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Sustained-release of sodium diclofenac from suppository

Toshiaki Nishihata, Hisayo Wada and Akira Kamada

Faculty of Pharmaceutical Sciences, Osaka University, 1-6 Yamadaoka, Suita, Osaka 565 (Japan)

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Summary

The increased solubility of sodium diclofenac in a suppository base in the presence of lecithin resulted in a slow release of sodium diclofenac from the base. In a study using dogs, the administration of a sodium diclofenac suppository prepared from triglyceride and lecithin as bases (lecithin suppository) at a dose of 2 mg of the drug/kg dog weight maintained the plasma diclofenac concentration within an effective pharmacological range for relatively long periods without a transient high diclofenac concentration in the plasma. The bioavailability of diclofenac after administration of the suppository containing lecithin was equivalent to that observed following the administration of a conventional suppository prepared with only a triglyceride as the base. Rat rectal mucosal damage caused by sodium diclofenac was moderated by the administration of the lecithin suppository, probably due to the low concentration of sodium diclofenac in the rectal fluid due to a slow release of sodium diclofenac from the lecithin suppository.

Introduction

Although the intensity of a pharmacological effect is related to the drug concentration at the site of action which is often also related to the drug plasma concentration, an ideal situation is obtained when the concentration in the body is

Correspondence: T. Nishihata, Faculty of Pharmaceutical Sciences, Osaka University, 1-6 Yamadaoka, Suita, Osaka 565, Japan.

continuously between the minimal effective and the maximal safe values. But when the drug has a relatively short elimination half-life, it is impossible to maintain the concentration within the therapeutic range, without the need of frequent dosing.

Recently, rectal administration of non-steroid anti-inflammatory drugs has increased. However, rectal administration of sodium diclofenac, an anti-inflammatory drug, in a commercial suppository caused rapid transient high plasma diclofenac concentrations, followed by relatively rapid elimination from the plasma in humans. Therefore, sustained-release of sodium diclofenac from a suppository base is more plausible to maintain an effective concentration without transient undesirable high concentrations and to avoid the inconvenience of frequent repetitive dosing. Since it has been reported (Horton and McClure, 1971; Furusawa et al., 1972; Nishihata et al., 1978) that the presence of lecithin in organic solvents increased the partitioning of anionic substances to the oil phase, sodium diclofenac suppositories prepared with a mixture of triglyceride base and lecithin was examined to obtain fundamental information regarding the use of a sustained-release suppositories for anti-inflammatory drugs.

Materials and Methods

Materials

Sodium diclofenac was obtained from Nippon Bulk Yakuhin (Osaka, Japan). Soybean lecithin was obtained from Wako Pure Chemicals (Osaka, Japan). Other reagents used were of analytical reagent grade.

Animals

Three male beagle dogs, 10–11 kg, were fasted for 16 h prior to experimentation for the absorption study and this absorption study was carried out by a cross-over method. For the historical studies, male Wistar rats, 200–225 g, were fasted for 24 h prior to experiments.

Preparation of suppository

Triglyceride (Witepsol H-15, Dynamit Novel, A.G. Chemische, Witter, F.R.G.) was used as the primary suppository base. When a mixture of triglyceride and lecithin was used as the suppository base, lecithin was mixed well with Witepsol H-15 at 50°C before adding sodium diclofenac. Suppositories for the dog study were prepared as follows: 25 mg of sodium diclofenac powder (77–144 μm) was added to 975 mg of molten base at 50°C and was mixed well for 2 h. Sodium diclofenac dissolved in the molten base containing 350 mg lecithin/g base, while sodium diclofenac was suspended in the triglyceride base alone. The molten suppository containing sodium diclofenac was poured into disposable plastic molds (Nichi Packing, Osaka, Japan), allowed to solidify at room temperature and then stored at 4°C until use. The dose of the drug in the suppository for dogs was 2 mg/kg dog weight. For the study in rats, the molten suppository containing 1.25 mg or 5 mg sodium diclofenac/g suppository was poured into a silicone-rubber tube (inner

diameter 2.5 mm) and allowed to solidify at room temperature. The dose of the drug in the suppository for rat was totally 2.5 mg/kg rat weight.

