Iontophoretic Delivery of Apomorphine II: An In Vivo Study in Patients with Parkinson’s Disease

Ronald van der Geest,1,2,4 Teus van Laar,3 Josy M. Gubbens-Stibbe,2 Harry E. Bodde,1 and Meindert Danhof2,5

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Purpose. Transdermal transport rates of the dopamine agonist R-apomorphine were determined in patients with idiopathic Parkinson’s disease (IPD). Apomorphine was applied by iontophoresis at two current densities.

Methods. In ten patients apomorphine was applied passively for one hour. Thereafter, in the first five patients, a current density of 250 μA.cm−2 was applied for one hour and a current density of 375 μA.cm−2 in the second group. The individual pharmacokinetic parameters were obtained separately following a 15-minute zero-order intravenous infusion of 30 μg.kg−1. Skin resistance was measured during current delivery. Current-induced irritation was measured by Laser Doppler Flowmetry (LDF). The pharmacodynamics were quantified by a unilateral tapping score. Qualitative clinical improvements (decreased tremor, rigidity or cramp) were also recorded.

Results. In all patients increasing plasma concentrations of R-apomorphine were found during the interval of current application. The maximum concentrations that were attained were related to the applied current density: 1.3 ± 0.6 ng.ml−1 at 250 μA.cm−2 and 2.5 ± 0.7 ng.ml−1 at 375 μA.cm−2. When the current was switched off all concentrations returned to baseline values in about 90 minutes. By mathematical deconvolution of the profiles it was shown that steady-state fluxes were reached within the one-hour interval of current driven transport. Steady-state fluxes were calculated to be 69 ± 30 nmol.cm−2.h−1 at 250 μA.cm−2 and 114 ± 34 nmol.cm−2.h−1 at 375 μA.cm−2. Individual drug input rates were inversely related to the overall resistance. Significantly elevated LDF values were found after patch removal, indicating mild current induced erythema. Only subtherapeutic plasma concentrations were obtained in all patients except for one.

Conclusions. The results show that current-dependent delivery of apomorphine is possible in vivo at acceptable levels of skin irritation. Excellent correlation was found between the calculated in vivo transport rates and the rates that were previously obtained in vitro.

Key Words: iontophoresis; Parkinson’s disease; human; pharmacodynamics; transdermal delivery; apomorphine.

INTRODUCTION

Dopamine agonists were developed in the early seventies for the treatment of Parkinson’s disease. Disease progression results in so-called “on-off” phenomena in over 50 percent of the patients over a period of ten years. These phenomena can not be treated effectively with oral dosing of levodopa (1). Apomorphine is currently the most effective dopamine agonist with a potency comparable to levodopa (2,3). Additionally, it has shown improvement in the treatment of on-off effects (4). However, systemic side effects such as nausea, vomiting and dizziness occur frequently.

Delivery of apomorphine is not without difficulty and different problems occur when the drug is dosed via different routes. These problems are mainly due to instability and—possibly as a result of this—local toxicity. Cotzias et al. showed that oral absorption is minimal and that the first-pass effect is high (5). At very high doses beneficial effects occur but long-term administration via this route is not possible due to drug-induced nephrotoxicity. The development of alternate routes of administration has resulted in a significant improvement of therapy, but the serious problems associated with long-term dosing have prevented its widespread acceptance.

Subcutaneous administration is currently the method of first choice but invariably results in the appearance of subcutaneous nodules. Responses comparable to subcutaneous administration were observed for sublingual, rectal and nasal administration. However, for sublingual administration, systemic side effects occurred more frequently and inconsistency of dissolution and unpleasant taste were noted (6). Furthermore, in a follow-up study 50 percent of the patients developed stomatitis (7). No local toxicity was observed following rectal administration (8). However, the limited acceptability of this route will probably limit its chronic use. A reduction of systemic side effects was observed for nasal administration (9). Prolonged use resulted in moderate to severe nasal irritation in all patients (10).

As described earlier, accurate control of the input rate of apomorphine will result in maximal benefit to the patient and minimal systemic side effects (11). In studies on the iontophoretic delivery of fentanyl in humans it has been shown that current-dependent delivery can be achieved with this technique (12). However, as for the other alternate routes, local toxicity may limit its success. Therefore, the applicability of this technique for the controlled delivery of apomorphine in patients with Parkinson’s disease will equally depend on the control of dosing and on local drug-induced toxicity. Therefore these two aspects should be studied concurrently.

The aim of this study was to explore the feasibility of in vivo iontophoretic apomorphine application for the treatment of patients with Parkinson’s disease. Constant apomorphine concentrations were applied at two current densities to investigate if transport rate can be controlled and manipulated by the externally applied current. Furthermore, the occurrence of possible side effects on the skin as a result of this application was determined.

MATERIALS AND METHODS

Patients

Ten patients with idiopathic Parkinson’s disease (IPD) were included (6 men and 4 women) with a mean age of 55 ± 5 (range 46–64) years. The mean weight was 73 ± 11 (range 52–91) kg and all patients were internally and neurologically...
stable. All patients gave informed consent. The protocol of the study was approved by the Medical Ethical Committee of the University Hospital of Leiden.

