The rats were fasted overnight prior to the experiments. Each animal was anesthetized with pentobarbital (50 mg/kg, intraperitoneally), and the carotid artery was cannulated with polyethylene tubing (PE-50; Clay Adams, Becton Dickinson & Co., Franklin Lakes, NJ, USA) in order to collect blood samples. The tube was filled with a heparin lock in order to prevent blood clotting. The solution consisted of 100 U/ml heparin in saline. A solution for injection was prepared by dissolving 150 mg of CPT-11 in sterilized, distilled water (20 ml). Kremezin suspension in water (150 mg/2 ml) or 2 ml of water as a control was orally administered to rats 30 min and 10 h prior to CPT-11 injection. CPT-11 was injected at a dose of 15 mg/kg via the caudal vein. Blood samples (approximately 0.2 ml) were collected through the carotid artery at 15, 30, and 45 min and 1, 2, 3, 4, 6, 8, and 12 h after administration of CPT-11. The samples were immediately centrifuged at 16,000 *g* and 4°C for 5 min, and the plasma was separated. Plasma samples were prepared for HPLC determination according to the described method [4]. After completing the blood collection periods, the rats were sacrificed and the intestinal contents were collected from jejunum, ileum, and colon. Kremezin was removed thoroughly from the intestinal contents so as not to affect the analysis. The concentrations of CPT-11 and its metabolites were determined by HPLC after homogenization of the fecal samples in acetonitrile. Each determination was performed at least three times to confirm the reproducibility. The samples were stored at −80°C until analysis.

Monitoring of CPT-11-induced diarrhea

Monitoring of CPT-11-induced diarrhea was performed according to our previously reported method [4]. Kremezin suspension (150 mg/2 ml) or the same volume of water was orally administered to rats three times per day throughout the experimental period. This treatment was begun at one day prior to CPT-11 injection. Animals were with free access to an ordinary diet and water. CPT-11 was injected via the caudal vein at a dose of 60 mg/kg per day for four consecutive days with a slow bolus injection. The change of body weight and the severity of diarrhea were checked two times per day. This grade assessment was performed according to the method as described by Kurita et al. [17]. The grade was follows: 0 (normal–normal stools or absent), 1 (slight—wet and soft stools), 2 (moderate—wet and unformed stools with moderate perianal staining of the coat), and 3 (severe—watery stools with severe perianal staining of the coat).

Data analysis

Unpaired student's *t* test and Williams' test were used to evaluate for significant differences in mean values. Diarrhea score data were analyzed using Wilcoxon's rank sum test. The significant level was set up at $P < 0.05$.

Results

Adsorption of CPT-11 and its metabolites onto Kremezin in vitro

To evaluate whether Kremezin adsorbs the camptothecin drugs, we examined the adsorption characteristics of Kremezin. Since the excretion of camptothecin drugs in cancer patients is approximately 10% of dose/day [25] (clinical dose of CPT-11 is approximately 200 mg/m^2), and Kremezin dose is 6 g/day, we set the camptothecin drugs/Kremezin ratio on 1:100 to 1:10,000. The camptothecin drugs were rapidly adsorbed, and the adsorption rates attained were 85% and up within approximately 60 min (Fig. 1). The adsorption capacities of Kremezin for all the camptothecin drugs showed saturation kinetic characteristics within 24 h after mixing. The maximum adsorption capacities of Kremezin for CPT-11, SN-38, and SN-38G were given 407, 398, and 852 mg per 1 g of Kremezin, respectively, by the double reciprocal plot of the concentration and the amount of the camptothecin drugs adsorbed onto Kremezin at a time point of 24 h after the mixing (Fig. 2). Since the dose of Kremezin is 6 g/day, we considered Kremezin have enough capacity to adsorb the camptothecin drugs. These results suggest that Kremezin could be a candidate as an adsorbent contributing to the adsorption and the excretion of the camptothecin drugs in vivo.

