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Effect of food on bioavailability of bioadhesive-containing indomethacin tablets in dogs

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Abstract

The effect of food on the bioavailability of bioadhesive containing indomethacin tablets was evaluated on five male beagle dogs. Indomethacin was administered intravenously at a dose of 15 mg and orally in the fasting state and after food intake as a bioadhesive tablet at a dose of 25 mg. After dosing, serial blood samples were collected for a period of 6 h. Indomethacin plasma concentration was determined by a sensitive high-performance liquid chromatographic assay. Food consumption dramatically reduced the area under the plasma concentration-time curve (AUC) and the maximum concentration (C_{max}) by 86 and 76%, respectively. No significant differences were observed in the time to peak concentration (T_{max}), mean residence time of the drug in the body (MRT), mean absorption time (MAT), elimination rate constant (K_{el}) and elimination half-life ($t_{1/2}$) between the fasting and postprandial states. The mean gastrointestinal time (MGT) was found to be 0.81 h. The absolute bioavailability of the indomethacin bioadhesive tablets in the fasting state and after meal was 85.4 and 11.8%, respectively. Complexation of the bioadhesive material with the food contents is the most plausible explanation for the decrease in the extent of absorption of indomethacin.

Keywords: Polycarbophil; Indomethacin tablet; Food effect; Bioavailability; Dog

1. Introduction

Bioadhesive polymers for drug delivery purposes are defined as synthetic or natural polymers that have the ability to adhere to a biological tissue for an extended period of time (Park and Robinson, 1984; Peppas and Buri, 1985). These polymers can adhere to gastric mucin/epithelial cell surfaces either by becoming sticky when placed in water and owe their bioadhesion to stickiness or through secondary chemical bonds especially hydrogen-bonding and also by binding to specific receptor sites on the cell surface. One such bioadhesive polymer is polycarbophil (Markus, 1965) which was shown to be effective for oral (Longer et al., 1985), ocular (Robinson and Lee, 1984) and rectal (Hosny, 1988; Hosny and Robinson, 1991; Hosny and Al-Angary, 1993) drug delivery.

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In our laboratory we developed polycarbophil-containing indomethacin tablets (Al-Meshal et al., 1992; Hosny and Al-Meshal, 1994a). These tablets were shown to disintegrate rapidly in less than 1 min, to reduce the incidence of indomethacin induced gastric ulcers, and could be prepared by direct compression. These tablets are also more bioavailable than the marketed capsules 'Indocid, MSD' showing 152% relative bioavailability (Hosny and Al-Meshal, 1994b).

No work has been carried out to demonstrate the effect of food on the bioavailability of bioadhesive-containing dosage forms. Therefore, the objectives of this study were two-fold: (1) to evaluate the effect of food on the bioavailability of indomethacin from bioadhesive-containing tablets; and (2) to determine the absolute bioavailability of indomethacin-containing bioadhesive tablets compared to i.v. injection of indomethacin solution under fasting conditions.

2. Materials and methods

2.1. Materials

Bulk polycarbophil was a kind gift from Lee Laboratories Inc. (Petersburg, VA, U.S.A.). Indomethacin was obtained from Al-Hikma Pharmaceutical (Amman, Jordan). Confortid 50 mg, i.v. injection was purchased from Dumex Ltd (Denmark). All other chemicals and solvents were of analytical and HPLC grade.

2.2. Animals

Five male beagle dogs, weighing between 7 and 10 kg, were used in the present study. Indomethacin was administered on three occasions separated by 2 weeks between each treatment. The animals remained in good health through the entire period of the study. The dogs were starved for about 18 h prior to the experiment, but allowed water ad libitum. During the experimental period each dog was placed in the upright position in the restrainer stand. The legs were shaven and a cephalic vein was cannulated using an 18-gauge cannula. The cannula was used for intravenous administration and blood sampling. The same five dogs were used throughout the intravenous and oral dosing experiments.

2.3. Study design and plasma samples

The three treatment periods were as follows: (a) indomethacin administered intravenously at a dose of 15 mg; (b) indomethacin administered p.o. in the fasting state as a bioadhesive tablet (containing 25 mg indomethacin manufactured in our laboratories for the purpose of this study); and (c) p.o. as a bioadhesive tablet (containing 25 mg indomethacin) 15 min after intake of 480 ml (16 oz.) of dog food mixed with an equal volume of water.

