International Journal of Pharmaceutics, 98 (1993) 113–120

IJP 03233

Percutaneous absorption of terodiline and the membrane-controlled transdermal therapeutic system

Taro Ogiso, Masahiro Iwaki, Tadatoshi Tanino, Mika Yatomi and Chisai Tsujimoto

Department of Pharmaceutics, Kinki University, Osaka (Japan)

(Received 7 July 1992)
(Modified version received 10 November 1992)
(Accepted 22 February 1993)

Key words: Terodiline; Percutaneous absorption; Membrane-controlled system; Microporous membrane; Rat

Summary

In an attempt to prepare a transdermal dosage form of terodiline which is extensively metabolized in man, the absorption of terodiline, an anticholinergic and calcium antagonist, through rat skin was estimated in vitro and in vivo. Terodiline penetrated rapidly through the skin from the gel formulation without enhancers (penetration rate, 167.6 μg/h per cm^2). Laurocapram, a potent enhancer, did not enhance the absorption in vitro. When the gel formulation (0.9 g) was applied to rat abdominal skin (6 cm^2), high plasma concentrations (C_{max}, 8.8 ± 3.4 μg/ml) of terodiline were observed for 24 h, thereby resulting in a high bioavailability equivalent to that after intravenous injection. The application of a transdermal therapeutic system, prepared using the gel formulation and a microporous membrane, gave a constant plasma level of terodiline, 250–820 ng/ml, for about 48 h, indicating that the membrane-controlled systems may be an efficient drug delivery system for treatment of urinary urge incontinence.

Introduction

Terodiline has both anticholinergic and calcium antagonist properties. In clinical trials terodiline has been shown to be effective in the treatment of urge incontinence (Ekman et al., 1980; Ulmsten et al., 1985; Gerstenberg et al., 1986). Since the incidence of urinary incontinence increases with age, particular attention has been paid to the pharmacokinetics of drugs for treatment of urinary incontinence in geriatric patients.

Terodiline is extensively metabolized, mainly by hydroxylation, demethylation and glucuronidation, in dog and man (Norèn et al., 1988). The percutaneous (p.c.) route avoids the first-pass phenomenon by which the liver can significantly reduce the amount of intact agent passing into the systemic circulation. Therefore, the transdermal route of administration may be useful for drugs with low bioavailability due to first-pass metabolism. The p.c. dosage form, as a rule, is convenient for application and so is suitable for geriatric patients. Thus, it is of increasing interest

Correspondence to: T. Ogiso, Department of Pharmaceutics, Kinki University, 3-4-1 Kowakae, Higashi, Osaka 577, Japan.

to develop a convenient and effective formulation for treatment of urinary incontinence. The elderly form an important target group for the treatment of urinary urge incontinence with drugs such as terodiline.

In the present study, the absorption characteristics of terodiline via rat skin were estimated in the presence or absence of absorption enhancers. In addition, transdermal therapeutic systems were prepared using two microporous membranes to achieve a sustained plasma concentration and the plasma concentrations were measured after p.c. application of the systems to rats.

Materials and Methods

Materials

Terodiline hydrochloride was a generous gift of Kissei Pharmaceutical Co. (Matsumoto, Japan). Tipepidine citrate, an internal standard for GLC, was obtained from Tanabe Pharmaceutical Co. (Osaka, Japan). Hiviswako 104, a gel base, and laurocapram were obtained from Wako Pure Chemical Industries (Osaka, Japan) and Nelson Research and Development Co. (Irvine, CA), respectively. Microporous membrane, made of polyolefin, Hipore (HP) 2100 (mean pore size, 0.23 μm; thickness, 100 μm) and Hipore (HP) 4050 (mean pore size, 0.30 μm; thickness, 50 μm) were generous gifts of Asahi Organic Chemicals (Tokyo, Japan). Other chemicals and solvents used were of reagent grade or HPLC quality. Free terodiline was prepared from the salt by extraction with hexane at alkaline pH, washing the extract with water and evaporation of hexane. Male Wistar rats, weighing 220–300 g, were used throughout this experiment. The animals had free access to MF diet (Oriental Yeast Co., Tokyo, Japan) for 3–4 days prior to and during the experiment.

