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Characteristics of intestinal absorption of adinazolam and in vivo evaluation of oral sustained release tablets of adinazolam in beagle dogs

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Summary

The characteristics of intestinal absorption of adinazolam in rats were investigated using an in situ intestinal loop method on the upper, middle and lower parts of the small intestine, and colon. The disappearance of the drug from the intestinal lumen was measured to estimate the absorption. Adinazolam was readily absorbed from various sites of the small intestine and colon indicating no absorption site specificity. Absorption followed first-order kinetics with a disappearance half-life of less than 15 min. Dose dependency or saturation of the absorption were not observed in the experimental concentration range of 5–1000 μg/ml. In one of the experiments to investigate the effect of postprandial administration, the intestinal absorption of adinazolam decreased somewhat when the administered solution contained either 5% bile powder or 5% polysorbate 80. In the biopharmaceutic study, the sustained release (SR) tablet significantly prolonged the plasma adinazolam concentration in beagle dogs in comparison to that of the rapidly disintegrating conventional tablets (conventional tablet) of adinazolam. The mean residence time (MRT) of adinazolam from the SR tablets was about 5-times greater than that of the conventional tablets.

Introduction

Adinazolam mesylate (adinazolam) is a new triazolobenzodiazepine that has the pharmacological properties of both an anxiolytic and antidepressant (Hester, 1979, 1980; Hester et al., 1980). Since the rapid elimination of adinazolam from blood after intravenous injection in the preliminary animal study indicated that a short duration of in vivo activity required frequent dosing, an oral sustained release (SR) formulation was desirable.

According to the guidelines for 'Design and Evaluation of Oral Sustained-Release Dosage Form' issued in Japan in 1987, the following biopharmaceutical studies are required to characterize the intestinal absorption of the active drug after oral administration: (1) location of major absorption sites or specificity in the site of absorption; (2) absorption rate; (3) whether absorption is non-linear due to saturation of absorption;

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(4) effect of postprandial administration on the absorption rate; and (5) the presence or absence of inactivation or metabolism of the drug in the gastrointestinal tract or its mucosa.

In the present study, therefore, we investigated the absorption characteristics of adinazolam in rats using in situ intestinal loop methods, as follows: (1) the absorption of adinazolam from various sites of rat intestine was observed to determine the absorption site specificity; (2) the effect of dose on the absorption was observed in order to estimate the absorption mechanism of the drug; and (3) the effect of bile or polysorbate 80 on the absorption of the drug was monitored to estimate the postprandial effect. Further, the evaluation of prototype SR tablets was performed in dogs by monitoring plasma adinazolam concentration, in comparison to rapidly disintegrating conventional tablets (conventional tablet).

Materials and Methods

Materials

Adinazolam mesylate milled (lot no. 64191) and alprazolam (lot no. 11928-DOP-137B) were supplied by The Upjohn Co. (MI, U.S.A.). Bile powder was purchased from Wako Pure Chemical Industries Ltd (Osaka, Japan). Polysorbate 80 (Tween 80) was obtained from Nikko Chemical Co., Ltd (Tokyo, Japan). Hydroxypropylmethylcellulose (HPMC) 2910 JP 4000 cps was purchased from Shin-Etsu Chem. Co., Ltd (Tokyo, Japan). Corn starch obtained from Nihon-Syokuhin-kako (Tokyo, Japan), and lactose purchased from Foremost Inc. (CA, U.S.A.) were JP and USP grade, respectively.

Animals

Male Sprague-Dawley rats, weighing 200–250 g, were fasted for 16 h prior to the experiment, but water was given ad libitum. Eight male beagle dogs, each weighing 10–11 kg, were used under postprandial conditions described later.

Preparation of drug solution administered in rats

The drug solution was prepared with isotonic phosphate buffer (pH 6.8). The concentration range of adinazolam in the solution was 5–1000 μg/ml.

In situ loop technique

After anesthetizing rats with sodium pentobarbital (30 mg/kg, i.p.), middle abdominal incision was performed. About 10 cm of intestinal loop was prepared and 1 ml of the drug solution was administered (Nishihata et al., 1986). The abdomen was then closed. The intestinal loop was excised at a designated time to determine the remaining amount of adinazolam. In the case of the absorption site specificity study, the concentration of drug solution administered was fixed at 250 μg/ml (1 mg/kg) at all parts of the intestinal loop. This dose is equivalent to the maximum daily dose in humans. The samples were collected at 5, 15 and 30 min after administration. In the case of the dose dependency study, the samples were collected at 2, 5, 10, 15 min for 5 μg/ml, 5, 15, 30 min for 50 and 250 μg/ml, and 15, 30, 60 min for 1000 μg/ml solution. After incision, the mucosa of the loop was rinsed with 15 ml of saline three times and the rinse solution was combined. The intestinal absorption characteristics of adinazolam were investigated at four different portions of the intestine: upper, middle and lower parts of the small intestine, and colon.

