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Rectal absorption of flurbiprofen, ketoprofen and indomethacin in polyacrylic acid aqueous gel preparation in rats

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Summary

The bioavailability on rectal administration of flurbiprofen (FP), ketoprofen (KP) and indomethacin (Ind) with polyacrylic acid aqueous gel base was investigated in rats. When FP, KP and Ind were administered rectally with gel base at various pHs (5.0–8.0), their bioavailabilities increased upon higher pH. In the rectal administration of FP, KP and Ind with gel base at various concentrations (viscosities: 0.5–2.0 w/v%), higher bioavailabilities were obtained at lower concentrations (viscosity) of gel base. In the rectal administration of Ind with gel base containing oleic acid (10 v/v%), the bioavailability was higher and longer than that with simple gel base; however, that of FP and KP did not change without or with oleic acid. In the in vitro release experiments using micropore membrane, the effect of gel concentration (viscosity) was evident; the higher the viscosity of the gel preparation, the slower the FP, KP and Ind release. The results suggest that the release rate from the gel preparation is rate-limiting in the rectal absorption of FP, KP and Ind in gel preparations in rats.

Thus, it can be assumed that polyacrylic acid aqueous gels are useful as a base for rectal administration of FP, KP and Ind.

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Introduction

Non-steroidal anti-inflammatory (NSAI) drugs such as flurbiprofen (2-(2-fluoro-4-biphenylyl) propionic acid: FP), ketoprofen (2-(3-benzoylphenyl)propionic acid: KP) and indomethacin (1-(*p*-chlorobenzoyl)-5-methoxy-2-methylindole-3-acetic acid; Ind) have been widely used in the treatment of rheumatoid arthritis, osteoarthritis and acute musculoskeletal disorders. In the usual oral administration of NSAI drugs, the tablets and capsules have led to peptic ulceration and anorexia. Other side-effects have involved the central nervous system, including headache, giddiness and blurring of vision, when the blood concentration is above the therapeutic levels. Rectal administration of NSAI drugs would be a favourable dosage route for patients with peptic ulcers, infants and children. Recently several reports have appeared concerning rectal administration of NSAI drugs using conventional suppository bases such as Witepsol or polyethylene glycol (Vidras et al., 1982; Caillé et al., 1980). In our previous paper, the rectal administration of ibuprofen with polyacrylic acid gel base, has been reported to be an effective method of administration (Hirano et al., 1980). Polyacrylic acid gel base which is group of carboxyvinyl polymer can be adjusted to a suitable pH and viscosity, and unpleasantness during rectal administration is minimal (Morimoto et al., 1980).

In this study, FP, KP and Ind gel preparations were used to obtain prolonged action by taking advantage of these gel characteristics, and the bioavailability of the gel preparation was examined after rectal administration.

Materials and Methods

Materials

Polyacrylic acid (Hiviswako 105) was obtained from Wako Pure Chemical Industries (Japan), flurbiprofen (FP) from Kakenyaku Kako (Japan), ketoprofen (KP) from Rhone-Poulenc (Japan) and indomethacin (Ind) from Sigma, St Louis, MO. Oleic acid was obtained from Wako Pure Chemical Industries (Japan).

Preparations

Polyacrylic acid aqueous gel base was prepared by adding 10% NaOH solution to each pH into various concentrations of Hiviswako 105 presoaked in distilled water at room temperature as described in a previous report (Morimoto et al., 1980). The pH of the gel bases were adjusted to 5.0, 6.5 and 8.0. The concentrations of gel bases were 0.5, 1.0 and 2.0 w/v%. In the case of the gel base containing oleic acid, oleic acid was emulsified in gel base (1.0 w/v%, pH 6.5) at a concentration of 10 v/v%. FP and KP were suspended in separate gel bases at a concentration of 50 mg/ml, and Ind at a concentration of 20 mg/ml. On the other hand, the base of Witepsol H-15 was melted, and FP and KP were suspended in the base by stirring at a concentration of 50 mg/ml, Ind at a concentration of 20 mg/ml. Then the preparations using Witepsol H-15 were cooled gradually in an injection cylinder (i.d. 4.7 mm). The viscosity of gel bases and gel preparations were measured by a

cone-and-plate viscometer (E type, Tokyo Keiki, Japan) at 37°C and the rate of shear of 38.4 s^{-1}.

