International Journal of Pharmaceutics, 84 (1992) 253–260

IJP 02831

Enhanced transdermal delivery of ketobemidone with prodrugs

Laila Bach Hansen [a], Ann Fullerton [a], Lona Louring Christrup [a] and Hans Bundgaard [b]

Departments of [a] Pharmaceutics and [b] Pharmaceutical Chemistry, The Royal Danish School of Pharmacy, Copenhagen (Denmark)

(Received 18 December 1991)
(Accepted 17 February 1992)

Key words: Ketobemidone; Skin penetration; Transdermal delivery; Prodrug; Narcotic analgesic

Summary

The feasibility of achieving transdermal delivery of the opioid analgesic ketobemidone was assessed in human skin penetration studies in vitro using both ketobemidone itself and three carbonate ester prodrugs formed at the phenolic hydroxyl group. Whereas ketobemidone itself only showed a limited ability to permeate the skin from either polar or apolar vehicles the ester prodrugs very readily penetrated through the skin from solutions in isopropyl myristate and, in particular, from ethanol and ethanol-water solutions. Thus, steady-state fluxes in the range of 40–140 μg ketobemidone base/cm^2 per h were observed for the ketobemidone esters from 20% w/v solutions in ethanol and ethanol-water (3 : 1 and 1 : 1 v/v) vehicles. The esters were rapidly hydrolyzed to the parent drug in the presence of skin enzymes and only free ketobemidone was detected in the receptor phase. The study demonstrates the feasibility of achieving transdermal delivery of ketobemidone based on the ready enzymatic conversion and the favourable skin penetration properties of the ester prodrugs which in turn are attributed to their high solubilities in both polar and apolar solvents.

Introduction

Much attention has recently been paid to the development of transdermal delivery systems of narcotic analgesics (Schulte et al., 1980; Sebel et al., 1987; Duthie et al., 1988; Ritschel and Barkhaus, 1988; Aungst et al., 1989; Mahjour et al., 1989; Rieg-Falson et al., 1989; Ritschel et al., 1989; Roy and Flynn, 1989a, b, 1990; Sugibayashi et al., 1989; Drustrup et al., 1991; Fullerton et al., 1991).

Correspondence to: L.L. Christrup, The Royal Danish School of Pharmacy, Department of Pharmaceutics, 2 Universitetsparken, DK-2100 Copenhagen, Denmark.

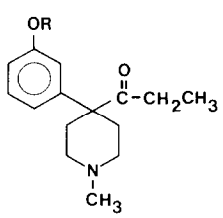
Transdermal administration may be a possible approach to overcome some of the disadvantages associated with the parenteral and peroral route of administration of strong narcotic analgesics such as side-effects caused by high peak plasma levels, the demand for frequent dosing due to short elimination half-lives and variable and incomplete oral bioavailability due to extensive first-pass metabolism.

A prerequisite for the development of a transdermal delivery system of these drugs is that the drugs are capable of penetrating the skin at a sufficiently high rate to obtain plasma concentrations in the therapeutic range.

Due to their favourable physico-chemical properties (water and lipid solubilities) and rela-

tively high potencies fentanyl and sufentanil may be successfully transdermally delivered (Sebel et al., 1987; Duthie et al., 1988; Roy and Flynn, 1989b, 1990). Similarly, the less potent but lipophilic drugs, methadone and pethidine, also show good skin penetration properties (Fullerton et al., 1991). In the case of morphine, which shows a very poor ability to pass across the skin (Roy and Flynn, 1989b), the prodrug approach has recently been shown to be an efficient means to improve its percutaneous absorption (Drustrup et al., 1991).

