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Transdermal iontophoretic delivery of sufentanil

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Summary

Iontophoresis promotes the penetration of charged and uncharged molecules through the skin using an electrical current application. In vitro assays were performed to investigate the influence of several electrical and physicochemical parameters on the transdermal permeation of sufentanil. Continuous current application strongly enhanced sufentanil flux through hairless rat skin as compared to passive diffusion. Direct current was more potent than pulse current to promote sufentanil transdermal permeation. An enhancement in current density applied induced an increase in the flux of the drug. When current application was terminated before the end of the experiment, the flux decreased but remained higher than diffusion flux. The pH of the medium affected diffusion and iontophoretic fluxes: in contrast with diffusion, acidic pH was more efficient for iontophoresis. An enhancement of drug concentration enhanced the iontophoretic flux. Application of direct or pulse current induced similar changes in skin permeability to water.

Introduction

Iontophoresis employs an electrical potential gradient to promote the penetration of charged and uncharged molecules across biological membranes such as the skin. It has been used with success for local delivery of drugs and more recently has been explored for transdermal systemic delivery as an alternative to conventional administration routes. Indeed, iontophoresis has been shown to be effective in the enhancement of transdermal delivery of several drugs including peptides (for review, see Banga and Chien, 1988; Yoshida and Roberts, 1992). The mechanism of the iontophoretic transport is not completely understood. The major factor determining the iontophoretic transport of an ionic drug is the electrochemical potential across the skin. The current induced water flux by electro-osmosis and probably an increased skin permeability also contribute to the transport of charged and uncharged molecules (for review, see Phipps and Gyory, 1992; Pikal, 1992).

Sufentanil is a potent synthetic narcotic widely used to induce profound anesthesia and analgesia. It has an ultrashort half-life, high volume of distribution and narrow therapeutic window. It

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undergoes extensive first pass metabolism after oral administration and is exclusively administered parenterally (Halliburton, 1988; Clotz and Nahata, 1991).

Recently, the transdermal delivery of sufentanil was investigated. Due to its lipophilic structure (K_p(octanol/water) = 2842), sufentanil can diffuse passively through human cadaver skin with a permeation coefficient in the range of 1.5×10^{-2} cm/h (Roy and Flynn, 1989, 1990). Significant plasmatic concentrations were detected in human volunteers after percutaneous absorption (Sebel et al., 1987). Since the drug is a weak base ($pK_a = 8.5$) and is ionized at acidic pH, its transdermal transport could be enhanced by anodal iontophoresis.

The aim of the present report was to determine whether transdermal permeation of sufentanil could be promoted by iontophoresis and to examine the effects of various electrical and physicochemical factors on the in vitro iontophoretic transport of sufentanil through hairless rat skin. The skin permeability after iontophoresis was also investigated.

Materials and Methods

Materials

Sufentanil citrate and [^{3}H]sufentanil were obtained from Janssen Pharmaceutica (Beerse, Belgium) and Janssen Biotech (Olen, Belgium), respectively. The radiolabelled sufentanil had a purity of approx. 99% and was used within 10 weeks. Tritiated water was bought from Amersham (Brussels, Belgium). All other chemicals were of the purest grade available. Male hairless rats (Iops mutant) were purchased from Iffa Credo (France).

Permeation apparatus

The transdermal permeation system consisted of a custom made horizontal cell with a donor compartment of 1.5 ml above a receptor compartment of 7.5 ml continuously stirred with a magnetic stirrer. The two chambers were separated by a 3 cm^2 area of abdominal skin freshly excised from hairless rat with the stratum corneum facing the donor side. Platinum (99.95% purity) electrodes of 1 cm × 1 cm were placed in each compartment (Mattey-Johnson, Vilvorde, Belgium).

Commercially available direct current outputs were used to provide constant direct current which varied from 0 to 2 mA. The pulsed current units were designed to provide adjustable current intensity with a maximum voltage drop of 21 V, a square wave form with a mean current intensity varying from 0 to 2 mA and variable frequencies and on/off ratios (Thysman and Préat, 1991; Préat and Thysman, 1992; Thysman et al., 1992).