The combined rinse solution of the loop segment was diluted in a volumetric flask with saline to a total volume of 100 ml. After centrifugation at 3000 rpm for 10 min, 1 ml of the supernatant was collected and 2 ml of acetonitrile was added gradually with mixing. Then 200 μl of the internal standard solution containing about 250 ng of alprazolam was added and thoroughly mixed. After centrifugation at 3000 rpm for 10 min, 2 ml of the supernatant was collected and evaporated by nitrogen gas. The residue was dissolved with 500 μl of the mobile phase and used as the assay sample for high-performance liquid chromatography (HPLC).

Formulations

Prototype oral SR tablets were developed using a hydrophilic polymer (HPMC 2910 4000 cps) to control the rate of drug release from tablets. The formulation, containing 15 mg of drug per

tablet, was designed to have a range of in vitro drug release rates as described in Results. Preparation of SR tablets was performed briefly as follows: adinazolam was granulated with corn starch using wet granulation technique, and then mixed with the appropriate amount of HPMC and lactose. Blended materials were compressed with a rotary compressing machine (Kikusui, Kyoto) to obtain the SR tablets.

The conventional tablets with rapid disintegration were also employed for in vivo bioavailability study.

In vitro dissolution study

The in vitro dissolution study was performed according to the method described in the JP XI dissolution test. The apparatus and conditions employed were as follows: The dissolution apparatus with an autosampler (Toyama Kagaku, Tokyo) was connected to a UV spectrophotometer (Shimadzu, Kyoto) and a personal computer (NEC, Tokyo). The machine system was adapted from the JP XI rotary basket method. Specifically, dissolution media, i.e., 900 ml of JP XI disintegration medium (pH 1.2), 900 ml of 0.1 M sodium phosphate buffer (pH 4.0), and 900 ml of JP XI disintegration medium (pH 6.8), were used at 37°C. The rotation speed of the basket employed was 100 rpm.

In the procedure, one tablet was used in each dissolution test, and each formulation and each condition were tested three times. As the apparatus with an autosampler and an autodetector was employed, the amounts of adinazolam dissolved were monitored automatically with a personal computer, and were assayed using the UV spectrophotometer. UV detection was performed at 246 nm for the sample in both JP XI disintegration medium (pH 6.8) and 0.1 M sodium phosphate buffer (pH 4.0), and at 263 nm for the sample in JP XI disintegration medium (pH 1.2).

In vivo absorption study of adinazolam in beagle dogs after oral administration

In this study, eight male beagle dogs, each weighing 10–11 kg, were used and the study was performed in cross-over fashion with the SR tablets and conventional tablets, at a dose of adinazolam of 15 mg for oral administration. Intravenous administration was performed using 5 mg adinazolam dissolved in 1 ml of saline. The drug was administered 0.5 h after feeding 250 g of assorted feed at 8:30 a.m. on the day of the experiment.

After oral administration of the SR tablets, 5 ml of blood was collected at 0.5, 1, 2, 3, 4, 6, 8, 12, and 24 h. On the other hand, after oral administration of the conventional tablet or intravenous administration of saline solution, 5 ml of blood was collected at 0.25, 0.5, 1, 2, 3, 4, 6, and 8 h. Blood samples were centrifuged at 3000 rpm for 10 min, and the plasma was transferred to test tubes and stored at −20°C prior to assay.

The dog plasma was assayed as follows: 1.5 ml of plasma was mixed well with 0.5 ml of internal standard solution and 0.5 ml of Na_2HPO_4 in a conical tube with a stopper. 6 ml of diethyl ether was added to the above aqueous phase, and the mixture was shaken for 10 min. After centrifugation at 3000 rpm for 10 min, 5 ml of organic solvent phase was collected in a conical tube and dried under nitrogen gas at room temperature. The dried residue was redissolved in 150 μl of mobile phase for HPLC assay. The correlation coefficient of regression analysis for calibration curve in the HPLC assay method was 0.9999 ($y = 3.65x + 3.62$), and the standard deviation of three measurements of each standard sample (2, 20, 100 and 200 ng/ml) was within the 5% of average. In this assay method, the lower detection limit was 2 ng/ml of adinazolam in dog plasma sample.