The purpose of the present study was to assess the feasibility of achieving transdermal delivery of ketobemidone (**I**). This strong narcotic analgesic which is equipotent with morphine (Eddy et al., 1957; Anderson et al., 1986) is usually given perorally or rectally but its bioavailability is incomplete and variable (Bondesson et al., 1980; Anderson et al., 1981, 1982). Since ketobemidone (**I**) shows a low lipophilicity (Hansen et al., 1991) it may be expected to have a limited skin permeability. Various carboxylic acid and carbonate esters of the drug with higher lipophilicities have recently been developed as prodrug forms (Hansen et al., 1991) and we have therefore included some of these derivatives (the carbonate esters **II–IV**) in the present in vitro human skin penetration study.



I R = -H

II R = -C(=O)-O-CH2CH3

III R = -C(=O)-O-CH2-CH(CH3)2

IV R = -C(=O)-O-CH2CH2CH2CH2CH2CH3

Materials and Methods

Apparatus

High-performance liquid chromatography (HPLC) was carried out using a system consisting of a Hitachi L-6200 Intelligent Pump, a Hitachi L-4000 variable wavelength UV-detector and a Hitachi Auto Sampler model 655A-40, using an injection volume of 20 μl. A deactivated reversed-phase Supelcosil LC-8-DB column (33 × 4.6 mm) (3 μm particles) equipped with a Supelguard 20 mm precolumn (both from Supelco Inc., U.S.A.) was used. Measurements of pH were performed at the temperature of study using a Metrohn type 632 pH Meter instrument. Homogenization of the skin specimens was carried out using a Mikro-dismembrator II (model B. Braun) equipped with a 7 ml teflon chamber and a chrome steel sphere with a diameter of 10 mm. Capacitance measurements of the skin mounted in the diffusion cells were carried out using a Digital Capacitance Meter (Lutron).

Chemicals

Ketobemidone hydrochloride was obtained from H. Lundbeck A/S, Copenhagen, Denmark. The free base form of ketobemidone was prepared by adding 3.5 ml of a 2 M sodium hydroxide solution to a solution of 2 g of ketobemidone hydrochloride in 25 ml of water. The precipitate formed upon standing for 4 h at 4°C was filtered off, washed with water and recrystallized from ethanol-water, m.p. 153–154°C (reported m.p. 150–151°C (Avison and Morrison, 1950)). The carbonate esters (**II–IV**) of ketobemidone were prepared as previously described (Hansen et al., 1991). The free base forms were obtained from the crystalline hydrochloric acid salts by extraction of basic solutions (pH 9) with methylene chloride. The free base forms were all oils.

Determination of solubilities

The solubility of ketobemidone base was determined in triplicate in isopropyl myristate, ethanol and ethanol-water mixtures (3:1 or 1:1 v/v) at 21 ± 1°C by placing excess amounts of the compound in 2–5 ml of the solvent. The mixtures were placed in an ultrasonic bath for 10 min and

then rotated on a mechanical spindle for 24 h and filtered. An aliquot of the filtrates was diluted with acetonitrile or water and analyzed by HPLC.

Preparation of human skin homogenate

Approx. 300 mg of skin specimens (3×3 mm^2) were placed in a teflon chamber containing a small chrome steel sphere. After freezing the skin by exposing the chamber to liquid nitrogen (approx. -200°C) for 1–2 min the chamber was placed in the Mikro-dismembrator apparatus and vigorously shaken for 60 s. This method produced a fine yellowish-white powder, which on lyophilization, lost approx. 65% in weight. After lyophilization the powder was suspended in 0.05 M phosphate buffer (pH 7.4) at a concentration corresponding to 5% w/v dry skin. After incubation at 5°C for 24 h the suspension was centrifuged for 10 min at 10000 rpm and the supernatant containing enzymes was removed. After dilution with phosphate buffer pH 7.4 to a concentration of 1% w/v dry skin, the homogenate was stored at -20°C until use. This method is a modification of a previously described technique (Johansen et al., 1986).

