Chapter 4

TRANSDERMAL IONTOPHORESIS OF ROTIGOTINE:
INFLUENCE OF CONCENTRATION, TEMPERATURE
AND CURRENT DENSITY IN HUMAN SKIN IN VITRO

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ABSTRACT

Iontophoretic transport of rotigotine across human stratum corneum (HSC) was studied \textit{in vitro} in side by side diffusion cells according to the following protocol: 6 hours of passive diffusion, 9 hours of iontophoresis followed by 5 hours of passive diffusion. A current density of 0.5 mA cm\textsuperscript{-2} was applied. The parameters studied were the influence of the rotigotine concentration in donor phase and the influence of the molecular weight of the co-ions. To this end Na\textsuperscript{+} was replaced by tetra ethyl ammonium (TEA\textsuperscript{+}) or tetra butyl ammonium (TBA\textsuperscript{+}) (both at pH 5 and 6). In addition, the influence of the acceptor phase temperature (32 °C \textit{versus} room temperature), the replacement of HSC by dermatomed human skin (DHS), and the relation between drug transport and current density were examined.

The estimated steady-state flux (Flux\textsubscript{ss}) gradually increased with the drug concentration in the donor phase in a linear manner. The flux was also linearly correlated with the applied current density providing a convenient approach to individual dose titration. The use of TEA\textsuperscript{+} as co-ion increased the rotigotine iontophoretic flux significantly, while TBA\textsuperscript{+} did not. Replacing HSC by DHS reduced the iontophoretic rotigotine transport, while an increase in temperature to 32 °C increased the rotigotine flux. The maximum Flux\textsubscript{ss} achieved was around 80 nmol cm\textsuperscript{-2} h\textsuperscript{-1} indicating that by means of iontophoresis, a therapeutic level of rotigotine might be achieved with a reasonable patch size.
A. INTRODUCTION

Rotigotine (the molecular structure of which is plotted in Fig. 1), is a potent and selective D-2 dopaminergic receptor agonist. It has a very low oral bioavailability (approximately 0.5% in rats (1)), due to an extensive first pass effect (2-5). Therefore an alternative delivery route that circumvents the gut wall and the hepatic circulation, is required. One of the most attractive routes is via the skin, since transdermal delivery has the advantage of a constant input into the systemic circulation, which reduces the development of side effects, such as dyskinesia, motor fluctuations, and resting tremor resulting from fluctuating drug concentration versus time profiles (6). Currently, a transdermal patch of rotigotine is in development in which the drug is delivered by passive diffusion (7,8). So far, it has been demonstrated that with this formulation a reduction in levodopa dosing can be achieved (8). However the use of rotigotine as mono-therapy has not yet been established. To achieve this goal, a further increase in the transdermal flux is required, which might be achieved by iontophoresis. In addition to an enhanced continuous transport, the application of iontophoresis allows dose titration by changing the current density (9), which makes individualized dosing feasible.

![Rotigotine Molecular Structure](image)

Fig. 1. Structure and physical properties of rotigotine HCl: M.W. = 351.93, $pK_a$=7.9 (N-protonation) and 10.3 (phenol group), $\log P$= 4.03.

In our previous study (10), we have reported on the influence of pH and NaCl concentration to the rotigotine iontophoretic transport. To obtain more information on the mechanism of rotigotine iontophoretic transport, we decided to study the influence of the following parameters on the iontophoretic rotigotine transport: rotigotine donor concentration; replacement of Na$^+$ by higher molecular weight co-ions, namely tetra ethyl ammonium (TEA$^+$) and tetra butyl ammonium (TBA$^+$); and the temperature of the acceptor phase. In order to determine whether the flux can be adjusted by changing the current density, the relationship between current density and iontophoretic flux of
rotigotine has also been studied. Finally, we have compared rotigotine iontophoretic transport in dermatomed human skin (DHS) to human stratum corneum (HSC).

