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SUSTAINED RELEASE SUPPOSITORY OF SODIUM DICLOFENAC: USE OF WATER ABSORBABLE POLYMER

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ABSTRACT

The investigation on the usefulness of water absorbable polymer (Poys® SA-20) for the preparation of sustained release suppository was performed. To prepare the sustained release suppository, sodium diclofenac solution is absorbed into the sphere polymer, and the particles of the polymer after dryness are suspended in the melted triglyceride suppository base, followed by solidification. The sustained release of sodium diclofenac from the suppository was confirmed by the in vitro release study with slow release of sodium diclofenac and by the in vivo absorption study in dogs with an avoidance

of transient high plasma diclofenac concentration and a prolong of plasma diclofenac concentration.

INTRODUCTION

Suppositories of sodium diclofenac (Voltaren®), which is anti-inflammatory drug, are widely used for clinical purposes. Since the disappearance of diclofenac after administration of Voltaren® is somewhat rapid (1), patients with rheumatoid arthritis sometimes do not sleep well due to the short-term action of Voltaren® (2). Therefore, a long-acting suppository of sodium diclofenac with sustained plasma diclofenac concentration would be helpful to the therapeutics of patients. Since an avoidance of the potency abuse in relating to the rapid transient high plasma diclofenac concentration is another important purpose, formulation of sustained release suppository of sodium diclofenac is desired.

In the present study, the preparation of sustained-release suppository of sodium diclofenac was performed using a water absorbable polymer, which incorporates drug into the polymer matrix.

MATERIALS AND METHODS

Sodium diclofenac was supplied by Ciba Geigy Japan (Takarazuka, Japan). Poys® SA-20 (water absorbable polymer), polyacrylic acid with intramolecular bridge, which is a white sphere (100 to 250 um diameter) with a specific gravity of 0.8 to 1.0 g/ml, was supplied by Kao Co. Ltd. (Tokyo, Japan). Triglyceride, Pharmasol B-115, was obtained from Nippon Fat &Oil Co. (Tokyo, Japan).

Since it was confirmed preliminary that the capability of the sphere polymer to absorb 0.5 %w/v sodium diclofenac solution was about 250g/g, 500 mg of the polymer is added to 100 ml of water containing 500 mg of sodium diclofenac. After drug solution was absorbed completely into the polymer, the swollen polymer was dried at 40°C under the vacuum condition. The water content of the dried materials was less than 1.5 %w/w. The content of diclofenac in the materials was 501.2 ± 1.4 mg/g.

Suppositories were prepared as follows: To prepare a conventional suppository (Supp-A), 500 mg of sodium diclofenac was suspended in 16 g of the melted triglyceride at 45°C. The 825 mg molten mass was poured into disposable plastic mold (Nichii Packing Co., Osaka Japan; 1.2 ml volume), and then was solidified

at room temperature. To prepare a sustained-release suppository (Supp-B), 1.0 g of the sphere polymer containing drug was suspended in 16 g of the melted triglyceride at 45°C. The 850 mg of the molten mass was poured into the plastic mold, and was solidified at room temperature.

The in vitro release study was carried out according to the method reported previously (3), which modified the method of Thomas et al (4). Briefly, a suppository was put in the cellulose membrane tubing (Nakarai Chemicals Co., Kyoto, Japan; Code No. 411-03 and type 20/32 with a diameter of 16 mm, wall thickness of 0.02 mm and pore size of 10,000 to 20,000 molecular weight cut offs), and incubated in 100 ml of 0.1 M sodium phosphate (pH 7.0) in a conical flask, which is shaken at 200 strokes/min, at 37°C. 100 ul of aqueous solution was collected at designated time intervals. A complete melting of each suppository in the cellulose membrane tube occurred within 20 min after incubation.