Measurement of in vitro transdermal transport of sufentanil

The horizontal diffusion cell described above was used to study the transdermal permeation of sufentanil. The donor compartment contained 40 or 400 μg/ml of sufentanil and 0.6 μCi/ml of [^{3}H]sufentanil as a radioactive tracer in a citrate buffer (0.01 M) at pH 3.5, phosphate buffer (0.01 M) at pH 7 or borate buffer (0.01 M) at pH 9. The receptor compartment was filled with an isotonic glucose solution buffered with a 0.06 M phosphate buffer at pH 7.4. The platinum electrodes were immersed in the solutions with the anode in the donor compartment and the cathode in the receiver compartment.

As stated in each experimental protocol, a direct current or a pulse current with an on/off ratio of 1:1 and a frequency of 2500 Hz were applied for 0, 1 or 6 h at a mean intensity of 0.5, 1 or 1.5 mA (i.e., a mean current density of 0.17, 0.33 or 0.50 mA/cm^2, respectively).

To evaluate the transdermal permeation of sufentanil, the drug concentration in the receiver chamber was monitored every 30 min for 6 h. Samples (0.4 ml) were taken from the receiver and replaced with a drug-free buffer. Sufentanil concentration was assessed by measuring the radioactivity in the samples mixed with a liquid scintillation cocktail (Ready Safe, Beckman) and counted in a liquid scintillation counter (Wallac 1410, LKB).

The results were expressed as a plot of the cumulative quantity of sufentanil (ng/cm^2) vs time (h). The steady-state fluxes of sufentanil (ng/cm^2 per h) were determinated from the slope

of the linear part of the plot using linear regression analysis ($r < 0.95$). The lag times were determined by extrapolation of the steady-state curves to the x-axis (Thysman et al., 1992).

In vitro study of skin water permeability

In order to ascertain whether skin water permeability was modified after iontophoresis, the donor compartment containing the anode was filled with 40 μg/ml sufentanil in a citrate buffer (0.01 M) at pH 3.5. A direct or pulse current (on/off 1:1, 2500 Hz) was applied for 30 min or 1 h at a mean current density of 0.33 mA/cm^2. The donor solution was then removed and replaced with tritiated water (0.7 μCi/ml).

The permeability of the skin to water was assessed by monitoring the radioactivity in the receptor compartment for 6 h. Water permeability (expressed in μl/cm^2 per h) was deduced from the linear part of the plot of cumulative quantity of water vs time (Thysman and Préat, 1991).

Statistics

The results are expressed as means $\pm$ SE. Fluxes were compared using the Anova test (Sheffe's test) ($p < 0.05$).

Results and Discussion

Influence of iontophoresis on the in vitro transdermal permeation of sufentanil

Iontophoresis significantly enhanced the in vitro transdermal absorption of sufentanil relative to passive diffusion. Indeed, the cumulative quantities of sufentanil (40 μg/ml at pH 3.5) detected in the receiver compartment after iontophoresis with both direct (0.33 mA/cm^2) and pulse current (1:1, 2500 Hz, 0.33 mA/cm^2) were significantly higher than after diffusion (Fig. 1). After a lag time of 2 h, the iontophoretic release profile of the drug was linear with time and thus the flux was constant for at least 4 h. The fluxes of drug were 0.8 ± 0.5, 101.5 ± 5.7 and 219.9 ± 34.8 ng/cm^2 per h after diffusion, pulse current or direct current application, respectively (Fig. 3).