Hydrolysis of ketobemidone esters in human skin homogenate

The hydrolysis of the esters was studied in human skin homogenate (1% w/v dry skin) at 37°C. The initial concentration of the compounds was 3×10^{-5} M. The reactions were initiated by adding 100 μl of a stock solution of the compounds as hydrochloric acid salts in water to 5 ml of preheated skin homogenate. The solutions were kept in a water-bath at 37°C and at appropriate intervals, 250 μl samples were withdrawn and deproteinized with 500 μl of a 2% solution of zinc sulphate in methanol-water (1 : 1 v/v). After mixing and centrifugation for 3 min at 13000 rpm, 20 μl of the clear supernatant was analyzed for intact ester by HPLC as described below.

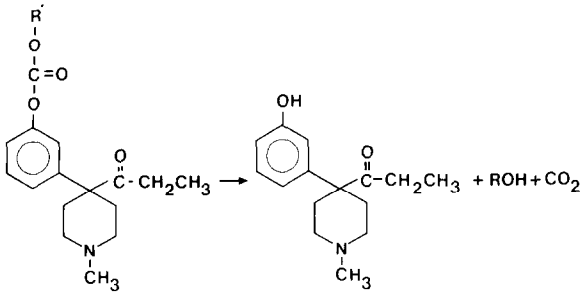
Permeation studies using excised human skin

Whole abdominal or breast human skin obtained from three women undergoing surgery was used. The skin was stored at -20°C and was allowed to thaw gradually to room temperature before use. All subcutaneous fat was removed and the skin cut into pieces. The excised skin was mounted in closed diffusion cells of the same type as those used by Franz (1975); they have an available diffusion area of 0.70 cm^2. The dermal side of the skin was exposed to the receptor medium (5.2 ml of 0.05 M isotonic phosphate buffer of pH 7.2) which was stirred magnetically and kept at a constant temperature of 37°C with a circulating water-bath. The skin in the assembled diffusion cells was initially screened for barrier integrity by measuring the capacitance. Only skin membranes with intact skin barrier properties were used.

The compounds studied were applied as solutions or suspensions; 200 μl was applied on the skin when using aqueous buffer and isopropyl myristate, whereas 1000 μl was applied with the ethanol and ethanol-water vehicles. The suspensions were stirred for 24 h prior to application to the skin surface. At appropriate intervals samples of 1 ml were withdrawn from the receptor phase and replaced with fresh receptor medium. The samples were stored at -20°C until they were analyzed for ketobemidone and ester content by HPLC. All experiments were carried out with three or five replications. All comparative studies were performed with skin obtained from the same donor.

Analysis of ketobemidone and its esters by HPLC

A reversed-phase HPLC procedure was used for the quantitative determination of ketobemidone esters and the parent drug. A deactivated Supelcosil column was eluted with a mobile phase consisting of a mixture of methanol (5% v/v), acetonitrile (15–40% v/v) and 0.1% phosphoric acid (55–80% v/v) containing triethylamine (10^{-3} M) in order to improve peak shape. The concentration of acetonitrile was adjusted for each compound in order to provide an appropriate retention time. The flow rate was 1–2 ml min^{-1} and the column effluent was monitored at 215 or 280 nm. Quantitation of the compounds was done by measurement of peak heights in relation to those of standards chromatographed under the same conditions.



Scheme 1.

Results and Discussion

Properties of ketobemidone esters

The three carbonate esters of ketobemidone (**II–IV**) included in this study have previously been shown to be rapidly converted to the parent drug by enzymatic hydrolysis in plasma (Scheme 1) (Hansen et al., 1991). The half-lives for their hydrolysis in 80% human plasma were less than 10 s. The esters were also found to be readily hydrolyzed by enzymes present in the skin. Thus, the half-lives observed in a 1% human skin homogenate at 37°C were 7.7 min (**II**), 6.6 min (**III**) and 9.6 min (**IV**).

The ester prodrugs are all much more lipophilic than the parent drug as illustrated by the partition coefficients in an octanol-pH 7.4 buffer system (Table 1). Likewise, the esters show a much higher solubility in both ethanol, ethanol-water mixtures and in the apolar isopropyl myristate than ketobemidone (Table 1). These higher solubilities are in harmony with the great difference in the melting points: whereas ketobemidone melts at 153–154°C the carbonate esters are all oils. These properties with respect to biphasic solubility and enzymatic hydrolysis should be favourable for skin penetration as indeed was also verified in the skin permeation studies.

