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Communication

Pharmacokinetics of formulated tenoxicam transdermal delivery systems

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Abstract

To investigate the feasibility of developing a new tenoxicam transdermal delivery system (TDS), the pharmacokinetics of tenoxicam from various formulated TDS were evaluated and compared with values following oral administration of tenoxicam and with application of a piroxicam plaster (Trast) marketed in Korea. Based on previous in-vitro study results, a mixture of diethylene glycol monoethyl ether (DGME) and propylene glycol monolaurate (PGML) (40:60) was used as a vehicle, and caprylic acid, capric acid, lauric acid, oleic acid or linoleic acid (each at 3%) was added as an enhancer. Triethanolamine (5%) was used as a solubilizer, and Duro-Tak 87-2510 as a pressure-sensitive adhesive. Among these fatty acids used for the formulation of tenoxicam TDS, caprylic acid showed the greatest enhancing effect; the area under the plasma concentration–time profile (AUC) decreased in the order of caprylic acid > linoleic acid ≥ oleic acid > lauric acid > capric acid. Compared with oral administration, maximum plasma concentration (C_{max}) was significantly lower, and time to reach C_{max} (T_{max}) delayed with all formulated tenoxicam TDS. All formulated TDS resulted in a lower AUC than with the oral formulation, except for TDS containing caprylic acid, although the difference was statistically significant only with capric acid. The AUC for all the formulated tenoxicam TDS was significantly higher than that of the piroxicam plaster; TDS with caprylic acid increased AUC 8.53-fold compared with the piroxicam plaster. Even though the T_{max} of tenoxicam TDS was not significantly different from that of the piroxicam plaster, C_{max} was higher; formulations containing caprylic acid and linoleic acid increased C_{max} by 7.39- and 8.76-fold, respectively. In conclusion, a formulation containing 1.5 mL DGME-PGML (40:60) with 3% caprylic acid and 5% triethanolamine mixed with 6 g Duro-Tak 87-2510 could be a good candidate for developing a new tenoxicam TDS to maintain a comparable extent of absorption to oral delivery while attaining a prolonged effect with fewer toxic events.

Introduction

Tenoxicam is an oxicam non-steroidal anti-inflammatory drug, with a structure closely related to that of piroxicam. Oxicam drugs are generally characterized by strong binding to plasma proteins and a long elimination half-life (Todd & Clissold 1991). The mean elimination half-life of tenoxicam is 67 h, which allows administration of a single oral daily dose of 20 mg (Valdes et al 1985; Nilson 1994). Tenoxicam is completely absorbed following oral administration; however, its use has been associated with a number of gastrointestinal disorders (Barclay & Traballi 1987; Caughey & Waterworth 1989).

Transdermal delivery has been recognized as an alternative route of administration, offering several advantages over oral administration, such as avoiding first-pass metabolism by the liver and enzymatic degradation by the gastrointestinal tract, and maintaining relatively constant plasma concentration in the body (Ansel et al 1995).

Because tenoxicam has a relatively large molecular weight (337.4 Da), high melting point (209–213°C), low intrinsic solubility in water (10 ± 0.006 mg mL^{-1}) and low intrinsic partition coefficient (0.42 ± 0.05), compared with ketoprofen (Cordero et al 1997), which is known to have high permeability, permeation was facilitated by using appropriate vehicles containing enhancers from our previous in-vitro studies (Gwak & Chun 2001, 2002).

Based on the results from the previous studies, the present study aims to evaluate the pharmacokinetic characteristics of pressure-sensitive adhesive (PSA) transdermal delivery systems (TDS) in rats, and compare them with pharmacokinetics from oral administration,

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and a piroxicam plaster (Trast) which is being marketed in Korea.

Materials and Methods

Materials

Tenoxicam and piroxicam were kindly provided by Dong-A Pharm. Ind. Co. Ltd (Yongin, Korea). Propylene glycol monolaurate (PGML, Lauroglycol 90) and diethylene glycol monoethyl ether (DGME, Transcutol P) were obtained from Gattefossé (Gennevilliers Cedex, France). The acetonitrile and methanol used were of HPLC grade. Caprylic acid, capric acid, lauric acid, oleic acid and linoleic acid were purchased from Sigma Chemical Co. (St Louis, MO, USA). Duro-Tak 87-2510 (copolymer: acrylate, functional group: -OH, 40.5% solution of non-crosslinking acrylic copolymer, 4500 cps, solubility parameter 16) was obtained from the National Starch and Chemical Company (Bridgewater, NJ, USA). Other reagents were of analytical grade.