Several investigators have previously reported

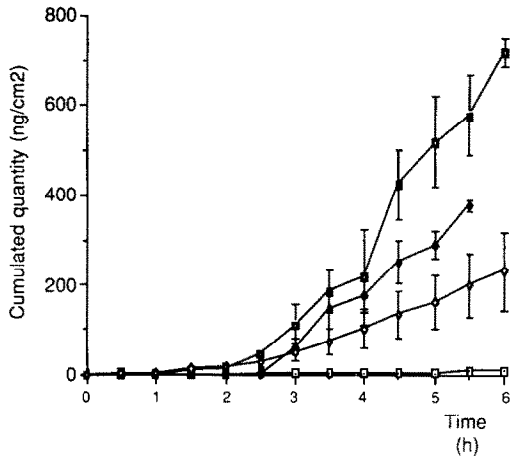

Fig. 1. Cumulative quantity of sufentanil (ng/cm^2) vs time (h) after passive diffusion (⊡) ($n = 4$), iontophoresis for 1 h with a direct current (0.33 mA/cm^2) (◇) ($n = 4$), iontophoresis for 6 h with a pulse current (on/off 1:1, 2500 Hz, 0.33 mA/cm^2) (♦) ($n = 6$) or with a direct current (0.33 mA/cm^2) (■) ($n = 6$). The donor compartment contained 40 μg/ml of sufentanil in a citrate buffer (0.01 M) at pH 3.5.

that iontophoresis promotes the transdermal flux of other opiates (Glikfeld et al., 1988; Phipps et al., 1989; Corish et al., 1990; Padmmanabhan et al., 1990; Phipps and Gyory, 1992; Préat and Thysman, 1992). The cumulative quantity of drug detected in the receptor compartment was the sum of the quantities that permeated via diffusion and by iontophoresis. The diffusion contribution of ionized sufentanil through the skin was low. The iontophoretic contribution resulted from electromigration and electro-osmosis.

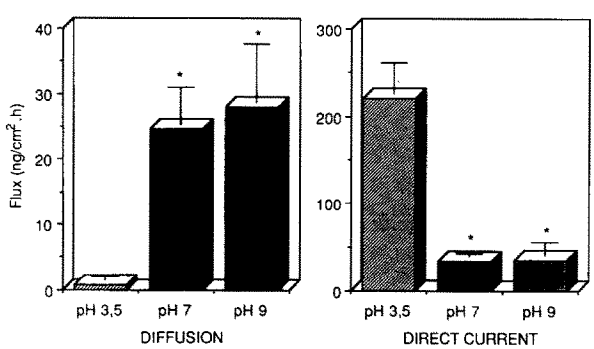

Fig. 2. Flux of sufentanil (ng/cm^2 per h) after diffusion or iontophoresis with direct current 0.33 mA/cm^2 at pH 3.5 (citrate buffer 0.01 M), pH 7 (phosphate buffer 0.01 M) or pH 9 (borate buffer 0.01 M) (* $p < 0.05$ vs pH 3.5) ($n = 5$).

The lag time observed can be explained by the thickness of skin membrane and partitioning properties between drug reservoir, stratum corneum and viable tissue.

The use of Pt electrodes results in the generation of hydronium ions at the anode and hydroxyl ions at the cathode. A buffer is thus necessary to avoid pH variations. Unfortunately, the use of buffer results in contamination of drug containing medium with co-ions which are usually more mobile than the drug ions (Phipps and Gyory, 1992). Therefore, the addition of citrate buffer in the donor medium could reduce the fraction of current carried by the sufentanil ion and thus the transdermal flux of sufentanil could also be diminished.

Influence of electrical factors on the in vitro iontophoretic transport of sufentanil

The influence of electrical factors such as current profile, current density and duration of iontophoresis on sufentanil iontophoretic transport was investigated.

Effect of the type of current The direct current was more efficient than pulse current to promote sufentanil permeation ($p < 0.05$) (Figs 1, 3 and 4). Therefore, most the experiments were performed with a direct current.

Pulse current has been widely used to allow the depolarization of the skin induced by the

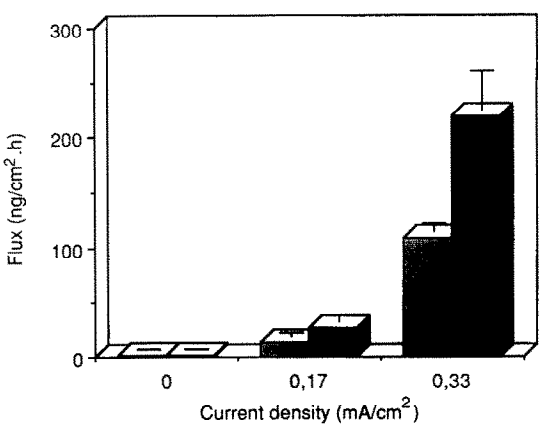

Fig. 3. Flux of sufentanil (ng/cm^2 per h) after iontophoresis with pulse (⊡) or direct (▨) current at a density of 0 ($n = 4$), 0.17 ($n = 6$) or 0.33 ($n = 6$) mA/cm^2. The donor was filled with 40 μg/ml of sufentanil in a citrate buffer (0.01 M) at pH 3.5.

