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Decreased bioavailability of carbamazepine suppository after its intrarectal and intracolostomal administration to rectal-resected or colostoma-constructed rabbits

Kazuki Nagasawa [a,*], Hirokazu Nakanishi [b], Ryoji Yamamoto [a], Sumiko Kintsuji [a], Sadaki Fujimoto [a]

[a] *Department of Environmental Biochemistry, Kyoto Pharmaceutical University, 5 Nakauchi-cho, Misasagi, Yamashina-ku, Kyoto 607-8414, Japan*

[b] *Department of Pharmacy, Kyoto-Katsura-Hospital, 17 Yamada-Hirao-cho, Nishikyo-ku, Kyoto 615-8258, Japan*

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Abstract

The pharmacokinetics of carbamazepine (CBZ), one of the useful analgesic adjunctive agents for palliative care, and its major active metabolite, CBZ-10,11-epoxide (CBZ-E), were investigated after the intrarectal and intracolostomal administration of CBZ to rabbits with rectal-resection or colostoma-construction. In rectal-resected rabbits, the bioavailability of CBZ and the plasma level of CBZ-E after rectal administration were significantly lower than those in normal rabbits, and furthermore these values after intracolostomal administration to colostoma-constructed rabbits tended to be lower than those in rectal-resected ones. This decreased bioavailability of CBZ was thought to be not due to an increased first-pass effect, but to the lower CBZ absorption ability in the upper rectum and colon, since absorption profile of CBZ was not affected by first-pass metabolism. When the dose was increased based upon the difference in the absolute bioavailability values in the rectal-resected and colostoma-constructed rabbits, the decreased plasma levels of CBZ were restored to the control levels incompletely, and the elimination of CBZ and CBZ-E was retarded. These findings suggest that owing to the similarity of their pharmacokinetics in rabbit and man, the increment of dosages of CBZ should be avoided, when CBZ suppositories are administered to rectal-resected or colostoma-constructed patients.

Keywords: Palliative care; Pharmacokinetics; Carbamazepine suppository; Carbamazepine-10,11-epoxide; Rectal-resection; Rabbit

1. Introduction

Recently, in Japan, the life style including diet pattern has been changing, decreased intake of dietary fiber and increased intake of animal protein being especially conspicuous. With this, together with some other factors, the number of

* Corresponding author. Tel.: +81-75-595-4648; fax: +81-75-595-4756

E-mail address: nagasawa@mb.kyoto-phu.ac.jp (K. Nagasawa).

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patients with colorectal tumors has been increasing (The Ministry of Health, Labour and Welfare Website, 2002). The standard therapy regimens for rectal tumor consist of surgical operation, chemotherapy, radiotherapy and thermotherapy (hyperthermia), depending on the tumor type and stage (Buyse et al., 1988; Scheithauer et al., 1993; Dahl et al., 1999; Douilard et al., 2000; van der Zee et al., 2000). Together with such therapies or at the terminal stage, on the other hand, palliative care for pain, fatigue, etc. is necessary for maintenance of a patient's QOL (World Health Organization, 1996). In general, pain management is performed following the guidelines of the WHO, and several analgesics and analgesic adjunctive agents are currently administered orally (Schipper et al., 1984; Zech et al., 1995). For patients who cannot take medicine orally and who have ileus, intravenous, subcutaneous or intrarectal administration is performed. In particular, considering a patient's QOL, the rectal route is one of the most useful ones, and the intrarectal or intracolostomal administration of medicine can prolong the patient's at-home day because it allows self-administration and therefore obviate the need of intervention of nurses or health professionals for its administration.

To our knowledge, however, there is very little information on the pharmacokinetics of analgesics, etc. after rectal administration in patients whom the rectum is resected or a colostoma is constructed (Hojsted et al., 1990). Therefore, in our previous study, we developed a rabbit model for rectal-resection and colostoma-construction, and demonstrated that the bioavailability of diclofenac sodium, one of the important analgesics for the management of the pain resulting from bone metastasis, was decreased after its intrarectal or intracolostomal administration to our model rabbits (Nagasawa et al., 2001).

Carbamazepine (CBZ) is a broadly used antiepileptic (Levy and Wurden, 1995), and is also often used as an analgesic adjunctive agent in palliative care for neuropathic pain due to tumor insult (Kloke et al., 1991). In our clinical experience, a CBZ tablet administered rectally to a consenting patient can relief his neuropathic pain (unpublished observation). Furthermore, several studies have demonstrated the usefulness of CBZ suppositories for palliative care (Walter, 1990; Ewoud et al., 1991; Storey and Trumble, 1992). However, whether or not the colorectal resection affects the bioavailability of CBZ after its intrarectal or intracolostomal administration has not been examined yet.

The aim of this study was to determine the change in the pharmacokinetics of CBZ and its major metabolite, CBZ-10,11-epoxide (CBZ-E), after intrarectal and intracolostomal administration of CBZ suppositories to our model rabbits.