Three male beagle dogs (10 to 11 kg) were fasted for 16 h prior to the administration of suppository for the cross-over study. After a rectal administration of a suppository at a dose of 25 mg of sodium diclofenac, 2 ml of blood was collected from

left fore-leg vein of dogs. The blood was centrifuged at 3,000 rpm for 5 min, to obtain plasma. To measure the plasma profile of drug concentration after intravenous administration, 1 ml of saline containing 5 mg of sodium diclofenac was injected from right fore-leg vein of dog.

The assay of diclofenac in plasma was performed by a high performance liquid chromatographic method reported by Yaginuma et al (5), with an assay limitation of diclofenac was 0.05 ug/ml in plasma.

RESULTS

The complete release of sodium diclofenac from Supp-A was observed within 3 h (Fig. 1). The apparent slow release of sodium diclofenac from Supp-A in spite of rapid melt of the suppository base during the release study seems to indicate that the release of drug through the cellulose membrane rather than a release from suppository is rate limiting step. Since the transport of drug through cellulose membrane is dependent on the concentration of drug dissolved inside of the tube, the method used in this study is able to be employed to compare the relative release rate between suppositories. The release of sodium

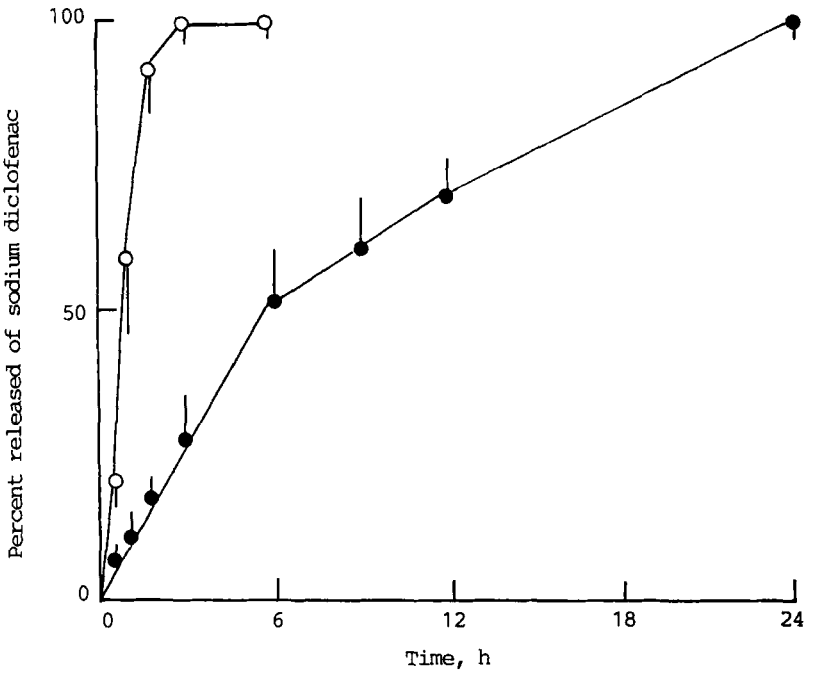

FIGURE 1

Release of diclofenac from Supp-A (o) and Supp-B (●) at 37°C. Each value represents the mean ± S.D. (n=3).

diclofenac from Supp-B delayed significantly in comparison to that from Supp-A (Fig. 1), and a complete release was observed within 24 hr. To characterize the in vitro release, a model-independent method which was reported by Tanigawara et al (6) and was based on the moment analysis, was employed, in which the release of the drug was defined by the mean in vitro release time (MRLT) with equation [1].

$$MRLT = \int_0^\infty t\,(dm/dt)\,dt \Big/ \int_0^\infty (dm/dt)\,dt \qquad [1]$$

where m is the mass of drug released at time t. The

MRLT was calculated in equation [1] by using a personal computer. The MRLT from Supp-B was 5.42 ± 0.21 h (n=3) which was significantly greater than that from Supp-B with 0.91 ± 0.14 h (n=3) ($p<0.005$, student t-test).