Influence of pH, magnesium oxide, and liquid food on adsorption

CPT-11 and SN-38 have been known to exist as a lactone form and a carboxylate form dependent upon pH. The lactone form and the carboxylate form predominate under acidic conditions and alkaline conditions, respectively [9]. The physical characteristics of the two forms show remarkable differences with regard to the

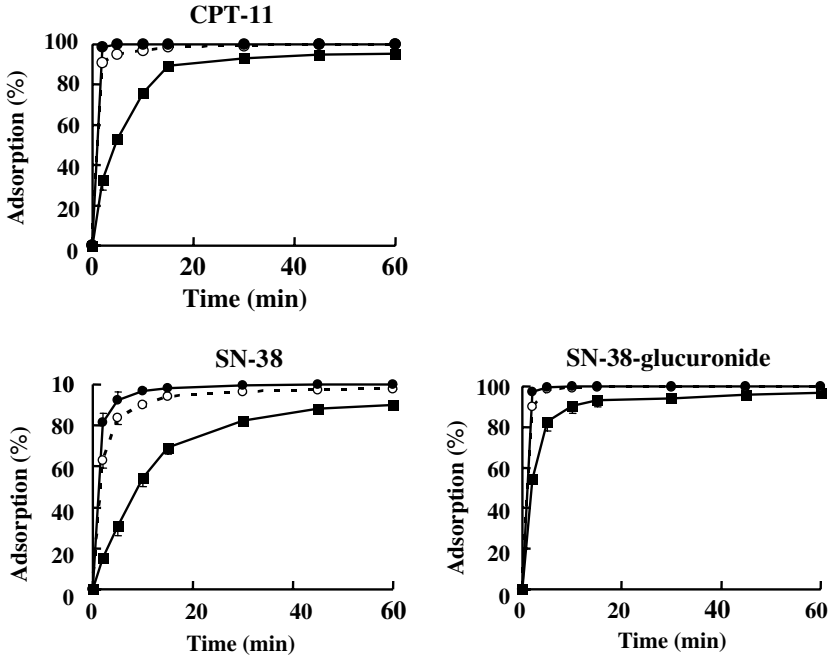

Fig. 1 Time course for adsorption (%) of the camptothecin drugs onto Kremezin at different ratios. CPT-11, SN-38, and SN-38-glucuronide were prepared at three different concentrations in phosphate buffered saline (pH 7.4). Five hundred milligrams of Kremezin was added to 10 ml of the solution; finally the ratios of Camptothecin drug/Kremezin were 1:100 (*filled square*), 1:1,000 (*open circle*), and 1:10,000 (*filled circle*). Each *point* and *bar* represents the mean and SD of six independent assays

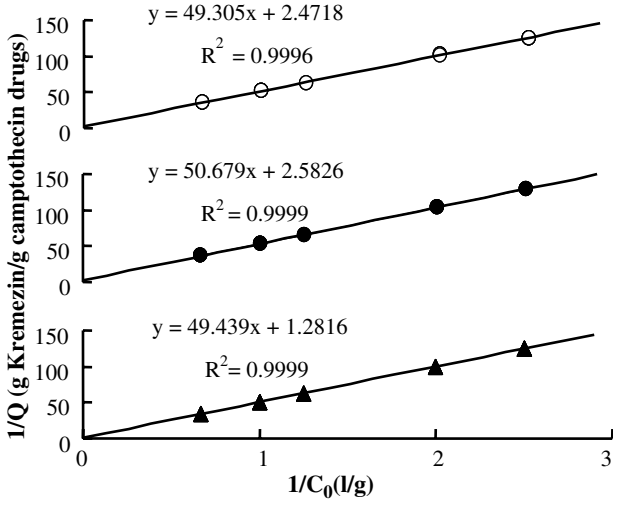

Fig. 2 Langmuir plot of adsorption of CPT-11 and its metabolites onto Kremezin. CPT-11 (*open circle*), SN-38 (*filled circle*), and SN-38-glucuronide (*filled triangle*) were prepared at five different concentrations in phosphate buffered saline (pH 7.4). Five hundred milligrams of Kremezin was added to 10 ml of the solution. Twenty-four hours later, the final concentrations of camptothecin drugs were determined. Data were plotted to the mass balance equation $Q = V(C_0 - C_f)/W$, where V is the volume of solution, C_0 is the initial concentration, C_f is the final concentration, and W is the weight of Kremezin