2. Materials and methods

2.1. Materials

Pure CBZ and CBZ-E were purchased from Wako Pure Chemical Ind., Osaka, Japan, and Sigma Chemical Co., St. Louis, MO, USA, respectively. Propentofylline powder (internal standard for high-performance liquid chromatography (HPLC)) was a kind gift from Hoechst Japan, Tokyo, Japan. Witepsol H-15 was obtained from Maruishi Pharmaceutical Co., Ltd., Osaka, Japan. All other chemicals were commercial products of reagent grade.

2.2. Animals

Male Japanese White rabbits (Japan SLC Inc., Hamamatsu, Japan) weighing 2.0–3.5 kg (mean, 2.5 kg) were used in all experiments. All experiments were approved by the Experimental Animal Research Committee of Kyoto Pharmaceutical University and were performed according to the Guideline for Animal Experimentation of Kyoto Pharmaceutical University.

In the intravenous (i.v.) and rectal (control, i.r.) experiments, animals had free access to water and were fasted overnight (about 24 h) prior to the experiments.

In the oral (p.o.) administration experiments, rabbits were pretreated by the method described by Maeda et al. (1977). Briefly, rabbits were fed a special diet, which was prepared by removing alfalfa from a commercial solid diet (RC4; Orien-

tal Yeast Co., Ltd., Tokyo, Japan), for a week of conditioning before the oral administration study. After being fasted overnight with water ad libitum, a rubber stomach tube, 25 cm in length and 5 mm in external diameter with a large hole on the side of the tip, was inserted into the stomach, and then 50 ml of warmed saline (37 °C) was instilled. The fluid in the stomach was then withdrawn by suction with a syringe. This procedure was repeated until the fluid withdrawn hardly contained any solid material. After gastric lavage, the rabbits were allowed water ad libitum and muzzled to prevent coprophagy during the night.

2.3. Animal operation

In the experiments involving rectal-resected or colostoma-constructed rabbits, the rabbits were surgically operated on as reported previously (Nagasawa et al., 2001). Briefly, under pentobarbital anesthesia (50 mg/kg, i.v.), midline laparotomy was performed. The arteries and veins in the mesorectum governing the resected rectum portion (approximately 10 cm length from 10 cm from the anus) were ligated, and then the portion in which the governing vessels were ligated was resected. In the rectal-resected rabbits, the upper (colonic side) and lower (rectal side) ends resulting from the resection were occluded by the Albert–Lembert method. On the other hand, in the colostoma-constructed rabbits, after resection of the rectal portion, the remaining lower end (rectal side) was ligated, and a colostoma was constructed using the upper end (colonic side) at the midline abdomen following the Hartmann method. After the operation, the rabbits were allowed water ad libitum and fasted overnight, the experiments being performed on the next day. After the experiments, an autopsy was performed, the leakage of the rectal contents, blood circulation and pathological condition of the operated portion being examined.

2.4. Animal experiments

An i.v. bolus of a CBZ solution in propylene glycol–pure water–ethanol (5:3:2; v/v/v, 25 mg/1.25 ml/kg) was injected via an ear vein. In the p.o. administration experiments, the CBZ solution as the same as the case in the i.v. administration (50 mg/2.5 ml/kg) was administered orally via gastric intubation. The CBZ suppositories (50 mg/kg), which were prepared using Witepsol H-15 as a suppository base as described by Shinoda et al. (1995) were inserted into the rectum or colostoma, and the anus or colostoma was immediately closed with adhesive (Aron Alpha®) to prevent expulsion of the suppositories. This procedure resulted in no detectable leakage of the rectal contents during the experimental period. In all cases, blood samples (approximately 1.0 ml) were collected directly from an ear vein in heparinized disposable plastic syringes at 0.083, 0.25, 0.5, 1, 2, 4, 6, 8, 10 and 24 h after each dose. The samples were immediately centrifuged, and the extracted plasma fractions were stored at -20 °C until the assay.

2.5. Assaying of CBZ and CBZ-E in plasma

The plasma CBZ and CBZ-E concentrations were determined by HPLC using the method reported previously (Ohnishi et al., 1999). Briefly, 0.1 ml of plasma was placed in a plastic centrifugation tube (1.5 ml), and then 0.5 ml of acetonitrile containing propentofylline (internal standard) (1 μg/ml) was added. After vigorous shaking for 30 s, the mixture was centrifuged at 14,000 rpm for 5 min at room temperature. Then, 20 μl of the upper liquid phase was injected into an HPLC apparatus (LC-6A; Shimadzu, Kyoto, Japan) equipped with an ultraviolet detector (SPD-6A; Shimadzu). The conditions for analysis were as follows: column size, 250×4.0 mm i.d.; packing, STR-ODS-II (Shinwa Chemical Industries, Ltd., Kyoto, Japan); mobile phase, acetonitrile–pure water (24:76; v/v); column temperature, 40 °C; flow rate, 1.0 ml/min; wavelength, 210 nm; and sensitivity, 0.00125 a.u.f.s. The retention times of CBZ-E, propentofylline and CBZ were about 10, 14 and 25 min, respectively. The coefficient of variation of assay was less than 3%, and the recovery rates of CBZ and CBZ-E in plasma averaged over 90%. The calibration curves for CBZ and CBZ-E (0.5–20 μg/ml) showed good linearity ($r^2 > 0.999$). The detection limits for

CBZ and CBZ-E were approximately 0.5 and 0.2 μg/ml, respectively.