Multiple blood samples (5 ml) were collected in evacuated glass tubes (heparinized vacutainers, Becton & Dickinson, CA, U.S.A.) before and at 0.25, 0.5, 0.75, 1.0, 1.5, 2.0, 2.5, 3.0, 4.0, 5.0 and 6.0 h after dosing. The plasma was then separated after centrifugation and stored frozen at −20°C pending analysis.

2.4. Analysis of plasma samples

Indomethacin plasma concentrations were measured using a specific, sensitive, and validated high-performance liquid chromatographic procedure (Al-Angary et al., 1990). This assay involves extraction of plasma samples enriched with itraconazole (internal standard), with diethyl ether after acidification with glacial acetic acid. Following evaporation to dryness, the residues were reconstituted in the mobile phase and aliquots were injected into the chromatograph and eluted with ethanol/water/glacial acetic acid (65:34:1%, v/v). The liquid chromatographic systems consisted of a model 6000A solvent delivery pump, model U6K injector, and model 481 UV detector, set at 254 nm. The column was a 4 μm C-18 reversed phase column (all from Waters Associates, Milford, MA, U.S.A.). The within-day coefficient of variation (CV) ranged from 2.7 to 5.7%, while the between-day CV ranged from 3.6 to 6.1%. The absolute recoveries ranged from 94 to 97% over the concentration range 0.1–10 μg/ml.

2.5. Pharmacokinetic analysis

Pharmacokinetic parameters for indomethacin following oral administration were determined from the plasma concentration-time data. The maximum plasma concentration (C_{max}) and the corresponding time (T_{max}) were obtained directly from the plasma concentration-time profiles. The area under the plasma concentration-time curve (AUC) and the area under the first moment curve (AUMC) were estimated according to the linear trapezoidal rule and extrapolated to infinity using standard techniques (Gibaldi and Perrier, 1982). The apparent elimination rate constant (K_{el}) was calculated by the technique of least-squares regression analysis. The data of plasma indomethacin concentrations after intravenous administration were analyzed by a linear two-compartment open model with elimination from the central compartment (El-Sayed et al., 1990). The mean residence time of the drug in the body (MRT), mean absorption time (MAT), mean gastrointestinal time (MGT) and absolute bioavailability (F) of the oral tablets were calculated using the following equations:

$$\mathrm{MRT} = \frac{\mathrm{AUMC}}{\mathrm{AUC}}$$

$$\mathrm{MAT} = \mathrm{MRT_{po}} - \mathrm{MRT_{iv}}$$

$$\mathrm{MGT} = \mathrm{MAT_{postprandially}} - \mathrm{MAT_{fasting}}$$

$$F = \frac{\mathrm{AUC_{po}}}{\mathrm{AUC_{iv}}} \cdot \frac{\mathrm{dose_{iv}}}{\mathrm{dose_{po}}}$$

where $\mathrm{MRT_{po}}$ is the mean residence time after oral administration and $\mathrm{MRT_{iv}}$ denotes the mean residence time after i.v. administration.

2.6. Statistical analysis

The effect of food on the pharmacokinetic parameters of indomethacin following oral administration was evaluated statistically using analysis of variance and unpaired Student's t-test on a microcomputer statistical package (SAS, Statistical Analysis System). Statistical differences were considered significant at the level of 0.05. Pharmacokinetic parameters are presented as mean ± SD.

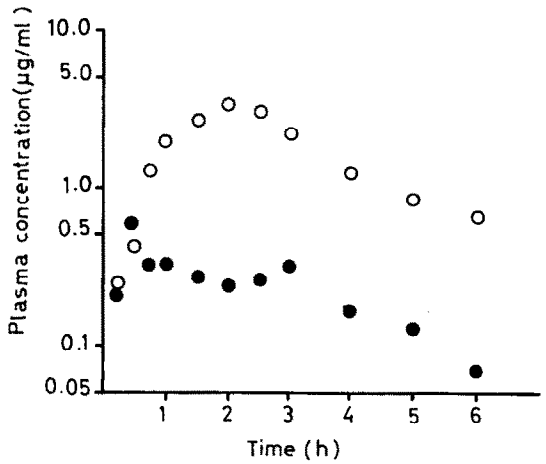

Fig. 1. Mean plasma concentration of indomethacin following oral administration of the bioadhesive tablets to five dogs in the fasting state (○) and postprandially (●).

3. Results

The mean plasma concentration-time curves for the five dogs following the oral administration of the bioadhesive tablets of indomethacin in the fasting and non-fasting conditions are shown in Fig. 1. Food consumption produced a significant reduction in indomethacin plasma concentrations from 0.5 h onwards ($P < 0.01$).

