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Percutaneous absorption of piroxicam from FAPG base through rat skin: effects of fatty acid added to FAPG base

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Abstract

A series of fatty acids (i.e., lauric, myristic, palmitic and stearic acid) decreased the release of piroxicam from FAPG (fatty alcohol-propylene glycol) base. The reason was due to an increase in lipophilicity of the base. The released piroxicam was found to be inversely proportional to the apparent viscosity of the ointments containing a fatty acid. However, these fatty acids enhanced the in vitro skin permeation of piroxicam. Lauric acid and myristic acid also promoted in vivo percutaneous absorption in rats. A small decrease in the release rate and high skin permeation compared to the control FAPG base (no fatty acid) were important in order to gain appreciable in vivo percutaneous absorption. The effect of fatty acid on the in vivo percutaneous absorption of piroxicam from the FAPG base can be estimated by comparing the in vitro rate of drug released from the base and the in vitro rate of drug absorption by the treated skin with those of containing no fatty acid.

Key words: Piroxicam; Percutaneous absorption; Pretreatment; Fatty acid; FAPG base; Released amount; Viscosity

1. Introduction

FAPG base (Katz et al., 1971) has been used as a topical vehicle for various corticosteroids (Coldman et al., 1971; Ostrenga et al., 1971; Rhodes et al., 1972; Henry, 1974) and indomethacin (Kaiho et al., 1986, 1987; Nomura et al., 1990). Oral administration of piroxicam has an irritational side-effect on the gastrointestinal mucosa (Schiantarelli and Cadel, 1981). A few traditional topical ointments of piroxicam have been prepared to prevent this side-effect (Tsai et al., 1985; Dallas et al., 1987). However, no information on the piroxicam FAPG ointment seems to exist. We selected piroxicam as a model drug to investigate the effect of a series of fatty acids (i.e., lauric, myristic, palmitic and stearic acid) on the percutaneous absorption of piroxicam FAPG ointment.

2. Materials and methods

Piroxicam (Pfizer, U.S.A.), indomethacin (Sumitomo, Japan), stearyl alcohol, stearic acid, palmitic acid, myristic acid, lauric acid, propylene glycol, PEG 400 and diethyl ether (Merck, Ger-

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many) were obtained commercially. All other chemicals were of analytical reagent grade. The cellulose membrane, C-110, was purchased from Visking Co., Ltd.

FAPG bases containing 1% piroxicam were prepared according to the following procedures. Stearyl alcohol (25%) and/or fatty acid (5%) were heated at 75°C; then piroxicam mixed with PG (70–75%), and previously heated to the same temperature, was added. The mixture was stirred until it congealed.

The diffusion cell used in the in vitro release experiment was similar to the Franz diffusion assembly (Chien et al., 1983). The Visking seamless cellulose tubing was used as the membrane. The test sample (1.5 g/2.43 cm^2) and the phosphate buffer (pH 7.4, 20 ml, containing 20% PEG 400) were poured into the upper donor and lower receptor container of the cell, respectively. The temperature of the solution was held at 37 ± 0.1°C, with stirring at 700 rpm. A sample solution (0.5 ml) was taken up at an appropriate time and assayed using a spectrophotometer (Hitachi 200-10, Hitachi Seisakusho Co., Ltd) at 365 nm.

In the measurement of the partition ratio, FAPG base (5 g) and aqueous piroxicam solution (10 ml, 10 μg/ml) were placed in a glass-stoppered test tube and shaken in a water bath at 60 ± 0.1°C for 2 h. The tube was removed and left at room temperature in a vertical position for 12 h to allow separation of the two phases. The amount of piroxicam in the water phase was determined with a UV spectrophotometer. The partition ratio (w/o) was calculated by comparison of the amount of piroxicam in the water phase (w) with that in the fatty alcohol and/or fatty acid phase (o).

A cone-and-plate viscometer (Brookfield RVT DVII, Brookfield Engineering Laboratories, Inc.) was used to determine the viscosity of piroxicam FAPG ointment at 34°C. The maximum shear rate was 38.4 s^{-1} with a sweeping period of 30 s.