Skin permeation

In these studies, excised human skin samples were used in a Franz-type diffusion cell apparatus. Each compound was studied in a polar (i.e., an aqueous phosphate buffer of pH 7.0) vehicle. The compounds **I–III** were also studied in an apolar (i.e., isopropyl myristate (IPM)) vehicle. In addition, compounds **I** and **II** were studied in ethanol and ethanol-water (3:1 and 1:1 v/v) vehicles. In the aqueous buffer vehicle the compounds were used in the form of their hydrochloric acid salts. Suspensions of ketobemidone base were applied in IPM, ethanol and ethanol-water vehicles whereas the free base forms of the esters were applied as solutions in these vehicles due to their high solubilities (Table 1).

The diffusion experiments showed that both ketobemidone and its esters are able to permeate human skin. The results obtained are shown in Figs 1–3 in which the cumulative amounts of ketobemidone (in μg ketobemidone base) measured in the receptor phase divided by the surface area of the diffusion cell are plotted against the time of sampling. The steady-state fluxes (F_{SS}) were obtained from the slopes of the linear portions of these plots. The permeability coefficients (K_P) for the steady-state delivery were obtained

TABLE 1

*Partition coefficients (P) and solubilities of the free base forms of ketobemidone and the carbonate ester prodrugs **II–IV** in various vehicles used in the skin permeation studies (at 21°C)*

Compound	log P [a]	Solubility (mg/ml)			
		IPM [b]	Ethanol	Ethanol-water (3:1 v/v)	Ethanol-water (1:1 v/v)
I	0.40	1.1	91	123	39
II	1.11	> 1000	> 1000	> 1000	> 1000
III	2.20	> 1000	> 1000	> 1000	> 1000
IV	3.20	> 1000	> 1000	> 1000	> 1000

[a] P: partition coefficient between octanol and an aqueous buffer of pH 7.4 (from Hansen et al., 1991).
[b] IPM: isopropyl myristate.

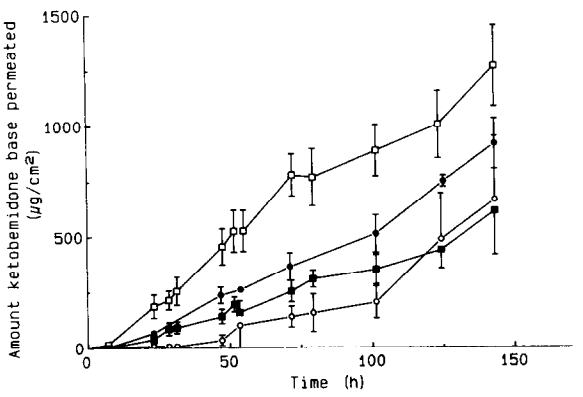


Fig. 1. Permeation profiles for ketobemidone (**I**) (○) and the esters (**II**) (■), (**III**) (□) and (**IV**) (●) through human skin from a 0.05 M phosphate buffer (pH 7.0) vehicle. The compounds were applied as solutions, containing the hydrochloric acid salts of the compounds at a concentration of 78–100 mg ml^{-1}. Error bars are ±S.D. (n = 3–5).

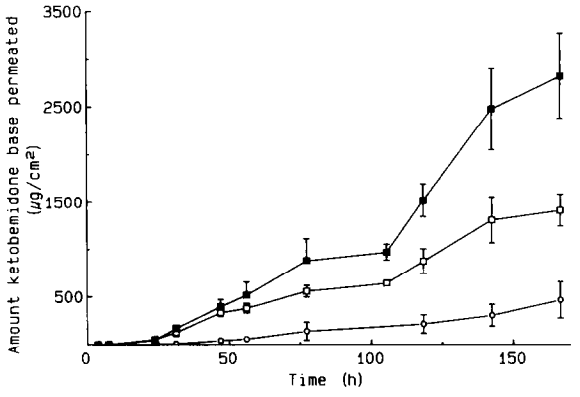


Fig. 2. Permeation profiles for ketobemidone (**I**) (○) and the esters (**II**) (■) and (**III**) (□) through human skin from an isopropyl myristate vehicle. Compound **I** was applied as a suspension of the free base form whereas compounds **II** and **III** were applied as solutions (500 mg free base ml^{-1}). Error bars are ±S.D. (n = 3).

