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EFFECTS OF THE ADMINISTRATION OF KETOPROFEN GEL ON THE PERCUTANEOUS ABSORPTION OF KETOPROFEN IN RABBITS

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ABSTRACT

The effects of the administration for a commercial ketoprofen gel on the percutaneous absorption of ketoprofen (through rabbit abdominal skin) were investigated. The AUC (area under the curve) value of absorbed ketoprofen for single topical administration of 6 g of ketoprofen gel applied with ODT (occlusive dressing technique) was found to be about 6-fold greater than that of repeated administration of 1.5 g of ketoprofen gel applied with ODT at 6 h interval in a day. It was about 14-fold greater than that of repeated administration of 1.5 g of ketoprofen gel applied without ODT at 6 h interval in a day. The experiment of volatilation of ketoprofen gels and the in vitro release test of ketoprofen gel applied with ODT and without ODT had been, in addition, respectively approached. The volatilation of solvent in the gel, as a result of this, may clearly be the primary factor for inducing a sharp descending of the plasma ketoprofen level following the Cmax

(maximum concentration) in the in vivo percutaneous absorption of ketoprofen gel; this factor also results in a lower plasma ketoprofen level for the gel applied without ODT than that with ODT.

INTRODUCTION

Oral administration of ketoprofen is very effective for the treatment of rheumatoid arthritis (1); it, however, has an irritational side-effect concerning gastrointestinal mucosa (2). The suppositories, ointments and enteric coated tablets of ketoprofen have been approached for preventing this side-effect during the last decade (2, 3, 4). No report on the effects of administration of ketoprofen gel on the percutaneous absorption of ketoprofen (through rabbit abdominal skin) has so far existed. A commercial ketoprofen gel was then selected as a model for investigating whether the single or repeated administration of the gel applied (with ODT and without ODT) shows a better percutaneous absorption of ketoprofen or not.

MATERIAL AND METHOD

Materials - Ketoprofen gel (3 %) was supplied by Heng Hsin Chemical and Pharmaceutical Co., Ltd. The cellulose membrane (Visking, C-110) was purchased from Visking Co., Ltd. All other chemicals were reagent grade products obtained commercially.

Topical administration - Male rabbits weighing between 1.8 and 2.2 Kg were used. The abdominal hair was clipped with an electric hair clipper without damaging the skin. Ketoprofen gel, 6 g, was spread on the skin (60 cm^2) with or without ODT (5) during 24 h for the single administration of the gel. For the repeated administration, 1.5 g of ketoprofen gel was accumulately applied on the skin (60 cm^2) at 6 h interval with or without ODT during 24 h. Blood samples (1.5 ml) were withdrawn

from the carotid artery at predetermined intervals, and the plasma samples were individually subjected to ketoprofen content measurement by HPLC. Areas under the plasma concentration curve (AUC) were determined by using the trapezoidal method.

Assay of ketoprofen - Plasma, 0.5 ml, was acidified with 1 ml 1 N HCl and mixed with 20 µl of internal standard (p - phenyl phenol, 0.05 mg/ml) methanol solution . The mixture was extracted with 7 ml cyclohexane-diethylether (70 : 30, v/v) mixture. An 5 ml aliquot of the organic layer was evaporated to dryness; The residue was redissolved in 2 ml of the mobile phase. 10 µl of this solution was injected into the HPLC apparatus (Milford, MA. USA). The conditions for analysis were as follows: colum, 15 cm x 3.9 mm i.d. 5-µM NOVAPAK C 18 colum; mobile phase, methanol-0.005 % acetic acid aqueous solution (65 : 35, v/v); flow rate, 0.7 ml/min; detector ultraviolet (265 nm). The signal from the detector was fed into an intergrator (Waters 740 DATA Module).

In vitro ketoprofen release test - The diffusion cell used was similar to the apparatus of Franz diffusion assembly (6, 7). The Visking seamless cellulose tubing was used as the membrane . The test gel sample (0.1 g/cm^2) was poured into the upper donor container of the cell covered (with ODT) or uncovered (without ODT) with a thin polyethylene film and 20 ml of the pH 7.4 phosphate buffers were poured into the lower receptor container of the cell. The temperature of the solution was held at 37 °C, with stirring at 700 rpm. A 0.5 ml of sample solution was drawm off at an appropriate time and replaced by equal volume of the diffusion medium. The samples were assayed with the spectrophotometer at a wavelength of 265 nm (3).

The volatility of ketoprofen gel - Ketoprofen gel, 0.24 g, was spread on a filter paper (dia. 1.76 cm) and allowed to stand at room temperature (20 °C), 55 % relative humidity. The weight of the gel was measured periodically.

