

Transdermal Delivery of Timolol and Atenolol Using Electroporation and Iontophoresis in Combination: A Mechanistic Approach

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Purpose. The purpose of this work was to study the effect of electroporation on iontophoretic transport of two β -blockers, timolol (lipophilic) and atenolol (hydrophilic), and to have a better understanding of the mechanism of combination.

Methods. The transdermal delivery of these β -blockers through human stratum corneum was studied in three-compartment diffusion cells. The transport of mannitol was evaluated to assess the electroosmotic flow.

Results. The iontophoretic transport of timolol was decreased by electroporation because the high accumulation of the lipophilic cation timolol in the stratum corneum resulted in a decrease of electroosmosis. In contrast, electroosmosis was not affected by atenolol, and the iontophoretic transport of atenolol was increased by electroporation.

Conclusions. Using two different β -blockers, we showed that lipophilicity and positive charges affect the electrotransport of drugs. Understanding the effect of the physicochemical properties of the drug, as well as the electrical parameters, is thus essential for the optimization of transdermal drug delivery by a combination of electroporation and iontophoresis.

KEY WORDS: transdermal drug delivery; electroporation; iontophoresis; electroosmosis; β -blockers.

INTRODUCTION

Transdermal drug delivery offers several advantages over traditional drug delivery systems such as oral delivery and injection, including elimination of hepatic first-pass metabolism, minimization of pain, and potential sustained release of drugs. However, because of the low permeability of the stratum corneum, different physical and chemical approaches have been developed to overcome the skin barrier and to have a better control of drug transport across the skin. Iontophoresis employs a low-density electrical current (from 0.1 to 0.5 mA/cm²) applied for a relatively long period (from minutes to hours). Electroporation consists in the application of short (from 100 μ s to less than 1s) high-voltage pulses (from about 100 to 1000 V) (1,2). The enhanced drug transport by electroporation results from the increased permeability of the electroporated skin, from electrorepulsion, and less

likely from electroosmosis. In contrast, the major mechanisms of iontophoretic transport are electrorepulsion and electroosmosis. At physiologic pH, the skin is negatively charged and cation permselective. Hence, current passage causes a net convective solvent flow in the anode-to-cathode direction, facilitating cation transport, inhibiting that of anions, and enabling the enhanced transdermal transport of neutral, polar solutes (3).

Because electroporation and iontophoresis have been individually shown to enhance transdermal drug transport, and because of their different mechanisms of action, their combinations have been hypothesized to be more effective than each of them alone. Specifically, electroporation may disorder the lipid bilayers of the skin and create new transport pathways in the skin, thus facilitating passage of current during iontophoresis and resulting in increased transdermal transport (4). A few studies explicitly focused on the combination of iontophoresis and electroporation to enhance transdermal drug delivery. The effect of electroporation on transdermal iontophoretic delivery of a few peptides and drugs, e.g., LHRH, salmon calcitonin, PTH, buprenorphine, dextran sulfate, defibrase, fentanyl, and sodium nonivamide acetate, was evaluated *in vitro* (5–11). Both an enhancing effect and no effect of electroporation on iontophoretic drug transport have been reported.

Timolol maleate and atenolol are β -adrenergic blocking agents used in the treatment of various cardiovascular disorders. With an oral bioavailability of 50%, the transdermal delivery of these drugs could be a potential alternative to oral delivery to increase therapeutic efficacy, bypassing hepatic first-pass metabolism and low oral absorption. The pK_a of timolol and atenolol are 9.2 and 8.6, respectively, and their logP 2.1 and –1.4 (12). Transdermal iontophoresis of timolol and atenolol has been studied: iontophoresis increased the transport, reduced the lag time, and allowed control of the delivery of the drug (13–17). As an alternative to iontophoresis or passive diffusion, the effect of electroporation on transdermal delivery of timolol was recently investigated (18). Even though the current application lasted for only 10 s, therapeutic fluxes of timolol (>50 μ g/cm²/h) through human stratum corneum were also achieved by electroporation.

