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Transdermal iontophoresis of fentanyl: delivery and mechanistic analysis

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Summary

Studies of electrical and physicochemical factors acting on the permeation kinetics of in vitro iontophoresis of fentanyl across hairless rat skin were performed. Iontophoresis increased the transdermal permeation flux of fentanyl as compared to the diffusion. An increase in the current density applied induced an enhancement of the flux through the skin. Continuous current was more potent than pulsed current (positive square wave 2.5 kHz on/off 1:1) at promoting fentanyl transdermal permeation. At the same current density (0.33 mA/cm^2), a decrease in the duration of iontophoresis application from 6 to 1 h reduced the cumulated quantity of drug detected in the receptor compartment but the flux remained higher than diffusion for at least 6 h. Iontophoresis and diffusion were compared when the drug was introduced into a donor solution at pH 7 or 3.5. Diffusion was higher at pH 7 than at pH 3.5. Iontophoresis was more efficient at acidic pH. The enhancement of the drug concentration in the donor compartment increased the flux through the skin. The mechanism of transport of fentanyl through the skin by iontophoresis was investigated. Electro-osmosis was not involved in the differences of kinetics observed after direct and pulsed current application since both induced the same water flux across the membrane. A period of iontophoresis shorter than 1 h did not modify the skin permeability. In contrast, the drug accumulated in the skin reservoir and was slowly released when the current was cut.

Introduction

Fentanyl is a synthetic narcotic widely used as both an analgesic and an anesthesic agent because of its rapid onset, short duration of action and high potency.

Its extensive first-pass hepatic metabolism vindicates the parenteral route of administration. A bolus injection is not adequate since the plasma concentration can reach toxic levels inducing central nervous sytem and respiratory depression and the short half-time of fentanyl (1.5–6 h) induces a rapid plasma level decrease (Bovill and Sebel, 1980; McClain and Hug, 1980; Holley and Van Steenis, 1988; Varvel et al., 1989).

Sustained release devices, including transdermal drug delivery, avoid these disavantages.

Transdermal delivery of fentanyl has been studied in vitro by Roy and Flynn (1990). A transdermal fentanyl delivery system (Transdermal Therapeutic System of fentanyl, TTS-

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Fentanyl, Alza Corp., Palo Alto, CA) has been developed for the management of moderate to severe pain (Duthie et al., 1988; Holley and Van Steenis, 1988). The mean serum fentanyl concentrations obtained from patients after placement of the fentanyl transdermal system increased during the first 14 h to reach a plateau. The serum level fell slowly after system removal at 24 h. The system allows significant plasma levels to be attained but the lag time observed and the lack of opportunity to modulate the rate of the release are important disavantages of this delivery system.

Iontophoresis is a process by which the transport of ions into or through skin is increased by the application of an external electrical field across the skin (Sims et al., 1991). It could be used to improve the transdermal administration of fentanyl since the drug is a weak base (pK_a = 8.43) (Mather, 1983) the major fraction of which is cationic in acidic medium.

The aim of the present report was to study the influence of electrical factors (current profile, current density and duration of current application) and physicochemical factors (pH of the donor phase and concentration of the drug in the reservoir) on the iontophoretic transport of fentanyl through hairless rat skin.

The mechanism of iontophoretic permeation of fentanyl was also investigated. Electro-osmosis, induced by the permselectivity of the skin, was studied in order to determine its contribution to the permeation kinetics of the drug through hairless rat skin.

The enhancement of skin permeation as a result of the electrical treatment and the release of fentanyl from the skin reservoir were also considered.

Materials and Methods

Chemicals

Fentanyl citrate was purchased from Janssen Pharmaceutica and [^{3}H]fentanyl citrate from Janssen Biotech (Beerse, Belgium). The [^{3}H]water was supplied by Amersham (Brussels, Belgium). The salts used to prepare the buffer (analysis grade) were obtained from UCB (RPL, Leuven, Belgium). All solutions were prepared in bidistilled water.

