Transdermal Permeation of Alniditan by Iontophoresis: In Vitro Optimization and Human Pharmacokinetic Data

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Purpose. The aim of this paper was to assess the feasibility of electrically enhanced transdermal delivery of alniditan, a novel 5 HT_{1D} agonist for the treatment of migraine.

Methods. An *in vitro* study was first performed to optimize the different parameters affecting iontophoresis efficiency. The mechanism of alniditan permeation by iontophoresis was investigated. Finally, a phase I clinical trial was performed to assess systemic delivery of alniditan by iontophoresis.

Results. i) *In vitro:* The optimal conditions were found with a buffer like ethanolamine at a pH of 9.5, with Ag/AgCl electrodes and a direct current application. Alniditan permeation was enhanced when increasing the current density, the duration of current application and the drug concentration. Iontophoresis slightly increased drug quantities in stratum corneum compared to passive diffusion but it strongly increased alniditan quantities in viable skin. ii) The objective to deliver *in vivo* 0.5 mg of alniditan within less than 1 h was reached but an erythema was detected at the anode.

Conclusions. This study demonstrates the feasibility of iontophoretic delivery system for antimigraine compounds.

KEY WORDS: transdermal drug delivery; alniditan; iontophoresis; migraine.

INTRODUCTION

Alniditan, a 5 HT_{1D} agonist is a novel chemical entity issue from Janssen Research for the treatment of migraine. Although widely used, oral treatment of an acute migraine attack may be unsatisfactory for several reasons. Patients with migraine often experience nausea and vomitting rendering the oral intake of drugs difficult. In addition, the gastric stasis which often occurs can hamper a good and reliable gastrointestinal absorption and reduce efficacy or slow down the effect onset of orally taken medicines. Self administration of a subcutaneous injection is often unacceptable from a patient point of view. Transdermal route of administration may be a good alternative to circumvent these problems. A classical transdermal administration would not be adequate because of the low permeability of the skin and the prolonged lag time resulting from the excellent barrier properties of the horny layer. Indeed, partition coefficient and solubility characteristics are the main physico-chemical properties determining the drug diffusion through the skin. Alniditan (two pKa: 8.3 and 11.5, mw: 302.42 and a partition coefficient (octanol/water at pH 8) of 1.59) (Fig 1) is ionized over a large pH range hindering its passive transdermal permeation.

Iontophoresis is a powerful technique to enhance percutaneous permeation of ionized drugs poorly absorbed by the skin (1,2). Application of an external electrical field provides an additional force which drives ions through the skin, modifies skin permeability and enhances solvent stream that can carry different species included neutral molecules (3).

The aim of the present paper was to assess the feasibility of electrically enhanced transdermal delivery of the antimigraine drug, alniditan. First, *in vitro* delivery was optimized by studying the influence of various electrical and physicochemical factors on its iontophoretic transport. Second, a phase I clinical trial was performed to assess systemic absorption of alniditan delivery by iontophoresis.

MATERIAL AND METHODS

Chemicals

Alniditan and [H^3] radio-labelled alniditan were supplied by Janssen (Beerse, Belgium). The [H^3]-water was purchased from NEN (Brussels, Belgium). The salts used to prepare the buffers (analysis grade) were obtained from UCB (RPL, Leuven, Belgium) for borate and citrate buffers and from Sigma Chemical Company (St Louis, MO) for ethanolamine buffer. All solutions were prepared in ultrapure water (Sation 9000, Sation, Barcelona, Spain). Glucose, NaOH and HCl (analytical grade) were obtained from Merck-Belgolabo (Overijse, Belgium).