In this work, the potential of the combination of these two electrically driving forces, electroporation and iontophoresis, was evaluated for the transdermal delivery of two β -blockers, timolol maleate (lipophilic model drug) and atenolol (hydrophilic model drug). The aims of this report were (a) to study the effect of electroporation on their iontophoretic transport and (b) to have a better understanding of the mechanism of combination. An *in vitro* three-compartment diffusion cell with human stratum corneum was used in order to mimic the *in vivo* situation. Based on previous work studying the transdermal delivery of timolol by electroporation (18) and iontophoresis alone (16), different combinations were tested. Because of the unexpected decrease of timolol iontophoretic transport by electroporation, a mechanistic study was performed based on the hypothesis that the electroosmotic flow was decreased by the higher accumulation of lipophilic cation timolol in the skin after electroporation. To check this hypothesis, the electroosmotic flow was evaluated by using the transport of a neutral molecule, i.e., mannitol.

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ABBREVIATIONS: E, electroporation; I, iontophoresis; E+I, combination of electroporation and iontophoresis; T, timolol; A, atenolol; M, mannitol; M+T, mannitol in the presence of timolol; M+A, mannitol in the presence of atenolol.

Then the effect of the physicochemical properties of the drug, i.e., the lipophilicity and the charge, was studied by comparing the transport of lipophilic timolol with that of a hydrophilic β -blocker, atenolol.

MATERIALS AND METHODS

Materials

Timolol maleate, atenolol, and D-mannitol were purchased from Sigma (St. Louis, MO). D-[14 C]Mannitol was obtained from Amersham Pharmacia Biotech (Buckinghamshire, England). The salts used to prepare the buffers and acetic acid (99–100%) were supplied by VWR (Leuven, Belgium). Platinum, silver, and silver chloride were obtained from Aldrich (Bornem, Belgium) and were >99.99% pure. HPLC grade acetonitrile (J. T. Baker, Deventer, The Netherlands) was used as a solvent in the HPLC analysis. All solutions were prepared with ultrapure water (conductivity 0.1 μ S/cm; Sation 9000, VWR, Leuven, Belgium). Dialysis membranes with a molecular weight cutoff of 5 kDa (Diacema, Munich, Germany) were used as a support.

Skin Preparation

Human stratum corneum was prepared as previously described (18). Briefly, human abdominal skin was obtained from plastic surgery and was prepared within 24 h. After removal of fatty tissue, the skin was dermatomed at 300 μ m (model 1993 dermatome, Robbins Instruments, Chatham, MA). To obtain isolated stratum corneum, dermatomed skin was incubated with its dermal side on paper soaked in a solution of 0.1% (w/v) trypsin (from bovine pancreas, T4665, Sigma, St. Louis, MO) in 0.15 M phosphate-buffered saline PBS overnight at 4°C and 1 h at 37°C. The stratum corneum was then carefully peeled off. The stratum corneum was treated with 0.1% (w/v) trypsin inhibitor solution (type II-S from soybean, T9128, Sigma, St. Louis, MO) in PBS. Then, it was washed twice with distilled water, blotted dry, and stored at room temperature in a silica gel-containing desiccator in N_2 in order to avoid oxidation of lipids.

