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Topical Delivery of Keloid Therapeutic Drug, Tranilast, by Combined Use of Oleic Acid and Propylene Glycol as a Penetration Enhancer: Evaluation by Skin Microdialysis in Rats

TERUO MURAKAMI, MAKIKO YOSHIOKA, RYOKO YUMOTO, YUTAKA HIGASHI, SADAYUKI SHIGEKI*, YOSHIKAZU IKUTA* AND NOBORU YATA†

*Department of Biopharmaceutics, Institute of Pharmaceutical Sciences, and *Department of Orthopedic Surgery, Hiroshima University School of Medicine, 1-2-3 Kasumi, Minami-ku, Hiroshima 734, Japan*

Abstract

Topical delivery of tranilast (*N*-(3,4-dimethoxycinnamoyl)anthranic acid), an inhibitor of collagen synthesis and a therapeutic drug for keloid and hypertrophic scar, was examined, in rats, with oleic acid alone or a combination of oleic acid and propylene glycol as penetration enhancer. Evaluation was by measurement of the concentration of tranilast in plasma and in the dialysate from skin microdialysis.

When tranilast at a dose of 1·5 mg was applied topically as an ethanol solution containing 5% polyvinylpyrrolidone on a dorsal skin surface (2·25 cm^2), the maximum concentration of tranilast in skin dialysate was approximately 2 μM. When 10 or 20% oleic acid was added to the same ethanol solution the maximum concentration of tranilast in the dialysate increased to 10–20 μM, and this value was further increased to 60 μM by the addition of a combination of oleic acid (10 or 20%) and propylene glycol (10%) to the solution. With the combination of oleic acid and propylene glycol the area under the plot of the concentration of tranilast in skin dialysate against time between 0 and 4 h (AUC_{0-4}) was more than 400-fold that after intravenous administration. The transdermal bioavailability of tranilast as assessed by the AUC_{0-4} of tranilast in plasma, was 0·2% of the dose applied in the ethanol solution, 3–5% of that applied in the ethanol solution containing oleic acid, and 14–16% of that applied in the ethanol solution containing both oleic acid and propylene glycol.

These results suggest that the topical delivery of tranilast with an absorption enhancer such as a mixture of oleic acid and propylene glycol might be a more effective medication than oral administration of tranilast for the treatment of keloid and hypertrophic scar.

Keloid and hypertrophic scar are clinically intractable diseases caused by abnormal proliferation of fibroblasts and production of collagen during granulation in the process of healing of injuries such as surgical wounds, burns and traumas (Murray et al 1981; Rockwell et al 1989; Dutubo-Brown 1990). These diseases cause disfigurement, itching and pain. Therapeutic drugs for keloid and hypertrophic scar involve triamcinolone acetonide (Cohen & Peacock 1990), a heparin-like substance (heparinoids).

Tranilast (*N*-(3,4-dimethoxycinnamoyl)anthranic acid), an anti-allergic drug used clinically in Japan to improve bronchial asthma, atopic dermatitis and allergic rhinitis, is now also used as a useful therapeutic drug for the treatment of keloid and hypertrophic scar, because the drug was found to suppress collagen synthesis specifically rather than the cell proliferation in cultured fibroblasts derived from keloid tissues in man (Azuma et al 1976; Waseda et al 1984; Suzawa et al 1992; Yamada et al 1995). Although peroral formulations of tranilast, such as capsules and granules, are available for

†Present address: Faculty of Pharmaceutical Sciences, Setsunan University, 45-1 Nagaotoge-cho, Hirakata, Osaka 573-01, Japan.

Correspondence: T. Murakami, Department of Biopharmaceutics, Institute of Pharmaceutical Sciences, Hiroshima University School of Medicine, 1-2-3 Kasumi, Minami-ku, Hiroshima 734, Japan.

clinical use, selective distribution of tranilast to restricted skin tissues such as keloid and hypertrophic scar would be unlikely after this mode of administration. We have previously examined the feasibility of iontophoretic transdermal delivery of tranilast for the therapy of keloid and hypertrophic scar and found that application of a dose of 12 mg once a week to affected parts for one or two weeks reduced patients' complaints of, for example pain and itching much more than oral administration of the much larger dose of 100 mg three times a day for several months (Shigeki et al 1997a). This finding indicates that topical delivery of tranilast to the affected parts substantially improves the efficacy of tranilast.

