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Short communication

Transdermal delivery of naloxone: ex vivo permeation studies☆

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Abstract

The purpose of this investigation was to study the feasibility of transdermal drug delivery of the potent opioid antagonist naloxone. The pharmacokinetic profile of naloxone makes it a suitable candidate for transdermal delivery. Ex vivo permeation of naloxone through excised rat skin was studied using a diffusion cell. Radiochemical assay of drug concentration and the use of rat as an animal model were adopted in this study. Naloxone possesses characteristics favorable to percutaneous absorption: i.e. a low molecular weight (327.37), water solubility and a good lipid–water partition coefficient of 12.94 ± 1.29 at pH 7.4. The flux ($\mu g/cm^2/h$) values varied from 6.59 ± 0.72 in control to 27.18 ± 4.26 in dimethyl formamide. The affinity of naloxone to skin in the presence of propylene glycol was decreased by 6.2 times compared to the control. Fourier transform infrared spectroscopy was used to study the effect of various sorption promoters on intercellular lipid pathways in skin. A change in lipid fluidization corresponding to broadening for both C–H symmetric (near 2850 cm^{-1}) and C–H asymmetric (near 2920 cm^{-1}) stretching was observed. An attempt was made to correlate the molecular weight of sorption promoters with skin affinity values of naloxone. © 1999 Elsevier Science B.V. All rights reserved.

Keywords: Diffusion study; Fourier transform infrared spectroscopy (FTIR); Naloxone; Skin permeation enhancement; Transdermal delivery

The opium group of narcotic drugs (narcotic analgesics) are among the most powerful analgesics; they are therapeutically effective but not without side/toxic effects. They find their clinical application in the management of different kinds

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of severe pain. However, non-medical use and development of tolerance are very common with narcotic analgesics. The potential for physiological and psychological dependence is very high. The most apparent side effects include nausea, vomiting, dizziness, mental clouding, hypotension and respiratory depression, resulting finally in coma (Reisine and Pasternak, 1996). Naloxone, a potent opioid antagonist, is used for the treatment of opioid abuse. It is not effective when administered perorally because of its high first pass metabolism, and it is currently administered either subcutaneously or intramuscularly. It has short biological half-life of 4–5 h; hence, repeated administration is necessary to obtain therapeutic efficacy and patient non-compliance will result in craving for drugs again. Therefore, the maintenance of constant blood levels of naloxone is axiomatic for better management of a de-addiction programme. Development of a transdermal delivery system would circumvent all the above problems and would result in better management and treatment of naloxone opioid addiction since the route of administration does not require much motivation on the part of the patient, avoids gastrointestinal absorption and maintains constant blood levels. Hence, the objective of this study was to develop an alternative delivery system for naloxone that would result in better therapeutic efficacy and demonstrate the feasibility of transdermal delivery of naloxone. In this investigation, the apparent partition coefficient of naloxone in different solvent systems was determined (Panchagnula, 1996). Ex vivo permeation studies of naloxone across excised rat skin were conducted. The effects of various sorption promoters on drug penetration into and permeation across the skin were determined. Finally, the affinity of the drug to skin was also determined and evaluated. Fourier transform infrared (FTIR) analysis has been used to investigate the fluidization of lipids of the stratum corneum in the presence of sorption promoters (Potts and Francoeur, 1992).

The Sprague-Dawley rat as an animal model and radiochemical assay were used in this study (Panchagnula and Ritschel, 1991). The apparent partition coefficient (APC) of naloxone was determined in the following systems: (1) mineral oil and distilled water; (2) isopropyl myristate and phosphate buffer pH 7.4; (3) n-octanol and phosphate buffer pH 7.4.

