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Evaluation of sustained-release granules of chlorphenesin carbamate in dogs and humans

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Summary

The bioavailability and pharmacokinetic properties of two sustained-release (SR) formulations of chlorphenesin carbamate (CPC) with different in vitro release rates were compared to those of an immediate-release (IR) formulation in beagle dogs and humans. Plasma levels of CPC were determined by HPLC assay. In humans, both SR formulations (SR-1 and SR-2), which have a difference in the rates of in vitro release, showed satisfactory maintenance of plasma concentrations with sufficient bioavailability as compared with the IR formulation, and their bioavailabilities relative to IR (relative bioavailability) were 1.00 and 0.86 for SR-1 and SR-2, respectively. Satisfactory maintenance of plasma concentration was also obtained in dogs, although the gastrointestinal transit time was shorter than that in humans. The relative bioavailabilities under fasting conditions in dogs were 1.05 and 0.90, respectively, and were almost the same in humans. The absorption from the small intestine and colon was almost complete for CPC in rats. It is suggested that the bioavailability of CPC was little affected by the gastrointestinal transit time. The reason that the bioavailability and pharmacokinetic properties of CPC in dogs were similar to those in humans might be due to the continuous absorption of CPC from these SR formulations after arrival in the colon. In this study, the dog was found to be a useful animal model for primary screening of SR formulations containing a drug which can be absorbed from the entire intestine, such as CPC.

Introduction

Chlorphenesin carbamate [3-(*p*-chlorophenoxy)-1,2-propanediol 1-carbamate, CPC] is a well-tolerated, orally active agent, which is effective in the treatment of skeletal muscle trauma and inflammation (Stern, 1963; Abruzzi, 1964). However, clinical use of CPC requires a daily dose of 750–1600 mg to be taken at three or four times (Stern, 1963). Therefore, the search for improved therapy and patient compliance has led to the development of sustained-release (SR) formulations of CPC which are administered less frequently than conventional dosage forms (twice a day).

Numerous studies have not dealt with the development of animal models suitable for the in-

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vestigation of the pharmacokinetics and the bioavailability of SR dosage forms (Cressman et al., 1971; Bialer, 1984; Uchida et al., 1986; Hossain et al., 1990). The dog, which has been shown to demonstrate absorption similar or dissimilar to that in human (Kaniwa et al., 1985; Ogata et al., 1985, 1986), is often used for bioavailability tests. That the gastrointestinal (GI) transit time in dogs is shorter than in humans (Dressman and Yamada, 1991; Dressman, 1986) has been attributed to the discrepancy between dogs and humans. Nevertheless, the dog has not been used successfully in various programs involved with the development of new SR formulations (Cressman et al., 1971; Morimoto et al., 1986). Therefore, it is important to study the relationships between the bioavailability of SR formulation in dogs and humans.

This study was undertaken in order to evaluate the dog as an animal model for the pharmacokinetic analysis of SR formulations of CPC. Two SR formulations with different in vitro release rates and an immediate-release (IR) formulation were administered to dogs and healthy volunteers. A comparative analysis was conducted between the pharmacokinetic parameters, and the sustained-release profiles of the dosage forms were analysed in dogs and humans. At the same time, biopharmaceutical and physiological factors, such as the sites of absorption and the GI transit, were also evaluated.

Materials and Methods

Chemicals

Chlorphenesin carbamate (CPC) was obtained from Taisho Pharmaceutical Co. Ltd (Omiya, Japan). The conventional tablet (Rinlaxer, lot 059) containing 250 mg of CPC also obtained from Taisho Pharmaceutical Co. Ltd (Omiya, Japan). Salicylazosulfapyridine (SASP) and sulfapyridine (SP) were purchased from Sigma (St. Louis, U.S.A.). All other reagents used were of analytical grade available from commercial suppliers.