B. MATERIALS AND METHODS

1. Materials

Rotigotine (HCl salt) was kindly supplied by Schwarz Pharma (Monheim, Germany). Silver and silver chloride (purity > 99.99%) were obtained from Aldrich (Borneum, Belgium). Ascorbic acid, sodium meta bisulphite, tetra ethyl ammonium chloride (TEACl), tetra butyl ammonium chloride (TBACl), trypsin (Type III, from a bovine pancreas) and trypsin inhibitor (Type II-S from soybean) were purchased from Sigma Chemicals (Zwijndrecht, The Netherlands). Dialysis membrane disks (cut off value of 5000 Da) were purchased from Diachema (München, Germany). HPLC grade acetonitrile was obtained from Rathburn (Walkerburn, UK). All other chemicals and solvents were of analytical grade. All solutions were prepared in Millipore water with resistivity of more than 18 MΩ.

2. Preparation of Dermatomed Human Skin (DHS) and Human Stratum Corneum (HSC)

Within 24 hours after surgical removal of the human skin (abdominal or breast skin from female donor, age: 38 ± 9 years), residual subcutaneous fat was removed. To avoid interference with contaminating subcutaneous fat the skin surface was carefully wiped with a tissue paper soaked in successively 70% ethanol and Millipore water. DHS was obtained by dermatoming the skin to a thickness of about 300 μm using a Padgett Electro Dermatome Model B (Kansas City, USA). In order to obtain HSC, DHS was incubated with the dermal side on Whatman paper soaked in a solution of 0.1% trypsin in 0.15 M phosphate buffered saline (PBS) pH 7.4 (NaCl: 8 mg ml⁻¹, Na₂HPO₄: 2.86 mg ml⁻¹, KH₂PO₄: 0.2 mg ml⁻¹, KCl: 0.19 mg ml⁻¹) overnight at 4 °C and subsequently for 1 hour at 37 °C after which HSC was peeled off from the underlying epidermis and dermis. Remaining trypsin activity was blocked by bathing in a 0.1% trypsin inhibitor solution in PBS pH 7.4. HSC was subsequently washed several times in water and stored in a silica gel containing desiccator in a N₂ environment to inhibit oxidation of HSC lipids.

3. In vitro Iontophoretic Studies

A 9-channel computer controlled power supply was used to provide a constant current (Electronics Department, Gorlaeus Laboratories, Leiden University, The Netherlands). A silver plate electrode was used as an anode and a silver/silver chloride electrode as a cathode.
All iontophoretic transport experiments were carried out by using three-chamber continuous flow through diffusion cells as previously described (11). HSC was used for all transport studies, except for one series of experiments in which DHS was used. HSC and DHS (⌀=18 mm, the diffusion area is 0.64 cm²) were hydrated for two hours in PBS pH 7.4 prior to mounting in the cells. Two pieces of HSC or DHS were placed between the anodal and the acceptor side, and between the acceptor and the cathodal side, with the dermal sides of HSC or DHS facing the acceptor compartment. At least three skin specimens were used for each experimental condition examined. Dialysis membrane (cut-off: 5000 Da) was used as supporting membrane. Rotigotine solution was applied at the anodal side. Rotigotine donor formulation was buffered with 5 mM citric acid. The cathodal side was filled with PBS pH 7.4. The acceptor chamber was continuously perfused using a peristaltic pump with PBS pH 7.4 at a flow rate of 6.5 ml h⁻¹. To maintain osmolarity an appropriate amount of D-mannitol was added to the donor solution. Unless specifically mentioned the acceptor phase was maintained at room temperature. The current was switched on for 9 hours after 6 hours of passive diffusion. The iontophoresis was followed by 5 hours of passive diffusion. Unless specially mentioned the current density used was 0.5 mA cm⁻². Samples were collected every hour with an automatic fraction collector (ISCO Retriever IV, Beun De Ronde BV, Abcoude, The Netherlands). During the experiments both the anodal and the cathodal compartment were magnetically stirred at 375 rpm. The composition of donor solutions for individual studies is outlined below.

a. The influence of rotigotine concentration
Rotigotine concentration of the donor solution was 0.5, 1 or 1.4 mg ml⁻¹. For the donor phase a pH of 5 was chosen. All studies were performed in the presence of 0.07 M NaCl.

b. The influence of different co-ions
0.07M NaCl was replaced by an equimolar amount of either TEACl or TBACl. All studies were carried out at pH 5 or 6 with a rotigotine concentration of 1.4 mg ml⁻¹.