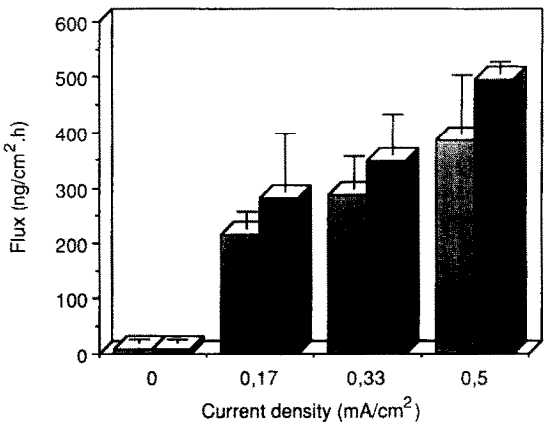

Fig. 4. Flux of sufentanil (ng/cm^2 per h) after iontophoresis with pulse (⊡) or direct (▨) current at a density of 0 ($n = 3$), 0.17 ($n = 5$), 0.33 ($n = 3$) or 0.50 ($n = 4$) mA/cm^2 The donor was filled with 400 μg/ml of sufentanil in a citrate buffer (0.01 M) at pH 3.5.

application of a direct electrical current, therefore decreasing the resistivity of the skin by reducing its capacitance (Yamamoto and Yamamoto, 1976). Even though most investigators did not compare the transport efficiency of direct or pulse current, it was reported that pulse current is more potent than direct current for promoting the transdermal permeation of several molecules such as insulin (Banga and Chien, 1988; Thysman and Préat, 1992). However, direct current appears to be at least as efficient as pulse currrent for smaller drugs (Bagniefski and Burnette, 1990; Pikal and Shah, 1991; Préat and Thysman, 1992). The iontophoretic transport of sufentanil was also always higher when a direct current rather than a pulse current was applied (Figs 1, 3 and 4). Thus, the iontophoretic delivery of a drug is affected by the current profile and its molecular weight (Yoshida and Roberts, 1992).

Effect of duration of application Direct current (0.33mA/cm^2) was applied for 0, 1 or 6 h and transdermal permeation of sufentanil was measured for 6 h. As previously reported, termination of the current did not cause the flux to return immediately to the passive control level (Wearley et al., 1989a; Green et al., 1992). Indeed, when the current was applied for 1 h, after a lag time of 2 h, the cumulative quantity of sufentanil detected in the receptor compartment

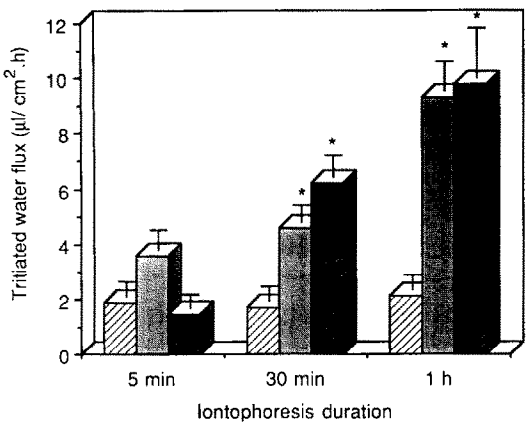

Fig. 5. Fluxes of tritiated water after 5 min, 30 min or 1 h diffusion (▨), or pulse current application (▩) or direct current application (0.33 mA/cm^2) (■) (2.5 kHz, on/off 1 : 1, 0.33 mA/cm^2). During diffusion or iontophoresis, the donor solution was filled with 40 μg/ml of sufentanil in a citrate buffer (0.01 M) at pH 3.5 and was then replaced by tritiated water (* $p < 0.05$ vs diffusion).

increased linearly with time at a rate much higher than diffusion. The flux measured was 55.1 ± 21.3 ng/cm^2 per h and remained significantly above the corresponding value for passive diffusion. An increased permeability of the skin (Fig. 5) or the release of this lipophilic drug from a reservoir formed in the skin during iontophoresis could explain these results.