Apparatus and procedures

A two-chamber plexiglass horizontal cell with stirring in the receptor compartment was used. The surface area of the membrane was 3 cm^2. Experiments were carried out with male hairless rat skins (mutant rat iops hairless from Iffa Credo, Brussels, Belgium). The 2–3 month old rats were killed by cervical dislocation. Their full thickness abdominal skin was excised and subcutaneous fat was removed carefully with scalpels and scissors. The skin specimens were mounted between the two compartments with the stratum corneum facing the donor phase. The electrodes were connected to a constant or pulsed current (positive square wave) power source and the current profile was controlled with an oscilloscope (HM 312 Hameg).

For all permeation studies, the receptor compartment was filled with phosphate buffer (0.24 M) at pH 7.4 made isotonic with glucose (0.22 M). A pair of platinum electrodes (1 cm^2) (Platinum pure, SA Johnson Matthey, Brussels, Belgium) was immersed in the solutions (the anode in the donor compartment and the cathode in the receptor compartment).

The upper reservoir was filled with 1.5 ml of the donor solution. Fentanyl and [^{3}H]fentanyl (0.3 μCi/ml) were introduced in a citrate buffer (0.01 M) at pH 3.5 or in phosphate buffer (0.01 M) at pH 7 at a concentration of 40 or 400 μg/ml. The mean density of current applied varied from 0 to 0.5 mA/cm^2. Continuous current and pulsed positive square wave (2.5 kHz on/off 1:1) were applied for 6 h.

To measure electro-osmosis during iontophoresis, the donor compartment was filled with citrate buffer (0.01 M) at pH 3.5 containing fentanyl (40 μg/ml) and [^{3}H]water (0.25 μCi/ml). Tritiated water fluxes were measured during in vitro iontophoresis of fentanyl for 6 h.

The integrity of the skin after in vitro iontophoresis was studied by measuring the tritiated water flux diffusion after either direct or pulsed current application for 0 min, 5 min, 30 min, 1 h

or 6 h at a mean density of current of 0.17 mA/cm^2. During iontophoresis, the donor compartment was filled with a fentanyl solution (40 $\mu g/ml$) in a citrate buffer (0.01 M) at pH 3.5. After switching off the electrical current, the donor compartement was emptied and $[^3H]H_2O$ (0.25 $\mu Ci/ml$) was introduced. For the duration of each current application, water diffusion was measured for 6 h and compared to water flux obtained after fentanyl diffusion performed for the same duration.

To investigate the reservoir capacity of the skin, direct current (0.33 mA/cm^2) was applied for 30 min or 1 h, with a donor compartment solution containing fentanyl (40 $\mu g/ml$) in a citrate buffer (0.01 M) at pH 3.5. After iontophoresis, the donor solution was completely removed, the sample skin was washed with citrate buffer and the donor compartment was filled with the same drug-free citrate buffer. The flux of fentanyl released from the skin reservoir was compared to that without renewal of the donor compartment.

Samples (0.4 ml) were taken from the receiver compartment at regular intervals of time and replaced with an equal volume of drug-free buffer. Liquid scintillation cocktail (Ready safe, Beckman, Belgium) was added to samples and counting was performed in a β-counter (LKB, Pharmacia). Quenching corrections were carried out.

The ratio of the cumulated quantities detected in the receptor compartment to the membrane area was plotted as a function of time. Fluxes were deducted from the linear portion of the curve. The results are expressed as means $\pm$ SE. Fluxes were compared to assess statistical differences using one-way analysis of variance and a Fisher t- test ($p < 0.05$).

Results and Discussion

Electrical factors

Current profile In vitro efficiencies of direct and pulsed current (2.5 kHz, on/off 1:1) to promote the transdermal permeation of fentanyl were compared. Fentanyl (40 $\mu g/ml$) was introduced in a citrate buffer (0.01 M) at pH 3.5. Iontophoresis was performed for 6 h with both current