Release experiments

The release rates of drugs from gel preparations were measured by a suppository release apparatus (Toyama Sangyo, Japan) according to the method of Muranishi et al. (1979). The gel preparation (5 ml) in a cylindrical cell was separated from the extraction phase by a membrane filter (FR 250 micro-filter, Fuji Photo Film, Japan). In the experiments using gel preparations with various pH values, the preparations were slowly stirred (50 rpm) to simulate rectal conditions, but stirring was not done in the experiments using gel preparations with various viscosity values and containing lipid.

Animal experiments

Wistar strain male rats weighing 230–260 g were used, and were fasted for 15 h prior to the experiments. Following the pentobarbital (50 mg/kg) anesthesia, each gel preparation was administered into a rectal loop (5 cm section above anus), which was isolated by ligation. Dosage for FP and KP preparations was 4 ml/kg of body weight and that for Ind was 1 ml/kg body weight. As comparative studies, 3 drugs were administered orally with gel base (1 w/v %, pH 6.5) and rectally with Witepsol H-15 to separate groups of rats. Blood samples (0.5 ml) were collected from the inguinal vein at 0.5, 1, 2, 3 and 5 h after administration.

Assay procedure

The quantity of FP was determined by the gas chromatographic method of Kawahara et al. (1975), and KP by the modified gas chromatographic method of Iguchi et al. (1967). Gas chromatography was carried out by a Shimazu GC-4 CMPF gas chromatograph, and dietyl phthalate was used as an internal standard. The quantity of Ind was determined by the fluorescence spectrophotometric method of Hucker et al. (1966).

Results

Rheological characteristics of polyacrylic acid aqueous gel

Fig. 1 shows the rheological characteristics of polyacrylic acid aqueous gel base (pH 6.5) and the preparations made by suspending FP, KP and Ind in gel base and measured with a cone-and-plate viscometer. The gel base is classified as a non-Newtonian liquid and its viscosity is constant over a wide range of pHs (4.5–12) (Morimoto et al., 1980). The apparent viscosity of gel base in the concentration range 0–2 w/v% increased with increase in the concentration of polyacrylic acid. The apparent viscosity of gel preparations made by suspending FP, KP and Ind in gel base were lower than that of simple gel base. The pH of gel preparations were also lower than that of the gel base. Particularly, the viscosity and pH of gel preparations with suspended KP decreased significantly.

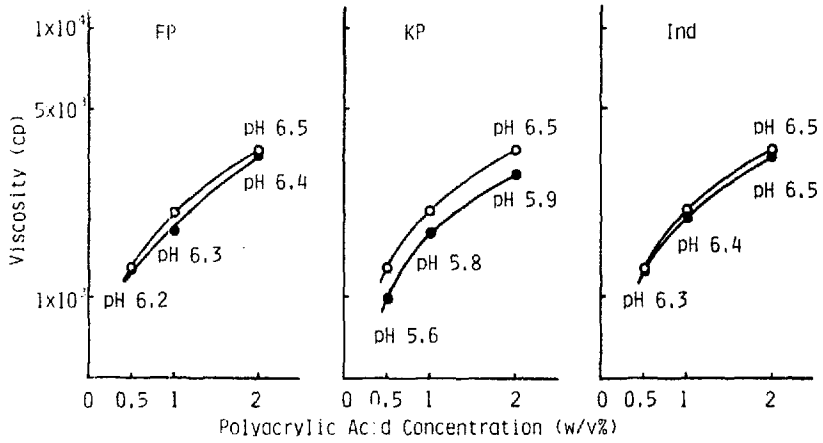

Fig. 1. Relationships among polyacrylic acid concentration, viscosity and pH in various gel bases and gel preparations. The viscosities of gel bases (●) and gel preparations (○) were measured with a cone-and-plate viscometer at a rate of shear of 38.5 s^{-1}. The pH value of gel base was pH 6.5. The gel preparations were prepared with gel base by suspending FP (50 mg/ml of gel), KP (50 mg/ml of gel) and Ind (20 mg/ml of gel). Viscosity is plotted semilogarithmically as a function of the concentration of polyacrylic acid.