Dosages

Three new experimental formulations of CPC, designated hereafter as an immediate-release (IR) formulation, IR, and two sustained-release (SR) formulations, SR-1 and SR-2, were in the form of uncoated and ethylcellulose-coated granules, respectively.

These products were prepared by the tumbling granulation method in our laboratory (Takashima et al., 1987). An aqueous solution of hydroxypropyl cellulose as a binder was gradually sprayed onto sugar crystals. Simultaneously, a mixed powder of CPC and corn starch was gradually sprinkled. After application, the CPC containing spherical granules (IR) were dried and sieved, and the IR was fed into the granulator. While the granules were being tumbled, a solution of ethylcellulose in ethanol was sprayed and at the same time hardened castor oil was gradually sprinkled to complete the coating. Finally the coated granules were dried at 70°C for 1 h to obtain SR formulations.

Physicochemical properties

The solubilities of CPC in 0.1 N HCl and McIlvaine buffer were determined by adding excess CPC to the media at 37°C. After equilibration the aliquot was filtered immediately using a membrane filter with pore size of 0.45 μm and diluted appropriately with the same medium, the samples were analyzed. For the measurement of partition coefficient, the initial concentration of CPC in the aqueous buffer layer was 3 mg/ml. The aqueous solution was added to the same volume of *n*-octanol saturated with the aqueous layer. After 2 h incubation, the partition coefficient was calculated from the determination of CPC concentration in the aqueous layer.

In vitro release study

The release of CPC from each formulation was measured according to the procedure of the paddle method (JP XI).

In all of the formulation dissolution tests, the dissolution medium was 900 ml of JP 1st fluid (JP XI) containing 0.01% polysorbate 80 at 37 ± 1°C, and the stirring speed was 100 rpm.

Absorption from the gastrointestinal (GI) tract

The absorption of CPC was studied essentially according to the procedure reported by Sakamoto et al. (1985). Male Wistar rats weighing between

200 and 250 g were used for the experiments. The rats were fasted for 17 h and had free access to water prior to the experiment. Under urethane anesthesia, both ends of the chosen GI parts were ligated to make loops after abdominal incision. Four parts of the GI tract, the stomach, the upper small intestine, the lower small intestine and the colon (each 5 cm in length), were used. Immediately after the operation, 0.5 ml of an aqueous solution of CPC (1.0 mg/ml) was introduced into each loop and the opening was ligated. 1 h after the operation, the loops were excised and their contents were removed. The amounts of drug in the loops, which had not been absorbed from each GI segment, were analysed using high-performance liquid chromatography (HPLC).

Dog studies

Four male beagle dogs weighing between 12.5 and 13.8 kg were fasted for 18 h prior to drug administration. The formulations were orally given to the dogs together with 20 ml of water. During the experiential period, access to food was not allowed but water was available ad libitum. At the designated time intervals, blood samples were withdrawn into heparinized syringes from the forefoot vein, and immediately afterwards the plasma portions were obtained by centrifugation (3000 rpm, 10 min) at 5°C. CPC levels in the plasma specimens were determined by an HPLC assay.

Oro-caecal transit time in dogs

The oro-caecal transit time was determined by measuring the time taken for the first detection of SP in dog plasma (SASP method: Kennedy et al., 1979). SASP was orally administered to dogs, which were fasted for 18 h before the study, in a 25 mg/kg dose. Each dog received 30 ml of water immediately after administration. Blood samples were taken with heparinized syringes at the designated time intervals after administration. The samples were centrifuged (3000 rpm, 10 min) and the separated plasma samples were kept at −20°C until assay. SP concentrations in plasma were determined by an HPLC assay (Mizuta et al., 1990).