Apparatus and Procedures for *In Vitro* Studies

A two chamber polycarbonate cell with stirring in the receptor compartment was used (4,5). Three cm^2 of abdominal skin freshly excised from 7–10 weeks old male hairless rats (Iffa Credo, St Germain-les-Arbresles, France) were inserted between the two compartments with the stratum corneum facing the donor. One cm^2 electrodes of platinum (Platinum pure, SA Johnson Matthey, Brussels, Belgium) or Ag/AgCl (Aldrich, Brussels, Belgium) were connected to a constant (direct) or pulsed (square wave, 2.5 KHz on/off 1/1) power source. Current density varied from 0 to 0.4 mA/cm^2 and was applied during various periods (from 0 to 1h30). Anode was introduced in the donor compartment whereas cathode was immersed in the receptor compartment (7.5 ml) filled with phosphate buffer 0.024 M isotonized with glucose. The upper reservoir was filled with 1.5 ml of the donor solution: alniditan (2.5, 5 or 7.5 mg/ml) and H^3-alniditan (1 μCi/ml) were introduced in citrate buffer at pH 5.5 or 7 (0.05 or 0.1 M), or in a borate buffer (0.05 or 0.1 M) at pH 9.5 or in an ethanolamine buffer (0.05M) at pH 9.5. Samples (0.4 ml) were withdrawn from the receptor compartment at regular intervals of times and replaced with an equal volume of drug-free buffer. Liquid scintillation cocktail (Ready Safe, Beckman) was added and counting was performed in a β-counter (Wallac 1410, LKB-Pharmacia). The ratio of the cumulative quantities detected in the receptor compartment

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to the membrane area was plotted as a function of time. The results are expressed as a mean ± SEM. Fluxes were calculated by: $\Delta Q/\Delta t$; with Q = cumulative quantities and Δt: interval of time between two measurements.

Stability of alniditan was checked by HPLC after a direct current iontophoresis with Ag/AgCl or Pt electrodes at a current density of 0.4 mA/cm^2 applied during 30 min, 1 h, 2 h or 6 h. Stability was also checked at different pH. No degradation was observed (data not shown). No tritium was released from radiolabelled alniditan after iontophoresis (data not shown).

To evaluate water transdermal permeation during and after iontophoresis, the donor compartment was filled with ethanolamine buffer (0.05 M; pH 9.5) containing alniditan (5 mg/ml) and tritiated water (1 μCi/ml). Direct current was applied for 1 h at a 0.4 mA/cm^2 current density with Ag/AgCl electrodes. Tritiated water cumulative quantities were measured during current application and for 5 h after current switching off. Fluxes were calculated by linear regression in the linear portion of the curves and compared to assess statistical differences using one-way analysis of variance and a Fisher t-test ($p < 0.05$). Skin integrity after 1 h iontophoresis (0.4 mA/cm^2) was studied *in vitro* by measuring tritiated water permeation after current switching off. During iontophoresis, the donor compartment was filled with an alniditan solution (5 mg/ml) in an ethanolamine buffer (0.05 M) at pH 9.5. After electrical current switching off, the donor solution was replaced with tritiated water (1 μCi/ml). Water diffusion was measured for 6 h and compared to water flux obtained with electrically untreated skin.

Quantification of alniditan in stratum corneum and viable skin was performed by stripping and tangential slicing technique described by Schaefer (6–8). Alniditan iontophoresis (7.5 mg/ml, 0.05 M ethanolamine buffer at pH 9.5) were performed at a 0.4 mA/cm^2 current density (Ag/AgCl electrodes) applied for 30 min, 1 h, or 1 h followed by 1 h passive diffusion. Iontophoresis were compared to passive diffusion performed during 1 or 2 h. Briefly, the skin was tape-stripped ten times. Each strip was counted for radioactivity (β-counter, Wallac 1410, LKB, Pharmacia). The remaining underlying skin tissue was flattened on a glass slide layed over dry ice. Four to five biopsies (0.5 × 0.5 cm) were taken. Ten slices (40 μm depth) were cut in a cryostat (2800 Frigocut, N Reichert-Jung) parallel to the skin surface. Corresponding slices from the different biopsies were combined and were counted for radioactivity.

In Vivo Study

The *in vivo* study investigated systemic absorption, topical reactions, overall tolerability and safety of alniditan after transdermal administration using iontophoresis on human volunteers. It was approved by Janssen Ethical Committee. The delivered dose was expected to be approximately 0.5 mg.

Eight healthy males and females (4/4) participated in this open trial. The age of the volunteers varied from 26.5 to 44.5 years, their weight between 59 and 86 kg and their height was included between 163 and 200 cm.

10 cm^2 hydrophilic polyurethane foam patches (Allevyn, Smith & Nephew, U.K.) were used. The anode foam patch was soaked with a solution containing 7.5 mg/ml of alniditan dissolved in an ethanolamine buffer pH 9.5 (0.05 M). The cathode foam patch was soaked in 0.9% NaCl. Ag/AgCl electrodes (2.5 cm × 2.5 cm) were inserted in the foam patches and connected to a direct current generator. Anode and cathode were applied on ventral side of the forearm of the volunteer. During two consecutive 30 min periods (separated by a 90 min interval), a direct current of 0.2 mA/cm^2 was applied. The patches were removed 90 minutes after the end of the second current application period.