HPLC assay

Samples for pharmacokinetic and stability studies were analysed using HPLC. Fifty microlitres of either piroxicam or tenoxicam (50 μg mL^{-1}), which was used as an internal standard (IS) for the tenoxicam and piroxicam assays, respectively, was added to 150 μL plasma samples. The samples were then acidified by adding 0.2 mL 0.1 N hydrochloric acid and extracted with 7 mL diethyl ether for 3 min using a vortex mixer. The tubes were centrifuged at 3000 rpm for 10 min. The organic layer was pooled in a conical borosilicate centrifuge tube, and back-extracted with 0.2 mL 0.02 N sodium hydroxide by vortex mixing for 3 min. After centrifuging for 10 min at 3000 rpm, 20 μL aqueous layer was injected onto the HPLC system.

The HPLC system consisted of a pump (model G1311A) and detector (model G1316A, both Agilent, Santa Clara, CA, USA) set at 355 nm. An ODS column (Luna C18, Phenomenex, Torrance, CA, USA) equipped with a C18 Radial Pak insert was used. The mobile phase was composed of pH 2.8 phosphate buffer and acetonitrile (55:45), delivered at a flow rate of 1.0 mL min^{-1}. The injection volume was 20 μL. Calibration curves were constructed based on the peak area ratios of the drugs to IS.

Preparation of tenoxicam transdermal delivery systems

Tenoxicam (45 mg) was dissolved in 1.5 mL DGME-PGML (40:60) containing 3% fatty acids and 5% triethanolamine, and then mixed with 6 g Duro-Tak 87-2510. Tenoxicam PSA TDS were prepared by casting the above solutions on a polyester release liner coated with silicone (Gelroflex ALU-PET 100 μ-2S DR; 3M, Saint Paul, MN, USA) using a casting knife. The area of the cast solutions was 10 cm × 16 cm, and the thickness spread was 300 μm. The solutions were set at room temperature for 10 min to evaporate the solvents, and then oven dried at 90°C for about 20 min to remove the residual organic solvents. The dried film was then transferred onto a backing film.

Stability of formulated tenoxicam transdermal delivery systems

The prepared tenoxicam TDS were stored at room temperature. The formulated TDS were cut into 1 cm × 1 cm pieces and dissolved in 30 mL methanol, immediately after preparation and at 15 and 30 days, by sonicating for 2 h. The solutions were assayed by HPLC.

Animal studies

Pharmacokinetic studies of tenoxicam TDS were carried out according to the Principles for Biomedical Research Involving Animals developed by the Council for International Organizations of Medical Sciences and had been approved by the Ethical Review Committee at the Ewha Womans University.

Male Sprague–Dawley rats weighing 250–300 g were obtained from Samtako Bio Co., Ltd (Osan, Korea). Rats were anaesthetized with ether (Daejung Chemicals and Metals, Siheung, Korea) and the jugular vein was cannulated using a polyethylene tube (0.76 mm i.d. × 1.22 mm o.d.; Becton Dickinson, San Jose, CA, USA). After surgery, each animal was housed in a separate cage. Animals were fasted overnight and for the first 6 h of the experiment, but were allowed water ad libitum. The rats were then divided into seven groups of six rats. Each group received one of the following: a piroxicam plaster (Trast), oral dosage form of tenoxicam (10 mg kg^{-1}), or TDS 1, 2, 3, 4 or 5, which, respectively, contained 3% caprylic acid, capric acid, lauric acid, oleic acid or linoleic acid, in DGME-PGML (40:60) containing 5% triethanolamine. For the administration of TDS or the piroxicam plaster, the hair of the abdomen was shaved carefully so that the stratum corneum remained intact. The size of formulated tenoxicam TDS applied to the shaved site of the rat was 3 cm × 3 cm; the piroxicam plaster was cut to 2.07 cm × 2.07 cm to ensure the equivalent dose as with the tenoxicam TDS based on the area of the plaster (81.012 cm^2) and drug amount (48 mg). Plasma samples (0.15 mL) were collected at predetermined time points and analysed by HPLC.

Pharmacokinetic analysis

Pharmacokinetic analysis was performed using WinNonlin (Version 1.1, Scientific Consulting Inc., Cary, NC, USA). The drug concentration–time curves were fitted to a one-compartment model with first-order absorption. The area under the plasma concentration–time profile (AUC) was calculated using the log-linear trapezoidal method.

Statistical analysis

All values are expressed as the mean ± s.d. The pharmacokinetic variables of all dosage forms were compared using the Kruskal–Wallis test followed by Dunn's post-hoc test. A P value of less than 0.05 was considered significant.

