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Investigation of sustained-release suppository of sodium diclofenac in humans

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Summary

A sustained-release suppository of sodium diclofenac prepared with a mixed base of glyceride and natural soya lecithin sustained the plasma diclofenac concentrations significantly in human subjects, with a three-times slower apparent absorption rate (absorption half-life: 2.9 h) in comparison with that after administration of a commercial suppository of sodium diclofenac (absorption half-life; 0.9 h). The addition of a high-melting point glyceride or hydrogenated soya lecithin in the suppository caused a slower apparent absorption rate of diclofenac with an absorption half-life of 6.3 h. Dissolution of diclofenac from the sustained-release suppository used in this study may occur according to the apparent leaching type mechanism proposed by Higuchi; i.e. the permeating rate of rectal fluid into the suppository's matrix may regulate the release of diclofenac from the suppository.

Introduction

Suppositories of sodium diclofenac (Voltaren), which is an anti-inflammatory drug, are widely used for clinical purposes. Since the disappearance of diclofenac after administration of Voltaren is somewhat rapid (Riess, 1978), patients with rheumatoid arthritis sometimes do not sleep well due to the short-term action of Voltaren. Therefore, a long-acting suppository of sodium diclofenac with sustained plasma diclofenac concentrations would be helpful to the therapeutics of many patients, since the disturbance of sleep at night may result in mental stress.

Recently, we have demonstrated (Nishihata et al., 1985) that a sustained-release suppository of sodium diclofenac containing lecithin as an additive in a glyceride base maintained the plasma diclofenac concentrations in dogs. Since it is considered that there are several physiological differences between the rectum of humans and dogs, we examined a sustained-release suppository of sodium diclofenac, which was reported previously (Nishihata et al., 1985), in human subjects. We further devised the sustained-release suppository

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of sodium diclofenac to maintain firmly the plasma diclofenac concentrations in human subjects.

Materials and Methods

Materials

Sodium diclofenac was supplied by Ciba-Geigy Japan Co. (Hyogo, Japan). Hydrogenated soya lecithin was supplied from Nikko Chemicals Co. (Tokyo, Japan). Natural soya lecithin was obtained from Wako Pure Chemicals Co. (Osaka, Japan). Glycerides used as suppository base were listed in Table 1. Other reagents used were of analytical grade.

Preparation of suppository of sodium diclofenac

The ingredients of the suppositories are described in Table 1. Suppositories of Code-1 and Code-5′ were prepared as follows: sodium diclofenac was suspended in each melted base described in Table 1 at 50°C, the molten mass was poured into disposable plastic molds (Nichi Packing Co., Osaka, Japan; 1.2 ml vol.), and then was solidified at 10°C. Suppositories of Code-2, Code-3 and Code-5 were prepared by dissolving sodium diclofenac in a variously melted base containing natural soya lecithin at 50°C as described previously (Nishihata et al., 1985). Suppository Code-4 was prepared by dissolving sodium diclofenac in a melted base after dissolving hydrogenated soya lecithin in the glyceride base at 80°C.

Dissolution study of sodium diclofenac from suppository

One gram of each test suppository wrapped with two sheets of gauze was immersed in a beaker containing 100 ml warm saline (38°C) and then 100 μl aliquots of saline which had been passed through a millipore filter (pore size: 0.5 μm) was collected at designated time intervals and assayed to determine the dissolution of sodium diclofenac.

Rectal absorption study

Six healthy male human subjects, 23–36 years old, were not allowed to take breakfast. Administration of suppository was carried out at 08.00 or 09.00 h, blood samples (2 ml) and urine samples were collected at designated time intervals, and then the blood was centrifuged to obtain plasma.

Assay

Assay of diclofenac was carried out by a high-performance liquid chromatography method described previously (Yaginuma et al., 1981) with minor modification (Nishihata et al., 1985). The assay limitation of diclofenac in plasma in the present study was 40 ng/ml.