After an intravenous injection of diclofenac at a dose of 5 mg, the profile of plasma diclofenac concentration (Fig. 2) was apparently fitted to one compartment open model (7), and elimination rate constant (ke) and the area under the curve plasma diclofenac concentration (AUC) were determined according to one compartment open model (Table 1).

After rectal administration of Supp-A. a transient high plasma diclofenac concentration was observed at 0.5 h to 1, followed by a rapid disappearance of diclofenac from plasma. After the rectal administration of Supp-B, a transient high plasma diclofenac concentration was avoided relatively and plasma peak level of drug was observed around at 2 to 3 h (Table 1). The pharmacokinetics parameters after the rectal administration of drug was obtained according to the one compartment open model with first-order absorption process, and the parameters were summarized in Table 1. A significant slow

TABLE 1

Pharmacokinetics parameters of diclofenac obtained from plasma concentration (shown in Fig. 2) after rectal administration of Supp-A and Supp-B in dogs (n=3).

	dose mg	Cmax μg/ml	Tmax h	ka h^{-1}	ke h^{-1}	AUC μg h/ml	BA[a] %
intravenous administration							
	5	--	--	--	0.61 ± 0.12	9.41 ± 1.26	100
rectal administration							
Supp-A	25	5.24 ± 1.40	0.67 ± 0.24	3.53 ± 0.86	0.49 ± 0.16	36.67 ± 7.16	78.0
Supp-B	25	2.23[b] ± 0.61	2.67[b] ± 0.47	0.45[b] ± 0.10	0.37 ± 0.11	28.44 ± 5.26	60.4

Cmax : plasma peak concentration of drug.
Tmax : time, when plasma peak concentration reach, after the administration.
a; BA (bioavailability) = $[(AUC)_r \times (Dose)_{iv}] / [(AUC)_{iv} \times (Dose)_r]$
$(AUC)_r$ and $(Dose)_r$: after rectal administration.
$(AUC)_{iv}$ and $(Dose)_{iv}$: after intravenous administration.
b; $p<0.01$ versus values after the administration of Supp-A.

absorption rate constant (ka) after an administration of Supp-B was observed in comparison to that of Supp-A, in spite of no significant difference of ke. However, the slight decrease of bioavailability after the administration of Supp-B was observed with a slight decrease of AUC value in comparison to that of Supp-A (Table 1). To estimate the in vivo residence time of diclofenac, a model-independent method which was reported by Yamaoka et al (8) and was based on the

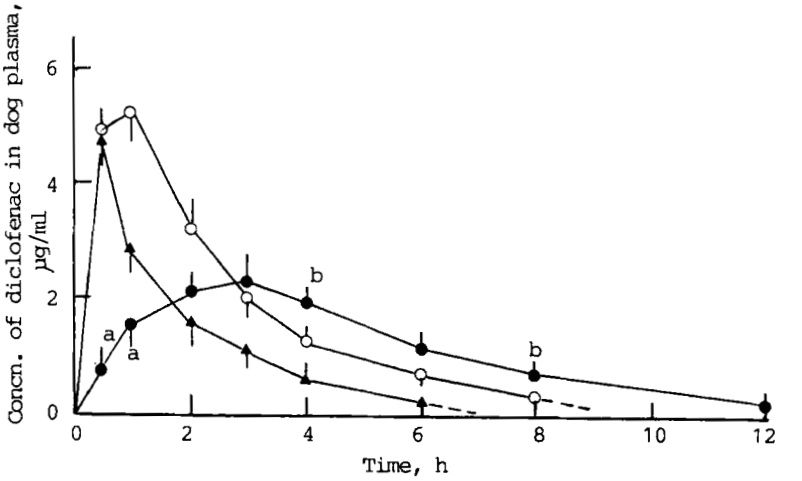

FIGURE 2

Plasma diclofenac concentration in dogs as a function of time after an administration of Supp-A (o) or Supp-B (●), at a dose of 25 mg of sodium diclofenac.
The closed triangles indicated the plasma diclofenac concentration after an intravenous administration of sodium diclofenac at a dose of 5 mg.
Each value represents the mean ± S.D. (n=3).
a; $p<0.01$ versus Supp-A. b; $p<0.05$ versus Supp-A.