HPLC assay of adinazolam

The adinazolam content of the sample was assayed by HPLC: A liquid chromatograph (Model LC-6A, Shimadzu) equipped with a UV detector (SAD-6A, Shimadzu), autoinjector (SIL-6B, Shimadzu), system controller (SCL-6B, Shimadzu) and chromatopac (CR-4A, Shimadzu) was used. The dimensions of the separation column were 4.6 mm i.d. × 125 mm length, and it contained reverse-phase column packing (LiChro CART Superspher 60 RP-8e). The mobile phase was a mixture of 0.05 M ammonium acetate buffer (700 ml) adjusted to pH 5.5, acetonitrile (300 ml)

and tetrahydrofuran (20 ml). The flow rate was 0.8 ml/min. Adinazolam was detected at 246 nm. A typical chromatogram of adinazolam is shown in Fig. 1A, and the calibration curve in Fig. 1B. Preparation of the assay sample is described above for the content assay. A 50 μl sample was injected into the column.

Statistical analysis

Statistical analysis were performed by Fisher's pairing t-test.

Results

Studies on the location of the major absorption site and on the absorption rate

The disappearance profiles of adinazolam from the each intestinal loop after administration of adinazolam solution at a concentration of 250 μg/ml are shown in Fig. 2 (C-1–4). The intestinal loops examined are classified as upper (C-2), middle (C-1), and lower (C-3) parts of the small intestine, and the colon (C-4, including a part of the rectum). Good absorption characteristics of adinazolam, as measured by disappearance of the drug, were observed at the upper, middle and lower parts of the small intestine as well as the colon. The disappearance of adinazolam occurred according to first-order kinetics as shown in Eqn 1. Apparent disappearance rate constants (k_a) were calculated by linear regression analysis from the slope of the straight line obtained in Fig. 2 according to Eqn 2:

$$d(A/A_0)/dt = -k_a(A/A_0) \quad (1)$$

$$\ln(A/A_0) = -k_a t \quad (2)$$

where A_0 and A represent the amounts of adinazolam administered and remaining at time t after administration, respectively. The disappearance half-life ($T_{1/2}$) of adinazolam from the loop was obtained from the following equation (Eqn 3):

$$T_{1/2} = 0.693/k_a \quad (3)$$

Both the disappearance rate constants and half-life of adinazolam at each site of intestine are summarized in Table 1. No significant difference in the disappearance rate constant was observed among each part of the intestine tested.

Dose dependency of the absorption from the middle part of small intestine

The disappearance profiles of adinazolam from the loop of the middle small intestine after administration at various doses are shown in Fig. 2 (A, B, C-1 and D). The concentration range of adinazolam examined was varied from 5 to 1000 μg/ml. It was also confirmed that the disappearance of adinazolam occurred according to first-order kinetics at all doses. As shown in Table 1, no significant differences in the disappearance rate constants of adinazolam were observed among the different concentrations tested.

Effect of bile on the absorption from the middle part of small intestine

In order to estimate the postprandial effect on the absorption of adinazolam, the influence of

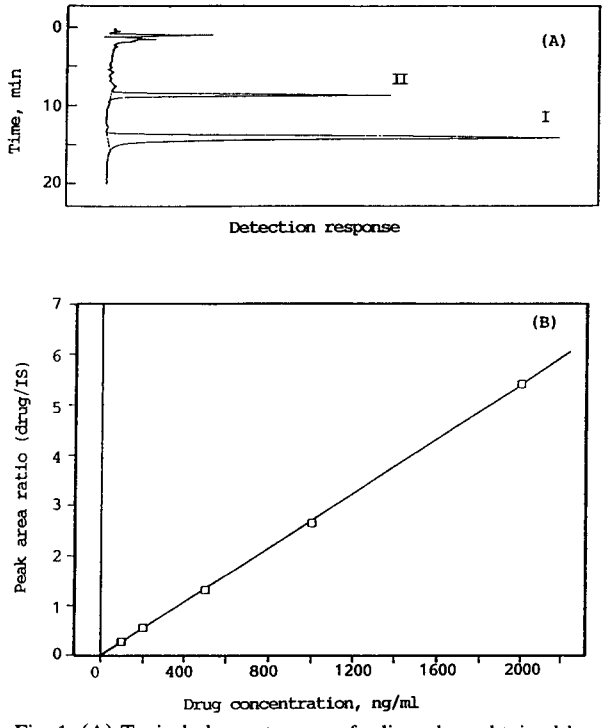

Fig. 1. (A) Typical chromatogram of adinazolam obtained by HPLC. I, adinazolam; II, alprazolam as the internal standard. (B) Calibration curve of adinazolam in the HPLC assay method. Regression analysis: $y = 3.69x + 6.66$ ($r = 0.9999$).