In this study, a sodium diclofenac suppository prepared with triglyceride base alone as base is referred to as a conventional suppository, and a sodium diclofenac suppository prepared with lecithin and triglyceride (3.5 : 6.5) as base is called a lecithin suppository.

Solubility of sodium diclofenac into suppository base

The solubility of sodium diclofenac in each base was determined at 38°C. Two grams of the molten base was incubated with 1 g of solid sodium diclofenac for 2 days without agitation. A 0.1 g liquid aliquot was collected carefully without agitation to prevent the collection of solid sodium diclofenac, and then incubated with 10 ml of 0.1 M phosphate buffer (pH 8.0) at 38°C to extract the diclofenac. Since the concentration of sodium diclofenac in the liquid reached a saturated concentration between 24 and 30 h, the solubility was determined by collecting the sample after 48 h incubation.

Release of diclofenac from suppository

This study was carried out by the method described by Thomas et al. (1971). Briefly, a 0.8 g suppository containing 10 mg sodium diclofenac was put in Visking tubing and incubated in 100 ml normal saline solution at 38°C. 100 μl of saline solution was collected at designated time intervals to determine the amount of diclofenac released. Since complete melting of each suppository in the Visking tube occurred within 15 min after the incubation, it seems that the melting process does not greatly affect the release of sodium diclofenac from the suppositories.

Absorption study in dogs

After administration of a suppository, blood samples were collected from the femoral vein at designated time intervals and centrifuged to obtain plasma. To determine the bioavailability of diclofenac after rectal administration, plasma concentrations of diclofenac were also measured after intravenous administration of sodium diclofenac at a dose of 1 mg/kg.

Assay of diclofenac

The assay of diclofenac was carried out using a high-pressure liquid chromatographic method described by Yaginuma et al. (1981). The assay limitation of diclofenac by this method was 0.04 μg/ml.

Histological study

This study was carried out according to the method described by Sithigorngul et al. (1983). Before rectal administration, the bowel contents in the lower rectum were evacuated by pressing down on the abdomen. A suppository having a dose described in the section on the preparation methods was administered into rectum and the anus was lightly ligated with thread to prevent leakage of suppository. At the designated times of 1 and 6 h after administration, the rat was lightly anesthetized

with ether and sacrificed by decapitation. The rectum and anus were removed as one segment with a length of approximately 2.5 cm. For light microscopy, pieces of the rectum were fixed in alcoholic Bouin's fixative, dehydrated, embedded in parrafin, sectioned, and mounted on slides using conventional histological methods. To assess damage to the rectal mucosa, sections were stained using the PAS method and Harris's hematoxylin (Humason, 1979). In 5 of 12 serial sections, the percent damage shown by mucosal epithelial cells was determined with a light microscope at a magnification of $\times 400$. With an ocular micrometer, 5000 μm of linear surface of the epithelium in each section was measured. Within this length, regions were measured which showed broken surface or cell detachment; this was repeated with each of the 5 sections on a given slide.

Results and Discussion

Solubility and release of sodium diclofenac

As shown in Fig. 1, the higher the content of lecithin in the triglyceride base, the greater the apparent solubility of sodium diclofenac. Since it has been suggested (Horton and McClure, 1971) that lecithin can interact with anionic substances and form a relatively stable complex in an organic solvent, the increased solubility of sodium diclofenac in the suppository base in the presence of lecithin may be due to the interaction of diclofenac and lecithin in base. The fact that the solubility of the free acid of diclofenac in triglyceride was not increased greatly by the presence of lecithin supports the above suggestion.