moment analysis was employed, in which behavior of drug in plasma was defined by mean in vivo residence time (MRSTrec) with equation [2].

$$MRSTrec = \int_0^\infty tCpdt / \int_0^\infty Cpdt \qquad [2]$$

where Cp is the plasma concentration of diclofenac at time, t. MRSTrec was calculated in equation [2] by using a personal computer. The MRSTrec of diclofenac after rectal administration of Supp-B was 7.47 ± 1.04 h (n=3) which was about four times greater than that after rectal administration of Supp-A with 1.92 ± 0.41

(n=4) ($p<0.005$, student t-test). It has also been suggested by Tanigawara et al (9) that the mean absorption time (MAT) was estimated with equation [3].

$$MAT = MRSTrec - MRSTiv \quad [3]$$

where MRSTiv is the mean in vivo residence time of diclofenac after intravenous administration, which was 0.94 ± 0.06 h (n=3). Thus, MAT after administration of Supp-B and Supp-B was about 6.5 h and about 1.0 h, respectively.

DISCUSSION

Formulation of Supp-B, in which sodium diclofenac was incorporated into water absorbable polymer, achieved the sustained release of diclofenac from the suppository. The mean in vitro release time of sodium diclofenac from Supp-B was prolonged with 5 times in comparison to that from Supp-A.

In the in vivo dog study, Supp-B was evaluated as the sustained release suppository of sodium diclofenac with an apparent slow absorption in comparison to that of Supp-A; i.e., the apparent slow absorption rate after administration of Supp-B seems to be due to the slow release of sodium diclofenac from Supp-B. In generally, the release of drug from suppository occurs

in following to the melting of the suppository base. Since sodium diclofenac is incorporated in the polymer sphere in Supp-B, however, water absorption rate into the polymer sphere after the melting of suppository base seems to regulate the release of drug. In the preliminary study, when the release of diclofenac from suppositories was investigated without use of cellulose membrane, 100 % release from Supp-A was observed within 1 h and that from Supp-B was observed within 3 h; i.e., the rapid release of diclofenac from Supp-B when the suppository was immersed directly in the medium may be due to the rapid swollen of the polymer with a large volume of water in surrounding directly. Since the a large volume of fluid is not expected in the rectal tract, it is considered that Supp-B was able to act as sustained release suppository in dogs.

REFERENCES

(1) Riess, W., Scand. J. Rheumatol., 22, 17 (1978).

(2) Nishihata, T., Keigami, M., Kamada, A., Fujimoto, T., Kamide, S., and Tatsumi N., Int. J. Pharm., 42, 251 (1988).

(3) Nishihata, T., Wada, H., and Kamada, A., Int. J. Pharm., 27, 245 (1985).

(4) Thomas W. H. and McCormack, R., J. Pharm. Pharmacol., 23, 490 (1971).

(5) Yaginuma, H., Nakata, T., Toya, H., Murakami, T., Yamazaki, M., and Kamada, A., Chem. Pharm. Bull., 29, 2974 (1981).

(6) Tanigawara, Y., Yamaoka, K., Nakagawa, T., and Uno, T., Chem. Pharm. Bull., 30, 1088 (1982).

(7) Yamaoka, K., Tanigawara, Y., Nakagawa, T., and Uno, T., J. Pharmacobio-Dyn., 4, 879 (1981).

(8) Yamaoka, K., Nakagawa, T. and Uno, T., J. Pharmacokin. Biopharm., 6, 547 (1978).

(9) Tanigawara, Y., Yamaoka, K., Nakagawa, T. and Uno. T., J. Pharm. Sci., 71, 1129 (1982).