In Vitro Model

Transport experiments were performed in a three-chamber continuous flow-through diffusion cell in order to mimic the *in vivo* situation. One piece of stratum corneum with a dialysis membrane used as a supporting membrane was placed between the outer chamber (anodal compartment) and the central acceptor chamber. Another piece of stratum corneum was placed between the central chamber and the other outer chamber (cathodal compartment). The central chamber was thermostated at 37°C. The exposed area was 0.64 cm^2 , and the acceptor volume and the donor volume were 0.5 ml and 2 ml, respectively. The donor solutions contained, unless specified, 40 mg of timolol maleate or atenolol per ml of a citrate buffer (pH 4.7; 12 mM 4 g NaCl/L). The acceptor chamber was filled with PBS, pH 7.4, and the cathodal compartment with 2 ml of the same buffer as in the anodal compartment. During the experiments, both anodal and cathodal chambers were magnetically stirred at 350 rpm (Variomag, Daytona Beach, FL). The acceptor flow rate was 6.5 ml/h; the acceptor compartment was connected to a frac-

tion collector (model 2128, BioRad, Richmond, CA) and sampled every hour. Because of the differences in skin permeability of different donors, human skin specimens from three different donors were used for each condition tested. A system with two pairs of electrodes was chosen for combination experiments. Platinum electrodes were used for electroporation and placed at 4 mm from the skin, and silver/silver chloride electrodes were used for iontophoresis and placed at 2 cm from the membrane (16,18).

Electrotransport Experiments

The power supply was a square-wave pulser combined with a current generator, controlled by a PC computer; by the use of a low current, it allowed monitoring of the resistance of the cell system during the experiments, and the maximal voltage drop was 10% (Moor Instruments, Axminster, England). Conditions for combination were based on the optimization of transdermal delivery of timolol by electroporation and the iontophoretic delivery of timolol *in vitro*. In electroporation followed by iontophoresis (E+I) combinations, after 6 h of passive diffusion, 10 pulses of 400 V \times 10 ms (spacing between pulses = 1 s, transdermal voltage = 86 V) were performed, immediately (30 s after the end of pulses) followed by iontophoresis (3 h \times 0.25 mA/ cm^2 or 9 h \times 0.5 mA/ cm^2); then passive diffusion was followed for at least 6 h (16,18).

Electroosmosis Studies

Because mannitol is a nonmetabolized neutral molecule, it is currently used as a marker for electroosmotic flow (19). Mannitol transport through human stratum corneum was measured for 6 h under electroporation and/or iontophoresis conditions. The donor compartment (anodal compartment) was filled with a solution of mannitol (24 mg/ml) and [14 C]mannitol (0.5 μ Ci/ml) in a citrate (12 mM, pH 4.7, 4 g NaCl/L) buffer. When mannitol transport was studied in the presence of the β -blocker, 40 mg/ml of timolol maleate or atenolol was added in the donor solution. The amount of [14 C]mannitol in each sample was determined by scintillation counting (liquid scintillation cocktail, Ready Safe, Beckman, Belgium; liquid scintillation counter Wallac 1410, LKB, Pharmacia, Uppsala, Sweden).

HPLC Analysis

The HPLC system consisted of an automatic injector, a gradient pump, and a UV detector (Bio-Tek Instruments, Milan, Italy). The wavelength was 270 and 294 nm for the analysis of atenolol and timolol maleate, respectively. An X-Terra RP C_{18} column was used (15 cm \times 3.0 mm, 3.5 μ m, Waters, Milford, MA). For the analysis of the samples containing timolol, a mobile phase consisting of acetonitrile/phosphate 50 mM, pH 3.0, buffer (25:75, v/v) was used as previously described (18). For atenolol, a mobile phase of acetonitrile/carbonate 50 mM, pH 6.0 buffer (10:90, v/v), was used. The flow rate was 0.5 ml/min and the injection volume was 50 μ l. Chromatography was performed at room temperature, and the retention time of timolol maleate and atenolol was 2.5 and 3.5 min, respectively. The calibration curves were linear ($r^2 > 0.999$) over the concentration range studied (1–100 μ g/ml). The intraday coefficients of variation were less than 3%. The

detection limits were 25 ng/ml and 100 ng/ml for timolol and atenolol, respectively.