Further, the higher the content of lecithin in the base, the slower is the release of sodium diclofenac from the base (Fig. 2). It has been suggested (Horton and

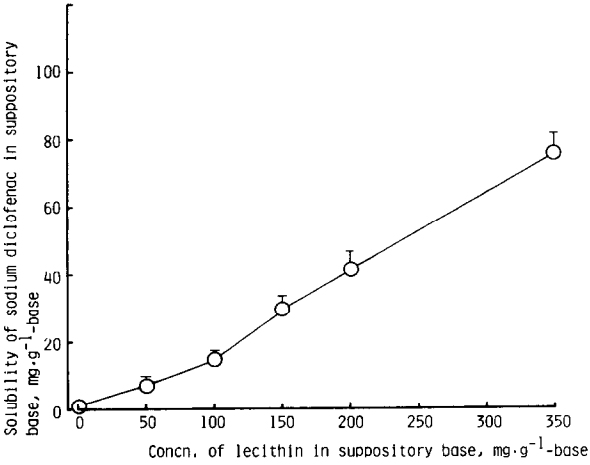

Fig. 1. Effect of lecithin on the solubility of sodium diclofenac into triglyceride suppository base at 38°C. Each value represents the mean $\pm$S.D. (n = 4).

McCure, 1971; Furusawa et al., 1972) that a complex of an anionic substance with lecithin can be formed and taken into the micellar aggregates in a bulk organic phase. An apparent slower release of diclofenac from a lecithin suppository may be due to the slow release of sodium diclofenac from micelles in the bulk triglyceride phase. Since it was observed that the release of diclofenac even from a lecithin suppository eventually reached 100% (Fig. 2), and that a melted lecithin suppository in the Visking tube resulted in greater turbidity to the naked eye according to the incubation periods, it may be considered that this observed turbidity of a melted lecithin suppository is due to the contact of possible micelles (aggregates) with water at the oil phase surface, resulting in the release of diclofenac. Therefore, it may be speculated that a possible stable lecithin micelle containing diclofenac in the oil phase released the diclofenac by destroying a micellar formation of lecithin in water when the micelles contact water, and the increase of the amount of lecithin in the suppository base suppresses the diffusion of the aggregates from the inner to the oil phase surface and/or suppresses the immersion of water into the bulk oil.

Absorption study of sodium diclofenac in dogs

The above findings indicate that the presence of lecithin in a triglyceride base resulted in a slower release of sodium diclofenac from the base. The plasma diclofenac concentration profile in dogs after rectal administration of the lecithin suppository was compared with that obtained after administration of a conventional suppository. In order to estimate the bioavailability of diclofenac after rectal administration, plasma diclofenac concentrations after intravenous administration were also determined.

It has been reported (Ishizaki, 1984) that the concentration of diclofenac in human plasma required to produce a suitable pharmacological response might be between 0.5 and 4 μg/ml. Since the conventional suppository was administered

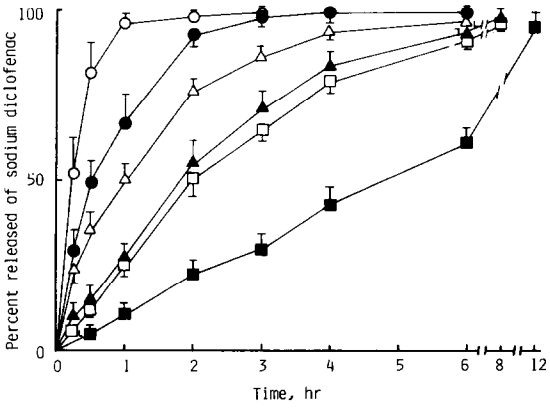

Fig. 2. Release of sodium diclofenac from a suppository at 38°C in the presence of following concentration of lecithin in the base: 0 mg (○), 50 mg/g (●), 100 mg/g (△), 200 mg/g (▲), 250 mg/g (□), and 350 mg/g (■). Each value represents the mean ± S.D. (n = 4).