Preparation of gel formulations and their transdermal systems

We have used Hiviswako 104 as a gel base which generally showed good drug release profiles. Hiviswako 104 was added to glycerin heated at 65°C and mixed vigorously. After cooling, the gel base was neutralized with triethanolamine. Free terodiline dissolved in propylene glycol was mixed with the gel base. In some formulations, laurocapram or lauric acid dissolved in propylene glycol with terodiline was mixed with the base. Details of the preparations are listed in Table 1.

TABLE 1

Composition of terodiline gel formulations

	Rp. 1	Rp. 2	Rp. 3
Glycerin (g)	63.27	63.27	63.27
Propylene glycol (ml)	30.0	25.0	28.58
Hiviswako 104 (g)	2.0	2.0	2.0
Triethanolamine (g)	2.73	2.73	2.73
Terodiline (g)	2.0	2.0	2.0
Laurocapram (g)	–	5.0	–
Lauric acid (g)	–	–	1.42

The transdermal system with or without a microporous membrane, containing 0.9 g of the gel formulation (terodiline, 18 mg) and having an absorption area of 6 cm^2 as depicted in Fig. 1, was prepared.

Intravenous (i.v.) and oral administrations

On the day before the experiment, the rat jugular vein was cannulated with silicon tubing (Upton, 1975). Terodiline hydrochloride was administered intravenously at a dose of 15 mg/kg and orally at 30 mg/kg in saline, respectively. Blood samples were collected periodically for 10 h (i.v.) and 28 h (p.o.) through the tubing. The plasma was separated immediately by centrifugation and stored frozen until assay.

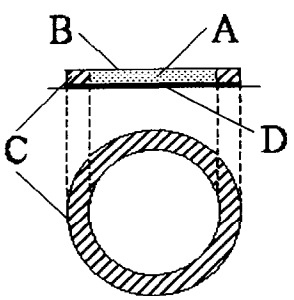

Fig. 1. Sectional view of transdermal system. (A) Gel formulation; (B) aluminum foil; (C) silicon rubber (2.76 cm i.d., 1.0 μm thickness); (D) microporous membrane.

In vitro p.c. penetration experiment

On the day before the experiment, the hair of the abdominal area of the rats was removed with an electric clipper and electric razor. On the next day, pieces (2 × 2 cm area) of full-thickness abdominal skin were excised from the rats. The adherent fat and other visceral debris were removed from the under surface. The dermal side of the skin was soaked in a buffer solution (0.85% NaCl-10 mM phosphate buffer, pH 7.4) for 12 h at 5°C. 0.25 g of gel formulation (terodiline 5 mg) was uniformly spread over the stratum corneum surface of the skin, mounted in a Franz diffusion cell (reservoir volume 13.0 ml; 1.0 cm i.d. O-ring flange), and occluded with a sheet of aluminum foil. Gentamicin sulfate solution (10 mg/ml, Sigma Chemical Co., St. Louis, MO) was added to the receptor fluid at a ratio of 1:100. The incubation was carried out at 37°C. Aliquots (100 μl) of the receptor fluid (0.85% NaCl-10 mM phosphate buffer, pH 7.4) were withdrawn periodically for 30 h.

In vivo percutaneous absorption experiment

On the day before the experiment, the rat jugular vein was cannulated with silicon tubing (Upton, 1975) and the hair of the abdominal area was carefully removed with an electric razor. On the next day, the transdermal system was applied to the rat abdomen. The system was fixed with an adhesive (Aronalpha, Konishi Co., Osaka, Japan) and immediately occluded with adhesive tape. Application of the system to the rat was performed for 48 h. Blood samples from the cannulated jugular vein were collected periodically for 48 h after dosing.

In vitro release test through microporous membrane

An aliquot (0.64 g) of the gel ointment was uniformly spread over a filter paper (No. 5C, Toyo Filter Co., Tokyo, Japan), Hipore 2100 or Hipore 4050 membrane. The filter paper and membranes were mounted in a Franz diffusion cell (reservoir volume, 10.5 ml; 1.6 cm i.d.) and occluded with a sheet of aluminum foil. The receptor solution was 0.85% NaCl-10 mM phosphate buffer, pH 7.4, supplemented with gentamicin sulfate solution. Aliquots (50 μl) of the fluid were withdrawn periodically for 8 h.