In the in vitro skin pretreatment experiment, the freshly excised rat skin was fixed in the diffusion cell and was respectively pretreated with FAPG base (1.5 g) containing various fatty acids (or none for the controls) for 12 h. The skin was then gently swabbed clean 20 times with cotton to remove the residual ointment. Subsequently, a 1% piroxicam FAPG ointment (1.5 g) containing no fatty acid was used as the model drug to penetrate the treated skin under the conditions of the in vitro release experiment described above. The rate of permeation (f_p) for each pretreatment was calculated from the slope of the linear region (Chow et al., 1984) of the profile of accumulated amount of permeated piroxicam vs time.

In the in vivo percutaneous absorption experiment, the 1% piroxicam FAPG ointment (4 g) containing various fatty acids or no fatty acid was spread on the dehaired abdominal skin (6 × 3.3 cm^2) using the occlusive dressing technique (Naito and Tsai., 1981). Blood samples (0.5 ml) were withdrawn from the carotid artery at predetermined intervals and the piroxicam content measured by HPLC (Hsu et al., 1991). The observed AUC (area under curve) value (AUC_0) for each ointment was calculated by the trapezoidal rule. The rate of skin permeation of a drug, R_p, is mathematically related to the rate of drug delivery from a matrix system, R_d, to the skin surface and the rate of skin absorption, R_a, by the following relationship (Chien, 1987):

$$1/R_p = 1/R_d + 1/R_a \quad (1)$$

On rearrangement of Eq. 1, the following equation was obtained

$$R_p = (R_d \times R_a)/(R_d + R_a) \quad (2)$$

The ratio of the relative rate of skin permeation of piroxicam for each FAPG ointment (containing a fatty acid; i) to the controls (containing no fatty acid; c) is expressed as:

$$R_{pi}/R_{pc} = (R_{di}/R_{dc}) \times (R_{ai}/R_{ac}) \times (R_{dc} + R_{ac})/(R_{di} + R_{ai}) \quad (3)$$

The amount of percutaneous permeation of drug is proportional to the AUC value (Schiantarelli et al., 1982; Hosoya et al., 1987); the ratio of the relative rate of skin permeation of piroxicam in Eq. 3 is expressed by the ratio of the relative AUC value for each ointment according to

$$AUC_{da}/AUC_c = (R_{di}/R_{dc}) \times (R_{ai}/R_{ac}) \times (R_{dc} + R_{ac})/(R_{di} + R_{ai}) \quad (4)$$

in which AUC_{da} and AUC_c are the AUC values for ointment containing a fatty acid and no fatty acid (controls), respectively. If the effect of added fatty acid only occurred on the rate of drug delivery or on the rate of skin absorption, the AUC values were correspondingly expressed as AUC_d or AUC_a and were calculated from the following equation, respectively.

$$AUC_d/AUC_c = (R_{di}/R_{dc}) \times (R_{dc} + R_{ac}) / (R_{dc} + R_{ai}) \quad (5)$$

$$AUC_a/AUC_c = (R_{ai}/R_{ac}) \times (R_{dc} + R_{ac}) / (R_{di} + R_{ac}) \quad (6)$$

The in vitro rate of drug release for the matrix dispersion-type piroxicam FAPG system is calculated from the following equation (Higuchi, 1961):

$$f_d = dq/dt = (ADC_s/2t)^{1/2} \quad (7)$$

where f_d (rate of release) is the amount of drug released (q) at time t (48 h) per unit area of exposure A denotes the initial concentration of drug (1% g/cm^3) C_s is the solubility of the drug (0.15% g/cm^3) in the external phase (PG) (Hsu et al., 1985) of the ointment and D represents the diffusion coefficient of the drug molecule in the vehicle and is calculated from the following equation (Higuchi, 1961; Tsuzuki et al., 1988):

$$q/t^{1/2} = (2ADC_s)^{1/2} \quad (8)$$

where the $q/t^{1/2}$ value was calculated from the slope of the linear q-$t^{1/2}$ profile obtained from the in vitro release experiment of each FAPG ointment.

