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Preparation and pharmacological evaluation of captopril sustained-release dosage forms using oily semisolid matrix

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Summary

The stability of captopril in the gastrointestinal (GI) tract was estimated by means of in vitro experiments to clarify the reasons why bioavailability of captopril was reduced when administered after meals. It was found that captopril became dramatically unstable in the presence of food, and that the addition of ascorbic acid to the system improved its stability. Oily semisolid matrix (OSSM) and enteric coated granules, ascorbic acid was formulated in both dosage forms, were prepared and administered to beagle dogs to ascertain the stabilization effect in vivo. Both prolonged-action dosage forms showed bioavailability improved, but ascorbic acid worked much more effectively with OSSM. The time courses of captopril plasma concentration, inhibition of angiotensin-converting enzyme (ACE) activity and the inhibition of pressor response to angiotension I (AI) were measured following single oral administration of captopril OSSM and conventional tablets (25 mg/T × 2) to non-fasting beagle dogs. The OSSM contained 50 mg of captopril and 250 mg of ascorbic acid. The beagle dogs were pretreated with i.v. administration of AI to obtain a simulated hypertensional state. The OSSM showed longer pharmacological action of captopril than the conventional tablets. The OSSM maintained more than 80% inhibition of ACE activity for over 8.5 h, while conventional tablets could maintain the same effect for only 2.5 h.

Introduction

An oral sustained-release dosage form of captopril using oily semisolid matrix (OSSM) was reported previously (Seta et al., 1988). In the OSSM, fine captopril crystals were suspended in an oily semisolid base composed of edible (soybean) oil and a thickening agent (glyceryl monostearate). Captopril OSSM showed the best bioavailability among the prolonged-action products evaluated, which consisted of coated slow-release (CSR) granules, modified release tablets, enteric coated granules and OSSM itself. But the area under the curve (AUC) of plasma captopril concentration for OSSM (0.83 $\mu g \cdot h/ml$) administered after meals was smaller than that of conventional tablets administered under the same conditions (1.4–1.7 $\mu g \cdot h/ml$). Therefore, even with OSSM the sustained plasma concentration was at a low and unsatisfactory level.

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In this paper, further study was made with OSSM in order to improve the bioavailability of captopril under non-fasting conditions. Many investigators have already reported on the effect of food intake on the bioavailability of drugs (Welling, 1984; D'Arcy and Merkus, 1980). The importance of effect of food on bioavailability should be emphasized especially in sustained-release dosage forms, since, it can hardly but be affected by food intake, for a sustained-release formulation that must be administered one or two times daily.

In general, factors reducing the oral absorbability of a drug by food intake are as follows. (1) Food intake delays gastric emptying time. (2) Increase of secretions into the gastrointestinal (GI) tract is related to food intake, and many secretions interact with drugs; for example, hydrochloric acid, bile salts, and digestive enzymes. (3) Food components may physically or chemically interact with drug molecules. For example, drug–protein complex formation results in a reduction of drug absorbability. (4) Ingested food may alter the pH in the GI tract. It may change the stability of a drug in the GI tract (Melander, 1978). (5) Food components may interfere with the transport of drugs through the GI membrane.

It has been reported that the bioavailability of captopril is reduced by co-administered food and antacid (Mäntylä et al., 1984). The mechanism of this reduction is considered to be complex formation of captopril with food components or secretions and/or degradation of captopril in the elevated pH environment caused by food or antacid. It is a well-known phenomenon that a co-administered stabilizer improves the bioavailability of a drug whose absorbability is decreased because of decomposition or inactivation in the GI tract (Poiger and Schlatter, 1978). Therefore, the stability of captopril in the GI tract was studied to improve the bioavailability of captopril sustained-release dosage form.

The effectiveness of captopril sustained-release formulations had already been evaluated by the plasma unchanged (free form) captopril concentration profile in our other study (Seta et al., 1988). Additional pharmacological studies have been made with beagle dogs to evaluate OSSM as a sustained-release dosage form, for the relationship between plasma concentration of captopril and inhibition of pressor response has not been perfectly clarified (Waeber et al., 1980; Richer et al., 1984).