Determination of terodiline

Terodiline in plasma and sample solution was determined by the GLC method of Karlèn et al. (1982), with modifications. Briefly, a 100 μl aliquot of plasma or 50 (or 100) μl of sample solution was mixed with 100 μl of the internal standard solution (tipepidine citrate, 20 μg/ml methanol) and 100 μl of methanol. After adding 0.5 N NaOH (0.4 ml) the mixture was extracted with hexane:ether (4:1, v/v, 5 ml). Following centrifugation, the supernatant was evaporated under reduced pressure and the residue was derivatized with a mixture of ethyl acetate (50 μl) and trifluoroacetic anhydride (50 μl) for 30 min at room temperature. After evaporation, the residue dissolved with a small volume of ethyl acetate was injected into the column (3 mm × 2 m) packed with 3% Silicon OV-17 on Uniport HP (100–120 mesh) on a gas chromatograph (Shimadzu GC-12A) equipped with a flame thermionic detector (FTD-8). The temperatures were: oven, 230°C; and injection port and detector, 250°C.

Pharmacokinetic and statistical analysis

The in vitro p.c. parameters were calculated from the penetration data by using the following equations:

$$D = \frac{\delta^2}{6\tau}$$

$$J_s = \frac{D \cdot k_m \cdot C_s}{\delta} = k_p \cdot C_s$$

where J_s is the penetration rate, k_m denotes the skin/vehicle partition coefficient of drug, D is the diffusion constant within the skin, τ represents the lag time and δ is the thickness (0.002 cm) of the stratum corneum, k_p denotes the permeability coefficient through the stratum corneum, and C_s is the drug concentration in the gel ointment.

Kinetic parameters were calculated by using the least-squares fit program, MULTI (Yamaoka

et al., 1981). The plasma concentration data after i.v. and oral administrations were fitted to the equations:

$$C_t = A \cdot e^{-\alpha t} + B \cdot e^{-\beta t}$$

$$C_t = A \cdot e^{-\alpha t} + B \cdot e^{-\beta t} - (A + B)e^{-k_a t}$$

where C_t is the drug concentration at time, t, A, α, B, and β denote the biexponential equation constants and k_a is the apparent absorption rate constant.

The area under the plasma concentration-time curve (AUC) after i.v. and oral administrations was calculated by the trapezoidal rule to the observed data point. The residual area beyond the last sampling time was estimated as C'/β, where C' is the last observed concentration. The absolute bioavailability was calculated using the AUC values. The area under the first moment curve (AUMC) and the mean residence time (MRT) were calculated by means of the following equations (Yamaoka et al., 1978; Benet and Galeazzi, 1979):

$$\text{AUMC} = \int_0^\infty t \cdot C \, dt$$

$$\text{MRT} = \frac{\text{AUMC}_{0-48}}{\text{AUC}_{0-48}}$$

The means of all data are presented with their standard deviation (mean ± SD). Statistical analysis was performed by using the non-paired Student's t-test, and a p value of 0.05 or less was considered to be significant.

Results

Plasma concentration of terodiline after single i.v. and oral administrations

The plasma concentration-time curves for terodiline after a single i.v. (15 mg/kg) and oral (30 mg/kg) administration are shown in Fig. 2. The plasma decay curves after i.v. and oral dosings showed biexponential kinetics. The pharmacokinetic parameters calculated by using the open two-compartment models are listed in Table 2 The bioavailability and $t_{1/2\,\beta}$ after oral dosing were 47.1% and 3.7 h, respectively, suggesting a relatively greater first-pass effect and apparently rapid elimination of drug after oral dosing.

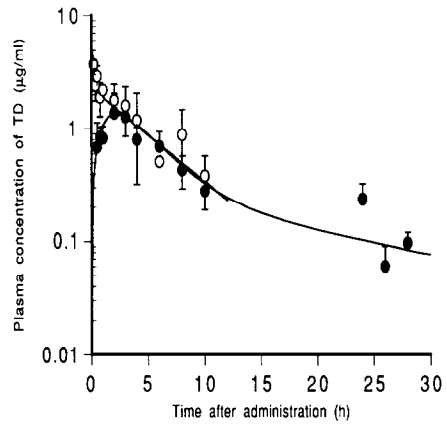

Fig. 2. Plasma concentration of terodiline after single i.v. (○) and oral (●) administrations. Each point represents the mean ±S.D. ($n = 4$ and 6). Dose: i.v., 15 mg/kg; oral, 30 mg/kg. Solid lines represent simulation curves.