reaction rate of the hydrolysis and lactonization of CPT-11 [1] and the protein binding to human serum albumin of CPT-11 [7]. Hence, we investigated the adsorption characteristics of both forms of CPT-11, SN-38, and SN-38G under the various pH conditions. Five hundred milligrams of Kremezin drastically adsorbed both the lactone form and the carboxylate form of the camptothecin drugs (5 mg), and their adsorption percentages were not less than 99.9%.

Kremezin physically contacts with food residues as well as the camptothecin drugs in the gastrointestinal tract. In case the intestinal contents interfere with the physical contacts between Kremezin and the camptothecin drugs, the adsorption capacity of Kremezin for the camptothecin drugs may be reduced. Therefore, in order to determine whether the digestive contents affect the adsorption capacity of Kremezin, we investigated the influence of Ensure Liquid™, a low-residue liquid food, on the adsorption capacity of Kremezin for the camptothecin drugs. As shown in Fig. 3, the adsorption rate of CPT-11 became slow with the increase in the volume of Ensure Liquid™. However, the final amounts of adsorption of the camptothecin drugs onto Kremezin at a time point of 4 h after mixing was not decreased by Ensure Liquid™. Further, we investigated the influences of magnesium oxide on the adsorption capacity of Kremezin because magnesium oxide is used for prevention of CPT-11-induced diarrhea by oral alkalization combined with control of defecation [26]. The adsorption of CPT-11, SN-38, and SN-38G onto Kremezin was not reduced by magnesium oxide (data not shown). In addition, desorption from Kremezin is also regarded to be the cause of the remaining camptothecin drugs. In this respect, we investigated the desorption of CPT-11, SN-38, and SN-38G from Kremezin. After complete adsorption by Kremezin, the solution was changed to PBS or Ensure Liquid™. Then, the concentrations of camptothecin

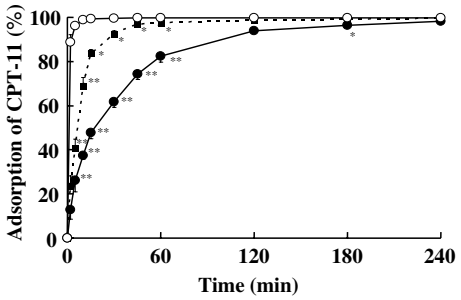

Fig. 3 Effect of liquid food (Ensure Liquid™) on adsorption of CPT-11 by Kremezin. CPT-11 was prepared in phosphate buffered saline (pH 7.4) and in Ensure Liquid™. Five hundred milligrams of Kremezin was added to 10 ml of the solution; finally the ratios of CPT-11/Kremezin were 1:1,000 (*open cirlce* phosphate buffered saline; *filled square* with 10% Ensure Liquid™; *filled circle* with 99.9% Ensure Liquid™). Each *point* and *bar* represents the mean and SD of six independent assays. The comparative adsorption in the presence and absence of Kremezin was analyzed by Williams' test. $*P < 0.05$; $**P < 0.01$, significantly different from the Kremezin absence group

drugs in the solution were measured. The desorption percentage was less than 1% throughout the observation period for 24 h (data not shown). These results indicate that Kremezin is suitable as an excellent adsorbent contributing to the adsorption of the camptothecin drugs in the body.