In this study the feasibility of topical delivery of tranilast with the aid of penetration enhancer was examined in rats; oleic acid alone or in combination with propylene glycol was used as penetration enhancer. The combined use of oleic acid and propylene glycol is already known to be a potent penetration enhancer for the transdermal absorption of hydrocortisone, 5-fluorouracil, triamcinolone acetonide, estradiol, nitroglycerine, etc. (Barry & Bennett 1987; Goodman & Barry 1988; Loftsson et al 1989a,b). The feasibility of topical delivery of tranilast was evaluated by measuring the concentration of tranilast both in plasma and in the dialysate obtained by skin microdialysis, using a probe implanted cutaneously. Microdialysis is accepted as a new technique for determining the unbound concentration of substances in extracellular space and biological fluids (Benveniste 1989; Benveniste & Huttemeier 1990). The use of microdialysis has also been extensively expanded in the field of skin study to monitor chemical events in skin tissues, e.g. histamine release in allergic reaction, detection of serological parameters, and evaluation of the transdermal absorption of drugs (Matsuyama et al 1994a,b; Meyerhoff et al 1994; Okahara et al 1995).

Materials and Methods

Materials

Tranilast was obtained from Kissei Pharmaceutical (Matsumoto, Japan). Other chemicals used were of reagent grade and were used without further purification.

Preparation of tranilast solution

For intravenous administration tranilast was dissolved at a concentration of 6 mg mL^{-1} in a 7 : 3 (v/v) mixture of 1% aqueous $NaHCO_3$ and ethanol. For topical application tranilast was dissolved at a concentration of 15 mg g^{-1} in ethanol containing 5% polyvinylpyrrolidone to increase the viscosity of the solution. Oleic acid alone (10 or 20%)or a mixture of oleic acid and propylene glycol (10 : 10% or 20 : 10%) were also added, as penetration enhancers, to the tranilast ethanol solution containing 5% polyvinylpyrrolidone.

In-vivo animal study

The dorsal skin hair of male Wistar rats, 230–270 g, was removed with clippers one day before the study. Rats were anaesthetized with pentobarbitone (40 mg kg^{-1}, i.p.) and a femoral artery or a vein, or both, were cannulated with polyethylene tubing (PE 50, Clay Adams, USA). The rats were then fixed in a prone position on a surface kept at 37°C. Skin microdialysis was performed as described previously (Okahara et al 1995) using a microdialysis device obtained from Carnegie Medicine (Stockholm, Sweden). The length of semi-permeable membrane of the microdialysis probe (CMA 10) was 4·0 mm; the molecular weight cut-off was 20 kDa. The microdialysis probe was implanted intracutaneously via a guide cannula. Tyrode solution (NaCl 0·8%, dextrose 0·1%, $NaHCO_3$ 0·1%, $CaCl_2$ 0·02%, KCl 0·02%, $MgCl_2$ 0·01%, $NaH_2PO_4.2H_2O$ 0·0066%) was perfused at a flow rate of 3 μL min^{-1} (single perfusion) by means of a micro-infusion pump (CMA 100).

Intravenous administration. Tranilast solution (0·25 mL) was intravenously administered at a dose of 1·5 mg per rat via a cannula inserted in a femoral vein. The dialysate from the outlet tubing of the microdialysis probe was collected every 10 min; blood was collected at appropriate times via a cannula inserted in a femoral artery.

Topical application. A solution of tranilast (1·5 mg) in ethanol (0·1 g) containing polyvinylpyrrolidone with or without oleic acid or oleic acid and propylene glycol was applied topically to a $1{\cdot}5 \times 1{\cdot}5$ cm^2 area of skin. Before topical application the microdialysis probe was implanted cutaneously at the centre of the area of application. The skin surface was covered with polyethylene film during the experiment (occlusive dressing technique). Dialysate was collected every 10 min for 4 h. Arterial blood was collected via a femoral artery cannula at appropriate times up to 4 h.