Blood samples, blood pressure measurements and electrocardiogram recordings were performed at specific time points until 6 h thereafter. Venous blood samples (5 ml) were taken from an anticubital vein (opposite to administration site) immediately before and at 30 min (end of first application period), 60, 90, 120 (just before second current application period), 150 (end of second current application period), 180, 210, 240, 300 and 360 min after start of first current application period. Blood samples were collected in heparinized tubes. Plasma concentrations of the test compound were determined by a radio-immunoassay (detection limit 0.10 ng/ml). Samples for haematological, biochemical and urinary safety analysis were collected on a pre-trial day and at a follow-up visit.

Volunteers remained in the clinical pharmacology unit until 4 h after start of first current application period. Upon removal of the patch, the skin occluded by the system was evaluated for evidence of local reactions (erythema, extent of erythema, edema, papules or itching and burning sensations). To evaluate tolerability, the volunteers saw the investigator for a follow-up visit, which was scheduled between 1 and 7 days after drug administration. Evaluation of the overall tolerability was based on adverse events. Any adverse event that had occured during the trial period was noted by the investigator.

The plasma concentration-time profile of alniditan after subcutaneous administrations was simulated using the linear superposition principle. For this, historical data after single subcutaneous doses of 0.6 to 1.0 mg of alniditan to healthy subjects, normalized to a dose of 0.5 mg, were used.

RESULTS AND DISCUSSION

A) *In Vitro* Optimization of Alniditan Transdermal Permeation

In order to optimize transdermal iontophoretic transport of alniditan, the effect of different electrochemical and physicochemical factors was investigated. The influence of pH, ionic strength, electrodes and buffers, current profile, current density, duration of current application and drug concentration was studied *in vitro*.

pH

In order to investigate influence of pH on alniditan permeation kinetics, alniditan, was introduced in citrate buffer at pH 5.5 or 7 and in a borate buffer at pH 9.5. Iontophoresis was performed with Pt electrodes during 1 h at a current density of 0.4 mA/cm^2 and was compared to diffusion. Small pH variations were observed in the donor compartment (not more than 0.5) and no variation in the receptor compartment.

The cumulative quantity of alniditan detected in the receptor compartment was significantly higher for iontophoresis experiments than diffusion. A cumulative quantity of 2.04 ± 1.02 μg/cm^2 was detected after 6 h passive diffusion. After iontophoresis, the cumulative quantities measured at 6 h were

32.78 ± 5.36, 33.52 ± 5.63 and 138.01 ± 10.73 μg/cm² at pH 5.5, pH 7 and pH 9.5 respectively. After current switching off, instantaneous amounts of permeated drug (first derivative or fluxes) decreased with time. This is probably due to the short current application and to the relative hydrophilicity of alniditan.

A highest iontophoretic permeation was observed at pH 9.5, at which the drug has a single positive charge (Fig.1). Therefore, following experiments were performed with a buffer at pH 9.5. As shown by Nernst-Planck equation (9), drug permeation depends on ion charge. However, this relation is not as simple in the case of a complex membrane such as skin. Different factors could explain the highest iontophoretic permeation at pH 9.5: i. a higher skin permeability at higher pH; ii. a higher electroosmotic flow due to a modification of permselectivity; iii. ionic strength differences between the different donor solutions. A study of water permeation was performed (5 mg/ml alniditan, 1h iontophoresis 0.4 mA/cm² followed by 5 h passive diffusion, Pt electrodes) in order to compare the convective flow of water as function of the pH. The higher cumulative quantity of water observed at pH 9.5 (37.8 ± 3.96 μl/cm2, 21.77 ± 4.01 μl/cm² and 17.06 ± 2.39 μl/cm² at pH 9.5, 7 and 5.5 respectively) indicating a higher skin permeability at pH 9.5. Iontophoretic transport of cationic drugs was already shown more efficient at high pH (10). However, the higher cumulative quantities observed at 1 h (when the electric field is switched off) at pH 9.5 (3.78 ± 0.68 μl/cm², 1.99 ± 0.72 μl/cm² and 1.32 ± 0.31 μl/cm² at pH 9.5, 7 and 5.5 respectively) could indicate modifications in electroosmotic flow and hence, that changes in permselectivity occur. It could be hypothesized the double charged alniditan has a higher affinity for the negative charges of the skin which would in turn hinder the iontophoretic mobility of double charged ions compared to single charged ions (11). Difference in transport number could also account for the difference in drug fluxes. As pH of the donor solution decreases (as H^+ concentration increases), the transport number of alniditan ion through the skin is expected to decrease as a result of competition with H^+. In addition, supply of competitive ions differed according to the buffer used: higher quantities of H^+ and Na^+ were present in pH 5.5 and pH 7 buffers than in the pH 9.5 buffer. (12)