Materials and Methods

Stability of captopril in vitro

Captopril was obtained from E.R. Squibb and Sons (Princeton, NJ, U.S.A.). Dog food, pancreatin and gall powder were purchased from Oriental Yeast Co. (Tokyo, Japan), Amano Pharmaceutical Co. (Nagoya, Japan), and Mikuni Chemical Co. (Tokyo, Japan), respectively, and used as received. Pancreatin was the Japanease Pharmacopoeia (JP X) grade. Screened additives were all reagent grade and purchased from Wako Pure Chemical Ind. (Osaka, Japan), except β-cyclodextrin (β-CD). The β-CD was a product of Sanraku-Ocean Co. (Tokyo, Japan). Dog food (10 g), pancreatin (2.8 g) or gall powder (2.8 g), was added to 100 ml of JP 2nd fluid (JP X), and suspended homogeneously using Physcotron NS-600 (Nichion-Irika Co., Funabashi, Japan, 10,000 rpm × 30 s). The initial concentration of captopril in each test fluid was 0.1 mg/ml and the fluids were incubated at 37 °C. Supernatant fluid of dog food was prepared as follows: 20 g of dog food was added to 100 ml of JP 2nd fluid (JP X), then homogenized using Physcotron (10000 rpm × 1 min). Homogenized fluid was centrifuged (3000 rpm × 5 min) to get the dog food supernatant. In the screening study of stabilizer, one aliquot of dog food supernatant and one aliquot of the JP 2nd fluid (JP X) solution of captopril with stabilizer were mixed to get a test solution, where the captopril concentration was 2 μg/ml and the molar ratio of captopril to stabilizer was 1 : 10. The 10 kinds of prepared test solutions had the same pH (about 6.6). They were incubated for 1 h at 37 °C, then the concentration of captopril was chromatographically determined.

Determination of captopril in the in vitro experiment was carried out essentially according to the *p*-bromophenacyl bromide (p-BPB) adduct procedure reported by Kawahara et al. (1981). The

HPLC system was a model LC-5A system (Shimadzu, Kyoto, Japan) equipped with an SPD-2A (UV-detector, 254 nm) and octadecylsilane reversed-phase column (A-312, Yamamura Chem. Lab. Co., Kyoto, Japan). Ethyl *p*-hydroxy benzoate was used as internal standard and the mobile phase was a mixture of acetonitrile–water–acetic acid (50 : 50 : 1 v/v/v).

Preparations

The materials used were all JP grade, except captopril. In the preparation of the OSSM containing ascorbic acid, ascorbic acid was mixed with captopril and the mixture was added to the oily solution (soybean oil and glyceryl monostearate). The other preparation procedure was the same as mentioned in our previous work in this series (Seta et al., 1988). The conventional tablet was a Captoril 25 mg tablet (Sankyo Co., Tokyo, Japan). Ascorbic acid containing captopril enteric coated granules were prepared as follows. A mixture of captopril (50 g), ascorbic acid (1000 g), microcrystalline cellulose (250 g) and carboxymethylcellulose calcium (450 g) was granulated with aqueous solution of hydroxypropylcellulose (conc. 7%, w/w) as a binder. The granules obtained were sieved to collect 12/24 mesh size fraction. The sieved granules were coated with hydroxypropylmethylcellulose phthalate (HP-55 Shin-Etsu Chem. Co., Tokyo, Japan, 10% w/w) solution in acetone–ethyl alcohol solution (1 : 1 w/w).

Dissolution test

For the dissolution test of OSSM, the rotating bottle method was adopted (NF XIV). The dissolution fluid was 60 ml of purified water and rotated at 20 rpm in 37 °C waterbath. The paddle method (JP X) was used with 500 ml of JP 1st and 2nd fluids in dissolution tests of enteric coated granules. The details of dissolution tests have already been reported in our previous work (Seta et al., 1988).