Analysis

The concentration of tranilast in the dialysate and plasma was determined by HPLC as described previously (Shigeki et al 1997a). Briefly, dialysate samples were injected directly on to the HPLC

column. Plasma (50 μL), obtained by centrifuging the blood sample at 3000 rev min^{-1} for 10 min, was deproteinized by addition of 100 μL acetonitrile. The mixture was again centrifuged, and the supernatant was injected on to the HPLC column. The TSK-GEL 80 TM (Tosoh, Japan) reversed-phase column was eluted with a 5 : 5 (v/v) mixture of acetonitrile and 1% aqueous acetic acid. Tranilast was detected at 360 nm.

Results

Intravenous administration of tranilast

The concentrations of tranilast in plasma and skin dialysate after intravenous administration of 1·5 mg (4·58 μmol) are shown in Figure 1. Tranilast disappeared biexponentially from plasma and dialysate. The dialysate/plasma concentration ratio of tranilast was constant (0·08 ± 0·01%; mean ± s.e.m.) during the experiment. Some pharmacokinetic parameters for tranilast in plasma obtained by two-compartment model analysis were: area under the plasma concentration–time curve ($AUC_{0-\infty}$), 12 675 ± 430 μM min; total plasma clearance, 0·33 ± 0·01 mL min^{-1} per rat; distribution volume of the central compartment Vd), 22·0 ± 6·4 mL min^{-1} per rat, elimination rate constant from central compartment, 0·016 ± 0·005 min^{-1}, and half-life of β phase, 51·9 ± 12·2 min. The AUC_{0-4} of tranilast in the skin dialysate was 14·4 ± 2·1 μM min (mean ± s.e.m., n = 3), or 0·09% of the plasma AUC. Thus, it was speculated that only a small amount of tranilast was distributed into the restricted skin tissue after intravenous administration, although the percentage recovery of tranilast by microdialysis was not determined.

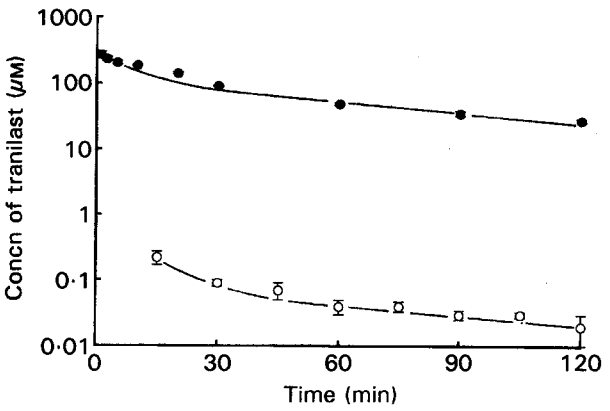

Figure 1. Concentration of tranilast in rat plasma (●) and skin microdialysate (○) after intravenous administration of 1·5 mg. Each value is the mean ± s.e.m. (n = 3).

Topical application of tranilast

Concentrations of tranilast in skin dialysate and in plasma after topical application of 1·5 mg (4·58 μmol) per rat are shown in Figure 2. Some pharmacokinetic parameters for tranilast in skin dialysate and plasma are listed in Table 1. As shown in Figure 2, in the absence of additives in the ethanol solution containing 5% polyvinylpyrrolidone, the maximum concentration of tranilast in dialysate was approximately 2 μM 4 h after application. When 10 or 20% oleic acid was added the maximum concentration of tranilast in the dialysate increased to approximately 10–20 μM 2 h after application. This maximum tranilast concentration was further increased to 60 μM 3 h after application by combined use of 10 or 20% oleic acid and 10% propylene glycol; addition of propylene glycol alone did not result in a significant increase compared with the value obtained in the absence of