Data Analysis

Fluxes of timolol, atenolol, and mannitol were calculated from the concentrations in the collecting tubes by using the equation: $J_F = F \cdot C_a / A$ where J_F is the flux through the membrane, C_a is the concentration of the permeant in the acceptor phase determined by HPLC, A is the skin area (0.64 cm^2), and F is the flow rate of PBS. When the flux reached steady state, this steady-state flux (J_{ss}) was obtained from the linear part of the plot of cumulative amount divided by the skin area ($\mu\text{g}/\text{cm}^2$) vs. time. The results were expressed as the mean \pm standard error of the mean. Statistical comparisons were made using the t test or ANOVA test. A probability value less than 0.05 was considered to be significant.

RESULTS AND DISCUSSION

Timolol Transport by Combination of Electroporation and Iontophoresis

Because of the differences between the mechanisms of action of electroporation and iontophoresis, it was hypothesized that combination of these two driving forces is more effective to enhance transdermal drug delivery. Whereas iontophoresis acts primarily on the drug by electrorepulsion and electroosmosis, electroporation acts on the skin by increasing its permeability and provides a local driving force for drug transport (4).

Electrical conditions for the combination were based on the previous experimental work on timolol transport by electroporation alone [10 pulses of $400 \text{ V} \times 10 \text{ ms}$ (18)] and by iontophoresis alone [9 h \times $0.5 \text{ mA}/\text{cm}^2$ (16)]. A first combination of electroporation and iontophoresis with these experimental conditions is presented in Fig. 1a. During the 6 h of passive diffusion, timolol steady-state flux through human stratum corneum was $3 \pm 2 \mu\text{g}/\text{cm}^2/\text{h}$. After electroporation alone, a steady-state flux of $40 \pm 14 \mu\text{g}/\text{cm}^2/\text{h}$ was obtained and remained constant for at least 15 h. Iontophoresis alone applied for 9 h resulted in a steady-state flux of $240 \pm 49 \mu\text{g}/\text{cm}^2/\text{h}$, but timolol flux decreased after the end of iontophoresis. When electrical pulses were applied before iontophoresis, a flux of $150 \pm 51 \mu\text{g}/\text{cm}^2/\text{h}$ was achieved. The benefit of the electrotransport over passive diffusion was clearly shown (ANOVA, $p < 0.01$).

Surprisingly, timolol flux obtained after a combination of electroporation and iontophoresis was lower than the flux obtained by the sum of those of electroporation alone and iontophoresis alone (t test, $p < 0.01$) and even lower than the iontophoretic flux (t test, $p < 0.01$). However, the drop of the resistance of the cell system in the combination experiments confirmed the hypothesis that electroporation applied before iontophoresis decreased skin resistance: in combination of electroporation and iontophoresis, the resistance of the cell system was 2200Ω 1 min after the pulse application; in the case of iontophoresis alone, the mean resistance was $15,000 \Omega$.

Another protocol of iontophoresis more acceptable for patients in clinical use, consisting in applying 3 h of iontophoresis with a current density of $0.25 \text{ mA}/\text{cm}^2$, was also applied