Captopril determination in plasma and urine

Each dosage form was administered to a group of male beagle dogs (3, 5 or 6 dogs, weighing between 9.3 and 13.2 kg) under non-fasting conditions. Other experimental conditions were the same as reported in a previous work in this series (Seta et al., 1988). Captopril concentration in plasma was determined by the fluorescent HPLC method, which was also described in our previous work in the series (Seta et al., 1988). Captopril in urine was derivatized into the adduct with p-BPB and then determined chromatographically. Procedure details of this method were reported previously (Kawahara et al., 1981).

Angiotensin-converting enzyme (ACE) activity measurement

An assay method of ACE activity reported by Lieberman (1975) was used in our experiment with some modification. It consisted of enzymatic hydrolysis of artificial ACE substrate hippuryl-L-histidyl-L-leucine (Hip-His-Leu) (Cushman and Cheung, 1971) and HPLC analysis of the resultant hippuric acid. ACE activity in vivo was determined with the same procedure as previously reported (Kawahara et al., 1985). Angiotensin I (AI) and Hip-His-Leu were purchased from Peptide Institute (Osaka, Japan) and used as received.

Inhibition of pressor response to AI

Three male beagle dogs (9.8, 10.2 and 11.9 kg) were treated surgically to measure their blood pressure directly with a pressure transducer (Nihon Kohden, TMI-BLH, Tokyo, Japan) (Koike et al., 1981). Three days after the surgery, intravenous administration of AI (0.3 μg/kg) was repeated at 10 min intervals until a constant pressor response was obtained. Then the captopril formulations were administered orally 30 min after a meal (100 g of dog food) and the time course of blood pressure, ACE activity and captopril concentration in plasma was recorded. Intravenous administrations of AI were continued after the dosing at the time when the blood specimens were withdrawn (0.5, 1.0, 1.5, 2.0, ..., 8.0 h). Administrations were carried out using cross-over between conventional tablets (25 mg × 2) and OSSM (50 mg of captopril) at one-week intervals.

Results and Discussion

In general, compounds having a sulfhydryl (SH) group easily undergo oxidation (Friend et al., 1972; Bergstrom et al., 1980). They tend to interact with various substances in the GI tract, for example, bile salts, digestive enzymes, proteins in food, etc.

Fig. 1 shows percent recovery of captopril in 3 kinds of fluids, containing homogenized dog food, pancreatin or gall powder. Captopril was found to be labile in all 3 fluids, but as is shown later, captopril was comparatively stable in phosphate buffer solution (pH 6.6). These results suggested that the interaction with dog food components mainly caused low bioavailability of captopril under non-fasting conditions. Dissolved captopril from the formulation unit may be decomposed enzymatically or form a complex with food proteins; in any case captopril will be inactivated by dog food components before absorption can occur.

A number of stabilizers were tested in attempts to improve the stability of captopril in the dog food supernatant. Remaining percents of captopril to the initial concentration are shown in Fig. 2. They were incubated for 1 h with or without stabilizer at 37 °C in 50% dog food supernatant solution. Of the 10 tested substances, the water-soluble antioxidants were found to be most efficient, i.e. ascorbic acid, erythorbic acid, their sodium salts and sodium sulfite anhydrous. From these, ascorbic acid was selected for further detailed study, because it was expected that its moderate pharmacological action would allow its use in fairly large amounts in the dosage form.

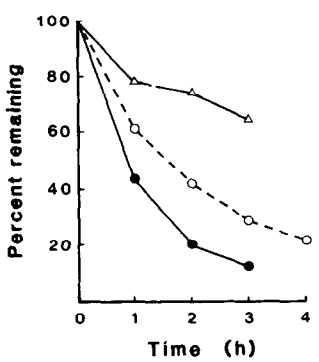

Fig. 1. Degradation of captopril in JP 2nd fluid in the presence of dog food (10 g/100 ml, ●———●), pancreatin (2.8 g/100 ml, ○------○) or gall powder (2.8 g/100 ml, △———△) at 37 °C.