Results and Discussion

Dissolution of sodium diclofenac from each suppository

We have reported (Nishihata et al., 1985) that suppositories of sodium diclofenac prepared with

TABLE 1

CODE AND CONSTITUENTS OF SUPPOSITORY

Code	Sodium diclofenac (mg)	Base (mg)	Glyceride	Soya lecithin	
				natural	hydrogenated
			% in base		
1	50	950	100 [a]	–	–
2	50	950	65 [a]	35	–
3	50	950	65 [b]	35	–
4	50	950	65 [b]	–	35
5	50	950	65 [c]	35	–
5′	50	950	100 [c]	–	–

[a] Novate (m.p. 33.5–35.5°C),

[b] Witepsol H-15 (m.p. 33.5–35.5°C),

[c] Mixture of 1 vol. of Witepsol H-15 and 3 vol. of Witepsol H-42 (m.p. 41.0–43.0°C) (1 : 3) mixture.

glyceride (Witepsol H-15) and natural soya lecithin (6.5 : 3.5) as the base released diclofenac with an apparent zero-order rate constant when the Thomas method (Thomas and McCormak, 1981) was used for dissolution experiments. A ratio of 6.5 glyceride : 3.5 lecithin in the base was employed in this study. Further, since rectal absorption of diclofenac after administration of the above reported sustained-release suppository occurred rapidly rather than at a rate expected from the dissolution study using the Thomas method in our previous study (Nishihata et al., 1985); the new method described in experimental section was employed for the dissolution experiment of sodium diclofenac from suppositories in the present study.

Dissolution of diclofenac from suppository of Code-1 occurred rapidly to more than 90% within 30 min, as shown in Fig. 1A. The addition of natural soya lecithin in the base of Code-1 or Witepsol H-15 (reported previously; Nishihata et al., 1985) delayed the dissolution rate of diclofenac from each suppository (Code-2 and Code-3). Suppositories of Code-1, -2 and -3 melted completely within 5 min in the warm saline with swelling of lecithin of Code-2 and Code-3 (naked eye observation). Slow dissolution of diclofenac from suppository of Code-4 was also observed without melting but with swelling (naked eye observation) probably due to hydrogenated soya lecithin which does not melt at 38°C. Although only slight dissolution of diclofenac from the suppository of Code-5′, which was prepared with only a high melting point glyceride base was observed (Fig. 1 and Table 1), dissolution of diclofenac from a suppository of Code-5, which was prepared by addition of natural soya lecithin to the base of Code-5′, was observed with swelling of the base (naked eye observation) (Fig. 1).

When the total amount of diclofenac released, Q′, was plotted against the square-root of time (incubation time), straight lines were obtained for each suppository, except for the final stage of the dissolution experiment (Fig. 1B). From the above findings including swelling of the base containing lecithins, an apparent leaching type of release mechanism proposed by Higuchi with Eqn. 1 may