Release experiments

Figs. 2 and 3 show the influence of pH and concentrations (viscosities) of gel bases on release experiments for FP, KP and Ind gel preparations. The effects of pH and concentrations of gel preparations were evident. The slower releases of FP, KP and Ind were shown on lower pH of preparations. On the other hand, at lower concentrations (viscosities) of the gel preparations, releases were higher.

Rectal absorptions

Fig. 4 shows the influence of pH of gel base on the plasma levels when FP, KP

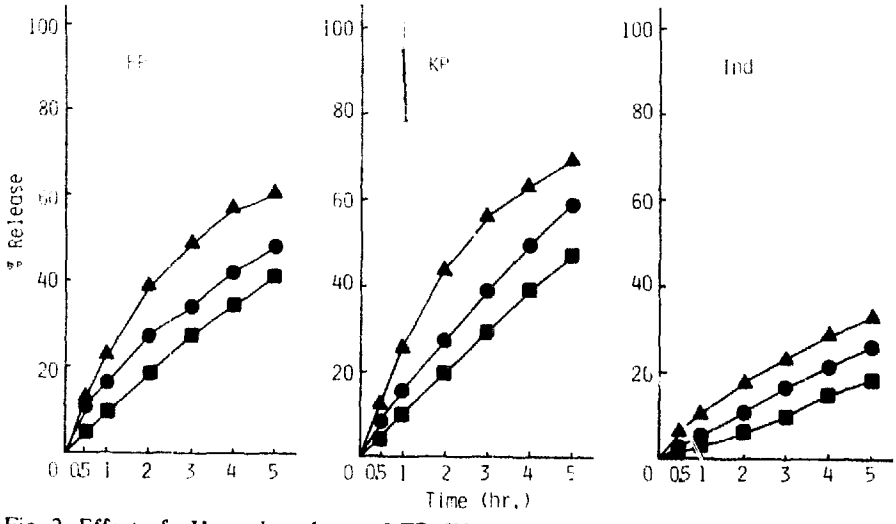

Fig. 2. Effect of pH on the release of FP, KP and Ind from gel bases. The concentration of polyacrylic acid in gel bases was 1.0 w/v%. The pH values of gel bases were: pH 8.0 (▲); pH 6.5 (●); and pH 5.0 (■).

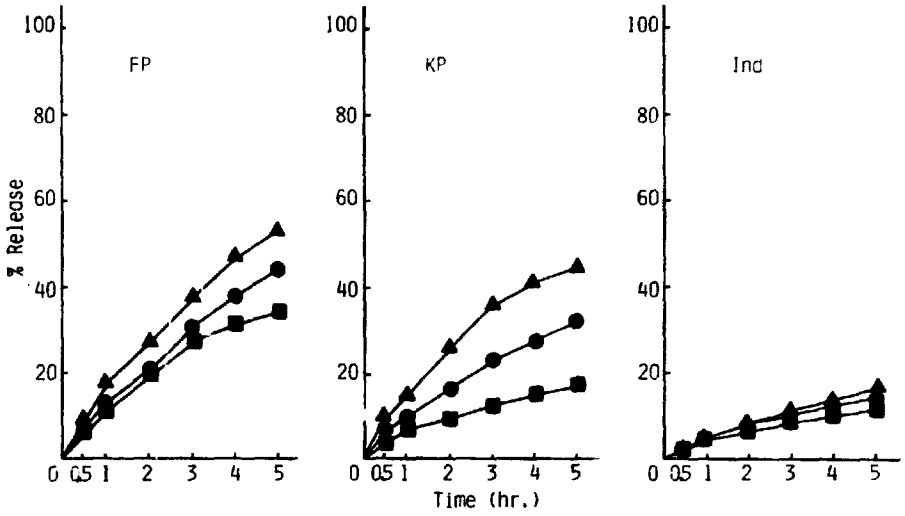

Fig. 3. Effect of concentration of polyacrylic acid on the release of FP, KP and Ind from gel bases. The concentrations of polyacrylic acid in gel bases were: 0.5 w/v% (▲); 1.0 w/v% (●); and 2.0 w/v% (■). The pH value of gel bases was pH 6.5.