2.6. Pharmacokinetic analysis

The peak plasma concentration (Cmax) and the time to reach Cmax (Tmax) of CBZ and CBZ-E were determined from the actual observed data. The areas under the plasma concentration–time curves from zero to infinity (AUC) for CBZ and CBZ-E were calculated by means of the trapezoidal rule with extrapolation to infinity with the elimination rate constant. The mean residence time from zero to infinity (MRT) of CBZ and CBZ-E, and the absolute bioavailability (F) of CBZ were estimated by a Moment analysis.

2.6.1. Statistical analysis

Data are expressed as means ± S.E. Comparisons between groups were made by means of one-way analysis of variance (ANOVA) followed by Fisher's Protected LSD test. Differences were considered to be statistically significant when $P < 0.05$.

3. Results

3.1. i.v. and p.o. Administration

The plasma concentration–time profiles of CBZ and CBZ-E in rabbits after i.v. and p.o. administration of a CBZ solution (25 and 50 mg/kg, respectively) are depicted in Fig. 1. The plasma concentrations of CBZ showed biphasic decreases for the i.v. and p.o. groups (Fig. 1A). Table 1 shows the pharmacokinetic parameters after i.v. and p.o. administration. The total clearance (CLtot) and distribution volume at steady state (Vdss) of CBZ after its i.v. administration were 0.563 l/h/kg and 1.28 l/kg, respectively. The Cmax and Tmax values of CBZ for the p.o. group were 31.9 μg/ml and 0.667 h, respectively. The F value of CBZ after p.o. administration was calculated to be 99.7%, and the MRT value for the p.o. group was approximately equal to that for the i.v. group. As shown in Fig. 1B, the plasma concentration–time curve of CBZ-E after p.o. administration of a CBZ solution was similar to that after i.v. administration, and there was no difference in the MRT value between the i.v. and p.o. groups (Table 1).

3.2. i.r. and Intracolostomal administration

As shown in Fig. 2A, the time course of the plasma CBZ level after the i.r. administration of a suppository (50 mg/kg) was monophasic. On i.r. administration to rectal-resected rabbits (i.r.r.) and intracolostomal administration to colostoma-constructed rabbits (i.s.), similar plasma concentration–time profiles were observed in comparison with that in the i.r. group, but the concentrations in the i.r.r. and i.s. groups were lower than those in the i.r. group. Furthermore, the plasma CBZ concentrations in the i.s. group tended to be lower than those in the i.r.r. group. Also, the plasma concentrations of CBZ-E in the i.r.r. and i.s. groups were less than that in the i.r. group, while there was no difference in the plasma level of CBZ-E between the i.r.r. and i.s. groups.

The Cmax and AUC values of CBZ in the i.r.r. and i.s. groups were significantly smaller than those in the i.r. group, and those in the i.s. group tended to be less than those in the i.r.r. group (Table 2). The F value for the i.r. group was significantly lower than those for the p.o. groups (Tables 1 and 2). The Cmax, AUC and F values decreased in the order of i.r. > i.r.r. > i.s. Although there were no differences in the Tmax and

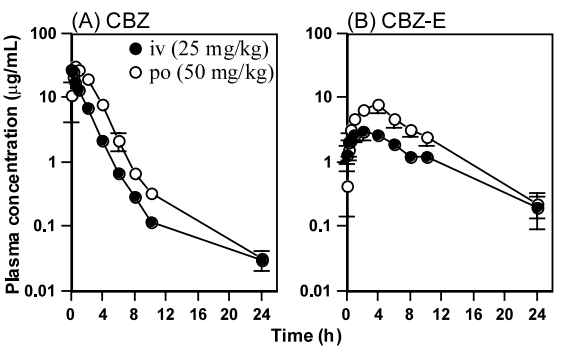

Fig. 1. Plasma concentration–time profiles of CBZ and CBZ-E after i.v. and p.o. administration of a CBZ solution (25 or 50 mg/kg) in rabbits. Each point represents the mean ± S.E. for three rabbits.

Table 1
Pharmacokinetic parameters of CBZ and CBZ-E after i.v. and p.o. administration of a CBZ solution (25 or 50 mg/kg) in rabbits

Parameter	CBZ		CBZ-E	
	i.v. (25 mg/kg)	p.o. (50 mg/kg)	i.v. (25 mg/kg)	p.o. (50 mg/kg)
Cmax (μg/ml)	–	31.9 ± 2.7	2.95 ± 0.82	7.74 ± 1.97
Tmax (h)	–	0.667 ± 0.167	2.67 ± 0.43	4.00
AUC (μg h/ml)	46.0 ± 5.6	91.6 ± 10.2	32.0 ± 6.1	69.6 ± 13.7
MRT (h)	2.24 ± 0.12	2.41 ± 0.10	8.14 ± 0.85	7.97 ± 1.66
Cltot (l/h/kg)	0.563 ± 0.078	–	–	–
Vdss (l/kg)	1.28 ± 0.25	–	–	–
F (%)	100 ± 12	99.7 ± 11.1	–	–

Each value represents the mean ± S.E. for three rabbits.