In the in vitro skin pretreatment experiment, from the viewpoint of Eq. 1, the in vitro rate of absorption (f_a) for each skin pretreatment with various fatty acid was calculated from the f_d value of the model ointment used to penetrate the treated skin (piroxicam FAPG ointment containing no fatty acid) and the in vitro rate of permeation (f_p) for each pretreatment condition described above, respectively. When the in vivo values of R_d and R_a in Eq. 4, 5 and 6 were substitued by the in vitro values of f_d and f_a, the following equations were obtained:

$$AUC_{da}/AUC_c = (f_{di}/f_{dc}) \times (f_{ai}/f_{ac}) \times (f_{dc} + f_{ac})/(f_{di} + f_{ai}) \quad (9)$$

$$AUC_d/AUC_c = (f_{di}/f_{dc}) \times (f_{dc} + f_{ac}) / (f_{dc} + f_{ai}) \quad (10)$$

$$AUC_a/AUC_c = (f_{ai}/f_{ac}) \times (f_{dc} + f_{ac}) / (f_{di} + f_{ac}) \quad (11)$$

The effects of fatty acid added to FAPG base can be estimated by comparing the calculated values of AUC_{da}, AUC_d, and AUC_a in Eq. 9, 10, and 11 with the observed value of AUC for each ointment.

3. Results and discussion

The piroxicam FAPG ointment containing no fatty acid showed the greatest release (Table 1 and Fig. 1) and the highest value of the partition ratio (Table 2). It is assumed that fatty acid added to the FAPG base increases the lipophilicity of the base and decreases the amount of released piroxicam. The ointment containing palmitic acid had the greatest value of the viscosity (Table 2 and Fig. 1). A similar result has been reported that the indomethacin FAPG ointment containing palmitic acid was more viscous than that of stearic acid or no fatty acid (Kaiho et al., 1987). Furthermore, the released piroxicam was found to be inversely proportional to the viscosity of the piroxicam FAPG ointment containing a particular fatty acid (Fig. 1). Because piroxicam in the FAPG ointment containing fatty acid had a similar partition ratio (ANOVA test, $p > 0.05$) as shown in Table 2, piroxicam having a similar thermodynamic activity in these bases, the piroxicam thereby released is proportional to the diffusion coefficient (according to Eq. 7) and is inversely proportional to the viscosity according to the Einstein Stokes equation (Higuchi, 1967).

It is clear that the rat skin pretreated with lauric acid led to an 8.7-fold increase in the penetrated amount of piroxicam relative to that of no fatty acid (Table 1); the pretreatment enhancing effect of fatty acid decreased linearly with increasing carbon number of the fatty acid from 12 to 18 ($r = 0.944$). Similar results have been reported for the percutaneous absorption of naloxone (Aungst et al., 1986).

Table 1
Comparison of the calculated values of AUC_{da}, AUC_d, and AUC_a with the observed value of AUC_0 for each ointment

Ointment [h]	q [a]	f_d [b]	Q [c]	f_p [d]	f_a [e]	AUC_0	AUC_d	AUC_a	AUC_{da}
1	2189.4 ± 117.2 [f]	25.1	35.3 ± 3.4	0.734	0.694	18.5 ± 3.4	–	–	–
2	1410.3 ± 105.8	15.6	308.3 ± 53.1	7.037	6.997	95.7 ± 12.9	18.2	149.8	132.2
3	1068.2 ± 54.2	12.5	153.3 ± 34.5	3.414	3.374	50.6 ± 4.2	18.0	81.4	72.7
4	145.8 ± 14.4	1.0	54.4 ± 8.3	1.708	1.668	11.4 ± 2.3	10.9	42.8	16.6
5	531.7 ± 50.2	6.1	39.8 ± 5.4	0.836	0.796	12.1 ± 1.3	17.0	21.1	19.3
							7093.4 [g]	4957.6 [g]	1902.6 [g]

[a] Released amount of piroxicam per unit area ($\mu g\ cm^{-2}$) during 48 h.
[b] Rate of drug release ($\mu g\ cm^{-2}\ h^{-1}$).
[c] Penetrated amount of piroxicam through pretreated skin ($\mu g\ cm^{-2}$) during 48 h.
[d] In vitro rate of drug permeation from the pretreated skin ($\mu g\ cm^{-2}\ h^{-1}$).
[e] In vitro rate of drug absorbed from the pretreated skin ($\mu g\ cm^{-2}\ h^{-1}$).
[f] Means ± S.E. ($n = 5$).
[g] Sum of squares: $\Sigma\ (y - AUC_0)^2$; y calculated value of AUC_d, AUC_a and AUC_{da} in Eq. 9, 10, and 11 for each ointment, respectively. AUC values expressed as $\mu g\ h\ ml^{-1}$.
[h] Ointment no. 1, 2, 3, 4 and 5 represent the ointment containing no fatty acid, lauric, myristic, palmitic and stearic acid, respectively.