Table 1

Comparison of AUC and Cmax Values in Each Condition

Administration	Topical Dose	Frequency	AUC (μg-h/ml)	Cmax (μg/ml)
Without ODT	6.0 g	1x[1)]	22.93 ± 5.45	1.78 ± 0.42
	1.5 g	4x[2)]	12.11 ± 3.46	0.81 ± 0.23
With ODT	6.0 g	1x	170.43 ± 24.3	9.82 ± 1.39
	1.5 g	4x	29.32 ± 4.89	2.36 ± 0.38

1) 1x is single dose in 24 h 2) 4x is four doses in 24 h
Data are the mean ± S.E. (n=5)

RESULTS AND DISCUSSIONS

According to the topical administration test, the AUC or Cmax values for ketoprofen gel applied as single administration with or without ODT were clearly greater than that of repeated administration (Table 1). The AUC value for ketoprofen gel applied as single administration with ODT was about 6-fold greater than that of repeated administration. The percutaneous absorption of a single greater dose of hydrocortisone has also been reported to increase over a lower dose applied three times (8). The AUC and Cmax values of absorbed ketoprofen for percutaneous absorption of ketoprofen gel applied with ODT as single or repeated administration were respectively greater than that without ODT. Especially, the AUC value for 6 g of ketoprofen gel applied as a single dose with ODT was 7.4-fold greater than that without ODT. The ointment of indomethacin or dinitrobutylphenol applied to the skin with ODT has been reported to promote the percutaneous absorption of indomethacin or dinitrobutylphenol for its skin hydration and temperature effects (5, 9). It is assumed here that when

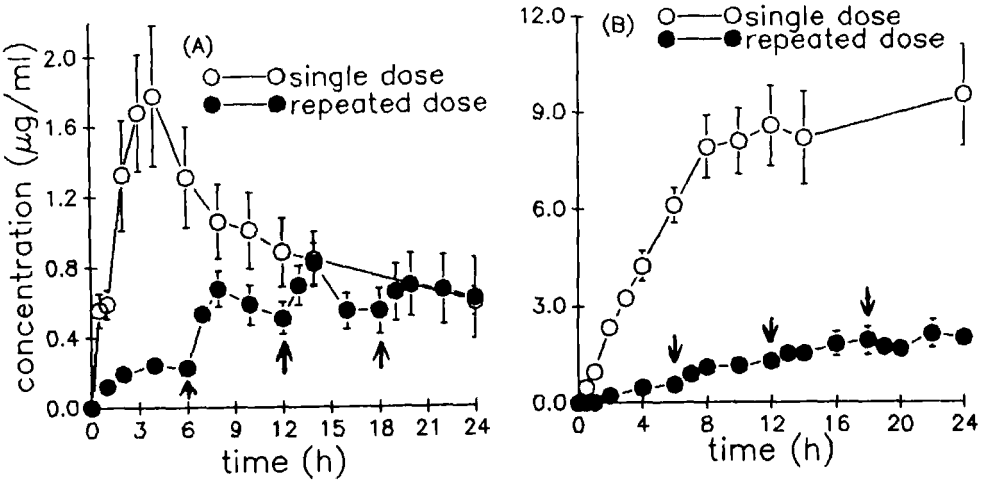

FIGURE 1

Percutaneous absorption of ketoprofen for single and repeated topical administration of the ketoprofen gel applied without ODT (A) and with ODT (B), respectively. Arrows represent the administration of ketoprofen gel after first ones. Vertical bars are standard errors (n = 5).

the ketoprofen gel has been applied as a single administration of a greater amount of gel with or without ODT, the ketoprofen gel on the skin will be less viscosity - owing to less volatilation of water or solvent in the gel and the skin being more hydrated than that of accumulately repeated administration of a lower amount of gel, respectively. This then results in the drug easily diffusing out of the gel and easily penetrating through the stratum corneum. These penetrated enhancing effects described above were, futhermore, much more potentiated by application of the ketoprofen gel with ODT than by that without ODT. Figure 1A indicates the plasma ketoprofen level ascending to a maximum level at the fourth hours after initial single administration of the ketoprofen gel (which was applied to the skin without ODT); the plasma drug level then