TABLE 2

Pharmacokinetic parameters following a single i.v. and oral administration of terodiline

Parameter	i.v.	Oral
A (μg/ml)	2.68 ± 0.52	5.38 ± 0.83
α (h^{-1})	4.64 ± 0.45	0.36 ± 0.17
B (μg/ml)	2.25 ± 0.49	0.32 ± 0.21
β (h^{-1})	0.19 ± 0.07	0.20 ± 0.03
k_a (h^{-1})	–	0.66 ± 0.11
V_1 (l/kg)	3.08 ± 0.37	–
V_2 (l/kg)	3.11 ± 0.85	–
k_{12} (h^{-1})	2.20 ± 0.42	–
k_{21} (h^{-1})	2.21 ± 0.27	–
k_{10} (h^{-1})	0.43 ± 0.24	–
$t_{1/2\beta}$ (h)	3.91 ± 1.24	3.65 ± 1.05
Cl_{tot} (1 kg^{-1} h^{-1})	1.29 ± 0.66	–
AUC (μg h ml^{-1})	15.17 ± 5.38	14.30 ± 4.81
AUMC (μg h^2 ml^{-1})	71.22 ± 27.11	227.61 ± 91.37
MRT (h)	4.44 ± 0.98	15.92 ± 3.76

k_a, absorption rate constant; V_1 and V_2, distribution volume of central and tissue compartments; k_{12} and k_{21}, distribution rate constants; $t_{1/2\beta}$, eliminations half-life at β phase; Cl_{tot}, total clearance; k_{10}, elimination rate constant from the central compartment. Each value represents the mean ± S.D. ($n = 4$). Dose: 15 mg/kg (i.v.) and 30 mg/kg (oral).

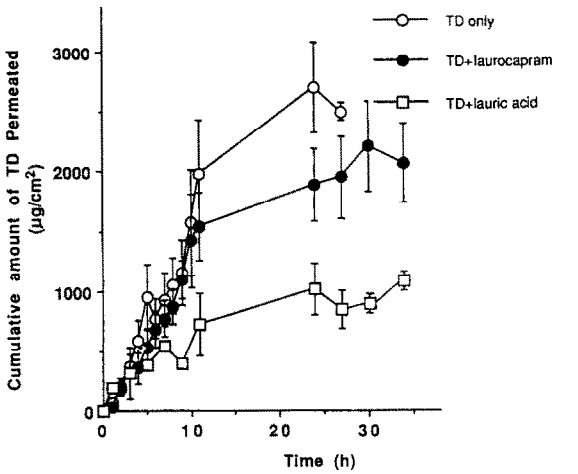

Fig. 3. Penetration profiles of terodiline (TD) through rat skin. Each point represents the mean ± S.D. ($n = 3$–6). Applied dose, 0.25 g/0.785 cm^2.

In vitro p.c. penetration

The in vitro p.c. penetration study was carried out to compare the penetration of the drug in the presence or absence of absorption enhancers, such as laurocapram and lauric acid. The penetration of terodiline was the greatest in the absence of these enhancers, as shown in Fig. 3. Laurocapram, a typical enhancer, showed no enhancement effect, while lauric acid dramatically decreased the penetration of the drug compared with that without enhancers. The penetration parameters are listed in Table 3. The drug penetrated through rat skin at a rate which can be

TABLE 3

In vitro percutaneous penetration parameters of terodiline through rat skin

Parameter	Rp. 1	Rp. 2	Rp. 3
J_s (μg/h per cm^2)	167.6 ±38.0	153.3 ±21.2	57.3 ±22.8
Lag time (h)	0.79± 0.40	1.31± 0.59	0.10± 0.00
K_p ($\times 10^{-3}$) (cm/h)	8.4 ± 1.9	7.7 ± 1.1	2.9 ± 1.1
K_m	20.0 ± 9.6	30.2 ±12.1	0.87± 0.36
D ($\times 10^{-6}$) (cm^2/h)	0.84± 0.70	0.51± 0.27	6.67± 2.56

J_s, penetration rate; K_p, permeability coefficient through skin: K_m, partition coefficient; D, diffusion constant within skin. Each value represents the mean ± S.D. ($n = 4$–6).