TABLE 2

Steady-state fluxes (F_{SS}) and permeability coefficients (K_P) for the steady-state phase of delivery of ketobemidone through human skin (obtained from one donor) from an aqueous buffer of pH 7.0 and from isopropyl myristate (IPM) (mean ± S.D. (n = 3–5))

Compound	F_{SS} (μg/cm² per h)		K_P (cm/h)	
	pH 7.0 buffer	IPM	pH 7.0 buffer	IPM
I	6.4 ± 2.7 [a]	3.3 ± 1.2 [b]	8.8×10^{-5}	3.1×10^{-3}
II	5.3 ± 1.9 [a]	20.1 ± 2.5 [c]	8.7×10^{-5}	5.5×10^{-5}
III	8.8 ± 1.3 [a]	9.6 ± 1.9 [c]	1.6×10^{-4}	2.8×10^{-5}
IV	6.8 ± 0.4 [a]		1.2×10^{-4}	

[a] The aqueous buffer solutions applied were not saturated. They contained the hydrochloric acid salts of the compounds at a concentration of 78–100 mg ml^{-1}.

[b] Saturated solution of the free base form (i.e., suspension).

[c] The IPM solutions applied were not saturated. They contained the free base form of the compounds at a concentration of 500 mg ml^{-1}.

TABLE 3

Steady-state fluxes (F_{SS}) and permeability coefficients (K_P) for the steady-state phase of delivery of ketobemidone through human skin (obtained from one donor) from ethanol and ethanol-water mixtures (mean ± S.D. (n = 3))

Compound	F_{SS} (μg/cm² per h)			K_P (cm/h)		
	Ethanol	Ethanol-water (3:1 v/v)	Ethanol-water (1:1 v/v)	Ethanol	Ethanol-water (3:1 v/v)	Ethanol-water (1:1 v/v)
I	14.8 ± 4.9 [a]	9.6 ± 1.6 [a]	8.0 ± 2.1 [a]	1.6×10^{-4}	7.8×10^{-5}	2.1×10^{-4}
II	47.7 ± 14.2 [b]	54.9 ± 13.9 [b]	41.3 ± 7.9 [b]	3.3×10^{-4}	3.7×10^{-4}	2.8×10^{-4}

[a] Saturated solution of the free base form (i.e., suspension).

[b] The ethanol and ethanol-water solutions applied were not saturated. They contained the free base form of compound **II** at a concentration of 200 mg ml^{-1}.

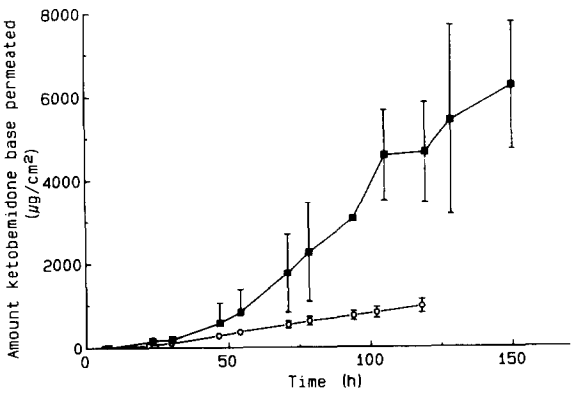


Fig. 3. Permeation profiles for ketobemidone (**I**) (○) and the ester prodrug (**II**) (■) through human skin from an ethanol-water (3:1 v/v) vehicle. Compound **I** was applied as a suspension of the free base form whereas compound **II** was applied as a solution (200 mg free base ml^{-1}). Error bars are ±S.D. ($n = 3$).