sharply descended to a lower level. This was done for the repeated administration of ketoprofen gel applied without ODT; the drug level descended following a maximum drug level had been reached. When the ketoprofen gel was applied as a single administration with ODT, the maximum concentration (8.24 μg / ml) of drug had been reached at the eighth hour after administration of the ketoprofen gel and kept it as a steady state drug level for a considerable period (Figure 1B). The plasma drug level has also been reported to have been maintained at a maximum steady state concentration for a considerable period after administration of its ointments or gels (5, 10, 11). When the ketoprofen gel was applied as a repeated administration with ODT, the plasma concentration of ketoprofen gradually ascended until a maximum level (1.91 μg / ml) of ketoprofen had been reached at the fourth administration of ketoprofen gel; it then kept it as a steady state plasma concentration for a considerable period (Figure 1B). The volatiled component in the ketoprofen gel according to the results , was assumed to have almost evaporated until 4 h after application of the gel in the case of without ODT and results in the ketoprofen gel become more viscosity and the dissolved drug precipitated from the gel (12). This then inducing the plasma ketoprofen level sharply descending until 4 h after single administration of the ketoprofen gel. This was confirmed by the volatility test of the ketoprofen gel which indicated the weight of the gel having sharply decreased until 4 h later; it then slowed down to a steady state weight until about 4 h later (Figure 2). Figure 3 shows the release amount - time profile for the ketoprofen gel which was applied to the skin with and without ODT in vitro, respectively. The release rate constant of ketoprofen (Table 2), during the diffusion period 0 to 4 h for the ketoprofen gel applied without ODT,

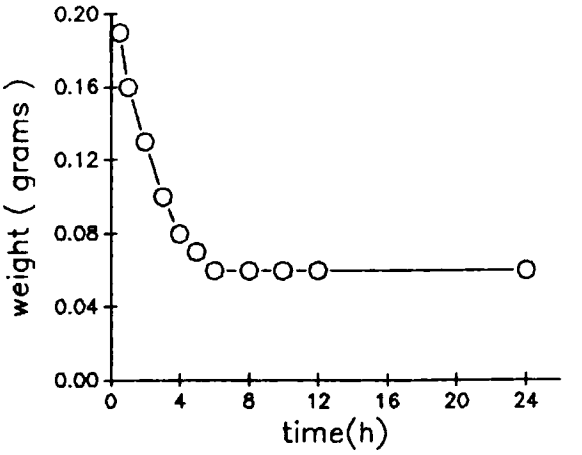

FIGURE 2

The remained weight of the ketoprofen gel versus the time after volatilation of the solvent in the gel.

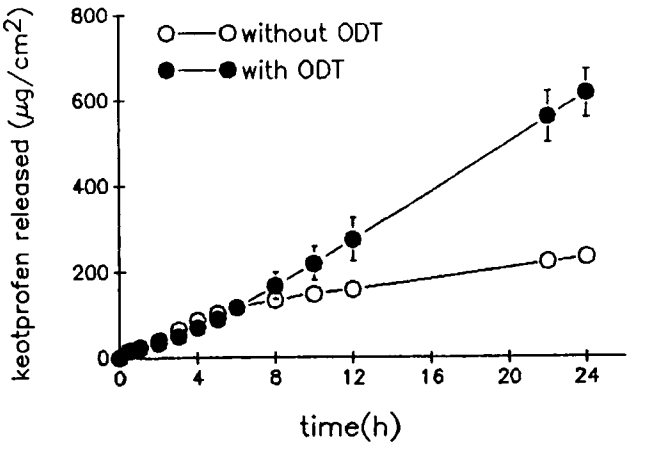

FIGURE 3

Effect of administration on the release of ketoprofen from ketoprofen gels. Vertical bars are standard errors (n = 3)

TABLE 2

Apparent Release Rate of Ketoprofen Gel in Each Condition

Administration	Duration of Release (h)	Release Rate (μg/h)	r*
without ODT	0 ~4	19.98 ± 2.23	0.996
	4 ~24	6.53 ± 0.58	0.997
with ODT	0 ~4	14.90 ± 1.46	0.993
	4 ~24	27.84 ± 2.78	0.999

* r is the correlation coefficient of the linear regression for the accumulated amount of drug vs time during each release period. Data are the mean ± S.E. (n = 3)

was found to be greater than that with ODT; on the contrary, the release rate constant for the ketoprofen gel applied without ODT during the diffusion period 4 to 24 h was less than that with ODT. During the diffusion period 0 to 4 h, it is assumed that the concentration of drug will be gradually increased with the gradual evaporation of the volatiled solvent in the gel (13) which was applied without ODT; this then resulted in the release rate of ketoprofen for the gel was greater than that with ODT. On the other hand, during the diffusion period was 4 to 24 h, it is assumed that the volatiled solvent in the gel applied without ODT was evaporated completely (Figure 2) ; this then resulted in the gel was more viscosity and the disslolved drug precipitated from the gel, then inducing less release of keotprofen than that with ODT.

In conclusion, when a commercial ketoprofen gel was used, 6 g of ketoprofen gel applied as a single administration to the rabbit abdominal skin was not only more convenient; it was also more ketoprofen penetrated through the skin than repeated

accumulated administration of 1.5 g of ketoprofen gel used at 6 hours interval in a day. Application of the ketoprofen gel to the skin with ODT was more effective than that without ODT. The effects of administration were very important in order to have the most therapeutic effective ketoprofen gel. This view point could be applied to other drugs or dosage forms applied to the skin.

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