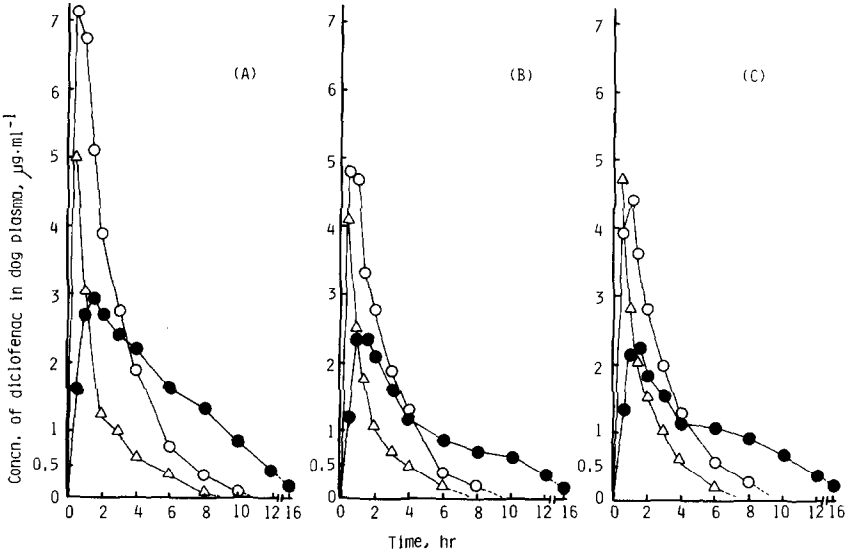

Fig. 3. Plasma diclofenac concentration in dogs as a function of time after administration of a conventional suppository (○) or a lecithin suppository (●) (see text) at a dose of 2 mg of sodium diclofenac/kg. △, represents the plasma diclofenac concentration after intravenous administration of sodium diclofenac at a dose of 1 mg/kg. In this study, 3 male beagle dogs were used as shown in A (10.2 kg body weight), B (10.1 kg), and C (10.9 kg).

clinically at a dose of 1 mg sodium diclofenac/kg in humans but it would be expected that the lecithin suppository would release sodium diclofenac very slowly, the dose of sodium diclofenac used in the dog study was 2 mg/kg to maintain an effective diclofenac concentration. As shown in Fig. 3, the administration of a conventional suppository resulted in a rapid initial increase of plasma diclofenac concentration and only maintained the effective concentration of more than 0.5 μg/ml for up to 5 h. On the other hand, although the administration of a lecithin suppository showed a lower maximum plasma diclofenac concentration compared to that following the conventional suppository, effective plasma diclofenac concentrations (more than 0.5 μg/ml) were maintained for about 12 h and diclofenac in the plasma was detected even 16 h after administration. This result indicates that rectal absorption of sodium diclofenac after administration of lecithin suppository is controlled by the release of sodium diclofenac from base.

The bioavailability of sodium diclofenac after rectal administration compared with that after intravenous administration in dogs is shown in Table 1. The bioavailability of diclofenac after the administration of lecithin suppositories was quite similar with that observed after administration of conventional suppositories.

Effect of sodium diclofenac suppository on surface integrity of rat rectal mucosa

It has been reported (Yaginuma et al., 1982) that serious rectal lesions and ulceration is often encountered after administration of sodium diclofenac supposito-

TABLE 1

BIOAVAILABILITY OF DICLOFENAC AFTER RECTAL ADMINISTRATION OF CONVENTIONAL SUPPOSITORY AND LECITHIN SUPPOSITORY

Administration	Dose (mg/kg)	Dog 1		Dog 2		Dog 3	
		AUC (μg·h/ml)	BA (%)	AUC (μg·h/ml)	BA (%)	AUC (μg·h/ml)	BA (%)
		[T_{max} (h), C_{max} (μg/ml)]					
intravenous administration	1.0	11.2	100	8.2	100	9.6	100
rectal administration							
conventional suppository	2.0	20.6	92.0	15.6	95.1	13.2	68.8
		[0.5,	7.16]	[0.5,	4.86]	[1,	4.57]
lecithin suppository	2.0	20.2	90.2	14.7	89.6	12.6	65.6
		[1.5,	2.97]	[1.5,	2.41]	[1.5,	2.24]