either bile or polysorbate 80 was investigated. The disappearance profiles of adinazolam from the loop of the middle small intestine after administration at a concentration of 250 μg/ml with either bile powder or polysorbate 80 are shown in Fig. 3. The concentration of bile powder in the administered solution was 1 or 5% w/v, and that of polysorbate 80 was 5% w/v. The disappearance of adinazolam was delayed by the addition of both 1 and 5% w/v of bile powder with a significant difference in the disappearance rate constant (Table 2). As shown in Fig. 3 and Table 2, the disappearance of adinazolam was also significantly delayed by the addition of polysorbate 80 in the administered solution.

In vitro dissolution of adinazolam from SR tablets

As shown in Fig. 4A, the complete dissolution of adinazolam from the conventional tablets was observed within 5 min in the media tested (Table

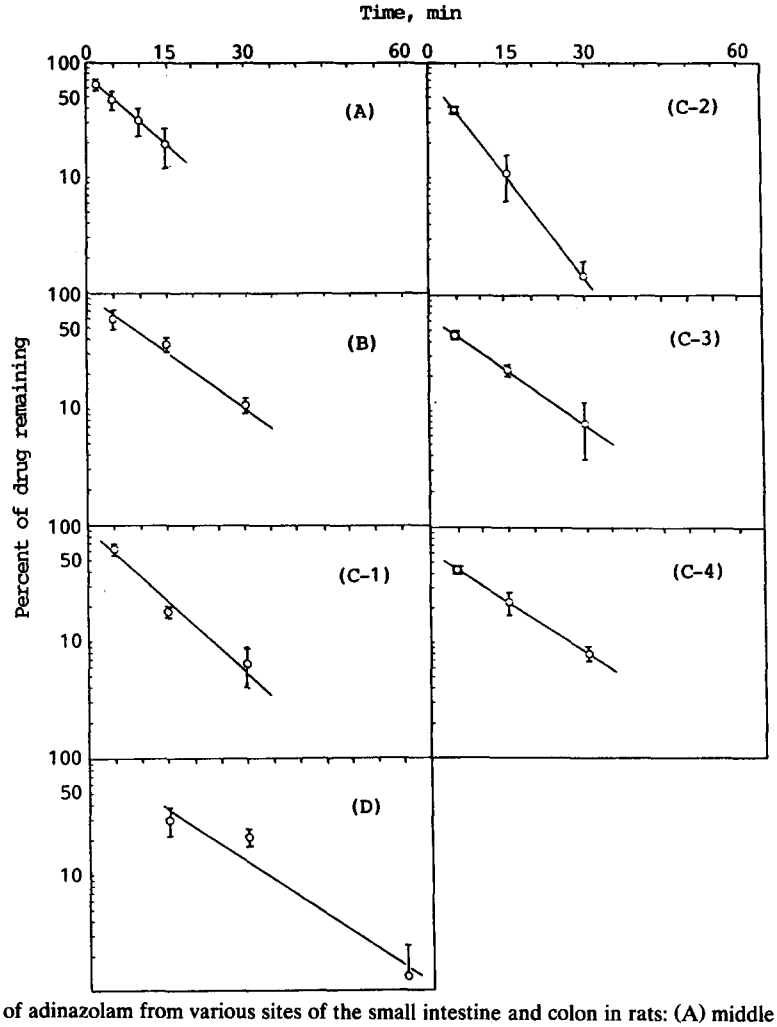

Fig. 2. Disappearance of adinazolam from various sites of the small intestine and colon in rats: (A) middle part, $y = -2.36x + 1.88$ ($r = 0.9991$); (B) middle part: $y = -1.81x + 1.96$ ($r = 0.9931$): (C-1) middle part, $y = -2.31x + 1.93$ ($r = 0.9857$): (D) middle part, $y = -1.88x + 2.07$ ($r = 0.9728$): (C-2) upper part, $y = -3.44x + 1.88$ ($r = 0.9998$); (C-3) lower part, $y = -1.83x + 1.80$ ($r = 0.9999$); (C-4) colon, $y = -1.72x + 1.77$ ($r = 0.9999$). Concentration of adinazolam: (A) 5 μg/ml; (B) 50 μg/ml; (C-1–C-4) 250 μg/ml; (D) 1000 μg/ml. 1 ml of the drug solution was administered to each loop. Each value represents the mean ± S.D. ($n = 3$). Regarding symbols without error bars, standard deviations (bars) are within symbols.