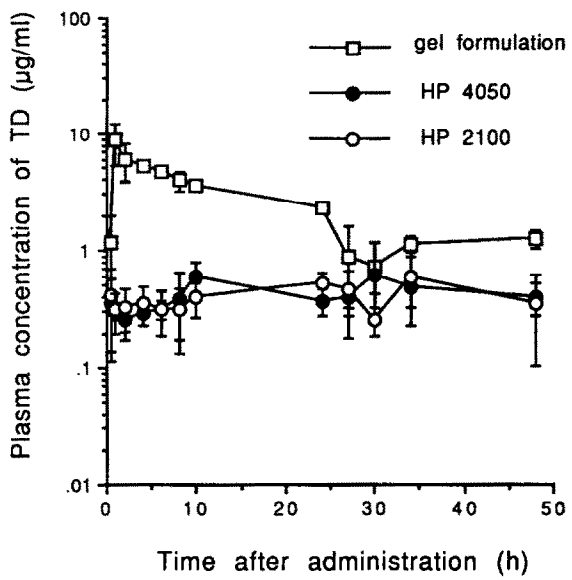

Fig. 4. Plasma concentration of terodiline after application of the transdermal systems. Each point represents the mean ± S.D. ($n = 3$–7). Applied formulation was 0.9 g/6 cm^2.

described fairly well by a zero-order kinetic profile during the first 12 h. This J_s value (167.6 μg/h per cm^2) for Rp. 1 was considerably larger than that of other drugs (Ogiso and Shintani, 1990; Diez et al., 1991), demonstrating the rapid penetration of terodiline through rat skin.

In vivo p.c. absorption

Rp. 1, which showed a large flux of terodiline in the in vitro experiment, was used for the in vivo absorption study. Additionally, in order to obtain a constant plasma concentration of terodiline for a prolonged period, a microporous membrane was adopted as a rate-controlling barrier. The transdermal systems prepared using the Rp. 1 formulation and microporous membranes were applied to the rat for 48 h. The plasma concentrations during a single p.c. application of the systems are shown in Fig. 4. The plasma levels of terodiline after application of the system (system 1) without microporous membranes were considerably high (C_{max}, 8.8 ± 3.4 μg/ml), while the plasma levels after application of the system (systems 2 and 3) with HP-2100 or HP-4050 membranes were low but constant for a long time; the plasma concentration range of 250–820 ng/ml

TABLE 4

Pharmacokinetic parameters after aplication of terodiline transdermal systems

Parameter	Transdermal system		
	1	2 [a]	3 [b]
C_{max} (μg/ml)	8.77 ± 3.37	0.70 ± 0.16	0.82 ± 0.21
AUC_{0-48} (μg h ml^{-1})	115.90 ± 4.74	19.72 ± 3.19	21.78 ± 4.61
MRT (h)	16.04 ± 1.08	23.72 ± 2.40	27.91 ± 6.22
Apparent bioavailability (%)	122.88 ± 9.74	25.00 ± 4.04	27.74 ± 5.92

[a] With Hipore 4050.[b] With Hipore 2100.
Each value represents the mean ± S.D. (n = 3–7). Applied gel formulation was 0.9 g (drug 18 mg)/6 cm^2.

was sustained for about 48 h. The pharmacokinetic parameters obtained are shown in Table 4. The MRT values (23.7 and 27.9 h), being apparent ones, for systems 2 and 3 were much greater than that (16.0 h, system 1) without membranes, indicating that the membrane-controlled systems may be an efficient drug delivery system for achieving a prolonged effect. The apparent bioavailability of terodiline after dosing of system 1 was 122.9 ± 9.7%, this value being significantly higher than that (47.1%) after oral dosing ($p < 0.01$).

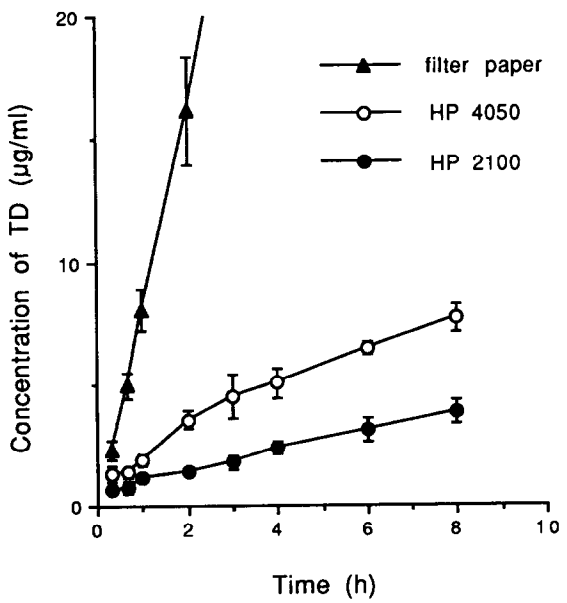

Fig. 5. Release profiles of terodiline through microporous membranes. Each point represents the mean ± S.D. (n = 3). Applied formulation was 0.64 g/2.0 cm^2.