Effect of Kremezin on pharmacokinetics of camptothecin drugs in rats

Considering the fact that Kremezin adsorbed the camptothecin drugs to a great extent in vitro, Kremezin may synergistically affect the pharmacokinetics of the drugs administered to rats. Hence, to evaluate this hypothesis, we measured the plasma concentration of camptothecin drugs after the administration of Kremezin. We preliminarily confirmed that Kremezin distributed thoroughly from duodenum to colon within 10 h in rats (data not shown). Therefore, Kremezin was orally administered 30 min and 10 h prior to CPT-11 injection. As shown in Fig. 4, contrary to our abovementioned hypothesis, the treatment with Kremezin had little effect on the plasma levels of CPT-11, SN-38, and SN-38G after intravenous administration of CPT-11.

Effect of Kremezin on the concentration of camptothecin drugs in rat intestinal contents

Of all the parts of the intestine including jejunum, ileum, and colon, the concentrations of the camptothecin drugs in the intestinal contents were significantly decreased by the treatment with Kremezin (Fig. 5).

Preventive effect of Kremezin on CPT-11-induced diarrhea

In keeping with the above results that Kremezin significantly decreased the remaining camptothecin drugs in the intestine, it is considered that Kremezin may prevent the CPT-11-induced diarrhea in patients who have undergone CPT-11 chemotherapy. Since the camptothecin drugs in the rat intestine were reduced to approximately 40–60% by the treatment with Kremezin,

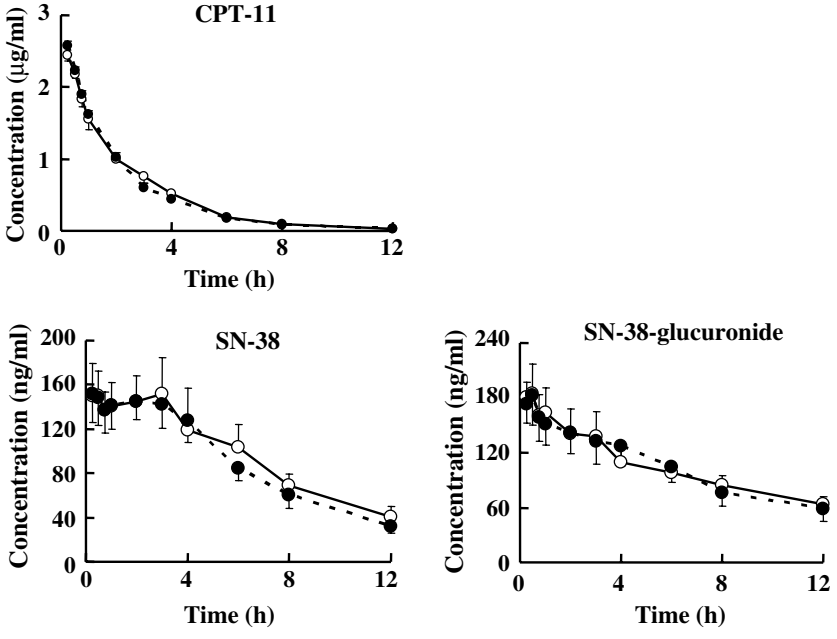

Fig. 4 Plasma concentration profiles of CPT-11, SN-38, and SN-38-glucuronide after intravenous administration of CPT-11 at a dose of 15 mg/kg to rats (*open circle* absence of Kremezin; *filled circle* presence of Kremezin). Each *point* and *bar* represents the mean and SEM from five rats