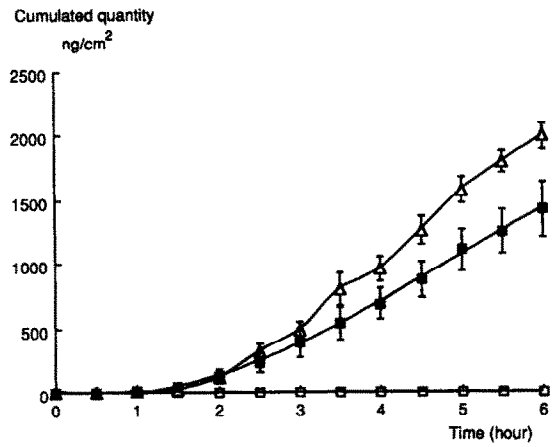

Fig. 1. Cumulated quantity of fentanyl detected in the receptor compartment vs time after diffusion (□), pulsed current (2.5 kHz on/off 1:1; 0.33 mA/cm^2) (■), or direct current application (0.33 mA/cm^2) (△). Fentanyl (40 $\mu g/ml$) was introduced in a citrate buffer (0.01 M) at pH 3.5 ($n = 5$).

profiles at a mean current density of 0.33 mA/cm^2. As shown in Fig. 1, current application greatly enhanced drug permeation through the skin as compared to diffusion. Without current treatment, the diffusion flux was 1 ± 0.3 ng/cm^2 per h. Direct current induced a higher transdermal flux of fentanyl (537 ± 31 ng/cm^2 per h) than pulsed current (378 ± 40 ng/cm^2 per h) ($p < 0.05$) (Fig. 1). The lag times measured were 2.09 ± 0.2 and 1.92 ± 0.4 h, respectively. The total cumulated quantity of drug detected in the receptor compartment is the sum of the quantities which permeated by diffusion and iontophoresis. The passive diffusion of cationic fentanyl across the hairless rat skin is extremely low because of the hydrophobic nature of the skin.

The skin has a specific behaviour under the influence of an electrical current. The stratum corneum acts like a capacitance and this polarization operates against the applied electrical field and greatly reduces the magnitude of the effective iontophoretic enhancement. This phenomenon prompted a number of authors to use a pulsed square wave current to allow the skin to release the electrical charges accumulated in the capacitance and reach its initial resistivity between each impulse (Yamamoto and Yamamoto, 1976, 1978; Liu et al., 1988; Chien et al., 1989).

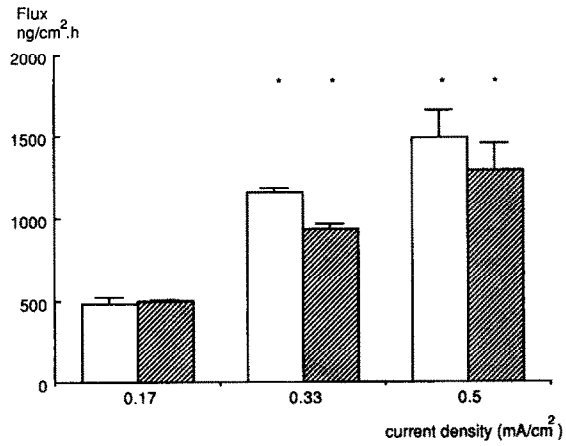

Fig. 2. Flux of fentanyl through hairless rat skin vs current density applied following direct current (□) or pulsed current (2.5 kHz on/off 1:1) (▨) iontophoresis performed for 6 h. Fentanyl (400 μg/ml) was introduced in a citrate buffer (0.01 M) at pH 3.5. (* $p < 0.05$ vs 0.17 mA/cm^2) ($n = 3$).

Pulsed current is more efficient than direct current in promoting the transdermal delivery of some drugs like peptides (Liu et al., 1988; Lelawongs et al., 1989; Wearley and Chien, 1990). In contrast, iontophoresis performed with direct current is more potent at inducing transdermal permeation of smaller molecules such as sodium and glucose (Bagniefski and Burnette, 1990; Pikal and Shah, 1991). The molecular weight of a molecule could be involved in the difference in efficiency between the current profiles (Pikal and Shah, 1990; Thysman and Préat, 1992).

Current density applied Iontophoresis was performed for 6 h. The donor compartment was filled with an acidic solution of fentanyl (400 μg/ml) in a citrate buffer (0.01 M) at pH 3.5. The mean current density of direct or pulsed current applied was enhanced from 0.17 to 0.5 mA/cm^2. The increase in current density enhanced fentanyl flux through the skin from 481.5 $\pm$ 43 to 1493 $\pm$ 172.5 ng/cm^2 per h for direct current and from 500 $\pm$ 7 to 1296 $\pm$ 168 ng/cm^2 per h for pulsed current (Fig. 2).