Assay for SP in dog plasma

To 200 μl of plasma was added 1 ml of 0.5 M Na_2HPO_4-KH_2PO_4 buffer (pH 7.4) and 2 ml of ethyl acetate. After shaking for 10 min and centrifugation at 3000 rpm for 10 min, 1 ml of supernatant fluid was transferred to a glass tube and evaporated to dryness under reduced pressure. The residue was dissolved in 200 μl of the mobile phase, which contained 0.2 μg of 4-hydroxyethyltheophylline as an internal standard (IS), and 50 μl of this solution was loaded onto the column. The HPLC assay was carried out using a Shimadzu LC-6A apparatus equipped with a reversed-phase column (TSK-gel LS-410, 150 × 4 mm i.d.) and a Nippon-Bunko Jasco UV-970 ultraviolet (UV) monitor (280 nm). Acetonitrile-H_2O-AcOH (10:89:1, v/v) mixture was employed as the mobile phase at a flow rate of 1.5 ml/min. The detection limit was 0.05 μg/ml for SP in dog plasma and the coefficient of variation over the concentrations measured was within the range 0.5–2.5%.

Human studies

15 male adult volunteers between the ages of 24 and 28 years old (mean 26.8 years) and weighing 58–78 kg (mean 65.2 kg) participated in the human studies. They were selected for the study on the basis of negative medical history and physical examinations, normal routine blood chemical analysis and morphology, and urine analysis. Written informed consent was obtained from each volunteer. Subjects were randomly divided into three groups, and were given each formulation (each containing 375 mg of CPC) following an overnight fast. Food was withheld for 4 h after the administration. In the human study, no alcoholic or caffeinated beverages were permitted from 2 days before the beginning until the end of each study. Blood samples were collected from the subjects at the designated time intervals, and plasma portions were separated immediately and frozen at −20°C until assay.

Assay for CPC in plasma

The plasma concentrations of CPC were determined by a normal-phase column liquid chromatographic method. The plasma specimens ob-

tained (0.5 ml) were diluted with an equal volume of *o*-methoxyphenylacetoamide (IS) aqueous solution (4 μg/ml in water), and 4 ml of ethyl acetate was added to the diluted plasma to extract CPC. The resulting mixture was then centrifuged at 3000 rpm for 10 min. The organic phase (3 ml) was then removed, and evaporated to dryness under reduced pressure. The residue was dissolved in dichloromethane (400 μl) and was applied onto the HPLC column. Analysis was performed on a Shimadzu model LC-6A liquid chromatograph and a Nippon-Bunko UV1-DEC-100 III spectrophotometer. The column contained a packing material consisting of Lichrosorb SI-100 (5 μm) for normal-phase chromatography. The mobile phase consisted of a dichloromethane-methanol mixture (200:3, v/v). The flow rate was set at 1.1 ml/min and peak detection was monitored at 230 nm. The lower limit of the assay was 0.05 μg/ml for CPC in the plasma and the coefficient of variation over the concentrations measured was within the range 0.5–3%.

Pharmacokinetic analysis

The pharmacokinetic parameters for SR and IR were determined using model-independent methods. The maximum plasma concentration (C_{max}) and time at which the maximum occurred (T_{max}) were determined from the individual plasma concentration-time profiles. The area under the curve (AUC) was calculated using the trapezoidal rule to the last blood collection point (24 h). The terminal half-life ($T_{1/2}$) was calculated according to an extrapolation method and the mean residence time (MRT) was computed using statistical moment theory (Yamaoka et al., 1978).

The plasma concentration-time curves obtained after oral administration of the CPC solution or conventional tablet were fitted to a compartment model using the MULTI program (Yamaoka et al., 1981).

Results

Physicochemical properties

The physicochemical properties of CPC are shown in Fig. 1. CPC was slightly soluble in water, but its partition coefficient was large in the physiological pH range. These characteristics remained almost constant, irrespective of pH change. Moreover, no degradation of CPC was observed over this pH range.