TABLE 1

Parameters for the disappearance of adinazolam from various sites of rat intestine after administration of 1 ml drug solution

Absorption site	Concentration of drug solution (μg/ml)	k_a (h^{-1}) [a]	$T_{1/2}$ (min) [a]
Upper part	250	7.9±1.6	5.4±1.1
Middle part	5	5.4±2.3	7.8±3.9
	50	4.1±0.8	10.2±2.2
	250	5.3±1.2	7.8±1.9
	1000	4.3±1.6	9.6±3.9
Lower part	250	4.2±1.5	9.6±4.4
Colon	250	4.0±0.4	10.8±1.2

Each value represents the mean±S.D. ($n = 3$). [a] No significant difference was observed among absorption sites and different concentrations tested.

3). The in vitro dissolution profiles of the SR tablets are shown in Fig. 4B. The times required for dissolution of 25, 50, and 75% of adinazolam from the SR tablets are summarized in Table 3. Regarding SR tablets, faster dissolution of adinazolam was observed in the media at low pH. To characterize the in vitro dissolution of adinazolam from the tablet, a model-independent method based on moment analysis which was reported by Tanigawara et al. (1982a) was employed. With this method, the dissolution of drug was defined by the mean in vitro dissolution time (MDT), which was determined using Eqn 4, as reported previously:

$$\mathrm{MDT} = \int_0^\infty t(\mathrm{d}m/\mathrm{d}t)\,\mathrm{d}t \Big/ \int_0^\infty (\mathrm{d}m/\mathrm{d}t)\,\mathrm{d}t \qquad (4)$$

where m is the mass of drug dissolved in solution at time t. MDT was calculated in Eqn 4 by using a personal computer. The results are summarized in Table 3.

In vivo absorption study in beagle dogs

Rapid intestinal transit is not appropriate for oral SR tablets, since the tablets may pass rapidly through the absorption site before completely releasing the drug. Since it has been reported that the intestinal transit time in beagle dogs under fasted conditions is often less than 3 h (Lui et al., 1986), the use of beagle dogs under such conditions is not appropriate to evaluate the SR tablets of adinazolam. In the preliminary study of this program, the plasma profiles of adinazolam

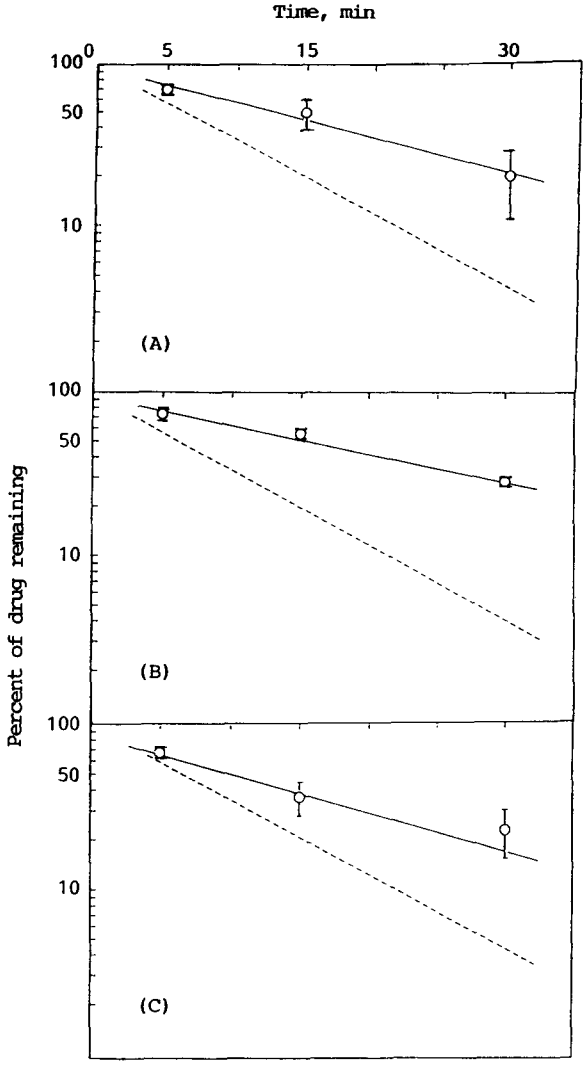

Fig. 3. Effects of bile powder and polysorbate 80 on the disappearance of adinazolam from the middle part of small intestine in rats: (A) 1% bile powder, $y = -1.11x + 1.89$ ($r = 0.9820$); (B) 5% bile powder, $y = -1.00x + 1.97$ ($r = 0.9912$); (C) 5% polysorbate 80, $y = -1.33x + 1.98$ ($r = 0.9896$) (---) control; $y = -2.31x + 1.93$ ($r = 0.9857$). The concentration of adinazolam was 250 μg/ml. 1 ml of the drug solution was administered to each loop. Each value represents the mean± S.D. ($n = 3$). Regarding symbols without error bars, standard deviations (bars) are within symbols.