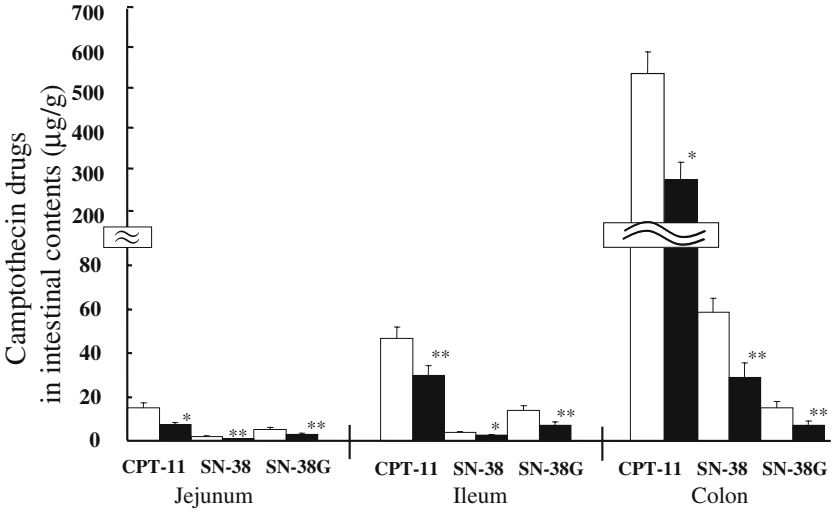

Fig. 5 Change in gastrointestinal concentrations of CPT-11, SN-38, and SN-38-glucuronide (SN-38G) after treatment with (*shaded bars*) or without (*open bars*) Kremezin in rats. The concentrations of camptothecin drugs in the jejunal, ileal, and colonic contents were determined 12 h after intravenous administration of CPT-11 at a dose of 15 mg/kg. Each determination was performed at least three times to confirm the reproducibility. The data are the mean ± SEM from five independent experiments. The comparative intestinal concentration in the presence and absence of Kremezin was analyzed by Student's *t* test. $*P < 0.05$; $**P < 0.01$, significantly different from the Kremezin absence group

we considered the frequency of the diarrhea would be reduced less than 50%. In order to validate this hypothesis, we investigated the preventing effect of Kremezin on the CPT-11-induced diarrhea in rats (Table 1). Control rats without CPT-11 did not have any diarrhea, whereas almost all rats with the single treatment of CPT-11 had a mild or moderate diarrhea within 96 h. However, in the group treated with Kremezin, the frequency of the diarrhea induced by CPT-11 was reduced by approximately 50%, and the degree of diarrhea grade was mild. Furthermore, the profile of the body weight changes was similar to that of the frequency of diarrhea induced by CPT-11 in the two groups of CPT-11 treated with or without Kremezin (data not shown). We thus concluded that Kremezin could mitigate the symptoms of CPT-11-induced diarrhea by decreasing the concentrations of the camptothecin drugs in the gastrointestinal tract.

Discussion

In this study, we investigated the adsorption capacities of Kremezin, an oral adsorbent, for the camptothecin drugs CPT-11, SN-38, and SN-38G in order to identify a method preventing CPT-11-induced diarrhea, and demonstrated that Kremezin mitigates the diarrhea induced by CPT-11 in rat. Diarrhea is a dose-limiting toxicity of CPT-11 treatment. Hence, the prevention of the diarrhea produces a great therapeutic benefit to

Table 1 Effect of Kremezin on severity of CPT-11-induced diarrhea in rats

Treatment group	*n*	Diarrheal score																			
		Day 1					Day 2					Day 3					Day 4				
		0	1	2	3	Mean	0	1	2	3	Mean	0	1	2	3	Mean	0	1	2	3	Mean
Control	6	6				0.00	6				0.00	6				0.00	6				0.00
CPT-11 + water	6	5	1			0.17	2	3	1		0.83	1	3	2		1.17	1	2	3		1.33
CPT-11 + Kremezin	6	6				0.00	5	1			0.17	4	2			0.33	4	2			0.33*

CPT-11 was administered at a daily dose of 60 mg/kg for four consecutive days to rats. The severity of diarrhea was checked two times per day, and the data of 12 h after for CPT injection are shown. Diarrhea score: *0* no diarrhea, *1* mild diarrhea, *2* moderate diarrhea, *3* severe diarrhea. The values are the number of animals with each score. The comparative diarrhea grade in the presence and absence of Kremezin was analyzed by Wilcoxon's rank sum test

$*P < 0.05$, CPT-11 alone versus CPT-11 with Kremezin

cancer patients. The course of diarrhea is intimately involved in CPT-11 and SN-38 excreted via the biliary route and/or the intestinal membrane route into the gastrointestinal tract. Therefore, the method excluding camptothecin drugs from the gastrointestinal tract is an important factor for the success of the chemotherapy using CPT-11.