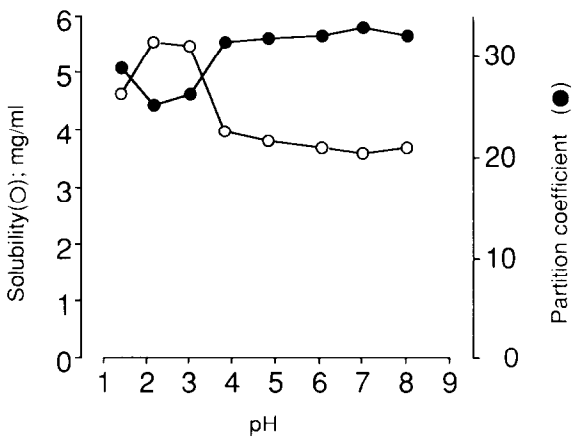

Fig. 1. Physicochemical characteristics of CPC.

In vitro release of CPC

Fig. 2 shows the release of CPC from a conventional tablet, IR formulation (IR) and SR formulations (SR-1 and SR-2) in a pH 1.2 dissolution medium containing 0.01% polysorbate 80. The conventional tablet and IR showed immediate and complete drug release within the first 15 min under these conditions. On the other hand,

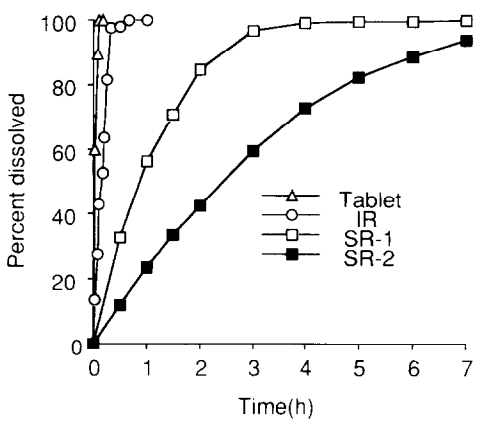

Fig. 2. In vitro dissolution of CPC from immediate-release formulations and sustained-release fromulations using the paddle method in JP XI 2nd fluid (pH 6.5).

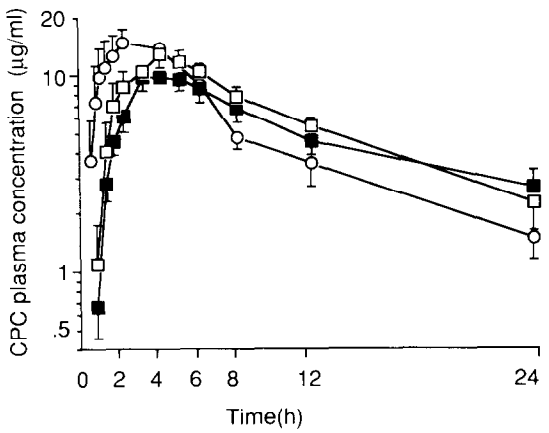

Fig. 3. Mean plasma concentration-time profiles of CPC obtained after administration of IR (○), SR-1 (□) and SR-2 (■) to four dogs.

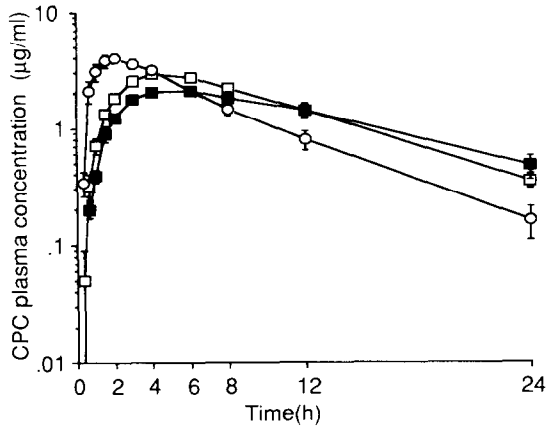

Fig. 4. Mean plasma concentration-time profiles of CPC obtained after administration of IR (○), SR-1 (□) and SR-2 (■) to five humans.

release was retarded by an increase in the amount of ethylcellulose film coating, and the times necessary for 50% release from SR-1 and SR-2 were between 1.0 and 3.0 h, respectively. Release was not influenced by the pH of the medium, since the solubility of CPC was not changed in the pH range of 1.0–8.0, as shown in Fig. 1.