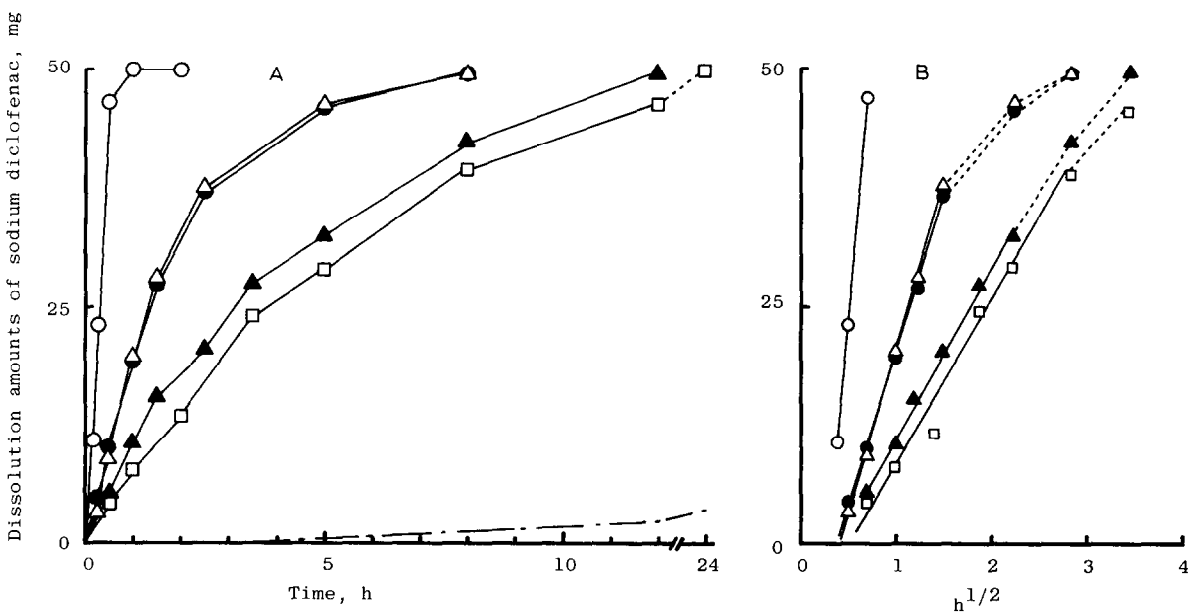

Fig. 1. A: dissolution of sodium diclofenac from suppositories of Code-1 (○), Code-2 (●), Code-3 (△), Code-4 (□), Code-5 (▲) and Code-5′ (·−·−·) as a function of time after the incubation. B: comparison of the dissolution profiles according to the square-root of time for each suppository shown in A. (Code 1: $y = 124.8 \times - 35.2$, $r = 0.999$, Code 2: $y = 35.7 \times - 19.7$, $r = 0.995$, Code 3: $y = 37.6 \times$, $r = 0.999$, Code 4: $y = 18.17 \times - 11.4$, $r = 0.995$, Code-5: $y = 19.06 \times - 7.41$, $r = 0.99$). Each value represents the mean of three experiments.

be applied for the dissolution of diclofenac from the suppositories containing lecithins of Code-2 to Code-5.

$$Q = \left[D\pi(2A - \pi C_s)C_s \cdot t/\tau\right]^{1/2} \quad (1)$$

where Q = the amount of drugs released after time t per units exposed area; D = the diffusitivity of the drug in the permeating fluid; τ = the tortuosity factor of the capillary system; A = the total amount of drugs present in the matrix per unit volume; C_s = the solubility of the drug in the permeating fluid, π: the porosity of the matrix.

$$Q' = Q \cdot S_q \quad (2)$$

where S_q = the total exposed area.

$$Q' = S_q\left[D\pi(2A - \pi C_s)C_s \cdot t/\tau\right]^{1/2} = kt^{1/2} \quad (3)$$

where k = the slope obtained from straight line in Fig. 1B.

The k may be an apparent total control factor for the dissolution of diclofenac from each formulation, i.e. a small value of k represents slow dissolution of diclofenac from the suppository. Since dissolution of diclofenac from suppository Code-5 was observed in spite of only slight dissolution of diclofenac from suppository of Code-5′ (not melted as described above) (Fig. 1A) and dissolution of diclofenac from suppositories of Code-2 and Code-3 occurred slowly in spite of rapid melting in the fluid, it seems to be clear that lecithin in those suppositories regulates the apparent dissolution rate of diclofenac from the matrix. Dissolution of diclofenac from suppositories occurred in the following order: Code-1 > Code-2 = Code-3 > Code-4 = Code-5. A detailed mechanism is not clear at the present time for the slow dissolution of diclofenac from the suppository containing lecithin. However, since diclofenac is dissolving in the base containing lecithin during the preparation, it may be possible that diclofenac in the anionic form complexes with lecithin in cation forms such as phosphatidylcholine and phosphatidylethanolamine in glyceride base as the organic phase, as proposed previously (Horton and McClore, 1971). Since the observed swelling