Bioavailability was determined according to following equation:
Bioavailability = $(AUC)_{rec} \cdot (dose)_{i.v.} / (AUC)_{i.v.} \cdot (dose)_{rec} \times 100$

ries. Therefore, to evaluate the clinical applicability of a lecithin suppository, a histological examination of the rectal mucosa was conducted.

Histological observations on rat rectal mucosa were performed at 1 and 6 h after the administration of each suppository to the rats and the changes in the mucosa were determined according to the methods described in the experimental section. Epithelial cells exposed only to the suppository base showed fewer surface discontinuities as compared with the control (Table 2). When the administration of a conventional suppository containing 5 mg sodium diclofenac/g suppository was administered at a dose of 2.5 mg sodium diclofenac/kg rat weight, about 30% of the mucosal surface was disrupted 1 h and 6 h after administration. When the lecithin suppository containing 5 mg sodium diclofenac was administered at a dose of 2.5 mg sodium diclofenac/kg rat weight, much less damage to the epithelial surface was seen (Table 2) at 1 h and 6 h after administration. Further, when administration of the conventional suppositories containing smaller amounts of sodium diclofenac (1.25 mg sodium diclofenac/g suppository) at a dose of 0.5125 mg sodium diclofenac/kg rat weight was carried out 4 times at 1-h intervals, much less damage to the epithelial surface was observed even at 6 h compared to that after one administration of a conventional suppository containing 5 mg of sodium diclofenac/g suppository at a dose of 2.5 mg sodium diclofenac/kg rat weight.

The more moderate damage to the mucosal tissue after administration of a lecithin suppository seems to be due to the low concentration of sodium diclofenac in the rectal fluid and the small accumulation of sodium diclofenac in rectal mucosa by the slow release of sodium diclofenac from lecithin suppository. It is also possible that lecithin may protect the mucosa from the action of sodium diclofenac since it

TABLE 2

EFFECT OF SODIUM DICLOFENAC SUPPOSITORY ON SURFACE INTEGRITY IN RAT RECTAL MUCOSA AS DETERMINED BY LIGHT MICROSCOPE

Treatment group	percent disrupted surface [a] after treatment (mean ± S.D.) ($n \geq 6$)	
	1 h	6 h
suppository base alone		
Witepsol H-15	1.02 ± 0.46	0.81 ± 0.54
Witepsol H-15 (65%) + lecithin (35%)	0.97 ± 0.66	1.04 ± 0.42
Sodium diclofenac suppository		
conventional suppository I [b]	31.41 ± 12.68	26.74 ± 11.92
conventional suppository II [c]	8.32 ± 4.72	9.1 ± 6.27
lecithin suppository [d]	4.68 ± 2.31	4.19 ± 1.76

[a] The percent disrupted surface refers to the length of measured surface which was discontinuous as a percentage of the total distance measured.

[b] Conventional suppository I containing 5 mg sodium diclofenac/g suppository at a dose of 2.5 mg sodium diclofenac/kg rat weight was administered once.

[c] Conventional suppository II containing 1.25 mg sodium diclofenac/g suppository at a dose of 0.5125 mg sodium diclofenac/kg rat weight was administered 4 times in 1-h intervals. Periods in Table was after first administration of suppository.

[d] Lecithin suppository containing 5 mg sodium diclofenac/g suppository at a dose of 2.5 mg of the drug/kg rat weight was administered once.

has been reported (Lichtenberger et al., 1983) that lecithin protected the ulceration in stomach by indomethacin.

Since the lecithin suppository showed less irritative effects on the rat rectal mucosa, it is possible that the administration of such a lecithin suppository may be desirable.

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