Thus, the electrical assistance produced an enhancement of the transdermal transport of fentanyl and the flux depended on the current density.

The density of current, expressed in mA/cm^2, represents the number of electrical charges travelling/unit time per unit surface. An enhancement in intensity allows an increase in the driving force to induce the movement of an ionized drug. The relationship between the intensity and flux has been experimentally verified by several authors (Gangarosa et al., 1980; Sanderson et al., 1987; Bannon et al., 1988; Del Terzo et al., 1989; Lelawongs et al., 1989; De Nuzzio and Berner, 1990). The application of current allowed the increase in permeation of the ions to be controlled. This phenomenon is one of the most interesting aspects of iontophoresis: the modulation of the current density applied allows one to regulate the quantity of the drug released from the device.

Duration of current application Fentanyl (40 μg/ml) was introduced into the donor compartment in a citrate buffer (0.01 M) at pH 3.5. Direct current (0.33 mA/cm^2) was applied for 0, 1 or 6 h in order to investigate the influence of the duration of current application. The fluxes across the skin were 1 $\pm$ 0.3, 146 $\pm$ 11 and 537 $\pm$ 31 ng/cm^2 per h, respectively ($p < 0.05$) (Fig. 3).

Without the application of current, trhe extent of diffusion was extremely low. Flux was greater when iontophoresis was applied for 6 h instead of

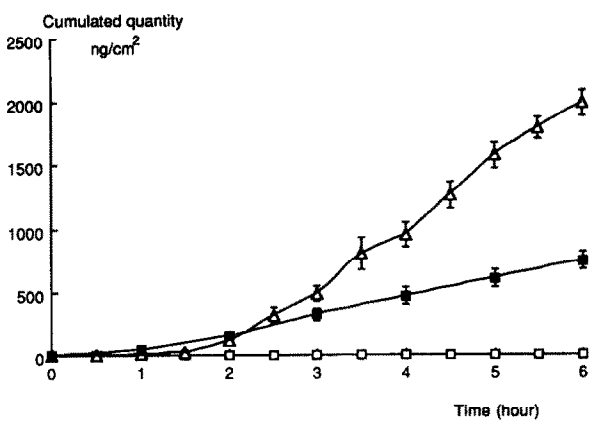

Fig. 3. Cumulated quantity of fentanyl detected in the receptor compartment vs time following direct current iontophoresis (0.33 mA/cm^2) performed for 0 h (□), 1 h (■), or 6 h (△). Fentanyl (40 μg/ml) was introduced in a citrate buffer (0.01 M) at pH 3.5 ($n = 5$).

1 h. The total quantity of charges permeating the skin increased on prolongation of the period of iontophoresis. When the current was applied for 1 h, a lag time of 1.2 ± 0.2 h was observed and the flux of permeation of fentanyl was maintained at the same rate for at least 4.5 h after switching off the current.

Further studies were performed for the purpose of ascertaining whether this could be induced by the enhancement in skin permeability following electrical treatment or by the release of drug bound to the skin reservoir.

Chemical factors

pH Diffusion and iontophoresis with a direct current (0.33 mA/cm^2) were performed at pH 3.5 (citrate buffer 0.01 M) and pH 7 (phosphate buffer 0.01 M). The concentration in the donor solution was 40 μg/ml. The diffusion fluxes measured at pH 3.5 and 7 were 1 ± 0.3 and 2.3 ± 0.6 ng/cm^2 per h, respectively ($p < 0.05$). The iontophoresis fluxes observed at pH 3.5 were greater (537 ± 31 ng/cm^2 per h) than at pH 7 (331 ± 82 ng/cm^2 per h) ($p < 0.05$).

Fentanyl is a weak base ($pK_a = 8.43$) (Mather, 1983). The proportion of drug ionized depends on the pH of the solution into which the species are introduced. During iontophoresis, mainly ionized drugs move under the influence of the voltage drop applied. However, only uncharged drugs travel through the skin by diffusion (Siddiqui, 1989).