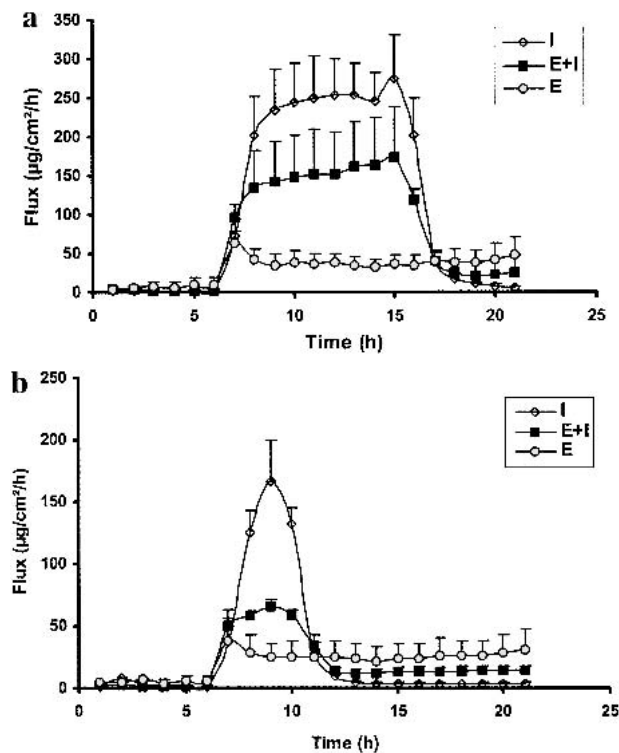


Fig. 1. Timolol fluxes after electroporation (E), iontophoresis (I), and a combination of electroporation and iontophoresis (E+I); experimental conditions used alone or in combination were (a) E, $400 \text{ V} \times 10 \text{ ms} \times 10$ pulses, and I, $9 \text{ h} \times 0.5 \text{ mA}/\text{cm}^2$ (mean \pm SEM, E: $n = 5$, I: $n = 6$, E+I: $n = 7$); (b) E, $400 \text{ V} \times 10 \text{ ms} \times 10$ pulses; I, $3 \text{ h} \times 0.25 \text{ mA}/\text{cm}^2$ (mean \pm SEM, E: $n = 5$; I and E+I, $n = 6$). Timolol maleate, $40 \text{ mg}/\text{ml}$, was introduced in a citrate buffer ($4 \text{ g}/\text{L}$ NaCl, pH 4.7).

alone or in combination with electroporation. Timolol flux after a combination of electroporation and iontophoresis was also lower than the flux obtained with iontophoresis alone (Fig. 1b). Cumulative quantities of timolol obtained at 21 h were 640 ± 82 and $483 \pm 46 \mu\text{g}/\text{cm}^2$, corresponding to transport by iontophoresis and by the combination of electroporation and iontophoresis, respectively; they were found to be significantly different (t test, $p < 0.01$). The measure of the resistance during the experiments also confirmed that a dramatic decrease in skin resistance was induced by electroporation.

The application of electroporation before iontophoresis has been previously reported to either increase drug transport or shorten the lag time or in some cases to have no effect on iontophoretic flux. The iontophoretic transport of LHRH, salmon calcitonin, dextran sulfate, and defibrase was increased by electroporation before iontophoresis (5,6,8,9). Fang *et al.* (11) showed that pulses of high voltages followed by iontophoresis did not result in increased transport of sodium nonivamide acetate over iontophoresis alone but shortened the lag time. In the case of buprenorphine, electroporation failed to enhance iontophoretic delivery through human epidermis (7).

Our results from the combination experiments were quite unexpected. Based on the rationale of combining two electrical methods acting by complementary mechanisms, an enhancement of iontophoretic transport of timolol by electroporation was expected. Nevertheless, timolol transport ob-

tained after a combination of electroporation and iontophoresis was lower than that obtained by iontophoresis alone for both conditions tested, indicating that application of electroporation before iontophoresis decreased the iontophoretic flux of timolol. The discrepancies in the literature suggest that the physicochemical properties of the drug, as well as the electrical parameters of electroporation and iontophoresis, could influence the transport resulting from the combination. They also indicate that a better understanding of the mechanism of transport by the combination is required to optimize drug delivery and, more particularly, to clarify the decrease in timolol transport observed when electroporation was applied before iontophoresis.

Mechanism of Timolol Transport by a Combination of Electroporation and Iontophoresis

Effect of Timolol on Electroosmosis

The combination of positive charge and lipophilicity, such as lipophilic β -blockers (e.g., propranolol) or peptides with lipophilic amino acids (e.g., nafarelin), has been previously reported to decrease electroosmosis during iontophoresis: the skin's negative charge can be reduced, neutralized, or even reversed by certain cationic, lipophilic species, resulting in an attenuation of electroosmosis by the association of these compounds with the negatively charged sites in the skin (3,13). Hence, it was hypothesized that the decrease in iontophoretic transport of timolol, a lipophilic cation, by electroporation could be explained by a decrease of electroosmosis after electroporation because of the accumulation of timolol in the stratum corneum. To check this hypothesis, electroosmotic flux was measured using mannitol as a tracer in the presence and in the absence of timolol.