Current Profile

Under the influence of an electrical current, stratum corneum acts like a capacitance and an electrochemical polarization may occur in stratum corneum. This phenomenon prompted a number of authors to use a pulsed square wave current. Moreover, some authors reported that pulsed iontophoresis may be clinically less irritating to humans. It has been suggested that a pulsed current is more efficient in promoting transdermal delivery of large molecules even though a direct current is more potent for smaller molecules (4,5).

Transdermal permeation of alniditan was studied by using a direct current or a pulsed current (2.5 KHz, on/off 1/1) at the same mean density, i.e. the same total amount of current applied. Cumulative quantities were higher after direct current application than pulsed current (data not shown). Thus, following experiments were performed with a direct current.

Current Density and Duration of Current Application

In order to investigate influence of current density, alniditan (5 mg/ml) was introduced in a borate buffer (0.1 M) at pH 9.5. Iontophoresis was performed during 1 h with Pt electrodes at 0.2 and 0.4 mA/cm². An increase in the applied current density was associated with an increase in the quantity of alniditan permeating through the skin (fig. 2).

Iontophoresis was performed during 0 min, 30 min, 30 min on/2h30 off/30 min on/2h30 off or 1h, at a mean current density of 0.4 mA/cm² with Pt electrodes and a direct current (fig.2). An increase in duration of current application was associated with an increase in drug cumulative quantities. Moreover, it is remarkable to observe the equivalence of cumulative alniditan quantities when iontophoresis was applied during 1 h or 30 min twice. A doubling in the pulse current application duration increased cumulative quantities by a factor two (data not shown). An increase in cumulative quantities was also observed when current was applied for 0 min, 30 min, 1h, 1h30 with Ag/AgCl electrodes and with an ethanolamine buffer (data not shown).

Electrodes/Buffer/Ionic Strength

Two types of electrodes are widely used in iontophoretic systems: inert (nickel, stainless steel or platinum) and reversible (e.g., Ag/AgCl) (1). Inert electrodes have the main disadvantage to induce electrolysis of water resulting in the production of H^+ at the anode and OH^- at the cathode. The production of these ions may reduce the flux of similarly charged solute ions (competition) and requires the use of a buffer to avoid pH

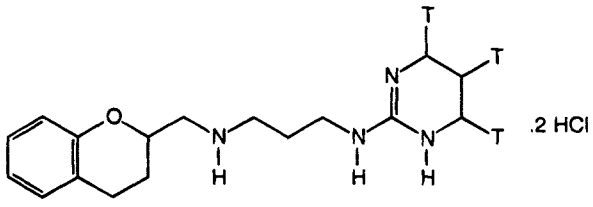

Fig. 1. Chemical structure of alniditan. T marks the position of tritium in the radiolabelled compound.

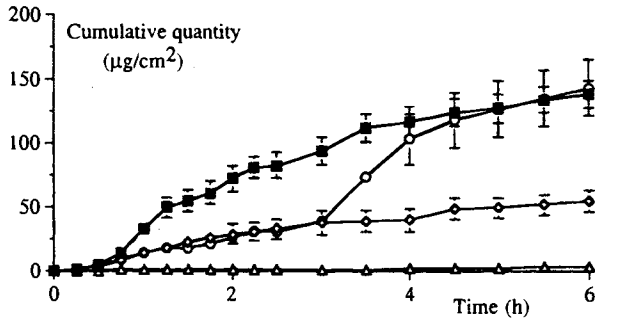

Fig. 2. Cumulative quantity (±SEM) of alniditan detected in the receptor compartment versus time after application of a direct current for 0 (open triangle), 30 min (open rhomb), 1 h (closed square) or 30 min on + 2h30 off + 30 min on + 2h30 off (open circle) (n = 5, 3, 7 and 3 respectively) at a mean density of 0.4 mA/cm² or 1 hour at a mean current density of 0.2 mA/cm² (open square; n = 3) with Pt electrodes. Alniditan (5 mg/ml) was introduced in a borate buffer (0.1 M) at pH 9.5.