MRT values among the i.r., i.r.r. and i.s. groups, the MRT values in these three groups were significantly greater than those in the i.v. and p.o. groups (Tables 1 and 2).

A similar tendency was observed in the parameters for CBZ-E after the i.r., i.r.r. and i.s. administration of CBZ suppositories (Table 2). However, the MRT value of CBZ-E in the i.s. group was significantly lower than those in the other two groups.

As a result of increasing the dose (100 mg/kg) in the i.r.r. groups, the plasma CBZ and CBZ-E concentrations increased significantly (Fig. 3). The Cmax value of CBZ tended to increase with the increased dose, and that of CBZ-E showed a significant increase (Table 3). The AUC values of CBZ and CBZ-E were approximately twofold increased, and that of the former was almost equal to that of the i.r. group (Tables 2 and 3). With the increased dose, the Tmax value of CBZ tended to be increase and that of CBZ-E significantly decreased, but those of both CBZ and CBZ-E were approximately the same as those in the i.r. group. There were no differences in the MRT values of CBZ and CBZ-E between the 50 and 100 mg/kg groups.

For the i.s. group, when the CBZ dose was increased to 150 mg/kg, the plasma levels of CBZ and CBZ-E were significantly greater than those of the 50 mg/kg group (Fig. 4). However, the decreases in their plasma level were retarded in comparison with in the 50 mg/kg group. The AUC values of CBZ and CBZ-E in the 150 mg/kg group were significantly greater than those in the 50 mg/kg group. The Tmax value of CBZ, and the MRT values of CBZ and CBZ-E in the 150 mg/kg group were about 2.6- and 1.5-fold, respectively, increased in comparison with those in the 50 mg/kg group (Tables 2 and 4).

Finally, we examined whether or not saturation kinetics were observed on the i.r. administration of CBZ by increasing the dose up to 150 mg/kg (Fig. 5 and Table 5). The plasma concentrations of CBZ and CBZ-E increased, and the elimination of the latter was apparently retarded with increasing the dose. The increase in the dose increased the Cmax, AUC and MRT of CBZ, and the increase in the AUC of CBZ was not linear (Table

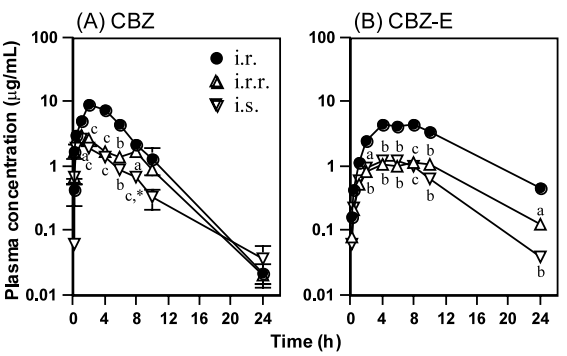

Fig. 2. Plasma concentration–time profiles of CBZ and CBZ-E after i.r. and i.s. administration of a CBZ suppository (50 mg/kg) in rabbits with or without rectal-resection or colostoma-construction. Each point represents the mean ± S.E. for three rabbits. (a) $P < 0.05$; (b) $P < 0.01$; (c) $P < 0.001$ (vs. i.r. group). *$P < 0.05$ (vs. i.r.r. group).

Table 2
Pharmacokinetic parameters of CBZ and CBZ-E after i.r. and i.s. administration of a CBZ suppository (50 mg/kg) in rabbits with or without rectal-resection or colostoma-construction

Parameter	CBZ			CBZ-E		
	i.r.	i.r.r.	i.s.	i.r.	i.r.r.	i.s.
Cmax (μg/ml)	8.88 ± 0.70	3.05 ± 0.59^{c}	2.58 ± 0.06^{c}	5.23 ± 0.22	1.18 ± 0.21^{c}	1.45 ± 0.31^{c}
Tmax (h)	2.67 ± 0.67	1.00^{b}	1.00^{b}	6.00 ± 1.16	8.67 ± 0.67	6.00 ± 1.16
AUC (μg h/ml)	56.3 ± 3.8	24.2 ± 3.3^{c}	15.9 ± 1.6^{c}	65.8 ± 9.3	17.9 ± 3.8^{b}	14.7 ± 3.9^{a}
MRT (h)	5.01 ± 0.28	5.86 ± 0.11	7.40 ± 2.21	9.87 ± 0.73	9.43 ± 0.25	$7.49 \pm 0.49^{b,*}$
F (%)	61.3 ± 4.2	26.3 ± 3.6^{c}	17.3 ± 1.7	–	–	–

Each value represents the mean ± S.E. for three rabbits.
[a] $P<0.05$;
[b] $P<0.01$;
[c] $P<0.001$ (vs. i.r. group).
* $P<0.05$ (vs. i.r.r. group).

5). Also, all the parameters of CBZ-E apparently increased with the increased CBZ dose, and the Cmax and AUC did not increase linearly.