After electroporation alone, steady-state fluxes of mannitol were found similar in the presence and the absence of timolol maleate, 444 ± 72 ng/cm²/h and 411 ± 74 ng/cm²/h, respectively (*t* test, *p* > 0.05; Fig. 2), indicating that timolol maleate does not affect mannitol transport by electroporation, very likely because of the low contribution of electroosmosis in mannitol transport by electroporation as compared to enhanced skin permeability (20). The transport of mannitol

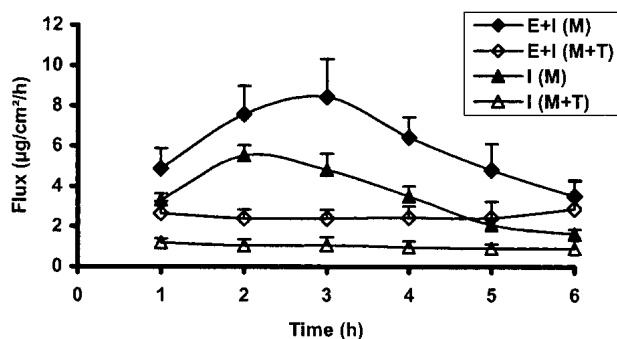


Fig. 2. Mannitol fluxes after iontophoresis (I) and combination of electroporation and iontophoresis (E+I) in the presence (M+T) and absence (M) of timolol; experimental conditions used alone or in combination were: E, 400 V \times 10 ms \times 10 pulses; and I, 3 h \times 0.25 mA/cm² (mean \pm SEM, *n* = 3). Donor phase composition, [¹⁴C]mannitol (0.5 μ Ci/ml) and mannitol (24 mg/ml) was introduced in a citrate buffer (4 g/L NaCl, pH 4.7) with or without timolol maleate (40 mg/ml).

in the presence and absence of timolol was always higher after the combination of electroporation and iontophoresis than after iontophoresis alone because of the increased skin permeability induced by electroporation. On the other hand, the presence of timolol decreased the electroosmotic flux during iontophoresis (*t* test, *p* < 0.01) as well as in the combination of electroporation and iontophoresis (*t* test, *p* < 0.01), consistent with the hypothesis that the accumulation of positively charged timolol in the stratum corneum by electroporation reduced the negative charges of the stratum corneum and hence induced a decrease of electroosmosis.

Effect of Timolol Concentration

The decrease of electroosmotic flow by iontophoresis of certain lipophilic, cationic compounds has been found to occur in a concentration-dependent fashion (13,21,22). Hence, the effect of timolol maleate concentration on the decrease of electroosmosis was investigated. Whereas in the previous experiments 40 mg of timolol maleate per milliliter of buffer were used, a lower concentration in the donor phase, i.e., 10 mg of timolol maleate per milliliter of buffer, was used (Fig. 3). As expected, with this concentration, timolol transport was lower: steady state fluxes were 7, 95, and 44 μ g/cm²/h after electroporation, iontophoresis, and a combination of electroporation and iontophoresis, respectively. Timolol fluxes after the combination were lower than those obtained by the sum of electroporation and iontophoresis alone (*t* test, *p* < 0.01) and even lower than fluxes obtained with iontophoresis only (*t* test, *p* < 0.01). This phenomenon observed previously was not decreased concomitantly with timolol maleate concentration, indicating that, even at lower concentrations, the accumulation of timolol in the stratum corneum by electroporation was high enough to induce the decrease of electroosmosis during iontophoresis.