Pharmacokinetic parameters in dogs and humans

The pharmacokinetic parameters of CPC in dogs and humans are summarized in Table 1. They were calculated on the basis of the one-compartment open model using the data on plasma concentration after the oral administration of CPC in tablet form to each human subject, and in aqueous solution form to each dog (250 mg/body), respectively. The difference in the parameters between dogs and humans was relatively small, except for the C_{max} and AUC. However, when both the values of C_{max} and AUC were normalized for body weight, they were almost the same.

Comparative pharmacokinetic evaluation of SR formulations in dogs and humans

Mean plasma concentrations obtained after single administration of the three kinds of experimental formulations to dogs and humans are presented in Figs 3 and 4, respectively. Tables 2 and 3 summarize the mean pharmacokinetic parameters.

After IR was administered to dogs (375 mg/body), the plasma concentration rose rapidly and reached the C_{max} within 4 h. The mean T_{max} value was 3.00 ± 0.58 h. In contrast, the absorption of CPC from both SR formulations was

TABLE 1

Pharmacokinetic parameters of CPC obtained after oral administration of CPC solution to four dogs and CPC tablet to five humans

Species	Dose 250 mg/body: fasting condition					
	K_a (h^{-1})	K_e (h^{-1})	$T_{1/2}$ (h)	C_{max} (μg/ml)	T_{max} (h)	AUC_{0-24} ($\mu g \cdot h$/ml)
Human	3.07 ± 2.63	0.25 ± 0.05	2.68 ± 0.86	3.78 ± 0.52	1.00 ± 0.58	20.72 ± 4.22
Dog	4.25 ± 0.99	0.25 ± 0.03	2.96 ± 0.41	15.16 ± 0.28	0.69 ± 0.12	94.16 ± 9.75

K_a, absorption rate constant; K_e, elimination rate constant; $T_{1/2}$, biological half-life; C_{max}, maximum plasma concentration; T_{max}, time to reach maximum concentration. Data are represented as mean ± S.E.

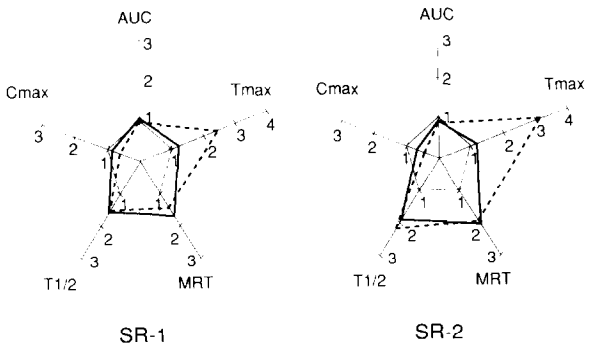

Fig. 5. Comparison of relative values of pharmacokinetic parameters (IR = 1) between humans (dashed line) and dogs (continuous line).

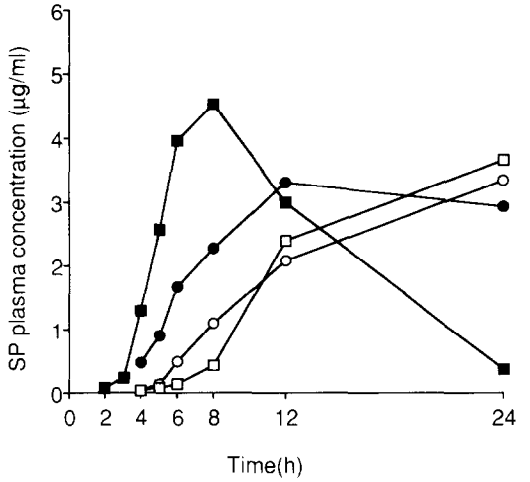

Fig. 6. Plasma SP concentration-time profiles of individual dogs after oral administration of SASP at a dose of 25 mg/kg.