by dividing the steady-state fluxes by the solubilities of the compounds in the vehicle when suspensions were used or by the concentration of the compounds in the vehicles when solutions were used. The values obtained for these parameters are given in Tables 2 and 3. It should be noted that only ketobemidone was found in the receptor phase in the experiments with the esters **II–IV**. This indicates complete hydrolysis of the esters through transport across the skin which is in agreement with the facile hydrolysis of the esters observed in the skin homogenates.

As seen from Table 2, the steady-state fluxes for ketobemidone and the esters are of the same magnitude (5.3–8.8 μg ketobemidone base/cm^2 per h) with an aqueous buffer vehicle of pH 7.0. In contrast, the fluxes obtained for the esters from the IPM vehicle were considerably higher than that for ketobemidone which is a result of the higher solubilities of the esters in IPM. The affinity of the esters for IPM is so high that the permeability coefficients are much lower than that for ketobemidone (Table 2).

The skin permeation behaviour of ketobemidone and the ethyl carbonate ester **II** was further studied in ethanol and ethanol-water vehicles. Ethanol has previously been reported to have an enhancing effect on drug transport across the skin (Ghanem et al., 1987; Pershing et al., 1990; Bommannan et al., 1991). The results obtained are listed in Table 3. As can be seen these vehicles provided a large enhancement in the fluxes, especially for the prodrug **II**.

Since the ethanol and ethanol-water solutions of compound **II** were not saturated it should be possible to obtain even higher fluxes by using more concentrated solutions. This was investigated with the compound in a separate experiment using skin samples from a different source (breast human skin). The flux obtained with a 20% w/v solution of compound **II** in ethanol-water (3:1 v/v) was 137.4 ± 10.9 μg/cm^2 per h. The difference between this value and that obtained in the previous experiment (54.9 ± 13.9 μg/cm^2 per h) may be ascribed to the different skin samples. Surprisingly, however, the flux observed with a 100% w/v solution of compound **II** was only 56.1 ± 2.7 μg/cm^2 per h. Thus, the steady-state flux does not appear to be proportional to the concentration of the compound in the donor phase in this high concentration range. The viscosity of the 100% w/v solution is higher than that of the 20% w/v solution and this factor may contribute to this unexpected finding. Further studies are certainly warranted to examine the influence of donor phase concentration on the rate of permeation.

The results obtained from the diffusion experiments show that it is possible to improve markedly the skin penetration of ketobemidone via the prodrug approach. The increased solubility of the esters in the vehicles combined with expected concomitant increase in solubility in the skin is most certainly responsible for the higher fluxes since the ability of the esters to partition into the skin is part of the driving force for diffusion.

The feasibility of obtaining transdermal delivery of ketobemidone via the prodrug approach can be assessed by comparing the daily doses of ketobemidone usually used via parenteral administration with those obtainable by transdermal delivery. If the area of the patch for transdermal delivery is 25 cm^2 and if a flux of 50 μg ketobemidone base/cm^2 per h is used, it would be possible to deliver 1.25 mg ketobemidone base/h or 30 mg over 24 h. This amount is in the range

of what is usually given (20–40 mg ketobemidone hydrochloride corresponding to 17–35 mg ketobemidone base) parenterally during 24 h.

Conclusions

The results obtained in this study indicate that the transport of ketobemidone through human skin can be markedly improved by using more lipophilic ester prodrugs. The fluxes observed in vitro for the ketobemidone esters suggest the feasibility of developing a transdermal delivery system for ketobemidone based on the good skin penetration properties and ready bioconversion of the ester prodrugs. It should also be pointed out that the fluxes might be further increased by the use of other vehicles than those studied here.

Acknowledgements

This study was supported by grants from H. Lundbeck A/S, Copenhagen, Denmark and the Danish Research Academy, Århus, Denmark.

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