Results and Discussion

Figure 1 shows the mean plasma concentration–time profiles after administration of the formulated TDS, the piroxicam plaster and the oral dosage form (10 mg kg^{-1}); the pharmacokinetic parameters are given in Table 1. The AUC differed significantly among the TDS ($P < 0.01$). From Figure 1 and Table 1, caprylic acid showed the greatest enhancing effect; the AUC decreased in the order of caprylic acid > linoleic acid ≥ oleic acid > lauric acid > capric acid. The AUC of TDS 1 (caprylic acid) was statistically higher than all the other TDS ($P < 0.05$). This result was totally different from that found in in-vitro studies, in which oleic acid had the greatest enhancing effect and caprylic acid showed the lowest enhancing effect (Gwak & Chun 2002).

In our previous in-vitro study, tenoxicam was saturated in the vehicle (propylene glycol) in the presence or absence of fatty acids, indicating that thermodynamic activity was maximized. The highest enhancing effect by oleic acid in-vitro was attributed mainly to barrier disruption. On the other hand, drug was completely dissolved in DGME-PGML (40:60) containing triethanolamine with/without fatty acids for the formulation of TDS in this study. Thus, permeation may be affected by the ratio of concentration to solubility of the drug in the vehicle as well as barrier disruption. C_{max} was also significantly different among the formulated TDS ($P < 0.05$), and was highest with linoleic acid. However, T_{max} did not differ among the TDS formulations, and ranged from 22.4 to 31.4 h.

Compared with oral administration, T_{max} was delayed with all formulated tenoxicam TDS, as shown in Table 1. The prolonged T_{max} indicated that the absorption rate was reduced with TDS. This interpretation was confirmed by the significantly lower C_{max} with all TDS formulations compared with oral delivery; TDS lowered the C_{max} to 13.1% (range 6.6–20.0%). In addition, TDS resulted in lower AUC compared with oral delivery, except for TDS 1 (caprylic acid), although the difference was statistically significant only with TDS 2 (capric acid).

PGML is an ester-type vehicle in which a small quantity of tenoxicam can be dissolved (solubility: 0.59 ± 0.008 mg mL^{-1}). Addition of DGME at a concentration of 40% increased the solubility to 1.52 ± 1 0.12 mg mL^{-1} (Gwak & Chun 2002). It has been suggested that DGME itself may not have a profound effect on the structural integrity of the skin, but that it eases the partitioning of a compound by increasing its solubility in the skin (Cho & Choi 1998). Many studies have shown that the addition of DGME at concentrations of 20–40% to the ester-type vehicles such as propylene glycol laurate, propylene glycol monocaprylate and PGML considerably increases the permeation flux of many drugs, including melatonin, ondansetron and ketorolac (Gwak et al 2002; Gwak et al 2004; Choi et al 2007).

The further addition of enhancers such as fatty acids and amines increased the flux of tenoxicam compared with our previous in-vitro study (Gwak & Chun 2001; 2002). The fatty acids are thought to increase the partitioning rate or disturb the skin by disrupting the tightly packed lipid regions of the stratum corneum. The amines are thought to increase the solubility, according to the equation $J_s = D\ K\ C / h$ where J_s is the flux, D is the diffusion coefficient, K is the skin–vehicle partition coefficient, C is the drug concentration in the vehicle

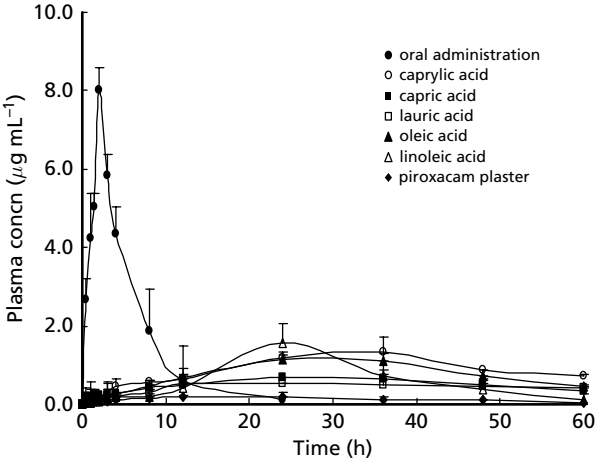

Figure 1 Mean pharmacokinetic profiles after administration of oral dosage tenoxicam, formulated tenoxicam transdermal delivery systems (TDS) and piroxicam plaster. Data are mean ± s.d. (n = 6).