The diffusion of ions through the membrane was extremely low due to the hydrophobicity of animal skin. As expected, the simple permeation flux of drug across hairless rat skin was greater when fentanyl was introduced into a solution at pH 7 than at pH 3.5 (Roy and Flynn, 1990). However, the iontophoretic fluxes were higher after introduction of the drug into acidic medium as a result of the gretear fraction of ions in this solution as compared to a neutral solution.

Concentration An increase in the concentration of drug from 40 to 400 μg/ml in the donor compartment induced a significant increase in drug permeation flux ($p < 0.05$). The flux was enhanced from 537 ± 31 to 1167 ± 27 ng/cm^2 per h when direct current (0.33 mA/cm$^{2)}$ was applied for 6 h and from 378 ± 48 to 936 ± 31 ng/cm^2 per h after pulsed current application for 6 h (2.5 kHz on/off 1:1 at a mean current density of 0.33 mA/cm^2) (Fig. 4).

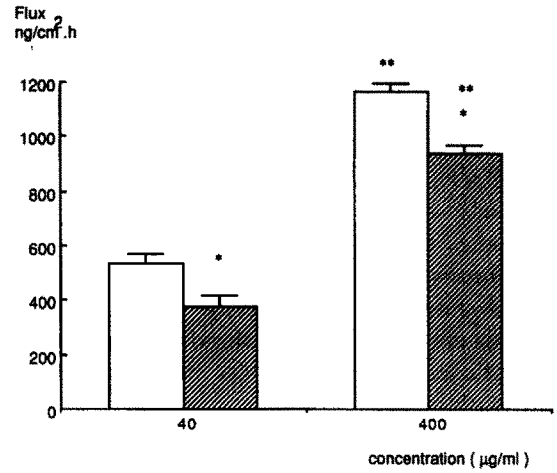

Fig. 4. Flux of fentanyl through hairless rat skin vs fentanyl concentration in the donor compartment after direct (□) or pulsed current (2.5 kHz on/off 1:1) (▨) iontophoresis performed for 6 h. The mean current density applied was 0.33 mA/cm^2. Fentanyl was introduced in a citrate buffer (0.01 M) at pH 3.5 ($n = 3$). (* $p < 0.05$ vs direct current; ** $p < 0.05$ vs 40 μg/ml).

The transport number depends on the concentration of ions. As the amount of fentanyl relative to the total amount of ions in the solution increased, its fractional contribution to the total transport of current increased (Kasting et al., 1988). The skin is not an inert tissue and presents some resistivity to ion movements. Moreover, many small ions present in the skin or added (buffer) transport part of the current. This could explain the lack of a strictly proportional relationship between the concentration and flux (Kasting and Bowman, 1988; Padmanabhan et al., 1990).

Mechanism

Electro-osmosis The skin is negatively charged since its physiological pH is higher than its pK value. From this charge, the cation permselectivity property of the skin emerges. The discontinuities in transport number between the membrane and the solution induce a concentration gradient across the membrane. This gradient leads to an

osmotic pressure which sets up an osmotic flow of water. Electro-osmosis operates from the anode to the cathode. Electro-osmosis could promote the migration of fentanyl and ion migration is a result of electrostatic repulsion and current-induced solvent flow (Liu et al., 1988; Pikal, 1990; Srinivasan and Higuchi, 1990; Sims et al., 1991).

Studies were performed to compare the electro-osmosis fluxes induced by either direct or pulsed current and to verify whether electro-osmosis could account for the differences in fentanyl fluxes through hairless rat skin obtained with both current profiles.

Skin presented an intrinsic permeability for water (2.3 ± 0.7 $\mu l/cm^2$ per h). Water fluxes through hairless rat skin measured during iontophoresis were higher than the intrinsic value. Direct and pulsed current application (mean current density 0.33 mA/cm^2) induced the same water flux through the membrane ($p < 0.05$). The fluxes observed during direct and pulsed current iontophoresis were 14.4 ± 1.1 and 15.2 ± 1.3 $\mu l/cm^2$ per h, respectively. Electro-osmosis could not account for differences between the kinetics obtained with both current profiles (Fig. 5).

Permeability of the skin to water The measurement of tritiated water flux is a good model to study the lesions induced by iontophoresis, since electrolytes and water follow the same pathway to travel through the skin. Therefore, in order to determine whether iontophoresis could enhance skin permeability and whether direct current could induce more skin damage than pulsed current, the water permeability of the skin was measured after iontophoresis.