c. The influence of acceptor phase temperature
Temperature of the acceptor phase was maintained either at room temperature or at 32 °C, the approximate temperature of HSC in vivo. The donor solution contained 1.4 mg ml⁻¹ rotigotine at pH 5 and 0.07 M NaCl.

d. The influence of using DHS compared to HSC
The iontophoretic rotigotine transport was examined across DHS. The donor solution contained 1.4 mg ml⁻¹ rotigotine at pH 5 and 0.07 M NaCl. The acceptor phase was maintained at a temperature of 32 °C.
e. The influence of current density
The current density applied was 0.125, 0.25 or 0.5 mA cm⁻². The donor solution contained 1.4 mg ml⁻¹ rotigotine at pH 5 and 0.07 M NaCl. The acceptor phase was maintained at a temperature of 32 °C.

4. Analytical Method
Collected samples during iontophoresis were injected directly into the HPLC system and analyzed by using a fluorescence detector (Jasco 821-FP, Gynkotek Separations, H.I. Ámbacht, The Netherlands) at excitation and emission wavelengths of 270 and 305 nm, respectively. The attenuation and gain were set at 1 and 10 respectively. A Superspher® 60, RP-select B, 75 mm-4 mm column (Merck KGaA, Darmstadt, Germany) was used. The mobile phase consisted of acetonitrile/0.1 M acetate buffer at pH 3.6 (40/60) v/v with a flow rate of 0.7 ml minute⁻¹. The calibration curves were linear (r>0.999) in the concentration range of 0.02 to 1.2 µg ml⁻¹. The intra and inter-assay variation were less than 5% for all concentrations tested. The detection limit under these conditions was 12 ng ml⁻¹.

5. Data Analysis
The flux and the cumulative amount of the iontophoretic transport of rotigotine were plotted as a function of time. From the latter plot, the estimated steady-state flux (Flux.ss) was calculated based on the permeation lag time method (12,13). The term estimated is given, as for most conditions, the real steady-state situation was not clearly observed during 9 hours of iontophoresis. For this reason the Flux.ss was calculated from the slope of linear portion of the plot between 5 and 9 hours of iontophoresis (r>0.999). All results were expressed as mean values ± standard deviations. Statistical analysis was performed by using one-way ANOVA followed by Newman-Keuls multiple comparison test. When a statistical analysis was performed for only 2 groups, a Student’s t-test was used. For all statistical analysis, the probability value of less than 0.05 was considered to be significant.

C. RESULTS

1. Effect of Rotigotine Concentration
The effect of concentration on rotigotine Flux.ss is presented in Fig. 2. It shows that by increasing of rotigotine concentration from 0.5, 1 and 1.4 mg ml⁻¹, the flux linearly increases (R²=0.87) from 22.7 ± 5.5 to 30.2 ± 3.5 and 53.2 ± 5.0 nmol cm⁻² h⁻¹, respectively.

2. Effect of Different Co-ions
Replacing Na⁺ by the larger co-ion TEA⁺ resulted in an increase of the rotigotine flux both at pH 5 and 6 (p<0.05). A further increase in molecular
weight of the co-ion by replacing Na\(^+\) by TBA\(^+\) did not result in a further increase in flux. In contrast, as shown in the flux \textit{versus} time profile in Fig. 3A and 3B, both at pH 5 and 6, the iontophoretic flux of rotigotine with TBA\(^+\) was even less than with TEA\(^+\). At both pH values, the values of rotigotine Flux\(_{ss}\) with TBA\(^+\) were not significantly different from the value with Na\(^+\) (p>0.05). Both for TEA\(^+\) and TBA\(^+\), the values of Flux\(_{ss}\) in pH 5 and 6 were similar (p>0.05). All the Flux\(_{ss}\) values are summarized in Table I.

**Fig. 2.** The correlation of Flux\(_{ss}\) \textit{versus} drug donor concentration during rotigotine iontophoresis at pH 5 in the presence of 0.07 M of NaCl. Data are presented as mean ± SD (n=6).