Rat skin for ex vivo permeation of naloxone was prepared by a procedure described earlier (Panchagnula and Patel, 1997) and used with diffusion cells (Erweka, Germany). Phosphate buffer pH 7.4 was used as receptor fluid and permeation studies were conducted by a previously described procedure (Panchagnula and Patel, 1997). Naloxone solution (200 μl; 20 mg/ml) was applied to the stratum corneum side in each of the donor compartments. Samples (100 μl) were withdrawn from the receptor compartment after 1, 2, 4, 6, 9, 12, 16, 24, 36, 48 and 72 h and analysed for drug content. At the end of the experiment, the amount of naloxone in the skin was also determined (Panchagnula, 1996). The permeation experiments were conducted using various sorption promoters (20 mg/ml; 100%): dimethyl sulphoxide (DMSO), *N*,*N*-dimethylacetamide (NN-DMAC), dimethyl formamide (DMFA) and propylene glycol (PG) (Ritschel and Hussain, 1988). Naloxone in triple-distilled water was taken as a control. Stratum corneum pieces (2×10 cm) were obtained from freshly excised dorsal skin (Scot et al., 1986) and then processed for FTIR studies by a method described by Walde et al. (1997). Dry stratum corneum films were incubated for 12 h in 2 ml of various sorption promoters, then removed and blotted dry on tissue paper. Finally, the films were immersed for 1–2 s in ethanol to remove all the excess adhering solvents to minimize solvent effect (Yokomizo, 1997). Spectral measurements (4000–800 cm^{-1}) were recorded in a Nicolet FTIR (Madison, USA) equipped with triglycine sulphate detector (100

Table 1
The apparent partition coefficients of naloxone in different systems

Solvent system	Apparent partition coefficient[a]
Mineral oil–distilled water	0.54 ± 0.15
Isopropyl myristate–buffer pH 7.4	1.80 ± 0.06
n-Octanol–buffer pH 7.4	12.94 ± 1.29

[a] Mean $\pm$ S.D., $n = 4$.

Table 2
Permeation parameters of naloxone and amount of drug present in the skin and receptor compartments, enhancement ratios and skin affinity values of naloxone in the presence of various sorption promoters (100%)

Sorption promoter	Lag time (h)[a]	Flux ($\mu g/cm^2/h$)[a]	Amount in skin ($\mu g/mg$)[a]	Amount in receptor compartment ($\mu g/g$)[a]	Skin affinity	Enhancement ratio
Control	0	6.59 ± 0.72	1.45 ± 0.870	490.74 ± 71.17	2.19	–
Dimethyl formamide	0.9 ± 1.30	27.18 ± 4.26[b]	3.84 ± 0.350[b]	2001.93 ± 258.31[b]	1.92	4.12
Dimethyl sulphoxide	0	22.27 ± 1.80[b]	1.02 ± 0.059	1673.04 ± 7.91[b]	0.61	3.38
N,*N*-Dimethyl acetamide	0	10.68 ± 2.35	2.17 ± 0.430	781.31 ± 107.53	2.81	1.62
Propylene glycol	6.5 ± 1.59[b]	14.22 ± 0.62[b]	0.496 ± 0.212	1022.79 ± 113[b]	0.47	2.16

[a] Mean $\pm$ S.D., $n = 3$–4.
[b] Statistically significant when compared to control ($p < 0.05$).