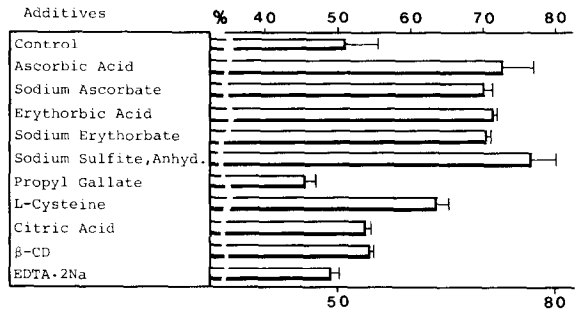

Fig. 2. Percent recovery of captopril in dog food supernatant solution in the presence of various additives after 1 h incubation at 37 °C; mean ±S.D., $n = 3$.

The stabilization effect of ascorbic acid on captopril in dog food supernatant is confirmed again in Fig. 3. Experimental conditions were the same as above and recovered percents of captopril after 3 h incubation in dog food supernatant free solution are also shown in Fig. 3. Even in dog food supernatant solution, the percent recoveries of captopril could be fitted to an apparent first-order plot. The regression lines were calculated

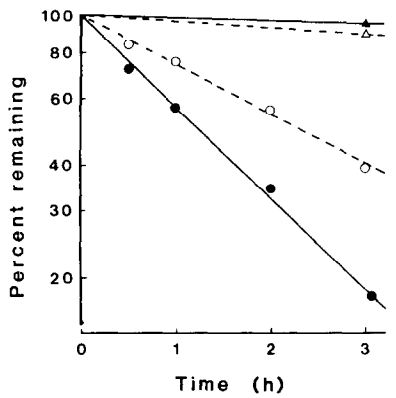

Fig. 3. Degradation of captopril in dog food supernatant in the presence of ascorbic acid at 37 °C, $n = 5$. Key: ●———●, no additive in dog food supernatant solution; ○------○, with ascorbic acid in dog food supernatant solution; ▲———▲, no additive in buffer solution (pH 6.6); △------△, with ascorbic acid in buffer solution (pH 6.6).

and the half-life periods obtained were 1.3 ± 0.1 h (mean $\pm$ S.D.) without ascorbic acid and 2.3 ± 0.3 h (mean $\pm$ S.D.) with ascorbic acid.

Therefore, it was concluded that addition of ascorbic acid to captopril solution containing dog food components is effective in its stabilization. The stabilization mechanism is still uncertain, but it is presumed that ascorbic acid inhibits the binding of the SH group of captopril to the SH groups present in food component. The similar effectiveness of other anti-oxidants supports this estimation, because binding between SH groups is simply oxidation.

Ascorbic acid was added to the OSSM formulation, which showed good efficiency in our previous paper (Seta et al., 1988), to enhance the bioavailability of the captopril sustained-release dosage form. Then the stabilization ability of ascorbic acid in vivo was ascertained by administration of OSSM containing ascorbic acid to beagle dogs. The dissolution behavior of the formulation was similar to previously reported OSSM which was ascorbic acid-free; that is, about 40% of the captopril was released within 3 h as measured by the rotating bottle method. Fig. 4 shows the time courses of captopril plasma concentration of 3 formulations in dogs; conventional tablets, OSSM containing ascorbic acid (250 mg), and enteric coated granules containing ascorbic acid (1000 mg). In the three trials 50 mg of captopril was administered 30 min after the meal. Conventional tablets and enteric coated granules were tried as a reference formulation. Conventional tablets and OSSM with ascorbic acid were administered to the same dog group. Among the 3 formulations, conventional tablets demonstrated the largest AUC (1.73 ± 0.16 $\mu g \cdot h/ml$), followed by OSSM (1.43 ± 0.14 $\mu g \cdot h/ml$), and finally enteric coated granules (1.02 ± 0.16 $\mu g \cdot h/ml$). However, OSSM exhibited the highest mean plasma concentration from 3 to 10 h after administration. Moreover, OSSM could maintain a steady concentration from 1 to 6 h after administration. The time course of enteric coated granules resembled that of OSSM, but its plasma captopril concentration was kept lower than that of OSSM. Thus, it was proved that ascorbic acid, added to prolonged-action formulations, could improve their bioavailability. In addition, ascorbic acid showed greater effectiveness in smaller amounts with OSSM than with enteric coated granules. The addition of ascorbic acid to the OSSM resulted in an increase of AUC about 1.7 times as high as that in OSSM without ascorbic acid. These results support our assumption that the degradation of captopril in the presence of food is the main reason for in vivo reduction in captopril absorption under non-fasting conditions.