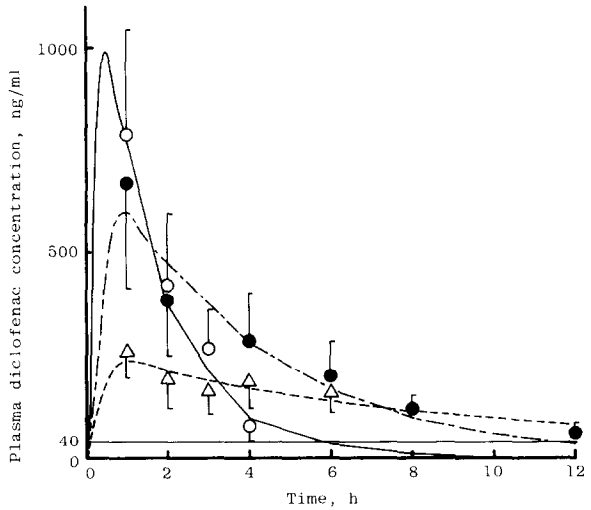

Fig. 2. Plasma diclofenac concentration in human subjects after rectal administration of suppositories of Code-1 (○), Code-2 (●) and Code-4 (△) at a dose of 50 mg sodium diclofenac. The number of subjects used in this study was 3 with weights of 54 kg, 58 kg and 76 kg. Each value represent the mean ± S.D. ($n = 3$). Lines, ———, ·—·—· and - - - - - - represent the expected plasma diclofenac concentration determined by the computer analysis.

of lecithin (naked eye observation) seems to regulate the dissolution of diclofenac from the matrix as described above, it may also be considered that

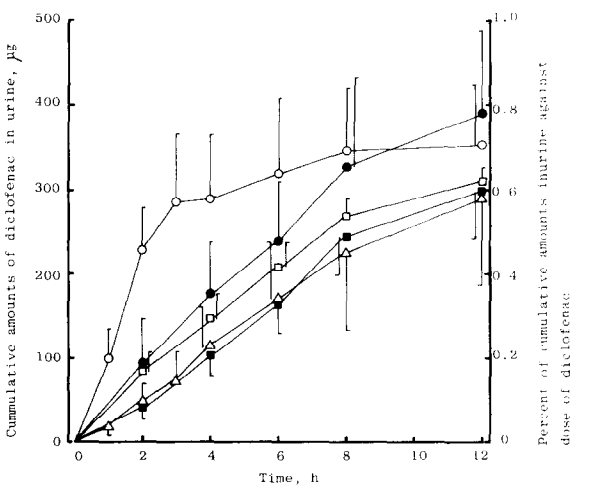

Fig. 3. Cumulative urinary excretion amounts of diclofenac in human subjects after administration of suppositories of Code-1 (○), Code-2 (●), Code-3 (□), Code-4 (△) and Code-5 (▲) at a dose of 50 mg sodium diclofenac. The number of subjects used in this study was 6 with weights from 54 to 76 kg. Each value represents the mean ± S.D.

TABLE 2

PHARMACOKINETIC PARAMETERS [a] OF DICLOFENAC OBTAINED FROM PLASMA CONCENTRATION (SHOWN IN FIG. 2) AFTER RECTAL ADMINISTRATION OF SUPPOSITORIES OF CODE-1, CODE-2 OR CODE-4 (SUBJECTS NUMBERS ARE THREE IN CROSS-OVER STUDY)

Code no.	C_{max} ($\mu g \cdot ml^{-1}$)	T_{max} (h)	k_a (h^{-1})	$t_{1/2}$ (h)	k_e (h^{-1})	$AUC_{0-\infty}$ ($\mu g \cdot h \cdot ml^{-1}$)
1	1.02 ± 0.39	0.5	0.76 ± 0.17	0.9	37.1 ± 18.1	1.71 ± 0.68
2	0.61 ± 0.22	1	0.24 ± 0.023	2.89	26.7 ± 7.62	2.09 ± 0.98
4	0.24 ± 0.066	1.25	0.11 ± 0.017	6.30	33.2 ± 14.4	2.11 ± 0.86

Pharmacokinetics parameters such as C_{max}, T_{max}, k_a, $t_{1/2}$, k_e and $AUC_{0-\infty}$ were determined by the computer analysis described in text. C_{max} = peak plasma diclofenac concentration; T_{max} = time with peak plasma diclofenac concentration; k_a = apparent absorption rate constant; $t_{1/2}$ = absorption half-life time; k_e = apparent elimination rate constant from plasma; AUC = area under the curve of plasma diclofenac concentration.

the k value expresses the permeating rate of fluid into the matrix; i.e. when the complex of diclofenac with lecithin contacts the permeating fluid, diclofenac is released rapidly due to unstable complex formation of diclofenac and lecithin in water.