Kremezin possesses an excellent adsorption capacity for various endogenous and exogenous compounds in vitro and in vivo. Hence, in this study, we chose Kremezin as a candidate adsorbent that contributes to the adsorption and the exclusion of the camptothecin drugs in the gastrointestinal tract. We investigated the adsorption characteristics of Kremezin in vitro and in vivo. Kremezin showed potent adsorption capacity for the camptothecin drugs under the experimental in vitro condition which supposes physiological properties (Figs. 2, 3). Furthermore, Kremezin significantly reduced the intestinal concentrations of the camptothecin drugs probably due to the adsorption in rats (Fig. 5). In addition, the plasma concentrations of the camptothecin drugs were slightly reduced by Kremezin in rats, but the reduction was not significant (Fig. 4). The influence of Kremezin on the enterohepatic circulation is considered to be negligible as to the evaluation of the pharmacokinetics of the camptothecin drugs. Therefore, these results suggest that Kremezin reduces the gastrointestinal toxicity induced by the camptothecin drugs without diminishing their antineoplastic effect.

Next, we examined the preventive effect of Kremezin on CPT-11-induced diarrhea. CPT-11 causes diarrhea as a result of the severe damage induced by the camptothecin drugs in both the small intestine and the colon in rats [10]. In this study, Kremezin significantly reduced the frequency and the grade of diarrhea (Table 1), but the reduction was not complete. Considering the failure of Kremezin to completely prevent diarrhea, the camptothecin drugs may not have been completely adsorbed by Kremezin. The remaining camptothecin drugs may damage intestinal cell, and subsequently cause diarrhea in some sensitive rats. The remaining camptothecin drugs may be due to the inhibition of physical contact with Kremezin, since the intestinal contents and/or the intestinal wriggle interfere with the approach of Kremezin to the camptothecin drugs. Generally, the adsorption capacity depends on the amount of Kremezin employed and on the concentrations of targeting substances. Hence, in case a large amount of Kremezin was administered, the toxic camptothecin drugs would be more effectively adsorbed by Kremezin in the body. In this study, we adopted the amount of Kremezin based on human parameters (converting body weight); then higher dose of Kremezin was not considered. Therefore further investigations are necessary.

Activated charcoal, an adsorbent which consists of carbon in the same as Kremezin, also prevents and/or mitigates the CPT-11-induced diarrhea [5, 6, 20]. However, the effects were weak or negative. On the other hand, our result and Maeda et al. [20] shows Kremezin can mitigate the CPT-11-induced diarrhea. Kremezin has been reported to show the strong adsorption capacity for substances with molecular weights of about 100–1,000 [12]. The molecular weights of CPT-11, SN-38, and SN-38G are within these ranges. In contrast, activated charcoal can adsorb substances with a larger range of molecular weights (several hundreds to million). Consequently, we considered that Kremezin is more useful for the adsorption of camptothecin drugs in clinical practice than activated charcoal.

In conclusion, Kremezin shows the potent adsorption capacities for CPT-11 and its metabolites. Kremezin is considered to be useful for mitigating-delayed diarrhea induced by the CPT-11 chemotherapy. However, it is difficult to directly extrapolate the effects of Kremezin shown in rats to those in human. Therefore, further investigations are necessary in order to determine the effect of Kremezin for the prevention of CPT-11-induced diarrheal symptoms in human.

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