Drug release through microporous membrane

Drug release through the membranes from the gel formulation (Rp. 1) was examined by using a Franz diffusion cell. The release profiles of terodiline through the membranes or a filter paper are shown in Fig. 5. The release rates (1.35 ± 0.28 μg/ml per h for HP-4050 and 0.46 ± 0.07 μg/ml per h for HP-2100) for drug through the porous membranes were significantly lower than that (7.56 ± 0.55 μg/ml per h) without the membranes, indicating that the membranes do act as a controlled-release barrier. The release rate through Hipore 4050 was slightly but significantly greater than that through Hipore 2100 ($p < 0.01$).

Discussion

Since urinary incontinence is a common problem in elderly patients, transdermal absorption studies of terodiline were initiated with a view to apply it to geriatric patients, who represent an important and sensitive target group for treatment.

Terodiline is almost completely absorbed from the gastrointestinal tract with about 90% bioavailability in man (Karlèn et al., 1982). After a single oral dosing to healthy volunteers, maximum serum concentrations (C_{max}) are usually reached within 4 h and the biological half-life is about 60 h. In rat, $t_{1/2}$ is 9.0–13.1 h after oral dosing of [^{14}C]terodiline (Sakai et al., 1987). The latter result was not consistent with our data. A reason for the discrepancy may be due to the fact that Sakai et al. (1987) measured total ^{14}C (drug + metabolites) in plasma. The apparent bioavailability of terodiline for the gel formulation (system 1) was over 100%. This value was compatible with that after oral dosing in human volunteers (90%) (Karlèn et al., 1982), but much larger than that (47.1%) after oral dosing in rat. These results indicate that terodiline was rapidly and

readily absorbed across rat skin, and perhaps across human skin. The high bioavailability should mainly be due to by-passing of the first-pass metabolism and the complete absorption of the drug. However, the extremely high value (> 100%) may in part be due to the variation of total clearance during application of the system or animal-animal variability.

The plasma terodiline concentrations 48 h after the transdermal systems were comparatively high (0.36–1.26 μg/ml), however, the data do not necessarily represent the sustained plasma concentration after that time. The cessation of application will result in the rapid elimination of the drug from plasma, since the drug is rapidly absorbed across skin (Fig. 4) and relatively quickly eliminated from plasma ($t_{1/2,\beta}$ 3.7 h).

The plasma concentrations of terodiline during the application of the gel formulation (system 1) were much higher than those during dosing of the systems with microporous membranes (systems 2 and 3), indicating that the microporous membranes are exceedingly effective as a controlled-release membrane. This is also clearly demonstrated by the fact that the release rates of terodiline through the membranes (7.09 and 2.42 μg/h per cm^2 for HP-4050 and HP-2100, respectively), calculated per unit area (cm^2), were much smaller than the skin penetration rate (167.6 μg/h per cm^2) of terodiline for system 1.

Estimation of serum steady-state concentrations (C_{ss}) from the oral data in man results in a $C_{ss,min}$ of about 230 ng/ml and $C_{ss,max}$ of about 300 ng/ml (Hallèn et al., 1988). Alternatively, the average steady-state serum concentration can be estimated from the AUC (single dose)/dosing interval to be 246 ng/ml (Hallèn et al., 1988). The C_{ss} has been reported to be 518 ng/ml in geriatric patients and 238 ng/ml in healthy volunteers given 12.5 mg twice per day orally (Hallèn et al., 1989). In this study, the plasma levels of terodiline after dosing of the transdermal systems with microporous membranes (systems 2 and 3) ranged from 250 to 820 ng/ml. Thus, these transdermal systems have the potential for efficient controlled release with an administration regimen of a single p.c. dose per 2 or more days for the treatment of urinary urge incontinence, assuming that the penetration of drug through human skin is lower than that through rat skin.

With the intention of improving the percutaneous absorption of terodiline in this experiment, absorption enhancers such as laurocapram and lauric acid were used. However, as a result these enhancers showed no enhancement effect, probably due to the excellent penetration characteristics (J_s = 167.6 μg/h per cm^2 and $k_p = 8.4 \times 10^{-3}$ cm/h) of this drug itself, as mentioned above.