changes. With Ag/AgCl electrodes, the redox-potential is lower than this of water and the electrode reacts itself. However, it is necessary to fix an initial pH and to provide at the anode a sufficient quantity of Cl^- easily obtained when the drug or the buffer is an hydrochloride salt (13). These chlorides precipitate with Ag^+ and prevent competition. Ag/AgCl electrodes can have two disadvantages: adsorption of the drug on the electrodes and release of chlorides at the cathode reducing the *in vitro* drug transport number by competition. Indeed, the drug transport number of an ion (t_i) represents the fraction of the total current carried by an ion (I_i) or in other words, the current efficiency for drug transport.

Under the minimal buffer concentration required, two types of electrodes (Pt and Ag/AgCl) and two buffers ($Na_2B_4O_7$/H_3BO_3 and ethanolamine/ethanolamine HCl) were compared.

Higher cumulative quantities were observed with Ag/AgCl electrodes and ethanolamine buffer as compared to Pt electrodes and borate buffer (fig. 3). This result may easily be explained by the current efficiency. If we calculate the current efficiency for the experiments shown in fig. 3, after 1 h iontophoresis, the current efficiency was about 0.6% and 1% with Pt and Ag/AgCl electrodes respectively (2). With inert electrodes (Pt), a 0.1 M buffer was necessary to maintain the pH instead of 0.05 M for reversible electrodes: additive competitive ions reduced the iontophoretic drug flux because they carried a fraction of the total current (12). With Ag/AgCl electrodes, ethanolamine/ethanolamine HCl buffer had two advantages: it avoided the presence of additive highly competitive ions like $Na_2B_4O_7$/H_3BO_3 buffer and provided chloride ions if needed (according to drug concentration and duration of current application).

Drug Concentration

Alniditan was introduced in the donor solution at a concentration of 2.5, 5 or 7.5 mg/ml in a borate buffer (0.1 M, pH 9.5). Iontophoresis was performed during 1 h at a mean current density of 0.4 mA/cm^2 with Pt electrodes. For Pt electrodes and Ag/AgCl electrodes (data not shown), the iontophoretic transport of alniditan was enhanced when its concentration increased. However, the increase did not seem to be proportional.

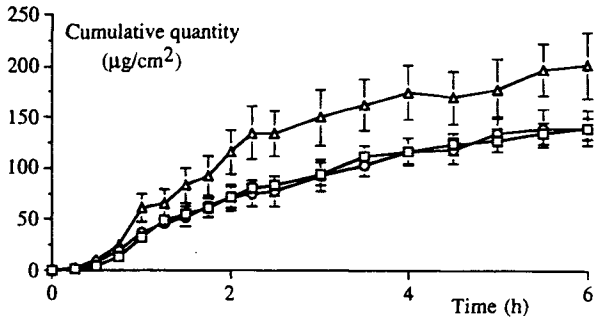

Fig. 3. Cumulative quantity (±SEM) of alniditan detected in the receptor compartment versus time after application of a direct current at a mean density of 0.4 mA/cm^2 with Pt or Ag/AgCl electrodes during 1 h. Alniditan (5 mg/ml) was introduced in a borate buffer (0.1 M) or in an ethanolamine buffer (0.05 M) at pH 9.5. With Ag/AgCl electrodes and borate buffer, a 0.007 M concentration of NaCl was added (open triangle: Ag/AgCl electrodes and ethanolamine buffer (n = 5); open circle: Ag/AgCl electrodes and borate buffer (n = 5); open square: Pt electrodes and borate buffer (n = 7)).

B) Mechanisms Involved in Alniditan Iontophoretic Transport

The enhancing effect of iontophoretic drug transport versus diffusion may be analysed by Nernst-Planck equation. However, other factors than diffusion and electrophoretic movement should be taken into account. Because skin is a negatively charged membrane, convective flow or electroosmosis through the skin may occur under current application. Moreover, iontophoresis may also increase skin permeability (3–5).

Tritiated water was introduced in the donor compartment at the beginning of current application or after current switching off in order to evaluate the contributions of electroosmosis and enhancement of skin permeability to water in alniditan iontophoretic delivery.