slower than that from IR. Mean T_{max} values after administration of SR-1 and SR-2 to dogs were 3.63 and 3.50 h, respectively. However, the difference in T_{max} between IR and SR formulations was not as large. As for C_{max}, the values for SR-1 and SR-2 were lowered to about 85 and 70% of that for IR, respectively, as the dissolution rate decreased. On the other hand, the AUCs for SR formulations did not markedly differ from that of IR in dogs. It could be concluded that both SR formulations showed good bioavailability for CPC in dogs.

After administration of SR-1 and SR-2 to humans, the plasma concentration also rose gradually: T_{max} was 4.40 ± 0.40 and 5.60 ± 0.40 h, and C_{max} was 2.98 ± 0.15 and 2.11 ± 0.18 μg/ml, respectively. AUC for SR-1 was observed to be the same as that for IR. Although AUC for SR-2 was slightly lower than that for IR, there was no great difference between both SR formulations in dogs or humans.

TABLE 2

Pharmacokinetic parameters of CPC obtained after oral administration of 375 mg of formulations IR, SR-1 and SR-2 to four dogs

Formulation	C_{max} (μg/ml)	T_{max} (h)	AUC_{0-24} (μg h ml^{-1})	F_{rel}	$T_{1/2}$ (h)	MRT (h)
IR	15.39 ± 1.40	3.00 ± 0.58	125.17 ± 16.51	1.00	3.45 ± 0.18	7.91 ± 0.55
SR-1	13.03 ± 0.94	3.63 ± 0.75	132.03 ± 9.60	1.05	5.30 ± 0.47	13.39 ± 2.04
SR-2	10.55 ± 0.86	3.50 ± 0.50	112.80 ± 11.40	0.90	6.51 ± 0.72	16.02 ± 2.96

Data are represented as mean ± S.E.

TABLE 3

Pharmacokinetic parameters of CPC obtained after oral administration of 375 mg of formulations IR, SR-1 and SR-2 to five humans

Formulation	C_{max} (μg/ml)	T_{max} (h)	AUC_{0-24} (μg h ml^{-1})	F_{rel}	$T_{1/2}$ (h)	MRT (h)
IR	4.80 ± 0.20	1.80 ± 0.38	35.25 ± 3.13	1.00	3.02 ± 0.38	7.22 ± 0.61
SR-1	2.98 ± 0.15	4.40 ± 0.40	35.08 ± 2.60	1.00	4.44 ± 0.43	10.46 ± 0.50
SR-2	2.11 ± 0.18	5.60 ± 0.40	30.43 ± 3.55	0.86	6.54 ± 1.41	14.00 ± 1.60

Data are represented as mean ± S.E.

Fig. 5 shows a comparison of the relative values of the bioavailability parameters (IR formulation = 1.0) between dogs and humans. In dogs and humans, $T_{1/2}$, MRT and T_{max} values for SR formulations were increased as compared with IR, whereas C_{max} values were decreased. The rank order of these parameters for the human and dog was the same, however, the relative values of T_{max} in beagle dogs for both SR formulations were lower than those in humans. Nevertheless, the AUC values for both SR-1 and SR-2 were almost equal to those for IR in both species. Furthermore, the differences between the bioavailability parameters in dogs and humans were not as large, except for the T_{max} values.

Oro-caecal transit time in dogs

Fig. 6 displays the plasma levels of SP in four dogs after oral administration of SASP. The mean value of the oro-caecal transit time, as judged by the initial detection of SP in the plasma, was found to be 3.5 ± 1.5 h in dogs (range 2.0–4.0 h).