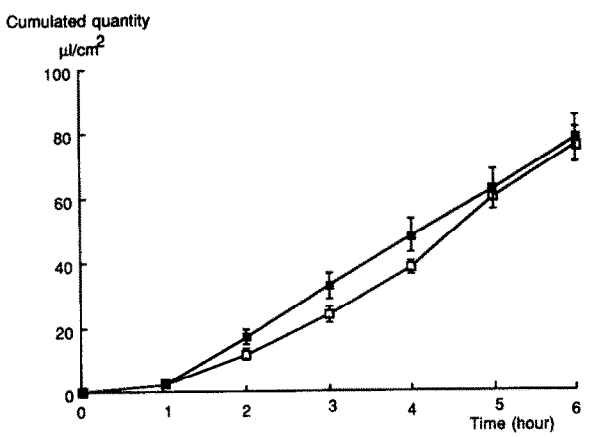

Fig. 5. Cumulated quantity of water permeating through the skin vs time during iontophoresis. Direct current (0.33 mA/cm^2) (□) or pulsed current (2.5 kHz on/off 1:1; 0.33 mA/cm^2) (■) was applied for 6 h. The donor compartment contained $[^3H]H_2O$ and fentanyl (40 $\mu g/ml$) in a citrate buffer (0.01 M) at pH 3.5 ($n = 5$).

The donor compartment was filled with an acidic fentanyl solution (citrate buffer 0.01 M at pH 3.5) and the current (0.17 mA/cm^2) was applied for several time periods. After switching off the current, the donor solution was removed and replaced by tritiated water.

Skin presents an intrinsic permeability for water: without current application, a water flux was observed (2.3 ± 0.7 $\mu l/cm^2$ per h). Current application for less than 1 h did not lead to an enhancement of water flux as compared to the intrinsic permeability. However, prolonged electrical treatment modified the water permeability of the skin, since after 1 or 6 h iontophoresis, the water fluxes were significantly different from the intrinsic permeability ($p < 0.05$) (Fig. 6).

In none of the cases examined did a direct current induce a significantly higher ($p < 0.05$) permeability of water through the skin than pulsed current (Fig. 6). Several studies have shown a lack of any significant alteration in skin permeability after application of a current of 1 mA/cm^2 for 10 min (Tyle, 1986) or after pulsed current application (1 mA, 2 kHz) for 3 h (Liu et al., 1988).

These results lead us to conclude that the differences in efficiency between the two current profiles cannot be explained by the presence of skin lesions induced by one of the current profiles. Direct current application for 6 h (0.33 mA/cm^2) induced a greater in vitro flux of fentanyl than a direct current for 1 h (Fig. 3). These results could be partly explained by the enhancement of skin permeability to aqueous solutions after prolonged electrical treatment (Fig. 6).

Reservoir The reservoir capacity of the skin is well known. It is assumed that drug binding takes place in the stratum corneum (Vickers, 1963).

When iontophoresis was performed for 1 h, a lag time of 1.2 ± 0.2 h was observed and the fentanyl flux measured through the skin re-

mained constant for at least 4.5 h (Fig. 3). We wished to verify whether this phenomenon resulted from an enhancement in skin permeability or the release of drug accumulated in the skin reservoir. Therefore, after iontophoresis application for 30 min and 1 h, the fentanyl donor solution was either left in place or removed and replaced by the same drug-free buffer.

As shown in Fig. 7, it appears that drug permeation after switching off the current resulted mostly from the emptying of the reservoir capacity of the skin. The fluxes measured after iontophoresis performed for 1 h were 104 ± 23 ng/cm^2 per h after renewal of the donor compartment and 146.5 ± 11.4 ng/cm^2 per h after diffusion of fentanyl. After performing iontophoresis for 30 min, the fluxes were 19.5 ± 12.2 and 44.9 ± 13.3 ng/cm^2 per h, after renewal and no renewal of the donor solution, respectively. The appearance of fentanyl in the receptor compartment after removing the donor solution confirmed that the reservoir capacity of the skin was