Tritiated Water Flux After Current Application

The donor solution containing alniditan (5mg/ml) in ethanolamine buffer (0.05M) at pH 9.5 was replaced with tritiated water after 1 h iontophoresis or diffusion. The passive permeation water flux observed on untreated skin (0.8 ± 0.2 μl/cm^2 per h) was significantly increased to 6.9 ± 0.5 μl/cm^2 per h after 1 h current application (mean current density of 0.4 mA/cm^2; Ag/AgCl electrodes).

This increase in transdermal water permeation is due to a skin permeability enhancement induced by current application.

As suggested from the shapes of the curves in figures 2 and 3, fluxes in alniditan decreased progressively with time, suggesting that increased permeability to alniditan is reversible.

Tritiated Water Permeation During and After Current Application

Iontophoresis was performed during 1 h at a mean direct current density of 0.4 mA/cm^2. The donor solution contained alniditan (5 mg/ml) in an ethanolamine buffer (0.05 M) at pH 9.5 and tritiated water. The water cumulative quantity measured after 1 h permeation through untreated skin (1.3 ± 0.2 μl/cm^2) was significantly increased by 1 h current application up to 4.0 ± 0.4 μl/cm^2 per h. This increase can be explained by a combination of electroosmosis and skin permeability enhancement.

C) Quantification of Alniditan Delivered by Iontophoresis in the Skin

The results of quantification of alniditan in stratum corneum and viable skin are shown in fig. 4. Immediately or 1 h after iontophoresis (performed during 30 min or 1 h at a current density of 0.4 mA/cm^2, Ag/AgCl electrodes, ethanolamine buffer pH 9.5, alniditan concentration: 7.5 mg/ml), the skin was directly tape stripped and frozen for further quantification. Iontophoresis were compared with 1 or 2 h passive diffusion.

In stratum corneum, iontophoresis induced a slight increase (as compared to diffusion) in alniditan quantity which remained unchanged even 1 h after current switching off. In viable skin, iontophoresis greatly increased the quantity of alniditan. The

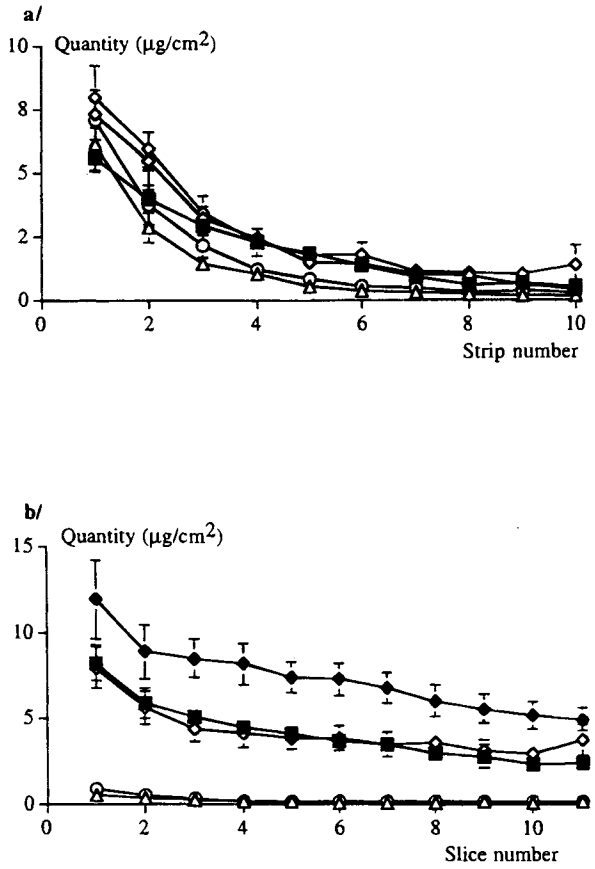

Fig. 4. Quantity of alniditan (±SEM) as function of stratum corneum strip (fig 4a) or epidermis and dermis depth (each slice is 40 μm depth) (fig 4b) after iontophoresis applied at a mean current density of 0.4 mA/cm^2 with Ag/AgCl electrodes during 30 min (close square), 1 h (close rhomb), 1 h followed by 1h diffusion (open rhomb), or after passive diffusion during 1 h (open triangle) and 2 h (open circle). Alniditan (7.5 mg/ml) was introduced in an ethanolamine buffer pH 9.5.

mean alniditan concentration found in viable skin increased from an order of magnitude up to 2 mg/cm^3.