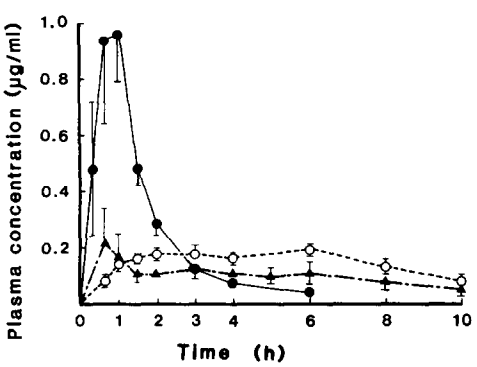

Fig. 4. Captopril plasma concentration after oral administration of oily semisolid matrix (○------○), enteric granules (▲-·-·-▲) and conventional tablets (●———●), mean of 6 beagles ($\bar{x} \pm$ S.E.), dose 50 mg, under non-fasting conditions.

The relationship between ascorbic acid content and captopril bioavailability was studied in OSSM formulations. Each formulation dosed the same amount of captopril (50 mg) and had nearly equal dissolution behavior. They were administered under non-fasting conditions to the same dog group. In Fig. 5, AUC_{0-10h} and cumulative urinary excretion percent (0–24 h) were plotted against ascorbic acid content. The data of ascorbic acid-free formulation (formulation A in Table 1) has already been reported in our previous paper (Seta et al., 1988); formulation B which contained 250 mg of ascorbic acid was mentioned in Fig. 4; formulation C which contained 500 mg of ascorbic acid was prepared and administered to achieve the third plot in Fig. 5. Results from both AUC and urinary recovery ratio indicated the same tendency; remarkable absorbability increases on adding the first 250 mg of ascorbic acid to the OSSM, followed by only slight increases on ad-

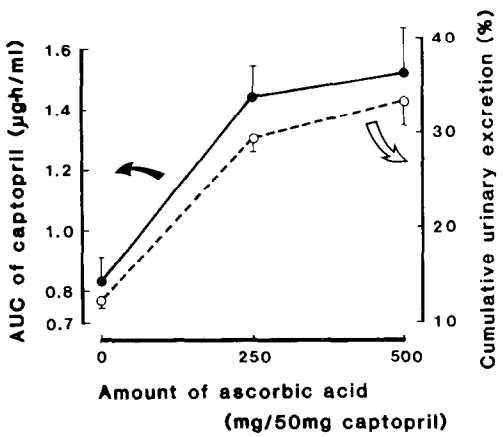

Fig. 5. Relationship between the bioavailability of captopril oily semisolid matrix and the amount of ascorbic acid formulated in the dosage form. Key: ●———●, AUC_{0-10h}; ○------○, cumulative urinary excretion (0–24 h).

dition of further ascorbic acid (500 mg). This result indicates a saturation of ascorbic acid effect to improvement of the captopril bioavailability when co-administered with food.