**Fig. 3.** The iontophoretic flux \textit{versus} time profiles of 1.4 mg ml\(^{-1}\) rotigotine in the pH 5 (A) and 6 (B) systems in the presence of 0.07 M of NaCl (open circle), TEACl (open square) and TBACl (close triangle). The current was switched on and off at 6 hours and 15 hours respectively. The error bar is the standard deviation of the mean (room temperature, n= 6).
Not only the flux, but also the shape of the curve is affected by changing the co-ions. As can be inferred from Fig. 3, after switching off the current, in the presence of Na\(^+\) co-ion, a slow decay in the rotigotine flux is observed both at pH 5 and 6. Interestingly, this decay is much faster when Na\(^+\) is replaced by either TEA\(^+\) or TBA\(^+\).

**Table I.** Iontophoretic rotigotine Flux\(_{ss}\) by the different in drug donor concentrations, acceptor phase temperature, skin membrane and current density.

<table>
<thead>
<tr>
<th>Conditions</th>
<th>Rotigotine Flux(_{ss}) (nmol cm(^{-2}) h(^{-1}))</th>
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<td>RTG conc. (mg ml(^{-1}))</td>
<td>Current density (mA cm(^{-2}))</td>
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<td>1.4</td>
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**Fig. 4.** The iontophoretic flux versus time profiles of 1.4 mg ml\(^{-1}\) rotigotine in the pH 5 system in the presence of 0.07 M of NaCl across HSC at room temperature (open square), across HSC at 32 \(^0\)C (open triangle) and across DHS at 32 \(^0\)C (close circle). The current was switched on and off at 6 hours and 15 hours respectively. The error bar is the standard deviation of mean (n= 6)
3. Effect of acceptor phase temperature

An increase in temperature of the acceptor phase from room temperature (20 °C) to 32 °C resulted in a significant increase in rotigotine iontophoretic transport. Flux_{ss} significantly increased from 53.2 ± 5.0 at room temperature to 80.2 ± 14.4 nmol cm\(^{-2}\) h\(^{-1}\) at 32 °C (p=0.0015). An increase in the acceptor phase temperature also results in a much faster decay of the flux during the post iontophoresis period. Likewise, after switching on the current, the flux increase was faster with an acceptor phase at 32 °C than at room temperature.

4. Effect of using DHS in comparison to HSC

As shown from the flux time profile (Fig. 4), the replacement of HSC by DHS changed the flux profile. The gradual increase in flux after switching on the current is much slower in DHS in contrast to HSC. Furthermore, the Flux_{ss} is significantly reduced from 80.2 ± 14.4 in HSC to 38.3 ± 4.1 nmol cm\(^{-2}\) h\(^{-1}\) in DHS (p<0.0001).

5. Effect of Using Different Current Density

The Flux_{ss} values were significantly different with the difference in current density (p<0.0001) and a linear correlation between current density and the rotigotine Flux_{ss} was observed with a correlation coefficient R\(^2\)=0.99 (see Fig. 5). All the Flux_{ss} values are summarized in Table I.

D. DISCUSSION

As previously reported, the value of the iontophoretic flux is determined by 4 contributing factors, namely electro-repulsion, electro-osmosis, convective flow and passive diffusion. All contributing factors are dependent on the concentration in the donor solution and for most drugs, a higher donor concentration results in a higher iontophoretic flux. However, for several drugs, especially compounds with high lipophilicity or molecular size, the opposite has been observed, namely that above a certain threshold an increase in concentration does not longer result in an increase and sometimes even a reduction in the iontophoretic transport. Propranolol (14), nafarelin (15), and leuprolide (16) are examples of drugs for which this type of cut-off phenomenon has been reported. Recently, ropinirole, another dopamine receptor agonist was also reported to have a reduced iontophoretic flux at a high drug concentration (17) resulting from a reduction in the contribution of electro-osmosis by neutralization of the negative charge of the stratum corneum.