Iontophoresis also altered somewhat the distribution of alniditan between the stratum corneum and the underlying tissue: of the radioactivity recovered in the skin following 1 h passive delivery, 88% was located in the tape-strips, 12% in the external viable tissues. The corresponding figures following 1 h iontophoresis were 23% and 77% respectively.

After current switching off, alniditan was progressively released and concentration gradient progressively decreased. The difference induced in drug quantity between iontophoresis and passive diffusion progressively decreased but was still present even 1.5 h after current switching off (and 30 min of current application). However, when electrical current is switched off, the permeation rate of drug may remain high until sufficient drug has desorbed from the skin and concentration gradient becomes equivalent to that of passive profile (14).

D) Human *In Vivo* Data

Phase one clinical trial was performed to evaluate whether 0.5 mg of alniditan could be delivered within a short lag time to reach the maximal plasma concentration. The optimum conditions found *in vitro* (Ag/AgCl electrodes, ethanolamine buffer pH 9.5) were used assuming that *in vitro* model would be predictive for *in vivo* studies: cumulative quantities of 50 to 100 μg/cm^2 detected *in vitro* would correspond, with a security factor due to the higher permeability of rat skin, to a delivery of 0.5 mg *in vivo* with a 10 cm^2 iontophoretic patch. The lag time was expected to be shorter *in vivo*. (15).

Tolerance

After patch withdrawal, there was no irritation at all at the cathode site. All subjects had erythema at the anode site persisting for approximately 48 h. There were no other topical reactions except for one subject who reported a prickling sensation at the application site and one subject who reported local irritation at the application site. The long lasting erythema could be due to the 9.5 pH ethanolamine buffer or to current application, or more likely to the drug itself by direct toxicity and/or vasoactive effect. This erythema could be a problem for future development of an iontophoretic delivery system of alniditan.

The adverse events reported were very mild and their nature (feeling of pressure in the head and neck) was very well in line with findings in previous trials with this compound. There were no clinically relevant changes in any of the investigated laboratory and cardiovascular safety parameters (data not shown).

Pharmacokinetic Data

The dose to be delivered was 0.5 mg. The mean plasma concentration profile after the iontophoretic administration is represented in fig 5. The plasma concentration, reached after the 30 min iontophoretic delivery, were equivalent to a stimulated subcutaneous administration of 0.5 mg repeated twice (fig 5).

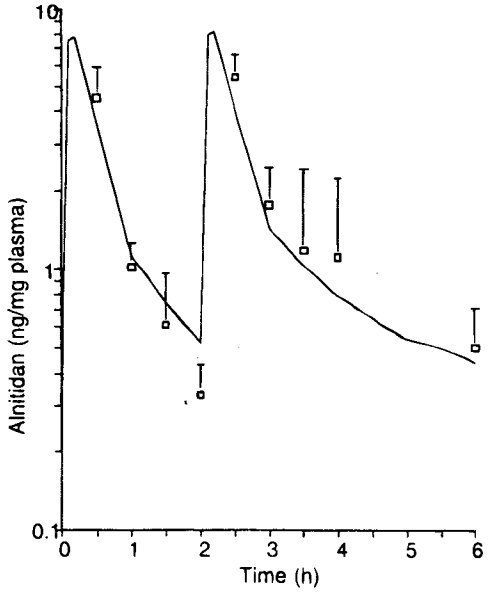

Fig. 5. Mean alniditan plama concentration and standard deviation (ng/ml) in healthy volunteers (n = 8) after iontophoretic delivery from 0 to 30 min and 120 to 150 min at 0.2 mA/cm^2 and simulation of a 0.5 mg subcutaneous injection at 0 and 120 min (open square) (see material and methods).

The mean plasma concentration measured at 30 min and 150 min were respectively 4.49 and 5.37 ng/ml. When the experiments were performed, they were thought to be within the therapeutic concentration which were estimated ranging between 5 and 20 ng/ml. Interestingly, the intra- and inter-individual variations in plasma concentration of alniditan were small, suggesting that iontophoresis allows to control alniditan transdermal delivery.

CONCLUSION

The *in vitro* study showed that alniditan transdermal permeation is greatly increased by application of electrical current. The efficiency of iontophoretic transport depended on electrochemical and physicochemical factors. The final objective of this study was to deliver by iontophoresis 0.5 mg of alniditan within less than 1 h. The *in vivo* trial indicated that the objective could be reached, eventhough an erythema was observed.

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