Further study was made to clarify the action of ascorbic acid on captopril absorption and disposition of captopril in the body. Captopril aqueous solution was administered orally to fasted male beagle dogs ($n = 6$, 9.7–13.2 kg) with a 2-way cross-over at one-week intervals; one group was given only captopril aqueous solution, and the other was given captopril and ascorbic acid aqueous solution. The dose of captopril was 18.75 mg and 125 mg of ascorbic acid was given 3 times during the experiment; the first dose at the same time as the captopril administration, and then 2 and 4 h after it. The time course of plasma

TABLE 1

Composition of captopril oily semisolid matrix dosage form

	Amount per single dose (mg)		
	A	B	C
Captopril	50	50	50
Ascorbic acid	–	250	500
Soybean oil	450	350	695
Glyceryl monostearate	250	100	200
Total/capsules	750/3cap	750/3cap	1445/5cap

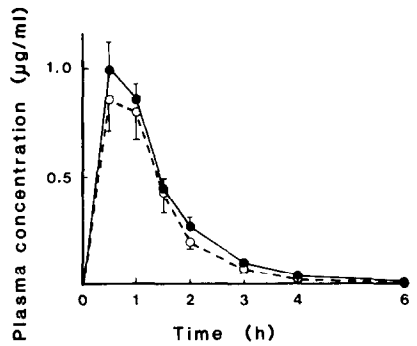

Fig. 6. Captopril plasma concentration after oral administration of captopril solution (18.75 mg/body) without (●———●) and with (○ – – ○) ascorbic acid (125 mg/body × 3); mean of 6 beagles ($\bar{x} \pm$ S.E.), under fasting conditions.

captopril concentration following the administration is shown in Fig. 6. There is no significant difference in the profile between administrations with and without ascorbic acid. The AUC, plasma peak concentration (C_{max}), and biological half-life ($T_{1/2}$) were calculated from the plasma concentration curve profiles shown in Fig. 6, and compared by Student's t-test at 5% significance level, but there was no significant difference between them. ACE activity was also measured at the same time. The inhibitory ratio of ACE activity was expressed as a remaining percentage of the ACE activity value measured just before captopril administration. The time course for remaining ACE activity is shown in Fig. 7. They also had similar profiles regardless of the co-existent ascorbic acid.

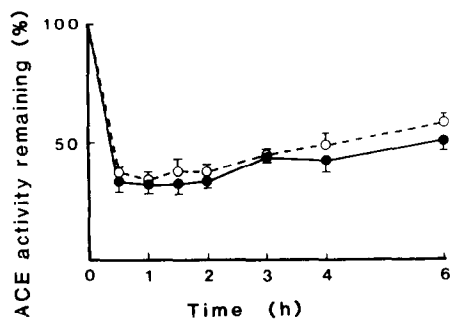

Fig. 7. Inhibitory percent of ACE activity in plasma after oral administration of captopril solution (18.75 mg/body) without (●———●) and with (○———○) ascorbic acid (125 mg/body × 3); mean of 6 beagles ($\bar{x} \pm$ S.E.), under fasting conditions.

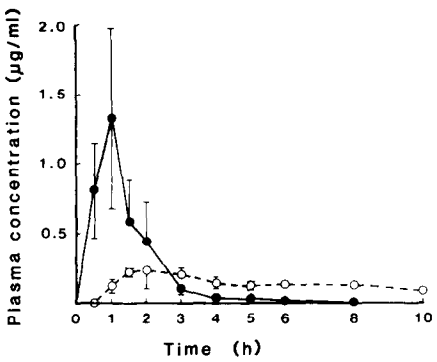

Fig. 8. Plasma concentration of captopril after oral administration of conventional tablets (●———●) and oily semisolid matrix (○------○) containing 50 mg of captopril in both formulations; mean of 3 beagles ($\bar{x} \pm$ S.E.), under non-fasting conditions.