In our previous study, we showed that the presence of rotigotine significantly reduces the electro-osmosis. This might be related to the lipophilic nature of rotigotine (log P=4.03), which facilitates the binding to the stratum corneum (10). Interestingly however, the data in Fig. 2 strongly suggest that the iontophoretic transport of rotigotine is proportionally increased by the increase
in drug concentration in the anodal compartment. This can be explained by the limited contribution of electro-osmosis to the total iontophoretic transport of rotigotine as we observed in the previous investigation to be smaller than 17% (10). Therefore, as the passive diffusion is negligible, electro-repulsion appears to be the main mechanism involved in the iontophoretic transport of rotigotine.

![Graph](image)

**Fig. 5.** The linear correlation between Flux\textsubscript{ss} versus current density on iontophoresis of 1.4 mg ml\textsuperscript{-1} rotigotine at pH 5 by the presence of 0.07 M of NaCl at 32 °C. The error bar is the standard deviation of mean (n= 5 - 6)

The use of TEA\textsuperscript{+} as co-ion increases the Flux\textsubscript{ss} of rotigotine compared to Na\textsuperscript{+}. This is presumably related to the smaller mobility of the two co-ions due to the larger molecular size and weight in comparison to Na\textsuperscript{+}. A smaller mobility will result in a reduced competition with rotigotine for charge transfer. This results in an increased iontophoretic transport. Interestingly, the replacement of Na\textsuperscript{+} by TEA\textsuperscript{+} in the donor solution resulted in a higher transport than replacement by TBA\textsuperscript{+}, although the TBA\textsuperscript{+} molecular size is larger than TEA\textsuperscript{+}. A similar situation has been encountered previously with iontophoretic transport of R-apomorphine (18). The reason behind this phenomenon is not clear. It might be that due to a higher lipophilicity of TBA\textsuperscript{+} relative to TEA\textsuperscript{+}, TBA\textsuperscript{+} partitions and binds more strongly in the stratum corneum, which might increase the possibility of ion competition to the rotigotine ion.

Another interesting phenomenon is that both TEA\textsuperscript{+} and TBA\textsuperscript{+} increase the decay in the rotigotine flux after switching off the current. In our previous study we have also observed this when the PBS pH 7.4 in the acceptor phase was replaced by PBS pH 6.2. We indicated that this is related to the increase in partitioning of rotigotine into the acceptor phase due to an increase in the solubility at pH 6.2 (10). From the results of the present study it can be concluded that the presence of TEA\textsuperscript{+} and TBA\textsuperscript{+} has also a positive influence on the partitioning of the drug from the stratum corneum into the acceptor phase.
This might be related to the structures of TEA$^+$ and TBA$^+$ as quaternary amines. Several quaternary amines are well known for having a surfactant action (19). Further studies are required to fully understand this phenomenon.

According to the Nernst-Planck equation, the electro-repulsion flux is directly proportional to the reciprocal of the absolute temperature according to the equation below (9):

\[
J_{\text{electro-repulsion}} = \frac{D z F C E}{kT}
\]

in which: $J_{\text{electro-repulsion}}$ is the electro-repulsion flux, $D$ is the diffusivity coefficient, $z$ is the ionic valence, $C$ is the molar concentration, $k$ is the Boltzman’s constant, $T$ is the absolute temperature, and $E$ is the electric field. Accordingly, if all other factors in equation 1 remain constant, increase in temperature from 20 °C to 32 °C will result in an approximately 4% reduction of the electro-repulsive flux. In contrast however, the iontophoretic flux was found to increase with increase in acceptor phase temperature. Thus, another factor in equation 1, most probably the ion diffusivity $D$, must increase to counteract the effect of the reduction in the reciprocal of $T$. The diffusivity of ions presumably increases in relation to the increase in the permeability of HSC due to the orthorhombic-hexagonal lipid phase transition between 30 °C and 35 °C in hydrated stratum corneum, which makes the lipid organization less dense (20). This might be particularly in favor for the iontophoretic transport of the larger ions. Moreover, the increase in temperature might also facilitate the rotigotine partition into the acceptor phase. This is indicated by the observed steeper increase of the flux when the current was switched on as well as the faster decay in flux during the post iontophoresis period (Fig. 4).