TABLE 2

Parameters for the disappearance of adinazolam from the middle part of rat small intestine after administration of 1 ml drug solution with bile powder and polysorbate 80

Surfactant	Concentration of drug solution (μg/ml)	k_a (h^{-1})	$T_{1/2}$ (min)
Control (without surfactant)	250	5.3 ± 1.2	7.8 ± 1.9
1% bile powder	250	2.6 ± 0.9 [a]	16.2 ± 7.5
5% bile powder	250	2.3 ± 0.2 [a]	18.0 ± 1.4
5% polysorbate 80	250	3.1 ± 1.2 [a]	13.8 ± 5.8

Each value represents the mean ± S.D. ($n = 3$). [a] $p < 0.05$ vs control.

in fasted dogs after oral administration of SR tablets were investigated. As shown in Fig. 5, plasma adinazolam concentration was not maintained under fasted conditions, probably as described with rapid intestinal transit in dogs under fasted conditions. When the SR tablet reaches the large intestine, it is not expected to become exposed to a large enough volume of intestinal fluid which is the driving force for drug release from the tablets.

The plasma adinazolam concentration profiles in dogs after oral administration of the SR tablet at a dose of 15 mg were compared with those after administration of the conventional tablets at a dose of 15 mg (Fig. 5). The pharmacokinetic parameters obtained from the plasma concentration profiles in dogs are summarized in Table 4. A significant decrease in the maximum plasma adinazolam concentration (C_{max}) and a significant delay in the time (T_{max}) to reach C_{max} were observed after administration of the SR tablet in comparison with those after the administration of the conventional tablet. No significant differences were observed in the area under the curve of plasma adinazolam concentration (AUC) determined using Eqn 5 (Yamaoka et al., 1978), and in the extent of bioavailability (EBA) determined using Eqn 6 (Yamaoka et al., 1978) between the SR and conventional tablets:

$$AUC = \int_0^\infty C_p dt \quad (5)$$

$$EBA = AUC_{po}DOSE_{iv}/AUC_{iv}DOSE_{po} \quad (6)$$

where C_p is the drug concentration in plasma at

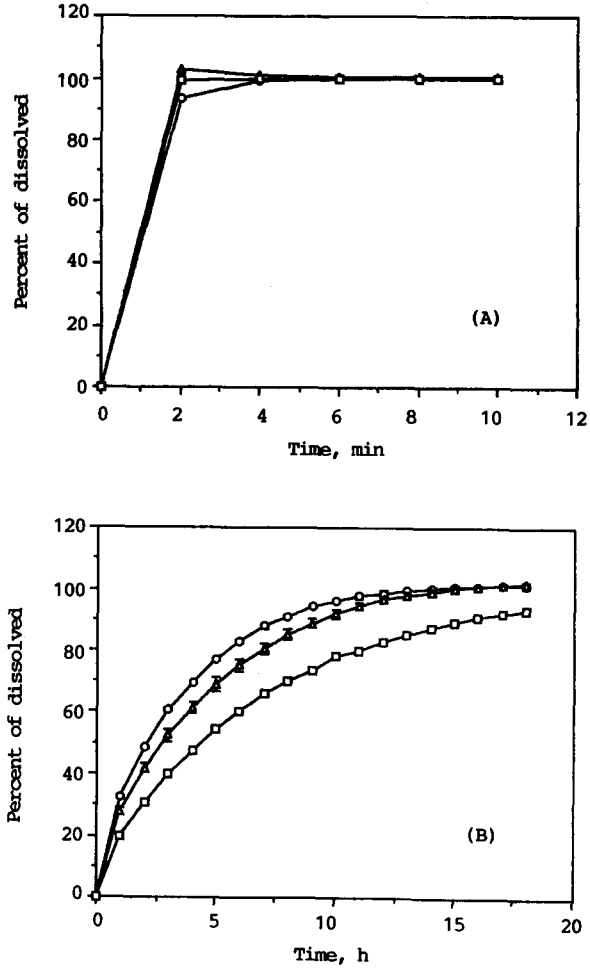

Fig. 4. Dissolution profiles of adinazolam from conventional tablets (A) and SR tablets (B) used in the dog study. (○) In JPXI disintegration medium (pH 1.2), (△) in 0.1 M sodium phosphate buffer (pH 4.0), (□) in JPXI disintegration medium (pH 6.8). Each value represents the mean ± S.D. ($n = 3$). Regarding symbols without error bars, standard deviations (bars) are within symbols.