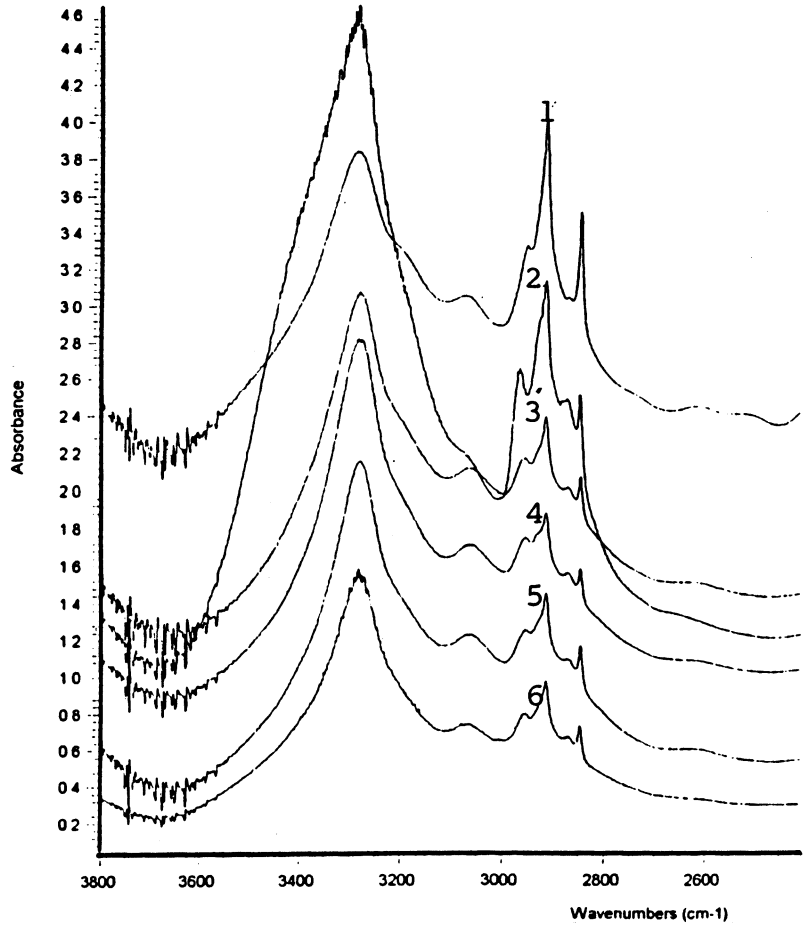

Fig. 1. FTIR spectra in the presence of various sorption promoters: 1, control; 2, PG; 3, n-hexane; 4, NN-DMAC; 5, DMFA; 6, DMSO.

scans with a resolution of 2 cm^{-1}). Peak positions were determined using the Nicolet Omnic software version 3.0. The data were analysed by one-way ANOVA followed by Scheffe's multiple range test using a computer program. A p-value of less than 0.05 was taken as being significant.

The APC values of naloxone in different solvent systems are listed in Table 1. Various solvent systems such as mineral oil, isopropyl myristate (IPM) and n-octanol have been used to relate partition coefficient to skin/transdermal absorption. The APC of drugs in mineral oil, n-octanol and IPM to some extent reflect the partitioning of drugs into the dead stratum corneum cells, intercellular spaces and into cells, respectively (Panchagnula and Ritschel, 1991). IPM is best related to skin/transdermal absorption because its polar and non-polar nature mimics the complex nature (polar/non-polar matrix) of the skin (Barry, 1983). The APC values of naloxone in all the solvent systems is a good indication that naloxone partitions well into the skin. An APC value of one or greater in IPM is generally required for optimal penetration into and permeation across the skin, which was observed in this case for naloxone. A comparatively high value of 12.94 ± 1.29 in the n-octanol–buffer system indicates that naloxone partitions into intercellular spaces. This, together with a very low APC value observed in mineral oil–water, indicates that naloxone perme-

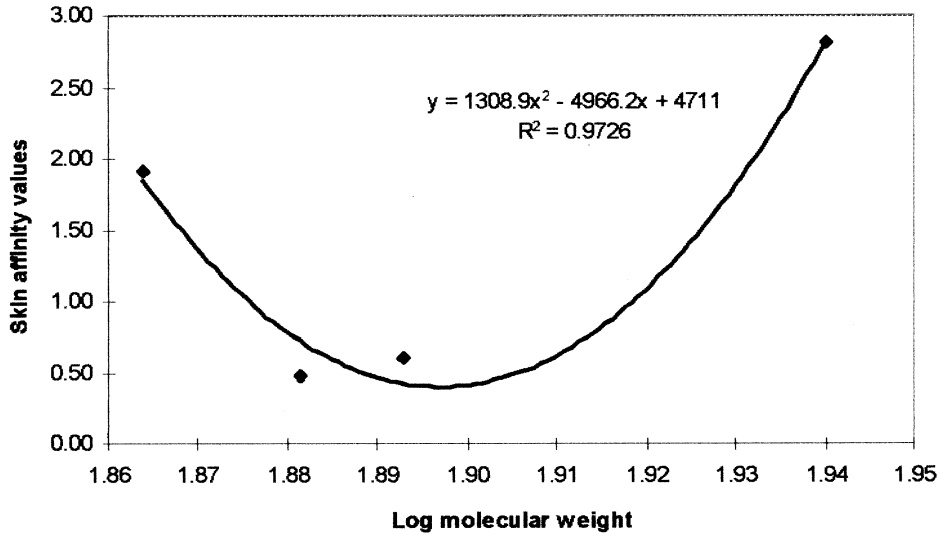

Fig. 2. Relationship between skin affinity values of naloxone and log molecular weight of various sorption promoters.