4. Discussion

In our previous study, we found that the bioavailability of diclofenac sodium suppositories after their i.r. and i.s. administration decreased, and this was thought to be due to an increased first-pass effect. Moreover, in both rectal-resected and colostoma-constructed rabbits, the plasma concentrations of diclofenac were increased to the normal rabbit level when the dose was increased based upon the ratio of the F values. These findings demonstrate the usefulness of our developed model rabbit, and suggest that when diclofenac sodium suppositories are administered to rectal-resected and colostoma-constructed patients, the dose should be increased (Nagasawa et al., 2001). CBZ is known to be metabolized to CBZ-E by CYP3A4 and CYP3A6 in man and rabbit, respectively (Lertratanangkoon and Horning, 1982; Kerr et al., 1994; Levy and Wurden, 1995; Wilkinson, 1996; Mesdjian et al., 1999). It has been reported that the bioavailability of CBZ is 75–85%, and that the first-pass effect is negligible (Saints et al., 1991; Kerr et al., 1994). In this study, we selected CBZ, which is one of the useful co-analgesics for the treatment of neuropathic pain and is not affected by first-pass metabolism, thereby differing from the case of diclofenac, and examined the pharmacokinetics of CBZ and CBZ-E in the rectal-resected or colostoma-constructed rabbits.

As shown in Fig. 1 and Table 1, the plasma concentration–time profiles of CBZ and CBZ-E after the p.o. administration were almost the same as those previously reported in man (Saints et al., 1991; Kerr et al., 1994), and the F value of CBZ

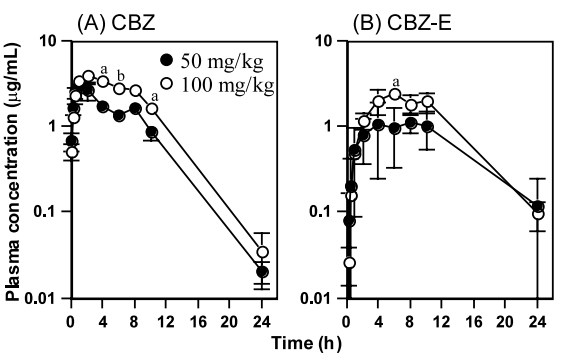

Fig. 3. Plasma concentration–time profiles of CBZ and CBZ-E after i.r.r. administration of a CBZ suppository (50 or 100 mg/kg) in rabbits with rectal-resection. Each point represents the mean ± S.E. for three rabbits. (a) $P<0.05$; (b) $P<0.01$ (vs. 50 mg/kg group).

Table 3
Pharmacokinetic parameters of CBZ and CBZ-E after i.r.r. administration of a CBZ suppository (50 or 100 mg/kg) in rabbits with rectal-resection

Parameter	CBZ		CBZ-E	
	50 mg/kg[b]	100 mg/kg	50 mg/kg[b]	100 mg/kg
Cmax (μg/ml)	3.05 ± 0.59	3.93 ± 0.71	1.18 ± 0.21	2.55 ± 0.38[a]
Tmax (h)	1.00	2.67 ± 0.67	8.67 ± 0.67	5.33 ± 0.67[a]
AUC (μg h/ml)	24.2 ± 3.3	40.7 ± 2.2[a]	17.9 ± 3.8	31.7 ± 7.0
MRT (h)	5.86 ± 0.11	6.41 ± 0.44	9.43 ± 0.25	8.58 ± 0.40

Each value represents the mean ± S.E. for three rabbits.
[a] $P < 0.05$ (vs. 50 mg/kg group).
[b] Data are cited from Table 2.

after p.o. administration was estimated to be approximately 100%. These results confirmed that the kinetics of CBZ and CBZ-E are similar in man and rabbit, and thus to investigate the pharmacokinetics of CBZ and CBZ-E in rabbits is very valid.

Following the i.r. administration of CBZ suppositories to normal rabbits, the time course of the plasma CBZ level was monophasic, differing from in the cases of i.v. and p.o. administration (Figs. 1 and 2). This was thought to be due to that in the case of i.r. administration, the distribution phase was offset by the absorption phase. The *F* value of CBZ after its i.r. administration was calculated to be 60%, this value being 75% of the in vitro release rate (about 80%) reported by Shinoda et al. (1995), whose base for CBZ suppositories was Witepsol H-15, i.e. the same as in our study. The Cmax of CBZ administered via the rectal route was less than that in the case of the oral route in non-operated rabbits. On the other hand, the Tmax value for the i.r. group was fourfold greater than that for the p.o. one (Tables 1 and 2). These results indicate that CBZ was well, but slowly, absorbed in the rectum from the suppositories.