TABLE 3

Time required for adinazolam dissolution of 25, 50 and 75%, and MDT with sustained release (SR) tablets

Condition and tablet	Dissolution time (min)				MDT (h)
	25%	50%	75%	100%	
In JP XI disintegration medium (pH 6.8)					
SR	88.0 ± 2.2	269.7 ± 13.4	588.5 ± 19.5		6.3 ± 0.1
Conventional				< 5	
In 0.1 M sodium phosphate buffer (pH 4.0)					
SR	51.1 ± 3.2	163.8 ± 13.0	346.7 ± 24.4		4.2 ± 0.3
Conventional				< 5	
In JP XI disintegration medium (pH 1.2)					
SR	39.8 ± 0.6	128.4 ± 2.0	280.0 ± 5.4		3.4 ± 0.1
Conventional				< 5	

Each value represents the mean ± S.D. ($n = 3$).

time t. $DOSE_{po}$ and AUC_{po} are the dose and AUC after oral administration, and $DOSE_{iv}$ and AUC_{iv} denote the dose and AUC after intravenous administration, respectively. AUC was calculated by the model-independent trapezoidal integration method using a personal computer. AUC for infinite time was obtained by single-exponential extrapolation of the terminal phase of the plasma adinazolam concentration curve.

To characterize the biopharmaceutics of adinazolam after administration of tablets, a model-independent method, based on moment analysis, was employed as reported by Yamaoka et al. (1978). In this method, the behavior of drug in

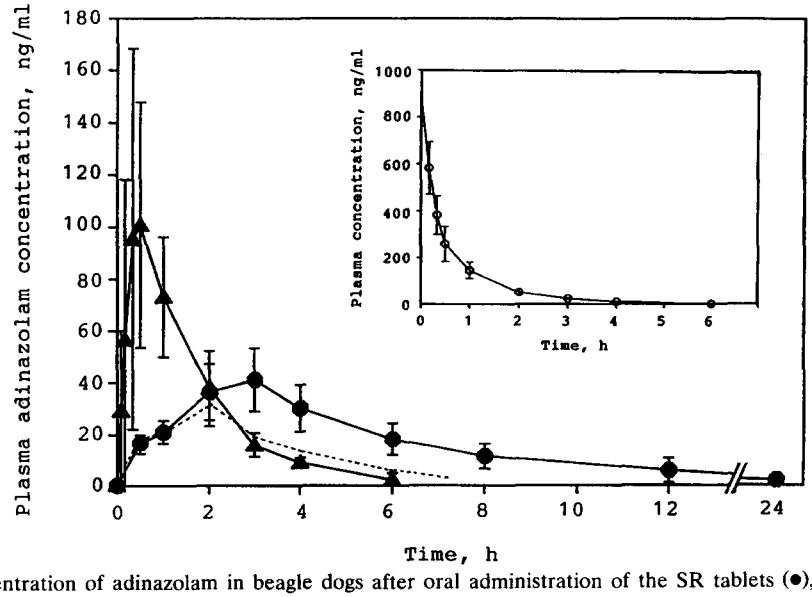

Fig. 5. Plasma concentration of adinazolam in beagle dogs after oral administration of the SR tablets (●), and the conventional tablets (▲) of adinazolam at a dose of 15 mg, under the postprandial condition described in Materials and Methods. The broken line represents the data after administration of the sustained release tablet under fasting conditions. For the intravenous study (○), 5 mg of adinazolam in 1 ml of saline was administered. The study was performed in a cross-over fashion with eight dogs. Each value represents the mean ± S.D..

TABLE 4

Pharmacokinetic parameters of adinazolam after intravenous or oral administrations in beagle dogs

Dosage form	Dose (mg)	AUC (ng h ml^{-1})	C_{max} (ng ml^{-1})	T_{max} (h)	MRT (h)	MAT (h)	$T_{1/2}$ (h)	EBA (%)
Intravenous administration								
Saline	5	451.3 ± 74.8	-	-	1.0 ± 0.1	-	0.4 ± 0.1	-
Oral administration								
(1) Conventional tablet								
	15	190.2 ± 50.6	130.0 ± 66.1	0.6 ± 0.3	1.8 ± 0.4	0.9 ± 0.4	0.8 ± 0.5	14.5 ± 4.4
(2) Sustained release tablet								
	15	278.2 ± 88.5	43.1 ± 11.9 [a]	2.6 ± 0.5 [a]	8.1 ± 4.1 [a]	7.1 ± 4.1 [a]	2.9 ± 1.4 [a]	21.3 ± 7.1