ates across the skin, possibly through an intercellular pathway (Barry, 1983), and does not form a reservoir in the skin (Ritschel et al., 1991).

Table 2 lists lag time (h) and flux (μg/cm^2/h) in the presence of various sorption promoters together with the amount of naloxone in the skin and in the receptor compartment (Ritschel et al., 1989). Enhancement ratios (Cornwell and Barry, 1995) and skin affinity of naloxone in the presence of the various sorption promoters was calculated (Panchagnula, 1996) compared with the control (Table 2). Permeation studies showed that NN-DMAC and DMSO have no significant effect on lag time, whereas PG significantly increases the lag time of naloxone. Although the lag time was 6.5 h in PG, which is statistically significantly different from control, it may not be of any clinical significance because of the nature of the therapeutic efficacy expected from transdermal delivery of naloxone. The flux values of naloxone in the presence of DMFA, DMSO and PG were significantly increased when compared to that of control ($p < 0.05$) and varied from 200 to 400%. Based on the amount of naloxone present in the skin, only PG decreased the affinity of naloxone for skin compared to that of control (more than 400%). Predictably the amount of naloxone present in the receptor compartment was highest in the presence of DMFA followed by DMSO and PG ($p < 0.05$). The skin affinity of naloxone in the control was 2.91, whereas the values were 0.47 and 0.61 in PG and DMSO, respectively. In the present case, normalization with donor phase concentration of naloxone is not necessary because the concentration of naloxone used in all permeation studies was the same (20 mg/ml). The effects of the sorption promoters were further evaluated by calculating the enhancement ratio (ER). The highest ER was observed with DMFA, followed by DMSO and PG. At the dose selected (20 mg/ml), the thermodynamic activity of naloxone may be less than the maximum value. In this case, the solvent system has no effect on the permeation of drugs across the skin and the drug with maximum solubility will have the greatest absorption. DMSO is known to be a potent sorption promoter; accordingly the flux was increased, a zero lag time and increased ER value were observed in the presence of DMSO. But these results are contrary to the observations reported by Aungst et al. (1986). With a flux of 20–30 μg/cm^2/h (see Table 2), blood naloxone levels of 13 ng/ml (range 2–13 ng/ml) can be achieved in a 70-kg patient. These concentrations very much translate into meaningful therapeutic plasma levels (extrapolated from the pharmacokinetic data

given in Table A-II-I of Goodman and Gilman, 1996)

The results presented in Fig. 1 compare the FTIR spectra in the C–H bond stretching region for an untreated sample with the spectra of samples treated with various sorption promoters. The broadening of peaks at 2850 cm^{-1} in the presence of the sorption promoters was seen compared to control (Knutson et al., 1985). This is due to increased fluidization, which is in agreement with previously reported results (Yokomizo, 1997). A plot of log molecular weight of sorption promoter versus skin affinity values (Fig. 2) shows a polynomial relationship ($R^2 = 0.9726$), indicating that the molecular weights of the sorption promoters are related to skin affinity values since these sorption promoters act as the driving force in partitioning drug into and permeation across the barrier layer. Further studies are in progress to investigate this relationship with drugs of various physicochemical properties. An attempt is also being made to correlate this relationship with ATR-FTIR and NMR studies of skin in the presence of sorption promoters. These studies will be published separately.

Based on flux, ER and skin affinity, DMFA, PG and DMSO are suitable for increasing the permeation of naloxone across the skin. However, a PG-based formulation with a suitable concentration of DMFA in which the thermodynamic activity of naloxone is maximal would be a better vehicle for the transdermal delivery of naloxone (Yokomizo, 1997).

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