It was shown that the observed AUC_0 value for the piroxicam FAPG ointment containing lauric acid was about 5-fold greater than that of no fatty acid (Table 1). It has been reported that lauric acid will increase the percutaneous absorption of naloxone and molsidomine (Aungst et al., 1986; Yamada and Uda, 1987). The values of AUC_{da}, AUC_d and AUC_a calculated using Eq. 9, 10 and 11 from the observed AUC values of the controls (AUC_c) and the values of f_d, f_a for each formula are listed in Table 1; their relationships among these calculated AUC values and the observed AUC_0 value for each formula are also shown in Fig. 2. The linear correlation ($r = 0.9996$) between the AUC_{da} and the observed AUC_0 values provides a method for estimating the observed AUC_0 value for the in vivo percutaneous absorption of piroxicam FAPG ointment containing a particular fatty acid. Furthermore, the calculated AUC_d value was more coincident with the observed AUC_0 values than that of the AUC_a value for the piroxicam FAPG ointment

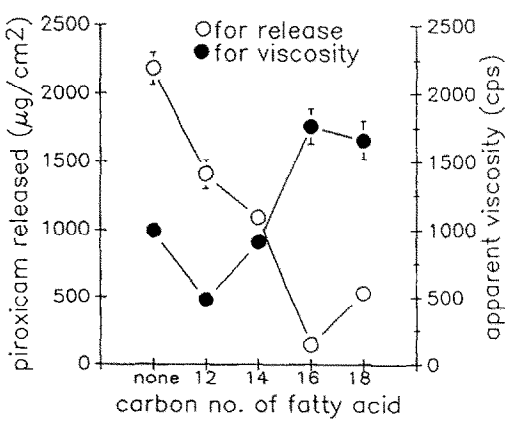

Fig. 1. Relationship between the released amount of piroxicam and the apparent viscosity of each piroxicam FAPG ointment. Each value represents the mean of five experiments with the standard error.

Table 2
Apparent partition ratio of piroxicam between water and FAPG base (water/base) and the viscosity of each ointment

	Ointment [a]				
	1	2	3	4	5
Partition ratio	2.14	0.55	0.76	0.54	0.67
S.E. ($n = 3$)	0.45	0.11	0.16	0.07	0.18
Apparent viscosity (cps)	992	480	909	1764	1661
S.E. ($n = 5$)	58	34	32	129	141

[a] Ointment no. 1, 2, 3, 4 and 5 represent the ointment containing no fatty acid, lauric, myristic, palmitic and stearic acid, respectively.

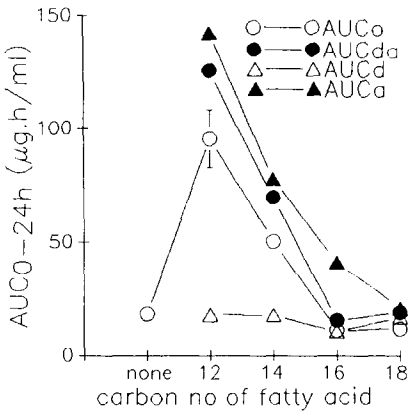

Fig. 2. Relationship between the values of AUC_0, AUC_d, AUC_a and AUC_{da} (Table 2) for each piroxicam FAPG ointment containing a fatty acid.

containing palmitic or stearic acid (Fig. 2 and Table 1); thus, the extent of the effect on the rate of release was greater than that of skin absorption. A similar result has also been reported for indomethacin FAPG ointment containing palmitic or stearic acid (Kaiho et al., 1987). In contrast, the calculated AUC_a value was more coincident with the observed AUC_0 value than that of AUC_d value (Fig. 2 and Table 1) for the ointment containing lauric acid; the extent of the effect on the rate of skin absorption should be greater than the effect on the rate of release.

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