Each value represents the mean ± S.D. ($n = 8$). [a] $p < 0.05$ vs conventional tablets.

plasma was defined by means of the in vivo residence time (MRT) determined using Eqn 7:

$$\text{MRT} = \int_0^\infty tC_p \, dt / \int_0^\infty C_p \, dt = \text{AUMC/AUC} \tag{7}$$

where C_p is the drug concentration in plasma at time t. MRT was obtained from the AUC and the area under the first moment curve (AUMC) for infinite time. The AUMC to the last measured plasma concentration was calculated according to the linear trapezoidal rule with addition of the correction term after the last measured point to infinity. The results are summarized in Table 4. The MRT of adinazolam after administration of the SR tablet was about 5-times greater than that after administration of the conventional tablet. This result indicates that the SR tablet maintained the plasma adinazolam concentration for an extended period of time.

It has also been suggested by Tanigawara et al. (1982b) that the mean absorption time (MAT) can be estimated with Eqn 8:

$$\text{MAT} = \text{MRT}_{po} - \text{MRT}_{iv} \tag{8}$$

where MRT_{po} and MRT_{iv} are the MRT after oral and intravenous administrations, respectively.

MAT after administration of the SR tablet was about 9-times longer than that after administration of the conventional tablet (Table 4).

Discussion

Because the oral SR formulation is designed to deliver the drug gradually into the body, drugs should have the following absorption characteristics: (1) no site specificity of intestinal drug absorption to reduce the effect of intestinal transit time; (2) rapid absorption rate from intestinal tract in comparison to the dissolution rate from SR tablet; and (3) no specific absorption mechanism so that the apparent drug absorption is controlled by the release rate of drug from the designed formulation.

Adinazolam was absorbed rapidly from rat intestine, and its disappearance half-life was less than 15 min. The absorption of adinazolam from various sites of small intestine and colon occurred apparently according to first-order kinetics. It was also confirmed that there is no specific absorption site for the intestinal absorption of adinazolam in the intestine.

The apparent absorption kinetics and the absorption rate of adinazolam were not affected by the dose administered to the loops, and there was no saturation of absorption even at the maximum dose examined (up to 1000 μg/ml in the admin-

istered solution). All of these results suggest that the absorption mechanism of adinazolam is passive diffusion. The absorption characteristics of adinazolam obtained indicate that this drug is suitable for an SR formulation.

It is well known that the intestinal absorption of poorly water-soluble drugs is enhanced by bile salts secreted postprandially (Amidon et al., 1982). Bile salts increase the apparent solubility of poorly water soluble drugs by including the drug into micellar complexes or emulsions. On the other hand, there is a little information on the reduction of drug absorption by bile salts (Levy et al., 1964). Adinazolam is very soluble in water (> 100 mg/ml) and readily absorbed from rat small intestine. Since it is also considered that adinazolam is involved in either a micellar complex or emulsion with bile salts or polysorbate 80, the decreased absorption of adinazolam on the addition of either bile or polysorbate 80 may be explained as follows: (1) the decrease in concentration of the free form of the drug results in a decrease in the apparent absorption rate constant as it is considered that the passive transport of drug depends on the drug concentration in the free form; and (2) even when other mechanisms, including the transport of drug from vehicle directly to the intestinal epithelium without the dissolution step into intestinal fluid, are involved in the absorption mechanism (Amidon et al., 1982), the absorption rate by these mechanisms should probably occur very slowly in comparison to the absorption rate of the free form in intestinal fluid. In the present study, it may be also considered that the degree of reduction in the absorption rate constant of adinazolam on the addition of bile or polysorbate 80 does not influence the design of oral SR tablets, since the absorption of adinazolam occurs rapidly even in the presence of bile or polysorbate 80. Thus, the bile secreted postprandially does not seem to influence the design of oral sustained release formulations of adinazolam.

In the in vivo absorption study in beagle dogs, the plasma adinazolam concentration after oral administration of the SR tablet was significantly prolonged, in comparison to that after the oral administration of the conventional tablets. The increase in MRT value after administration of the SR tablet, which was more than 5-times greater than that of the conventional tablet, seems to be due to the apparent slow absorption. This was represented by the high values of MAT. This apparent slow absorption also appears to be due to the slow dissolution of adinazolam from the SR tablets. The results obtained from the in vivo study indicate that the sustained medication of adinazolam is achieved by the administration of the SR tablets, used in the present study.

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