Effect of current density The influence of current intensity on the iontophoretic transport of sufentanil was investigated. The mean density of direct and pulse currents varied from 0.17 to 0.67 mA/cm^2.

At 0.67 A/cm^2 (2 mA), the resistance of the skin increased with time and the voltage drop had to be increased to more than 20 V, impairing continuous application of a 0.67 mA/cm^2 current density. Nevertheless, a current density of 0.5 mA/cm^2 is often recommended as an upper limit to avoid skin lesion.

When increasing the current density from 0.17 to 0.5 mA/cm^2, the cumulative quantities and fluxes of sufentanil increased (Figs 3 and 4) for both drug concentrations (40 or 400 mg/ml) and both current profiles (direct or pulse current). The lag time was not significantly modified. These results indicate that the delivery of sufentanil could be controlled by appropriate manipulation of the current density.

The Nernst-Planck equation predicts that the flux of drug is proportional to the electrical potential difference. A relationship between flux and current density has been demonstrated by a number of investigators under different experimental conditions (Bellantone et al., 1986; Burnette and Marrero, 1986; Del Terzo et al., 1989; Siddiqui et al., 1989; Wearley et al., 1989a; Corish et al., 1990; Green et al., 1992; Thysman et al., 1992).

Influence of physicochemical factors on the in vitro iontophoretic transport of sufentanil

The effect of physicochemical factors such as pH, drug concentration and drug lipophily on sufentanil iontophoretic transport was investigated.

Effect of pH The total flux of the drug is the sum of the flux of drug diffusing through the skin (mainly in its unionized form) and that transported by the electrical current. Given that the degree of ionization of a solute with a moderate dissociation constant is dependent upon pH, the pH is a critical determinant of the iontophoretic flux for a given solute (Phipps and Gyory, 1992). Since the pK_a of sufentanil is 8.5, the percentage of unionized form is 99.99, 97 and 31% at pH 3.5, 7 and 9, respectively. As expected, according to Fick's law of diffusion, the extent of diffusion was greater at pH 7 and 9 than at pH 3.5. Similar findings were reported by Roy and Flynn (1989, 1990).

In contrast, iontophoretic transport was greater with an acidic solution of sufentanil than with a neutral or basic solution. When a direct current (0.33 mA/cm^2) was applied continuously, the flux of sufentanil (40 μg/ml) was much higher at pH 3.5 than at pH 7 or 9 (Fig. 2). The enhancement ratio (iontophoretic flux/diffusion flux) was 300, 1.4 and 1.3 at pH 3.5, 7 and 9, respectively. As the fraction of ionized sufentanil decreased, the electromigratory contribution to the total flux droped significantly, indicating that the imposed electrical field did not substantially influence the flux of the compound in its unionized form (enhancement ratio, 1.3).

In addition to influencing the state of charge of the drug, the pH of the donor medium can also affect the permeability of the skin which seems pH dependent. The concentration of fixed charges within the skin could be pH dependent as could be the electro-osmotic flux, therefore reducing the iontophoretic flux of cationic drugs at low pH (Burnette and Marrero, 1986; Wearley et al., 1989b; Phipps and Gyory, 1992; Pikal, 1992). However, the influence of increased concentration of competitive H^+ ions and the decrease in permselective properties of the skin at pH 3.5 appear to be negligible with sufentanil as with other compounds (Bellantone et al., 1986; Del Terzo et al., 1989; Siddiqui et al., 1989; Wearley et al., 1989b; Corish et al., 1990; Thysman and Préat, 1991).