When DHS was used instead of HSC, the iontophoretic profile in time changed dramatically. At least three factors can play a role in this situation. Firstly, the increase in thickness of the membrane from approximately 40 μm in a fully hydrated HSC (21) to approximately 300 μm in DHS may reduce the permeation of ions thereby reducing the iontophoretic transport of rotigotine. Secondly, the absence of a vascular skin clearance in the dermis impairs rotigotine partition into the acceptor phase. Thirdly, as the tissue body fluid is at a pH of around 7.4, due to the pKa of rotigotine at 7.9 (10), a significant (approximately 24%) fraction of drug molecules is neutral, reducing the iontophoretic transport and the rate of rotigotine partition into the acceptor phase. As a result of these three factors, the viable part of the skin acts as a depot for rotigotine resulting in a slow increase in flux during iontophoresis and also a slow decay in flux during the post iontophoresis phase. As has been shown for R-apomorphine (22), the absence of the vascular clearance plays a prominent role in the iontophoretic profile. Specifically after switching on the current in the in vivo situation, the iontophoretic flux response is more similar to that in HSC than that in DHS.
As commonly reported (17,23), the flux was linearly correlated with the applied current density. According to Phipps and Gyory (24) the flux of the drug ion depends in a linear fashion on the applied current density and the drug transport number according to the equation:

\[ J_d = \frac{I_d \cdot I}{F \cdot Z_d} \]  

(2)

Where \( J_d \), \( I_d \) and \( Z_d \) are the flux, the transport number and the valence of rotigotine cation, \( I \) is the current density and \( F \) is the Faraday constant. By using the equation above the transport number of rotigotine during iontophoresis can be estimated from the slope in Fig. 5. The transport number was 0.4% indicating that only a small fraction of the total current was carried by rotigotine.

The linearity between current density and flux is an important feature for the iontophoretic delivery of rotigotine, given the widely variation in the dose requirements of individual patients with Parkinson’s disease. As already discussed above the dose requirement differs depending on the individual patient, on the phase of therapy, and on the disease progression. When using a transdermal iontophoretic system, dose titration can easily be managed by changing the current density, which is a very important advantage in the delivery of dopamine receptor agonists.

The maximum \( \text{Flux}_{ss} \) achieved in this study was approximately 80 nmol cm\(^{-2}\) h\(^{-1}\). This was achieved at a donor concentration of 1.4 mg ml\(^{-1}\) in the anodal compartment at pH 5 and the acceptor fluid at 32 °C. According to Calabrese et al. (6), the dose required to maintain the therapeutic level of rotigotine varied between 0.5 – 5.6 \( \mu \)g kg\(^{-1}\) body weight per hour. Therefore, a patient with 70 kg body weight needs between 35 – 392 \( \mu \)g of rotigotine per hour as maintenance dose. If we assume that the value of the \( \text{Flux}_{ss} \) in vitro could be achieved in the in vivo situation, we estimate a transport rate of 28 \( \mu \)g per hour per cm\(^2\) of iontophoretic patch. Thus, by using an iontophoretic patch with a size of 10 – 15 cm\(^2\), which seems to be quite feasible to be developed clinically, a therapeutic concentration might be achieved.

In summary, the iontophoretic flux was proportionally increased with rotigotine concentration in the anodal compartment. The flux was also linearly correlated with the current density applied providing a convenient manner to program the individual dose titration. Replacement of Na\(^+\) by TEA\(^+\) increased the rotigotine flux due to a decreased competition for charge transfer. The presence of TEA\(^+\) and TBA\(^+\) in the donor phase resulted also in a faster flux decay during the post iontophoretic period probably due to a weak surfactant action of those co-ions. The use the DHS instead of HSC reduced the rotigotine iontophoretic transport and resulted in a slower increase in flux during iontophoresis and also in a slower decay in flux during post iontophoresis period. This might be due to the thickness of the membrane and the possibility of more drug deposition presence in the epidermal and dermal part. Finally,
iontophoretic delivery is a quite feasible and promising delivery tool for rotigotine as the therapeutic level might be achieved by using a 10 – 15 cm$^2$ of patch.

E. ABBREVIATIONS

HSC : Human stratum corneum  
DHS : Dermatomed human skin  
Flux$_{ss}$ : Estimated steady-state flux

F. ACKNOWLEDGMENTS

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G. REFERENCES