Effect of Physicochemical Properties of the Drug on Mechanism of Transport

Effect of Atenolol on Electroosmosis

As mentioned previously, the permselectivity of the skin can be altered during iontophoresis by some lipophilic, cationic peptides (e.g., nafarelin) and β -blockers (e.g., propranolol). Their positive charges, which can neutralize the negatively charged sites in the skin, and their hydrophobic groups, allowing anchoring to the skin, ensure a tight association, thereby decreasing electroosmosis. Drug lipophilicity appears to be essential to this phenomenon: the parent peptide LHRH and the relatively hydrophilic β -blockers atenolol and nadolol did not affect electroosmosis (21,22).

Hence, to confirm the hypothesis that both positive charge and lipophilicity were critical to decrease the electroosmotic flux and drug transport in combination of electroporation and iontophoresis, the transport of mannitol by iontophoresis combined with electroporation was determined in the presence of atenolol, a hydrophilic β -blocker that does not affect the iontophoretic delivery of mannitol. The transport of mannitol by a combination of electroporation and iontophoresis was not decreased in the presence of atenolol (Fig. 4), indicating that, contrary to timolol, atenolol did not affect the electroosmotic flow.

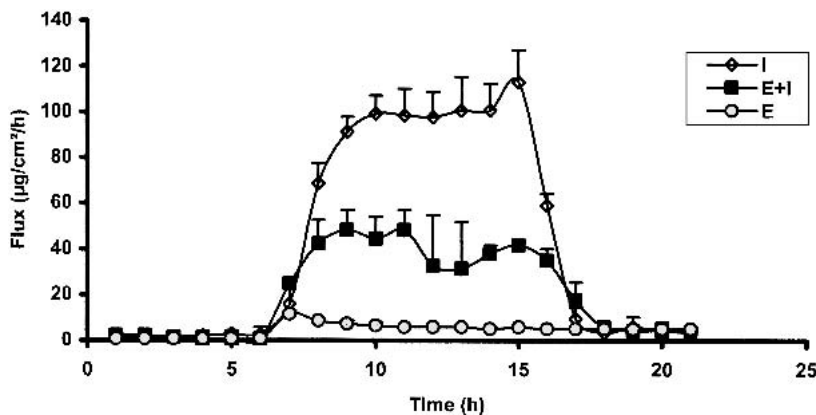


Fig. 3. Timolol fluxes after electroporation (E), iontophoresis (I), and combination of electroporation and iontophoresis (E+I); experimental conditions used alone or in combination were E, 400 V \times 10 ms \times 10 pulses; and I, 9 h \times 0.5 mA/cm² (mean \pm SEM; E, n = 4; I and E+I, n = 3). Timolol maleate, 10 mg/ml, was introduced in a citrate buffer (4 g/L NaCl, pH 4.7).

Atenolol Transport by the Combination of Electroporation and Iontophoresis

Atenolol transport by a combination of electroporation and iontophoresis was then studied in order to compare the result of 3 h of iontophoresis with a current density of 0.25 mA/cm² applied alone with that in combination with electroporation. Contrary to timolol, atenolol flux after combination of electroporation and iontophoresis was higher than after iontophoresis or electroporation (Fig. 5), consistent with the electroosmosis studies. Cumulative quantities of atenolol obtained at 20 h for iontophoresis alone (1089 \pm 54 μ g/cm²) and combination of electroporation and iontophoresis (2459 \pm 125 μ g/cm²) were significantly different (*t* test, *p* < 0.01). The transport and electroosmosis experiments with the hydrophilic β -blocker atenolol suggest that the lowering effect of electroporation on iontophoretic transport of timolol was related to the inhibitory effect of this positively charged lipophilic drug on electroosmotic flux. The comparison of the effect of electroporation on iontophoretic transport of timolol and atenolol indicates that the efficiency of the combination of electroporation and iontophoresis depends on the physi-

cochemical properties of the drug, in particular its charge and its lipophilicity. However, further experiments using drugs with different physicochemical properties should be performed to consolidate our hypothesis.