After the i.r.r. and i.s. administration of CBZ suppositories, the plasma concentration–time profiles of CBZ and CBZ-E were similar to those in the i.r. group, but their levels were apparently lower (Fig. 2). There was a small, but significant, difference in the plasma CBZ level between the i.r.r. and i.s. groups, while the plasma CBZ-E concentrations with i.s. administration were the same as those with the i.r.r. administration. Although this inconsistency in the plasma level between the parent compound and the metabolite was thought to be due to the small difference in the plasma CBZ levels resulting in no difference in the CBZ-E levels between the two administration routes, the detailed mechanisms remain unknown. Regarding the pharmacokinetics among the i.r., i.r.r. and i.s. groups, the plasma level, Cmax, AUC and *F* value of CBZ, and the plasma level, Cmax and AUC of CBZ-E decreased in the order of i.r. > i.r.r. > i.s. (Table 2). We confirmed that the temperature (average, 38 °C) of the colostoma in the colostoma-constructed rabbits did not differ from the rectum one (average,

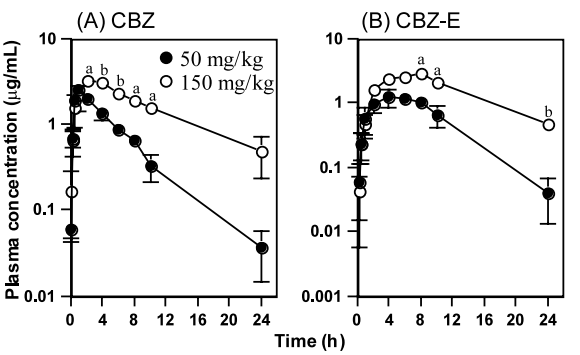

Fig. 4. Plasma concentration–time profiles of CBZ and CBZ-E after i.s. administration of a CBZ suppository (50 or 150 mg/kg) in rabbits with rectal-resection. Each point represents the mean ± S.E. for three rabbits. (a) $P < 0.05$; (b) $P < 0.01$ (vs. 50 mg/kg group).

Table 4
Pharmacokinetic parameters of CBZ and CBZ-E after i.s. administration of a CBZ suppository (50 or 150 mg/kg) in rabbits with colostoma-construction

Parameter	CBZ		CBZ-E	
	50 mg/kg[c]	150 mg/kg	50 mg/kg[c]	150 mg/kg
Cmax (μg/ml)	2.58 ± 0.06	3.47 ± 0.20[a]	1.45 ± 0.31	3.01 ± 0.48
Tmax (h)	1.00	2.67 ± 0.67	6.00 ± 1.15	5.33 ± 1.76
AUC (μg h/ml)	15.9 ± 1.6	45.0 ± 6.0[b]	14.7 ± 3.9	42.8 ± 4.6[b]
MRT (h)	7.40 ± 2.21	12.0 ± 3.3	7.49 ± 0.49	11.7 ± 0.6[b]

Each value represents the mean ± S.E. for three rabbits.
[a] $P<0.05$;
[b] $P<0.01$ (vs. 50 mg/kg group).
[c] Data are cited from Table 2.

37 °C) in the non-operated rabbits, which affects the melting rate of suppositories. Therefore, the absorption of CBZ in the upper rectum and colon was indicated to be poor. The mechanisms concerning the shortening of the Tmax of CBZ and CBZ-E in the i.r.r. and i.s. groups, and the MRT in the i.s. group have not been clarified yet (Table 2).

In our previous study (Nagasawa et al., 2001), we examined the effects of operation, that is, inflammation, etc. on the pharmacokinetics of diclofenac in rats, which is not affected by first-pass metabolism, differing from in rabbits and human subjects (Peris-Ribera et al., 1991). As a result, the plasma concentrations of diclofenac in rectal-resected rats did not change compared with those in non-operated rats. Furthermore, alfa-1 acid glycoprotein is known to increase with inflammation (Takada, 1987). Hooper et al. (1975) reported that the majority of CBZ was found to bind to albumin in plasma. Thus, we thought that the changes in the pharmacokinetics of CBZ and CBZ-E in rectal-resected rabbits observed in this study were not due to the effects of operation.

Furthermore, we investigated whether or not the decreased plasma concentrations in rectal-resected and colostoma-constructed rabbits could be reversed by increasing the administration dose. The dose for correcting the plasma levels of CBZ was decided by calculation based upon the difference in the F values between the i.r., i.r.r. and i.s. groups. In the i.r.r. group, increasing the dose from 50 to 100 mg/kg resulted in significant increases in the CBZ and CBZ-E concentrations, but their concentrations, and Cmax and AUC values were apparently lower than those in the i.r. group (Figs. 2 and 3, and Tables 2 and 3). Moreover, when the dose was increased from 50 to 150 mg/kg with i.s. administration, the plasma levels, and Cmax and AUC values of CBZ and CBZ-E significantly increased, but they did not increase to the respective values in the 50 mg/kg group (Figs. 2 and 4, and Tables 2 and 4). On the other hand, the MRT values of CBZ and CBZ-E in the i.s. group were significantly prolonged when the dose was increased to 150 mg/kg. These results

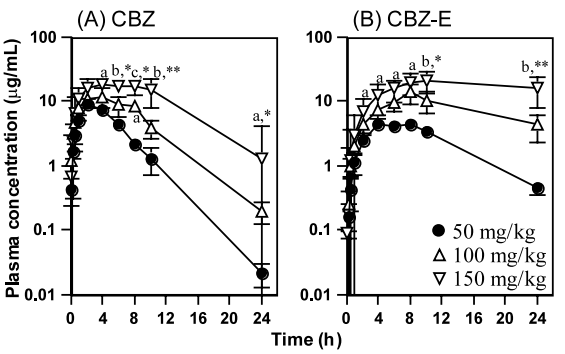

Fig. 5. Plasma concentration–time profiles of CBZ and CBZ-E after i.r. administration of a CBZ suppository (50, 100 or 150 mg/kg) in rabbits. Each point represents the mean ± S.E. for three or four rabbits. (a) $P<0.05$; (b) $P<0.01$; (c) $P<0.001$ (vs. 50 mg/kg group).*$P<0.05$; **$P<0.01$ (vs. 100 mg/kg).