Rectal absorption of sodium diclofenac in human subjects

Plasma diclofenac concentrations and cumulative urinary excretion of diclofenac in human subjects after administration of each suppository as listed in Table 1 are shown in Figs. 2 and 3, respectively. Since suppositories of Code-2 and Code-4 showed similar dissolution profiles with suppositories of Code-3 and Code-5, respectively, in the above study (Fig. 1A), suppositories of Code-1, Code-2 and Code-4 as three types of suppositories were examined for determination of plasma diclofenac concentrations. When suppositories of Code-2 or Code-4 were administered, plasma diclofenac concentrations were maintained without significant transient peak levels in comparison with the rapid increase of plasma diclofenac concentrations followed by a rapid decrease after administration of a suppository of Code-1. Pharmacokinetic parameters (Table 2) were obtained by using the computer analysis developed by Yamaoka et al. (1981). An apparent absorption rate constant after administration of a suppository of Code-1 was greater than that after the administration of Code-2 which was followed by Code-4. However, there is no significant difference in terms of an apparent elimination rate constant from plasma and the bioavailability estimated by the AUC method among the three suppositories.

Urinary excretion of diclofenac also occurred rapidly when a suppository of Code-1 was administered among the suppositories in Table 1 (Fig.

TABLE 3

COMPARISON OF APPARENT URINARY EXCRETION RATES ($\Delta U/\Delta t$), WHICH WERE CALCULATED WITH URINARY EXCRETION OF DICLOFENAC (ΔU) FOR 2 h (Δt) FROM FIG. 3, WITH ABSORPTION RATE CONSTANT (k_a) FROM TABLE 2 AND WITH k VALUE OBTAINED DISSOLUTION STUDY IN FIG. 1

Code	$\Delta U/\Delta t$ ($\mu g/h$)	$\frac{(\Delta U/\Delta t)(\text{Code-2–5})}{(\Delta U/\Delta t)(\text{Code-1})}$	$\frac{k_a(\text{Code-2–5})}{k_a(\text{Code-1})}$	$\frac{k(\text{Code-2–5})}{k(\text{Code-1})}$
1	136.8	1	1	1
2	48.9	0.357	0.316	0.286
3	41.7	0.305	–	0.301
4	23.7	0.173	0.145	0.146
5	21.6	0.158	–	0.152

3). Urinary excretion of diclofenac after administration of suppositories of Code-4 or Code-5 occurred more slowly than those following the administration of Code-2 and Code-3. Urinary excretion of diclofenac for 24 h after administration of each suppository was around 0.7% against total dose. When an apparent urinary excretion rate of diclofenac for the first 2 h after administration was compared with absorption rate shown in Table 2, the ratio of apparent urinary excretion rate of diclofenac after the administration of suppositories of Code-2 and Code-4 against the rate after administration of suppository of Code-1 showed quite similar ratios of absorption rate constants after administration of Code-2 and Code-4 against the rate constant after administration of Code-1, as shown in Table 3.

Since it is considered that the amount of diclofenac excreted in the urine is dependent on its plasma concentration and the plasma concentration may also be dependent on the amount absorbed, especially during the earlier stages after administration, it may be possible to estimate the relative absorption rate of diclofenac from the relative urinary excretion rates of diclofenac during the earlier stages after administration. Therefore, from the urinary excretion data it is expected that absorption of diclofenac after the administration of suppositories of Code-3 and Code-5 occurred in a similar manner to those after the administration of Code-2 and Code-4, respectively.

From the above findings including plasma diclofenac concentrations reported in Fig. 2, it appears that sustained-release suppositories of Code-2 and Code-3 are effective in humans for about 10 h and suppositories of Code-4 and Code-5 act effectively for more than 12 h after administration, since the minimum effective plasma diclofenac concentrations may be about 50 ng/ml in humans (personal communication from Ciba-Geigy, Japan). Further, the ratio of k values obtained from suppositories of Code-2 to Code-5 against that from Code-1 in Fig. 1 also showed similar ratios to those obtained by comparison of the apparent urinary excretion rates (Table 3), suggesting that the method used in this study for the dissolution experiment is suitable for the relative estimation of sustained dissolution of sodium diclofenac from the suppository containing lecithin in the rectal lumen.

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