Table 1 Pharmacokinetic parameters of formulated tenoxicam transdermal delivery systems (TDS), oral delivery and piroxicam plaster. In the TDS 3% fatty acid was used in diethylene glycol monoethyl ether/propylene glycol monolaurate (40:60) containing 5% triethanolamine. Data are mean ± s.d. (n = 6)

	AUC (μg h mL^{-1})	C_{max} (μg mL)	T_{max} (h)
Oral tenoxicam	97.09 ± 13.17	8.00 ± 1.03	3.60 ± 2.15
TDS 1 (caprylic acid)	105.64 ± 24.69[b]	1.32 ± 0.46[a]	31.24 ± 5.48[a]
TDS 2 (capric acid)	54.92 ± 14.64[b,c]	0.68 ± 0.25[a]	31.40 ± 11.26[a]
TDS 3 (lauric acid)	64.43 ± 4.37[b,c]	0.53 ± 0.35[a]	22.37 ± 19.51[a]
TDS 4 (oleic acid)	71.82 ± 13.63[a,b,c]	1.14 ± 0.18[a]	25.42 ± 2.94[a]
TDS 5 (linoleic acid)	72.07 ± 10.82[b,c]	1.57 ± 0.75[a]	26.85 ± 4.86[a]
Piroxicam plaster	12.39 ± 1.67	0.18 ± 0.004	17.31 ± 2.25

AUC, area under the plasma concentration–time curve; C_{max}, maximum plasma concentration; T_{max}, time of C_{max}. [a]$P < 0.05$ vs oral administration; [b]$P < 0.05$ vs piroxicam plaster; [c]$P < 0.05$ vs TDS 1.

and h is the thickness of the skin (Aungst et al 1990; Barry 1983; 1987).

The pKa of tenoxicam is about 5.5 (Albengres et al 1993), indicating that its solubility increases dramatically above pH 6. In our in-vitro studies solubility increased exponentially from pH 6 to 9 (Gwak & Chun 2002). The pH of tenoxicam was 7.95–8.10 in DGME-PGML (40:60) containing 3% fatty acid and 5% triethanolamine, compared with 4.42 in DGME-PGML (40:60).

Piroxicam and tenoxicam have similar pharmacokinetic parameters, characterized by significant protein binding (98.2 and 98.4%, respectively), volume of distribution (0.14 and 0.15 L kg^{-1}), total clearance (0.12–0.18 and 0.10–0.25 L h^{-1}) and half-life (57 ± 16 and 66 ± 16 h). The typical dose of both drugs is 20 mg once a day (Albengres et al 1993).

As shown in Figure 1 and Table 1, the AUC of all the formulated tenoxicam TDS was significantly higher than that of the piroxicam plaster; caprylic acid as the fatty acid increased the AUC by 8.53 times compared with the piroxicam plaster. Even though the T_{max} of tenoxicam TDS was not significantly different from that of the piroxicam plaster, C_{max} was much higher; formulations containing caprylic acid or linoleic acid increased C_{max} by 7.39- or 8.76-fold, respectively. Based on these results, it is expected that the same blood concentration as from the piroxicam plaster could be obtained with tenoxicam TDS but with much a smaller dose of tenoxicam.

The stability of formulated tenoxicam TDS was also evaluated. As shown in Table 2, the concentration remaining after 30 days' storage was 92–99% of the initial concentration, which was not degraded significantly, regardless of the formulations.

In conclusion, a formulation containing 1.5 mL DGME-PGML (40:60) with 3% caprylic acid and 5% triethanolamine mixed with 6 g Duro-Tak 87-2510 could be a good candidate for developing a new tenoxicam TDS that achieves bioavailability comparable to oral delivery but with a prolonged effect and fewer toxic events. Furthermore, this formulation could result in at least an 8-fold higher blood concentration than the piroxicam plaster with a comparable duration of action.

Table 2 The stability (% remaining) of formulated tenoxicam transdermal delivery systems (TDS) containing 3% fatty acid in diethylene glycol monoethyl ether/propylene glycol monolaurate (40:60) containing 5% triethanolamine. Data are mean ± s.d. (n = 3)

	Day 15	Day 30
TDS 1 (caprylic acid)	103.1 ± 9.8	99.0 ± 7.2
TDS 2 (capric acid)	99.3 ± 6.3	92.1 ± 2.8
TDS 3 (lauric acid)	102.2 ± 7.9	98.8 ± 6.5
TDS 4 (oleic acid)	99.0 ± 10.1	101.1 ± 3.2
TDS 5 (linoleic acid)	98.3 ± 5.9	96.1 ± 4.3

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