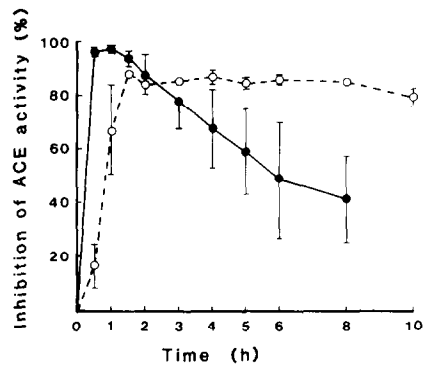

Fig. 9. Inhibitory percent of plasma ACE activity after oral administration of conventional tablets (●———●) and oily semisolid matrix (○------○) containing 50 mg of captopril in both formulations; mean of 3 beagles ($\bar{x} \pm$ S.E.), under non-fasting conditions.

The results shown in Figs. 6 and 7 lead us to the conclusion that ascorbic acid in captopril OSSM is pharmacologically inactive except for its inherent antiscorbutic action. This means that ascorbic acid does not affect the series of pharmacokinetic processes of captopril. In other words, absorption, distribution, metabolism and elimination of captopril is not changed by the co-existence of ascorbic acid.

OSSM (formulation B in Table 1) and conventional tablets were administered to beagle dogs under non-fasting conditions, the beagles being pretreated by AI administration. Captopril plasma concentration (Fig. 8), inhibitory ratio of plasma ACE activity (Fig. 9) and inhibitory ratio of pressor response to AI (Fig. 10) were measured at appropriate time intervals after administration of OSSM or conventional tablets. Both inhibitory ratios were expressed as percentages of the state just before administration of each dosage form.

As for the captopril plasma concentrations shown in Fig. 8, the time courses were similar to the results shown in Fig. 4. Conventional tablets, which were used as a reference formulation (25 mg × 2), exhibited a C_{max} at 1 h post-administration and then captopril disappeared rapidly from the blood circulation. In contrast, OSSM could maintain a nearly steady concentration from 1 to 10 h. ACE activity (Fig. 9) was perfectly inhibited by captopril in the plasma at 0.5 and 1 h from conventional tablet administration, but it decreased to 80% after 3 h, and to 50% after 6 h. On the other hand, the percent inhibition caused by captopril OSSM administration reached about 90% after 1.5 h and was maintained above 80% until the end of the observation period (10 h post-administration). The same tendencies can be observed on the inhibitory ratio of pressor response to AI (Fig. 10). With conventional tablet administration, the effect of inhibition to pressor response reached a maximum at 1–1.5 h after administration. After that the inhibitory ratio decreased to

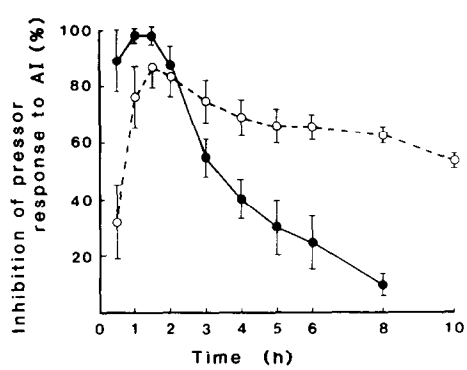

Fig. 10. Inhibitory percent of pressor response to i.v. administered AI (AI) after oral administration of conventional tablets (●———●) and oily semisolid matrix (○------○) containing 50 mg of captopril; mean of 3 beagles ($\bar{x} \pm$ S.E.), under non-fasting conditions.

below 10% at 8 h after administration, meaning that blood pressure again rose due to the action of the AI administered periodically since the formulation had been given. But with OSSM administration, the inhibition ratio decreased at a very gradual rate, OSSM exhibiting 60% inhibition ability from 1 to 8 h after administration. The period over which the percent inhibition was more than 60% was about 2.5 h with conventional tablets and about 7.5 h with OSSM.

From the results described above, the effectiveness of OSSM containing ascorbic acid was confirmed as a sustained-release dosage form. At the same time it was shown that the plasma concentration of captopril was a useful index in estimating the antihypertensive action of captopril, at least in studies using dogs.

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