Absorption from the gastrointestinal (GI) tract

Fig. 7 shows the difference of the absorption site on the fraction of CPC absorbed by the loop method in rats. No degradation was noted at any loop of the GI tract. The fractions absorbed 1 h after introduction into each GI loop estimated using the four chosen segments, the stomach, upper intestine, lower intestine and colon, were

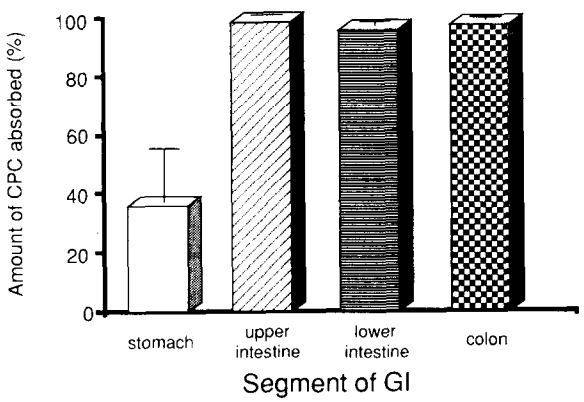

Fig. 7. Total absorption of CPC over 60 min at four segments of gastrointestinal (GI) tract in rats ($n = 3$) (data represent the mean ± S.E.).

35.8 ± 17.9, 98.5 ± 0.5, 95.7 ± 1.0 and 97.2 ± 1.0%, respectively. It was confirmed that CPC can be rapidly and completely absorbed from the entire intestine, except for the stomach.

Discussion

Previous studies with sustained-release dosage forms of aminorex fumarate and valproic acid showed that the dog was a good animal model for the absorption rate but not for the extent of absorption (Cressman et al., 1971; Bialer et al., 1984). Moreover, Morimoto et al. (1986) reported that when 4 mg molsidomine was given as SR beads to dogs, satisfactory prolongation of an effective plasma concentration could not be observed; in particular, the AUC was only about one half of that of the tablet. As previously suggested by Morimoto et al. (1986), two reasons for the decrease of AUC in the case of those SR dosage forms could be considered. First, the SR dosage forms may have passed through the absorption site (small intestine) before the release of the drugs is completed. Second, the elimination rate constant of the drugs themselves in dogs may be so large and the absorption rate constant (or release rate) so small that the plasma concentration cannot be maintained at an effective level.

In our experimental formulations, T_{max} was delayed and C_{max} was lowered in dogs and humans as the in vitro release rates decreased. Furthermore, the two SR formulations showed a very good in vivo sustained-release profile (Figs 3 and 4). In dogs, however, the average T_{max} values with IR were more retarded than that predicted with the solution. The reason for this unexpected result is probably related to the aqueous solubility of CPC. The dose of CPC for dogs was equivalent to that for humans in our study (375 mg/body wt). Excess of dose to dogs might be expected to inhibit considerably the dissolution of CPC, and hence its absorption rate. A trend toward a reduction in the rate or extent of absorption due to the intake of a low fluid volume following other IR products, for example, of theophylline, amoxicillin and erythromycin, has also been reported (Welling et al., 1975, 1977, 1978). This property

appears to be common to this type of compounds. On the other hand, the hydration level might have little effect on the T_{max} of SR, since they can release CPC slowly enough to dissolve it in the GI tract. According to the in vitro release rates, a slight difference in the AUC values between SR formulations was also detected. Other workers (Buhrer et al., 1966; Arlington et al., 1971) have reported that, when given as a solid formulation orally, absorption was essentially complete in both dogs and humans. It can therefore be presumed that IR also underwent complete absorption in our study. SR-1 showed complete absorption, whereas SR-2 exhibited slightly lower absorption compared with the IR in dogs and humans, as judged on the basis of the AUC values to the last sampling point. These findings were confirmed by the relative bioavailability (F_{rel}) calculated from the ratio of the AUC data obtained after administration of SR-1 and SR-2 to those of the IR: 1.05 and 0.90 in dogs and 1.00 and 0.86 in humans, respectively (Tables 2 and 3). The SR formulations, SR-1 and SR-2, showed a similar extent of absorption in both species.