The drug should penetrate mainly via a lipoidal pathway, i.e., transcellular route, since the free drug has a lipophilic nature. However, the rapid penetration of terodiline during the initial time period might be ascribed to the rapid absorption of drug dissolved in solvent via the appendageal route, since the flux through the hair follicles is much greater than that through the stratum corneum during the early stages of the diffusion process (Barry, 1983). The relatively low flux of terodiline after application of the gel formulation with laurocapram and lauric acid may be explained by the slow release of drug from the formulation, based on the high lipophilicity of the enhancers.

In conclusion, the present study of p.c. terodiline has shown that the drug is rapidly absorbed through rat skin without enhancer, resulting in an appreciably high bioavailability. The transdermal systems with porous membranes were found to be useful in terms of the sustained absorption of terodiline, longer duration of effective plasma levels and comparatively high bioavailability. The transdermal systems have the potential to be used as an efficient drug delivery system.

References

Barry, B.W., *Skin Transport. Dermatological Formulations: Percutaneous Absorption,* Dekker, New York, 1983, pp. 95–126.

Benet, L.Z. and Galeazzi, R.L., Noncompartmental determination of the steady state volumes of distribution. *J. Pharm. Sci.,* 68 (1979) 1071–1074.

Diez, I., Colom, H., Moreno, J., Obach, R., Peraire, C. and Domenech, J., A comparative in vitro study of transdermal absorption of a series of calcium channel antagonist. *J. Pharm. Sci.,* 80 (1991) 931–934.

Ekman, G., Andersson, K.-E., Rud, T. and Ulmsten, U., A double blind cross-over study of the effects of terodiline in women with unstable bladder. *Acta Pharmacol. Toxicol.,* 46 (Suppl. 1) (1985) 39–43.

Gerstenberg, T.C., Klarskov, P., Ramirez, D. and Hald, T., Terodiline in the treatment of women urgency and motor urge incontinence. A clinical and urodynamic double-blind crossover study. *Br. J. Urol.,* 58 (1986) 129–133.

Hallèn, B., Guilbaud, O., Strömberg, S. and Lindeke, B., Single-dose pharmacokinetics of terodiline, including a stable isotope technique for improvement of statistical evaluations. *Biopharm. Drug Dispos.,* 9 (1988) 229–250.

Hallèn, B., Bogentoft, S., Sandquist, S., Strömberg, S., Setterberg, G. and Ryd-Kjellèn, E., Tolerability and steady-state pharmacokinetics of terodiline and its main metabolites in elderly patients with urinary incontinence. *Eur. J. Clin. Pharmacol.,* 36 (1989) 487–493.

Karlèn, B., Andersson, K.-E., Ekman, G., Strömberg, S. and Ulmsten, U., Pharmacokinetics of terodiline in human volunteers. *Eur. J. Pharmacol.,* 23 (1982) 267–270.

Ogiso, T. and Shintani, M., Mechanism for the enhancement effect of fatty acids on the percutaneous absorption of propranolol. *J. Pharm. Sci.,* 79 (1990) 1065–1071.

Norèn, B., Strömberg, S., Ericsson, Ö. and Lindeke, B., Biotransformation of terodiline. *Acta Pharm. Suec.,* 25 (1988) 281–292.

Sakai, A., Hara, Y., Nishiyama, M., Ujiie, A., Ikeda, S., Jin, Y. and Esumi, Y., Studies on the metabolic fate of [^{14}C]terodiline: I. Absorption, distribution and excretion of [^{14}C] terodiline hydrochloride in rats. *Iyakuhin Kenkyu,* 18 (1987) 113–137.

Ulmsten, U., Ekman, G. and Andersson, K.-E., The effect of terodiline treatment in women with motor urge incontinence. *Am. J. Obstet. Gynecol.,* 153 (1985) 619–622.

Upton, R.A., Simple and reliable method for serial sampling of blood from rats. *J. Pharm. Sci.,* 64 (1975) 112–114.

Yamaoka, K., Nakagawa, T. and Uno, T., Statistical moments in pharmacokinetics. *J. Pharmacokinet. Biopharm.,* 6 (1978) 547–558.

Yamaoka, K., Tanigawara, T., Nakagawa, T. and Uno, T., A pharmacokinetic analysis program (MULTI) for microcomputer. *J. Pharmacobio-Dyn.,* 4 (1981) 879–885.