The pharmacokinetic parameters of indomethacin following oral administration of the bioadhesive tablets with and without food intake are listed in Table 1. Food dramatically reduced the area under the plasma concentration-time curve (AUC) (11.79 ± 5.69 and 1.61 ± 1.43 μg h ml^{-} for the fasting state and after meal, respectively) and the maximum plasma concentration (C_{max}) (3.90 ± 1.36 and 0.94 ± 1.7 μg/ml for the fasting state and non-fasting conditions, respectively). No significant differences were noted in the T_{max}, MRT, MAT, K_{el} and $t_{\frac{1}{2}}$ parameters between the fasting and non-fasting dogs. The mean gastrointestinal time (MGT), which is the difference in absorption time between the fasting and postprandial states, was found to be 0.81 h.

Table 1
Mean pharmacokinetic parameters of indomethacin following oral administration of bioadhesive tablets (containing 25 mg indomethacin) to five fasting dogs before and after food

Parameter	Fasting		Food	
	Mean ± SD	CV (%)	Mean ± SD	CV (%)
AUC (μg h ml^{-1})	11.79 ± 5.69	48.2	1.61 ± 1.43 [a]	88.6
C_{max} (μg/ml)	3.90 ± 1.36	34.7	0.94 ± 1.17 [a]	124.0
T_{max} (h)	1.90 ± 0.55	28.8	2.20 ± 1.35	61.4
MRT (h)	3.57 ± 0.67	18.9	3.92 ± 1.59	40.7
MAT (h)	2.13 ± 1.41	66.2	2.94 ± 1.75	59.5
K_{el} (h^{-1})	0.36 ± 0.00	16.3	0.42 ± 0.13	30.1
$t_{\frac{1}{2}}$ (h)	1.96 ± 0.35	17.7	1.76 ± 0.56	31.7
F (%)	85.40 ± 47.20	55.2	11.80 ± 9.10 [a]	77.7

Mean ± SD of five dogs.
[a] Significantly different; $P < 0.005$.

The absolute bioavailability of the indomethacin bioadhesive tablets in the fasting state and after meal was 85.4 ± 47.2 and 11.8 ± 9.1%, respectively.

4. Discussion

The results of this investigation demonstrate that food consumption dramatically reduced the extent of absorption of indomethacin from the bioadhesive tablets. The area under the plasma concentration-time curve (AUC) and the C_{max} were reduced by 86 and 76%, respectively. Although the time to maximum plasma concentration (T_{max}) increased by 16% postprandially, this change was not statistically significant. Nevertheless, interdog variation in T_{max}, determined as CV, was large after meal (61.4%) compared to the fasting dogs (28.8%).

The possibility of a decrease in the extent of absorption as a consequence of the delay in gastric emptying is remote, since the T_{max}, MRT and MAT remained unchanged between the two treatment periods. The mean absorption time in fasting dogs was 2.13 ± 1.41 h, which was 49 min shorter than after food intake (2.94 ± 1.75 h). This shows that food intake delayed the absorption process of indomethacin bioadhesive tablets, the delay being represented by the mean gastrointestinal time, MGT (0.81 h). Nevertheless, this delay was not statistically significant ($p = 0.4415$ for MAT).

The most plausible explanation for the significant decrease in bioavailability (F) of indomethacin bioadhesive tablets (86% decrease relative to the fasting dogs) is the complexation of the bioadhesive material with the food contents. There may be other reasons for the low bioavailability of these bioadhesive tablets after meal. One of the reasons is the effect of food on increasing pH of the gastric contents which consequently influences the surface charge of both gastric mucus and polymer (Ch'ng et al., 1985). The food also affects the degree of hydration of the bioadhesive polymer (Chen and Cyr, 1970) and its viscosity (James and Marriot, 1982), which in turn are critical for its adhesive strength. As shown previously (Smart et al., 1984), higher pH values disfavor adhesion between gelatin gels and plates coated with p75 SCMC and tragacanth. Also, it has been reported (Park and Robinson, 1985) that polycarbophil exhibited maximum bioadhesion at pH much lower than its pK_a value (4.7) and better adhesion occurred in the stomach than in the intestine (Rao and Buri, 1989).

In conclusion, polycarbophil-dietary component interaction seems to be the main reason for the low bioavailability of these indomethacin tablets when administered after food intake. Also, the effect of dietary component on the physiological conditions that affect the bioadhesive characteristics of polycarbophil should not be overlooked.

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