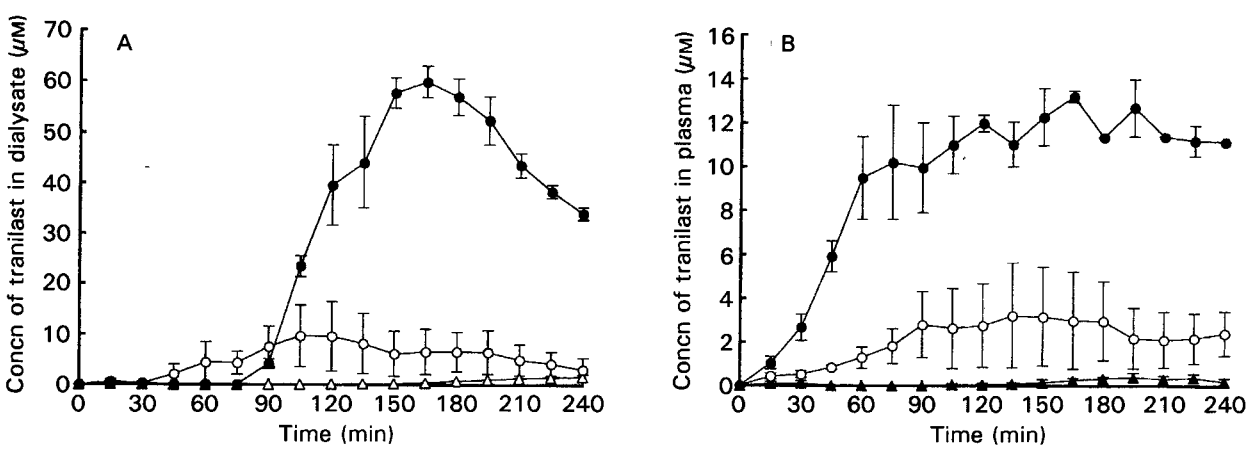

Figure 2. Concentration of tranilast in rat skin microdialysate (A) and plasma (B) after topical application at a dose of 1·5 mg (4·58 μmol) in combination either with oleic acid alone or with a mixture of oleic acid and propylene glycol. Oleic acid (%)–propylene glycol (%) in ethanol solution containing 5% polyvinylpyrrolidone: △ or ▲, 0–0%; ○, 20–0%; ●, 20–10%. Each value is the mean ± s.e.m. (n = 3 or 4).

Table 1. Pharmacokinetic parameters of tranilast in rats after topical application of 1·5 mg.

	Oleic acid/propylene glycol ratio (%:%)*						Intravenous†
	0–0	0–10	10–0	10–10	20–0	20–10	
Skin Dialysate							
Maximum concentration (μM)	1·7 ± 0·5	0·3 ± 0·3	19·6 ± 16·0	57·0 ± 15·1	9·7 ± 6·1	59·9 ± 3·1	–
Time of maximum concentration (min)	240	240	165	180	105	165	–
Area under the concentration–time curve from 0–4 h (μM min)	102 ± 1	86 ± 16	2190 ± 116	5392 ± 97	1240 ± 253	6525 ± 5	14·4 ± 2
Ratio of areas under the concentration–time curves, topical/intravenous	7	6	156	423	86	453	1
Plasma							
Maximum concentration (μM)	0·4 ± 0·2	1·4 ± 1·3	5·6 ± 1·1	11·3 ± 0·4	3·3 ± 2·4	13·2 ± 0·3	–
Time of maximum concentration (min)	195	240	195	135	135	165	–
Area under the concentration–time curve from 0–4 h (μM min)	36 ± 0	95 ± 77	819 ± 11	2141 ± 227	493 ± 167	2411 ± 648	15 383 ± 648
Ratio of areas under the concentration–time curves, topical/intravenous	0·002	0·006	0·053	0·139	0·320	0·157	1

*In ethanol solution containing 5% polyvinylpyrrolidone. These preparations (0·1 g) containing 1·5 mg tranilast were administered topically on 2·25 cm^2 dorsal skin surface. † Tranilast was administered intravenously at a dose of 1·5 mg per rat. Each value is the mean ± s.e.m. (n = 3).

additives. For all topical preparations delivery of tranilast to the restricted skin, as evaluated by determination of AUC_{0-4} for the skin dialysate, was far greater than after intravenous administration. In particular, combined use of oleic acid and propylene glycol resulted in more than 400-fold increase in AUC_{0-4} compared with that after intravenous administration. There was no significant difference in the enhancing potency of 10 or 20% oleic acid in the presence of 10% propylene glycol, although fluctuation of tranilast concentrations in the dialysate was less when 20% oleic acid was used. Findings were similar for tranilast plasma concentrations. The transdermal absorption of tranilast, evaluated by determination of AUC_{0-4} for plasma, also increased in parallel with the data from the dialysate in the order ethanol solution < solution containing oleic acid < solution containing oleic acid and propylene glycol (Table 1).