and Ind gel preparations were administered rectally in rats. The higher plasma levels were obtained by the gel preparations at higher pH. The plasma level reached a peak at 1 or 2 h, except for the Ind preparation with gel base at pH 8.0 in which the plasma level reached a peak at 3–5 h and tended to be prolonged. Rectal administration of FP and KP gel preparation showed higher plasma levels than with oral administration. However, with regard to the Ind preparation, only at pH 8.0, were plasma levels obtained rectally higher than those after oral dosage.

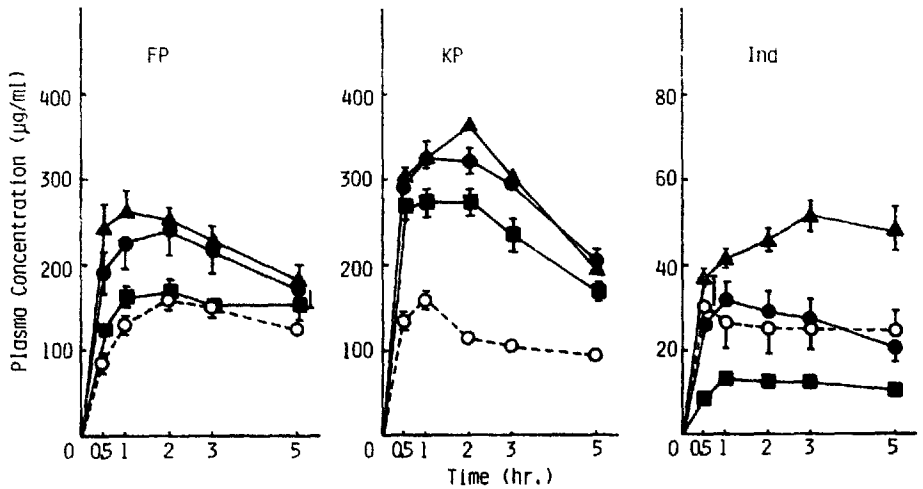

Fig. 4. Plasma concentrations of FP, KP and Ind following rectal administration with gel bases at various pHs and oral administration (○) in rats. The concentration of polyacrylic acid in gel bases was 1.0 w/v%. The pH values of gel bases were: pH 8.0 (▲); pH 6.5 (●); and pH 5.0 (■). FP, KP and Ind were administered at a dose of 200, 200 and 20 mg/kg body weight, respectively. Each value represents the mean ± S.E. of 6 rats.