Table 5
Pharmacokinetic parameters of CBZ and CBZ-E after i.r. administration of a CBZ suppository (50, 100 or 150 mg/kg) in rabbits

Parameter	CBZ			CBZ-E		
	50 mg/kg	100 mg/kg	150 mg/kg	50 mg/kg	100 mg/kg	150 mg/kg
Cmax (μg/ml)	8.88 ± 0.70	13.2 ± 3.6	19.1 ± 1.21^{a}	5.23 ± 0.22	13.9 ± 4.79	21.3 ± 3.5^{a}
Tmax (h)	2.67 ± 0.67	4.50 ± 1.26	5.33 ± 2.40	6.00 ± 1.15	8.50 ± 0.50^{a}	10.0^{b}
AUC (μg h/ml)	56.3 ± 3.8	118 ± 33.3^{a}	$282 \pm 38^{b,*}$	65.8 ± 9.3	248 ± 97	1727 ± 908^{a}
MRT (h)	5.01 ± 0.28	6.35 ± 0.11^{a}	$8.53 \pm 0.56^{c,*}$	9.87 ± 0.73	15.3 ± 2.6	74.0 ± 35.1^{a}

Each value represents the mean ± S.E. for three or four rabbits.
[a] $P<0.05$;
[b] $P<0.01$;
[c] $P<0.001$ (vs. 50 mg/kg group).
* $P<0.01$ (vs. 100 mg/kg group).

indicate that the plasma levels of CBZ could not be corrected by increase in the dose based upon the bioavailability. This phenomenon agrees to the findings of Bernus et al. (1996), Bertilsson (1978), by whom it was reported that the extent and rate of CBZ absorption is related to the dose (Bernus et al., 1996), and high doses can lead to incomplete absorption and delay in peak time, probably due to incomplete dissolution of the compound in the gastrointestinal tract (Bertilsson, 1978). As shown in Fig. 5 and Table 5, in non-operated rabbits, increasing the dose to 150 mg/kg led to non-linear kinetics of CBZ and CBZ-E, as indicated by the increased MRT values of CBZ and, especially, CBZ-E. These findings suggest that the pharmacokinetics of CBZ are linear up to the dose of 100 mg/kg and that those of CBZ-E are linear up to 50 mg/kg in the case of i.r., i.r.r. and i.s. administration of CBZ. This non-linear kinetics of CBZ and CBZ-E in rabbits is thought to be due to saturation of the elimination of CBZ and CBZ-E including the metabolism of CBZ-E to further metabolite(s) downstream of the CBZ-E metabolism pathway, because the elimination of CBZ-E was apparently delayed. Moreover, CBZ-E is known to be an active compound and to contribute to the adverse reaction of CBZ. Therefore, these findings suggest that the high dose of CBZ should be avoided and alternatively, increasing number of dose might be recommended.

In conclusion, it appears that the bioavailability of CBZ and the plasma level of CBZ-E, following the i.r.r. and i.s. administration of CBZ are decreased, and that their decreased plasma concentrations cannot be completely restored, and the elimination of CBZ and CBZ-E is retarded with an increased dose. Since the pharmacokinetics are similar to those in man, it is recommended that when increase of the plasma level of CBZ is needed, increment of the dosages should be avoided, when CBZ suppositories are administered to rectal-resected or colostoma-constructed patients.

References

Bernus, I., Dickinson, R.G., Hooper, W.D., Eadie, M.J., 1996. Dose-dependent metabolism of carbamazepine in humans. Epilepsy Res. 24, 163–172.

Bertilsson, L., 1978. Clinical pharmacokinetics of carbamazepine. Clin. Pharmacokinet. 3, 128–143.

Buyse, M., Zeleniuch-Jacquotte, A., Chalmers, T.C., 1988. Adjuvant therapy of colorectal cancer. J. Am. Med. Assoc. 259, 3571–3578.

Dahl, O., Dalene, R., Schem, B.C., Mella, D., 1999. Status of clinical hyperthermia. Acta Oncol. 38, 863–873.

Douilard, J.Y., Cunningham, D., Roth, A.D., Navarro, M., Lames, R.D., Karasek, P., Jandik, P., Iveson, T., Carmichael, J., Alakl, M., Gruia, G., Awad, L., Rougier, P., 2000. Irinotecan combined with fluorouracil compared with fluorouracil alone as first-line treatment for metastatic colorectal cancer: a multicentre randomised trial. Lancet 355, 1041–1047.

Ewoud, J.H., Albertus, G.B., Douwe, D.B., 1991. Pharmacokinetics of rectal drug administration. Part 1. Clin. Pharmacokinet. 21, 11–26.