Discussion

After intravenous administration of tranilast the distribution volume of the central compartment (Vd_c) and the distribution volume at steady state (Vd_{ss}), estimated by use of the equation $Vd_{ss} = Vd_c (1 + k_{12}/k_{21})$, were 22 mL and 48 mL per rat, respectively. These relatively small distribution volumes suggest that the selective distribution of tranilast from plasma into the restricted skin tissues such as keloid and hypertrophic scar would not be expected. In fact, the concentration of tranilast in the skin dialysate after intravenous administration was fairly low compared with the concentration in plasma, although the percentage recovery by microdialysis in-vivo was not determined in this study.

We have previously reported that transdermal iontophoretic delivery of tranilast is a useful treatment for keloid and hypertrophic scar (Shigeki et al 1997a,b). In that study, only 1·75% of the tranilast in the dose (12 mg per rat) was recovered in the skin after 30-min iontophoresis at 2 mA. However, such treatment once or twice a week reduced the patient's complaints of pain and itching. The above findings indicate that local delivery has an advantage over other routes of administration in such treatment of skin disease. In iontophoretic delivery the iontophoresis drug electrode must be fixed firmly to the surface of the affected parts. Furthermore, surface areas of commercially available drug electrodes are limited, whereas the size and shape of keloid and hypertrophic scar vary substantially among patients. For these reasons, and because the surfaces of the affected parts are not always flat, in that study iontophoresis was

applicable only to small, relatively flat affected areas. For this reason the feasibility of topical application of tranilast was examined, because such medication could be applied to affected parts of any size or shape. In this study the mixture of oleic acid and propylene glycol was found to result in topical and transdermal delivery of tranilast greater than that obtained by use of iontophoresis.

It is already known that oleic acid and a mixture of oleic acid and propylene glycol increase the permeability of the skin to many compounds (Barry & Bennett 1987; Goodman & Barry 1988; Loftsson et al 1989a,b) and oleic acid is known to be a penetration enhancer for polar to moderately polar compounds (Ongpipattanakul et al 1991). Kim et al (1996) reported that oleic acid in ethanol–water systems enhanced the rate of permeation of the skin by hydrophilic and lipophilic compounds, with more enhancement for hydrophilic compounds. The mixture of oleic acid and propylene glycol used here substantially facilitated the transdermal absorption of tranilast, a weakly acidic compound with a pK_a value of 3·7 (Table 1). After studies by infrared spectroscopy and differential scanning colorimetry, increased lipid-chain disorder in the stratum corneum, as a result of lowering the lipid transition temperature, and increased conformational freedom or flexibility of the endogenous lipid alkyl chains have been proposed as possible mechanisms of enhancement of the permeability of the skin to oleic acid (Francoeur et al 1990; Mak et al 1990; Ongpipattanakul et al 1991; Koyama et al 1994; Lin et al 1995; Maitani et al 1996). Ogiso et al (1995) reported that oleic acid dramatically removes ceramides which are the intercellular lipids, and suggested that the removal of intercellular lipids would cause dilation of adherent cornified cells and enhance the penetration through the intercellular pathways and follicles. The action of propylene glycol when used as a co-solvent with oleic acid is not yet fully understood, but it is considered that it enhances intracellular drug mobility and aids the transport of oleic acid to the site of action, making the combination of oleic acid and propylene glycol an effective accelerant (Goodman & Barry 1989).

It is also known that there are marked species differences in skin permeability and even regional variation in skin permeability in man (Wester & Maibach 1975; Sinha et al 1978; Rougier et al 1986; Harada et al 1993). Although keloid surfaces in particular lack accessory structures such as sweat glands and follicles (Murray et al 1981; Rockwell et al 1989), it could be expected that oleic acid is a useful penetration enhancer even for these surfaces, because, as described above, oleic acid facilitates the transdermal penetration of compounds through the stratum corneum. Another possible problem in the use of penetration enhancers for man will be the skin irritation which might result. In a preliminary study, we examined the possibility of skin irritation by a mixture of oleic acid and propylene glycol (each 5% in ethanol) in volunteers (Shigeki et al 1997b). No skin irritation was observed when the mixture was applied topically without the occlusive dressing technique. Although there are many differences between characteristics of rat skin and keloid tissue in man, the topical delivery of tranilast with an absorption enhancer such as a mixture of oleic acid and propylene glycol might be a beneficial substitute for oral administration of tranilast, and an effective medication for treatment of keloid and hypertrophic scar.

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