Several workers have recently reported on GI motility (Hossain et al., 1990; Sugito et al., 1990; Heinamaki et al., 1991; Wilding et al., 1992). GI transit from the mouth to the colon has been estimated to be 8–10 h, with transit being approx. 2–4 h in the small intestine of humans (Ch'ng et al., 1985). Sommers et al. (1990) reported that the mean GI transit time, as estimated based on the time of first detection of SP, was found to be 5.9 h in humans (range, 4.0–9.0 h). On the other hand, GI transit time in dogs was determined to be between 2.0 and 4.0 h in this study (Fig. 6), which is in good agreement with the results reported by Mizuta et al. (1990). A considerable difference in the GI transit time was found between dogs and humans (Dressman, 1986). The present study also demonstrates that GI motility in dogs is faster than that in humans. However, after administration of SR formulations to dogs (Fig. 3), satisfactory prolongation of an adequate CPC plasma concentration was observed and the AUCs were almost equivalent compared with that of the IR formulation. This might suggest that a large portion of CPC released from the SR formulations continued to be absorbed after arrival in the colon. As shown in Fig. 7, the transport of CPC across the intestinal membrane is little influenced by the GI sites. CPC was well absorbed, even from the rat colon, and was not considered to exhibit the so-called 'window effect' which is seen in some drugs, such as riboflavin, digoxin and furosemide (Hirtz, 1984). Such drugs are not absorbed all along the GI tract, but only in a definite segment, so that the drug may leave the segment before the whole dose has been absorbed. As for CPC, the absorption site was considered to be broad enough to justify the use of SR dosage forms.

The pH varies along the GI: it is a common belief that the pH is low in the stomach and increases sharply beyond the pylorus. The drug may be less available for absorption in terms of solubility or partitioning as a function of pH. Before the in vivo studies were conducted, it was confirmed that the solubility and lipophilicity of CPC were almost constant and adequate within the physiological pH range (Fig. 1). This finding indicates that the CPC could dissolve evenly in the luminal fluid during transit. In addition, CPC might be sufficiently lipophilic to be absorbed from all parts of the GI tract (Fig. 1). From these findings, the physicochemical properties of CPC were considered to be only slightly affected by the GI pH change.

From the above, the similarity in the extent of absorption from the SR formulations to that from IR in dogs and humans may be due to the fact that the absorption of CPC was only slightly affected by GI physiology, such as gastric acidity, intestinal pH and gastrointestinal transit time. In addition to the excellent physicochemical properties of the CPC itself, the elimination half-life of CPC was similar in dogs and humans. The values of the elimination constant of CPC in dogs and humans after solution and rapid-release tablet administration were 0.25 ± 0.03 and 0.25 ± 0.05 h^{-1}, respectively (Table 1). With respect to drug disposition, this is also considered to be comparable in dogs and in humans; orally absorbed CPC is thought to be excreted mainly into the urine as a glucuronide (Buhler, 1964).

In conclusion, this study shows that the dog is

a good animal model for predicting the extent and rate of CPC absorption from SR formulations in humans. This could be attributed to the fact that the half-life of CPC is similar in dogs and humans, and that the absorption of CPC was not site-specific. Therefore, the plasma CPC levels after the administration of SR formulations could be prolonged for up to 24 h in both species. In addition, the similarity in extent and rate of absorption may be due to the fact that the absorption of CPC from SR formulations was not affected by the pH of the GI tract. These results of studies in dogs could provide useful information regarding the performance of the SR dosage forms in humans. Thus, unlike other drugs such as molsidomine, valproic acid and aminorex fumarate, in the case of SR dosage forms containing a drug like CPC which can be absorbed from the entire intestine, the dog can be used as an animal model in formulation studies.

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