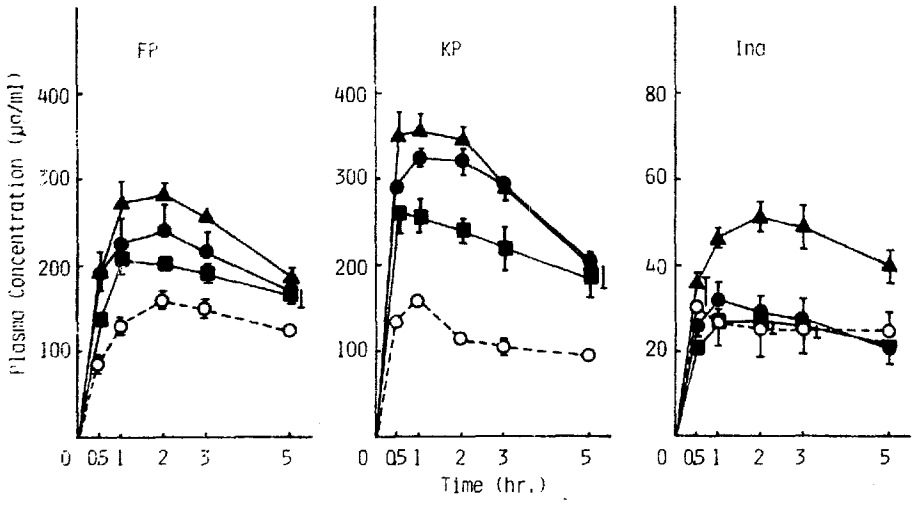

Fig. 5. Plasma concentrations of FP, KP and Ind following rectal administration with gel bases at various concentrations of polyacrylic acid and oral administration (○) in rats. The concentrations of polyacrylic acid in gel bases were: 0.5 w/v% (▲); 1.0 w/v% (●); and 2.0 w/v% (■). The pH value of gel bases was pH 6.5. FP, KP and Ind were administered at a dose of 200, 200 and 20 mg/kg body weight, respectively. Each value represents the mean ± S.E. of 6 rats.

Fig. 5. shows the influence of concentrations (viscosities) of gel bases on plasma levels when FP, KP and Ind gel preparations were administered rectally in rats. As the concentration of the preparation was lowered, the plasma levels of FP, KP and Ind at maximum increased. The plasma levels of FP and KP in the 0.5 w/v% preparation, where the viscosity is lowest, decreased rapidly after passing the peak and reached the levels of the 2 w/v% preparation, where the viscosity is highest, at 5 h after administration.

Fig. 6 shows the plasma levels when FP, KP and Ind were administered rectally with gel base (1 w/v%, pH 6.5), gel base containing 10 v/v% oleic acid and Witepsol H-15. The gel base containing 10 v/v% oleic acid did not affect the absorption of FP and KP compared with the gel base (1 v/v%, pH 6.5); however, it promoted the absorption of Ind, and had a prolonged action of Ind. The plasma levels of FP and KP on administration with Witepsol H-15 were lower than those with all gel preparations. The rectal administration of Ind with Witepsol H-15 indicated high peak plasma levels (C_{max}) and large areas under the plasma concentration–time curves (AUC); however, the plasma level was less prolonged than in the case with the gel base containing 10 v/v% oleic acid.

Bioavailability of rectal administration

The bioavailability of various preparations of FP, KP and Ind in rats are summarized in Table 1. The C_{max} and the AUC of FP and KP after rectal administration of 3 kinds of gel preparation were about 2 times greater than those after oral administration. In the case of the rectal administration of the Ind gel preparation containing oleic acid, c_{max} and the AUC were also about 2 tirnes greater

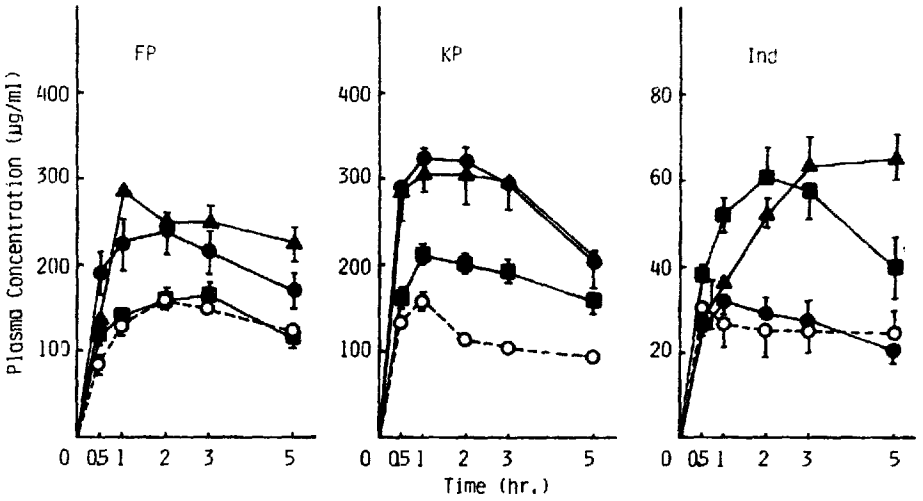

Fig. 6. Plasma concentrations of FP, KP and Ind following rectal administration with various bases in rats. FP, KP and Ind were administered at a dose of 200, 200 and 20 mg/kg body weight, respectively. Each value represents the mean ± S.E. of 6 rats. ●, 1.0 w/v% pH 6.5 gel base; ▲, 1.0 w/v% pH 6.5 gel base containing 10 v/v% oleic acid; ■, Witepsol H-15; ○, oral administration.

than those after oral administration of gel preparation. On the other hand, the AUC of FP and KP after rectal administration of gel preparations were greater than those with Witepsol, whereas the AUC of Ind were about the same as that with Witepsol.