CONCLUSION

Because of the differences between the mechanism of action of electroporation and iontophoresis, it was hypothesized that combination of these two driving forces was more effective and could produce a synergistic effect on drug transport. However, a lower transport of timolol was observed with the combination of electroporation and iontophoresis than with iontophoresis alone. The lowering effect of the combination was explained by an accumulation of positively charged timolol in the stratum corneum amplified by electroporation and a decrease of electroosmotic flux during iontophoresis. In contrast, the transdermal transport of hydrophilic β -blocker atenolol is increased by electroporation because the electroosmotic transport is not affected by the presence of

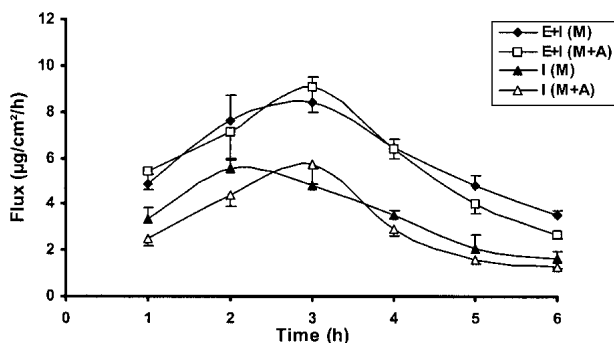


Fig. 4. Mannitol fluxes after iontophoresis (I) and combination of electroporation and iontophoresis (E+I) in the presence (M+A) and in the absence (M) of atenolol; experimental conditions used alone or in combination were E, 400 V \times 10 ms \times 10 pulses; and I, 3 h \times 0.25 mA/cm² (mean \pm SEM, n = 3). Donor phase composition: [¹⁴C]mannitol (0.5 μ Ci/ml) and mannitol (24 mg/ml) was introduced in a citrate buffer (4 g/L NaCl, pH 4.7) with or without atenolol (40 mg/ml).

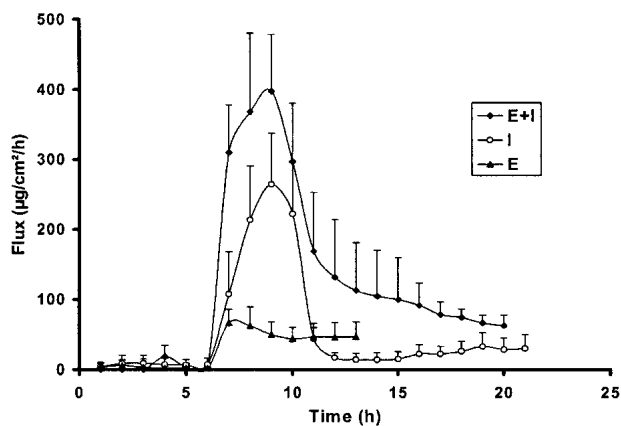


Fig. 5. Atenolol fluxes after electroporation (E), iontophoresis (I), and combination of electroporation and iontophoresis (E+I); experimental conditions used alone or in combination were E, 400 V \times 10 ms \times 10 pulses; and I, 3 h \times 0.25 mA/cm² (mean \pm SEM, n = 3). Atenolol, 40 mg/ml, was introduced in a citrate buffer (4 g/L NaCl, pH 4.7).

atenolol. Using two different β -blockers, we showed that the physicochemical properties of the drug affected the mechanism of drug transport by the combination of electroporation and iontophoresis. Both the lipophilicity and the positive charges are important parameters able to affect the electrotransport of the drug. Understanding the effect of the physicochemical properties of the drug, as well as the electrical parameters, is thus essential for the optimization of transdermal drug delivery by a combination of electroporation and iontophoresis.

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