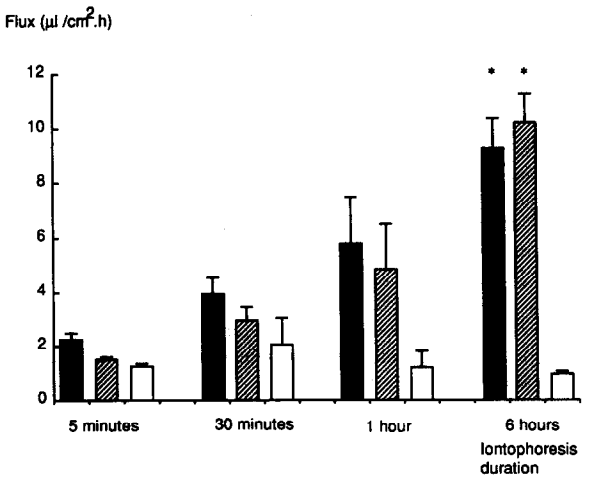

Fig. 6. Flux of water through the skin after iontophoresis performed for several time periods. For each iontophoresis duration, diffusion (□), direct current (0.17 mA/cm^2) (▨) or pulsed current (2.5 kHz on/off 1:1; 0.17 mA/cm^2) (▨) were applied. The donor solution (fentanyl 40 µg/ml in a citrate buffer 0.01 M at pH 3.5) was removed after iontophoresis for 5 min, 30 min, 1 h or 6 h and replaced with [^{3}H]H_2O. The water flux was then measured for 6 h (* $p < 0.05$ vs diffusion) ($n = 4$).

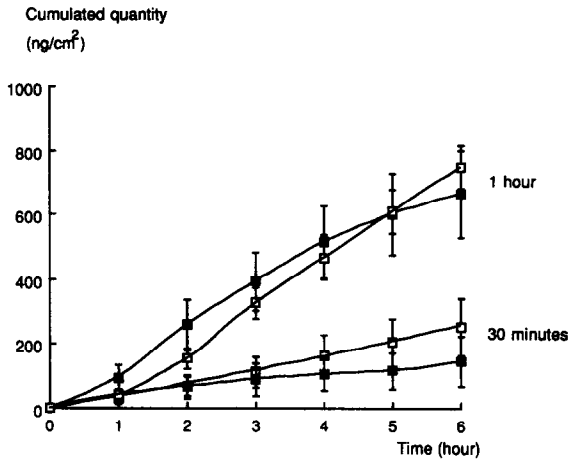

Fig. 7. Cumulated quantity of fentanyl detected in the receptor compartment after direct currrent iontophoresis (0.33 mA/cm^2). The current was applied for 1 h or 30 min. After swithing off the current, the donor solution (40 µg/ml in a citrate buffer 0.01 M at pH 3.5) left was in place in the donor compartment (□) or replaced with drug-free citrate buffer (■) ($n = 4$).

the factor leading to the slow release of drug bound to the stratum corneum.

Holley and Van Steenis (1988) described a slow decline of fentanyl serum concentrations in patients who received fentanyl transdermally. This could be explained by continued absorption from a skin depot of the drug after removal of the transdermal system (TTS-fentanyl) as may be expected for a lipid-soluble drug such as fentanyl (Vickers, 1963; Rougier et al., 1983; Holley and Van Steenis, 1988; Tojo et al., 1988; Walter and Kurz, 1988).

Conclusions

Even though fentanyl could be efficiently transdermally administered using devices releasing the drug by diffusion, it has been demonstrated that iontophoresis can improve the pharmacokinetic profile for the transdermal administration of this narcotic drug (Thysman et al., 1993).

The kinetics of fentanyl permeation through the skin depends on the current profile, current density and duration of current application. Ion-

tophoresis decreases the lag time as compared to a fentanyl-TTS patch.

Direct current is more potent than pulsed current in promoting the transdermal permeation of fentanyl through hairless rat skin. Neither electro-osmosis nor greater skin permeability induced by direct current application could account for these differences.

When iontophoresis is applied for 1 h, the in vitro release of fentanyl from hairless rat skin occurs even after the current has been switched off due to the skin reservoir capacity of the skin being more influential than increased permeability of the skin.

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