Hojsted, J., Rubeck-Petersen, K., Rask, H., Bigler, D., Christensen, C.B., 1990. Comparative bioavailability of a morphine suppository given rectally and in a colostomy. Eur. J. Clin. Pharmacol. 39, 49–50.

Hooper, W.D., Dubetz, D.K., Bochner, F., Cotter, L.M., Smith, G.A., Eadie, M.J., Tyrer, J.H., 1975. Plasma protein binding of carbamazepine. Clin. Pharmacol. Ther. 17, 433–440.

Kerr, B.M., Thummel, K.E., Wurden, C.J., Klein, S.M., Kroetz, D.L., Gonzales, F.J., Levy, R.H., 1994. Human liver carbamazepine metabolism, role of CYP3A4 and CYP2C8 in 10,11-epoxide formation. Biochem. Pharmacol. 47, 1969–1979.

Kloke, M., Höffken, K., Olbrich, H., Schmidt, C.G., 1991. Anti-depressants and anti-convulsants for the treatment of neuropathic pain syndrome in cancer patients. Oncology 14, 40–43.

Lertratanangkoon, K., Horning, M.G., 1982. Metabolism of carbamazepine. Drug Metab. Dispos. 10, 1–10.

Levy, R.H., Wurden, C.J., 1995. Carbamazepine, interactions with the other drugs. In: Levy, R.H., Mattson, R.H., Meldrum, B.S. (Eds.), Antiepileptic Drugs, 4th ed. Raven Press, New York, pp. 543–554.

Maeda, T., Takenaka, H., Yamahira, Y., Noguchi, T., 1977. Use of rabbits for GI drug absorption studies. J. Pharm. Sci. 66, 69–73.

Mesdjian, E., Seree, E., Charvet, B., Mirrione, A., Bourgarel-Rey, V., Desobry, A., Barra, Y., 1999. Metabolism of carbamazepine by CYP3A6: a model for *in vitro* drug interaction studies. Life Sci. 64, 827–835.

Nagasawa, K., Nakanishi, H., Matsuda, T., Takara, K., Ohnishi, N., Yokoyama, T., Fujimoto, S., 2001. Pharmacokinetics of diclofenac after its intrarectal and intracolostomal administration to rabbits with rectal resection or colostoma construction. Biopharm. Drug Dispos. 22, 31–39.

Ohnishi, N., Yonekawa, Y., Nakasako, S., Nagasawa, K., Yokoyama, T., Yoshioka, M., Kuroda, K., 1999. Studies on interactions between traditional herbal and western medicines. I. Effects of Sho-seiryu-to on the pharmacokinetics of carbamazepine in rats. Biol. Pharm. Bull. 22, 527–531.

Peris-Ribera, J.E., Torres-Molina, F., Carcia-Carbonell, M.C., Aristorena, J.C., Pla-Delfina, J.M., 1991. Pharmacokinetics and bioavailability of diclofenac in the rat. J. Pharmacokinet. Biopharm. 19, 647–665.

Saints, M., Thummel, K.E., Levy, R.H., 1991. Metabolism of carbamazepine by hepatic and intestinal P4503A4. Pharm. Res. 8, S239.

Scheithauer, W., Rosen, H., Kornek, G.-V., Sebesta, C., Depisch, D., 1993. Randomised comparison of combination chemotherapy plus supportive care with supportive care alone in patients with metastatic colorectal cancer. Br. Med. J. 306, 752–755.

Schipper, H., Clinch, J., McMurray, A., Levitt, M., 1984. Measuring the quality of life of cancer patients: the functional living index-cancer: development and validation. J. Clin. Oncol. 2, 472–483.

Shinoda, M., Akita, M., Hasegawa, M., Nadai, M., Hasegawa, T., Nabeshima, T., 1995. Pharmaceutical evaluation of carbamazepine suppositories in rats. Biol. Pharm. Bull. 18, 1289–1291.

Storey, P., Trumble, M., 1992. Rectal doxepin and carbamazepine therapy in patients with cancer. N. Engl. J. Med. 18, 1318–1319.

Takada, K., 1987. Basic and Clinical Pharmacokinetics. Yakugyojihosha, Tokyo, pp. 118–122.

The Ministry of Health, Labour and Welfare Website, http://www.mhlw.go.jp/, 4 February 2002.

Dutch Deep Hyperthermia Group, van der Zee, J., Gonzalez, G.D., van Rhoon, G.C., van Dijk, J.D., van Putten, W.L., Hart, A.A., 2000. Comparison of radiotherapy alone with radiotherapy plus hyperthermia in locally advanced pelvic tumours: a prospective, randomized, multicentre trial. Lancet 355, 1119–1125.

Walter, L.O., 1990. Carbamazepine suppository. Neurology 40, 1472.

Wilkinson, G.R., 1996. Cytochrome P4503A (CYP3A) metabolism: prediction of in vivo activity in humans. J. Pharmacokinet. Biopharm. 24, 475–490.

World Health Organization, 1996. Cancer Pain Relief, 2nd ed. World Health Organization.

Zech, D.F.J., Grond, S., Lynch, J., Hertel, D., Lehmann, K.A., 1995. Validation of World Health Organization guidelines for cancer pain relief: a 10-year prospective study. Pain 63, 65–76.