Influence of drug concentration In order to analyse the influence of drug concentration on the iontophoretic transport of sufentanil, the fluxes of sufentanil were measured at a drug concentration of 40 and 400 μg/ml in a citrate buffer (0.01 M) at pH 3.5. The diffusion of the drug increased from 0.8 ± 0.5 to 8.5 ± 5.6 ng/cm^2 per h. The fluxes increased from 219.9 ± 34.8 to 347.3 ± 73.2 and from 101.5 ± 5.7 to 286.0 ± 60.5 ng/cm^2 per h when a direct and a pulse current, respectively, were applied at a current density of 0.33 mA/cm^2 (Figs 3 and 4).

Thus, when iontophoresis was applied, a 10-fold increase in sufentanil concentration was associated with a 2-fold increase in transdermal fluxes. This increase results from a 10-fold increase in passive diffusion as predicted by Fick's diffusion law and an increased iontophoretic flux. The Nernst-Planck equation predicts that the ion flux through an inert membrane is directly proportional to the concentration. This was verified for various molecules. However, other authors have reported that the iontophoretic flux across skin membrane does not always depend linearly on drug concentration (Bellantone et al., 1986; Del Terzo et al., 1989; Wearley et al., 1989b; Préat and Thysman, 1992; Thysman et al., 1992). This could partly be explained by the fact that ions other than the drug contribute to current transport. The fraction of current carried by a drug is largely determined by the concentration and the mobility of counter- and co-ions in the donor medium, skin body and receptor medium (Phipps and Gyory, 1992).

Lipophilicity of the drug Fentanyl and sufentanil are synthetic opiates with similar molecular weights (284 vs 297) and pK_a values (8.5 vs 8.9) but with different partition coefficients (K_p(octanol/water (pH 7.4)) 717 vs 2842, respectively) (Roy and Flynn, 1989). Fick's diffusion law indicates that the lipophilicity of a drug influences its transdermal permeation: the greater the partition coefficient, the higher the diffusion flux. As expected, sufentanil diffused more readily across the skin than fentanyl (Roy and Flynn, 1990; Préat and Thysman, 1992). However, the iontophoretic flux of sufentanil was always lower than fentanyl flux under the same experimental conditions (Préat and Thysman, 1992) suggesting that more hydrophilic drugs are more readily transported by the current (Del Terzo et al., 1989).

Tritiated water fluxes after sufentanil iontophoresis with a direct or a pulse current

The measurement of passive water flux is classically used to estimate the barrier function of the skin. Without current, tritiated water flux was low (Thysman and Préat, 1991). Current application at 0.33 mA/cm^2 for 5 min did not significantly modify this flux relative to passive diffusion. In contrast, when the skin was exposed to current passage (0.33 mA/cm^2) for 30 min or 1 h, significantly elevated water fluxes were observed compared to the diffusion control (Fig. 5). It has also been reported previously that passive fluxes measured after iontophoresis are higher than the pre-iontophoretic passive fluxes, indicating that the 'intrinsic permeability' of the skin increases after current application. These results suggest that besides diffusion due to a chemical potential gradient, electromigration due to an electric potential gradient and solute transfer due to convective solvent flow, increased skin permeability can contribute to the iontophoretic transport of sufentanil (Pikal and Shah, 1990; Phipps and Gyory, 1992; Pikal, 1992).

Interestingly, the water fluxes measured after direct or pulse current application were not sig-

nificantly different. Thus, alterations in skin barrier function induced by the current cannot account for the differences measured in the iontophoretic transport of sufentanil with a direct or pulse current.

Conclusions

In conclusion, the results presented in this paper demonstrate that iontophoresis is an effective method to enhance the delivery of sufentanil. The iontophoretic transport of ionized sufentanil was much greater than the passive diffusion of non-ionized drug.

The effect of various electrical and physicochemical factors on sufentanil iontophoretic transport was analyzed. The delivery of sufentanil through the skin increased with current density and duration of iontophoresis, suggesting that transdermal iontophoresis could be an effective means of controlling sufentanil delivery. Direct current was more efficient than pulse current. Iontophoretic delivery of sufentanil increased with drug concentration and was higher at acidic pH. Prolonged application of the current increased skin permeability.

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