TABLE 1

BIOAVAILABILITY OF VARIOUS PREPARATIONS OF FP, KP AND IND IN RATS

Base		t_{max} (h)	C_{max} (μg/ml)	AUC_0^5 (μg·h/ml)	$AUC_0^5/AUC_{0p.o}^5$
FP	1%, pH 6.5 gel (oral adm.)	2	158.11 ± 15.62	646.57 ± 59.47	
	1%, pH 8.0 gel (rectal adm.)	1	261.43 ± 23.59 **	1077.31 ± 67.54 **	1.67 ± 0.19
	1%, pH 6.6 gel containing oleic acid (rectal adm.)	1	284.17 ± 6.91 **	1170.25 ± 31.04 **	1.81 ± 0.17
	Witepsol (rectal adm.)	3	163.47 ± 16.11	645.17 ± 30.96	1.00 ± 0.10
KP	1%, pH 6.5 gel (oral adm.)	1	158.00 ± 13.97	555.50 ± 40.13	
	1%, pH 8.0 gel (rectal adm.)	2	360.10 ± 6.39 **	1380.04 ± 43.93 **	2.48 ± 0.20
	1%, pH 6.5 gel containing oleic acid (rectal adm.)	1	306.27 ± 21.57 **	1346.81 ± 125.02 **	2.42 ± 0.29
	Witepsol (rectal adm.)	1	212.00 ± 8.74 *	885.60 ± 20.70 **	1.59 ± 0.12
Ind	1%, pH 6.5 gel (oral adm.)	0.5	30.26 ± 6.81	121.94 ± 27.71	
	1%, pH 8.0 gel (rectal adm.)	3	51.35 ± 4.08	219.51 ± 17.16 *	1.80 ± 0.43
	1%, pH 6.5 gel containing oleic acid (rectal adm.)	5	64.85 ± 5.20 **	251.08 ± 23.51 **	2.06 ± 0.51
	Witepsol (rectal adm.)	2	60.06 ± 6.93 *	242.65 ± 34.38 *	1.99 ± 0.53

Each value represents the mean ± S.E. Statistical significance of differences from the oral administration with 1%, pH 6.5 gel is as follows: * $P < 0.025$, ** $P < 0.01$.

Discussion

In in vitro release experiments, the higher the viscosity of the gel the slower was the drug release obtained (Fig. 3). Brunner and Speiser (1976) and Hirano et al. (1980) reported that higher viscosity gel preparations presented slower drug release in in vitro experiments on resorcinol and ibuprofen release from aqueous gel preparation, and their results are in agreement with ours in this report. On the other hand, the drug release of lower pH gel preparation was delayed (Fig. 2), and this is also consistent with the previous report (Hirano et al., 1980). It is considered that FP, KP and Ind, which are weakly acidic drugs, are more dissolved in the gel base of pH 8.0 than in that of pH 5.0, so that the release rates of FP, KP and Ind with the gel base of pH 8.0 are higher than that of the gel base of pH 5.0. As regards to the rectal absorption, the higher plasma levels were obtained by the gel preparations at higher pH and lower viscosity (Figs. 5 and 6). These results of absorption experiments correlate with those of release experiments, and it is suggested that the release rate of FP, KP and Ind from gel preparations is a rate-determining factor in the rectal absorption of FP, KP and Ind in rats.

The bioavailability data suggest that rectal administrations of the FP, KP and Ind gel preparations were superior to oral administration of the gel preparations or rectal administration with Witepsol.

Consequently, when FP, KP and Ind gel preparations using a polyacrylic acid aqueous gel base are administered in rats, the control of plasma concentration on time course should be easy. Also, gel preparations proved highly useful as a preparation to be rectally administered with reduced side-effects and prolonged action.

Acknowledgement

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