**Materials**

R-apolomorphine was obtained from OPG B.V. (Utrecht, Holland), N-propylnorapomorphine was obtained from Research Biochemicals International (RBI), (Natick, USA). Tetra-c-tymnammoniumbromide (TOABr) and diphenylborinic acid ethanolamine ester (DPBBA) were obtained from Aldrich (Bornem, Belgium). Sterile aqueous apomorphine formulations were prepared at the Department of Clinical Pharmacy and Toxicology of the University Hospital of Leiden. The formulations contained 15 mM apomorphine, 140 mM NaCl, 0.1 % sodium meta bisulfite and 5 mM citrate buffer pH 5. This formulation was derived from previously performed in vitro transport experiments, in which human stratum corneum and Ag/AgCl electrodes were used (11). In the patient study, open chamber Trans-Q® patches, containing Ag/AgCl electrodes, with a skin exposed surface area of 20 cm², were kindly provided by Iomed Inc. (Utah, USA). The anodal compartment was filled with 3 ml of the formulation. The cathodal compartment was filled with 0.9% sterile saline (NPBI, Emmen-Colpasum, The Netherlands). A (pulsed-) constant current carry-on power supply ($V_{max}= 27$ Volts, $I = 0$–$10$ mA) was manufactured by the electronics department of the Gorlaeus Laboratories (Leiden, The Netherlands).

**Iontophoretic Application and Pharmacokinetics**

Each patient received R-apomorphine intravenously (30 µg.kg⁻¹) and by transdermal iontophoresis according to a randomized cross-over design. The wash-out period between each treatment was at least one week. All dopaminergic medication was stopped at 24:00 hours, the night before the study day. Thirty mg t.i.d. domperidone, a peripheral dopamine antagonist, was administered starting two days before each session and was stopped at the end of each treatment.

For the iontophoretic treatment, application at two current densities was tested. For safety reasons the first five patients were treated with the lowest current density. The anodal compartment was filled with 3 ml of the apomorphine solution. The two patches (anode and cathode) were applied and on the volar side of the forearm. An i.v. catheter was inserted in the opposite arm for blood sampling and the infusion of saline. Blood samples were obtained at 0, 20, 40, 60, 70, 80, 90, 100, 110, 120, 125, 130, 135, 140, 150, 155, 185, 210, 240, 275, and 315 minutes. Patches were applied at $t = 0$. Electrical current was applied during one hour starting at $t = 60$ min. Resistances were measured at $t = 65$, 90 and 115 minutes. Resistance data were corrected for the voltage drop across the electrode-electrolyte interface. This voltage drop was 1.2 Volts. Local skin erythema was assessed visually and quantified by laser Doppler flowmetry (LDF) (Diodopp, Appli.Laser Technology, The Netherlands), before and after current application ($t = 0$, 245 and 317 minutes).

The pharmacokinetic parameters of apomorphine were determined under intravenous infusion. The patient was given a zero-order intravenous infusion of 30 µg.kg⁻¹ for 15 minutes through a permanent catheter in the forearm vein of one arm. A second i.v. catheter was inserted in the opposite arm. The other i.v. catheter was again used for blood sampling and infusion of saline. 5 ml blood samples were obtained at 0, 3, 7, 11, 15, 19, 23, 27, 31, 35, 40, 45, 50, 60, 70, 85, 105, 130, 160, 200, 225 and 260 minutes.

All blood samples were collected in tubes containing 5 mg of sodium metabisulphite and 15 mg of EDTA and were placed in ice immediately. Plasma was obtained from the blood samples by centrifugation. At the end of the session all plasma samples were stored at $-70$°C.

**Pharmacodynamics**

A unilateral tapscore was performed by pressing, as quickly as possible and with one hand, two buttons that are 30 cm apart. The number of taps during 30 seconds, using the arm that was most affected by the disease, was used as effect parameter (13). The tapscore was assessed at $t = 0$, 5, 9, 17, 25, 33, 42, 52, 72, 90, 132, 180, 227 and 262 minutes for the i.v. infusion and at $t = 0$, 22, 42, 72, 82, 92, 112, 132, 152, 187, 232, 277 and 317 minutes for the iontophoretic application. An increase of at least 25% compared to the tapscore at $t = 0$ was defined as a positive clinical response. Clinical improvement (decreased tremor, rigidity or cramp) was recorded using standard rating scales (14). The blood pressure was monitored and adverse effects (nausea, dizziness) were also recorded.

**Drug Analysis**

An enantio-selective assay according to Van der Geest et al. (15) was used for the quantification of R-apomorphine in plasma. Briefly, the method was as follows: 30 µl of internal standard N-propylnorapomorphine (2 mg/ml) was added to 1 ml of plasma sample. The samples were extracted with 0.5 ml DPBBA buffer and 1.5 ml TOABr. The pH of the buffer was 8.45 for plasma analysis and 9 for urine analysis. After 2 min of shaking and 15 min of centrifugation at 5°C, the organic phase was taken off and 3 ml of octanol and 0.5 ml of aqueous phase (0.05 M H3PO4, 0.1 % sodium-metabisulphite and 0.01 % EDTA) were added. After 2 min of shaking and 15 min of centrifugation at 5°C, 50 µl sample was injected into the HPLC system.

The HPLC system consisted of a Spectroflow 400 solvent delivery system (Applied Biosystems, Ramsey, NJ, USA), a WISP™-710 B autosampler (Millipore-Waters, Milford, MA, USA) and an Antec Electrochemical Detector (Antec, Leiden, The Netherlands). The chromatograms were recorded by a Chromatopack C-R3A reporting integrator (Shimadzu, Kyoto, Japan). For the separation of R-apomorphine a 10-µm Chiralcel OD-R chiral column (200 mm × 4.6 mm I.D.) (Diacel Chemical Industries, LTD. Tokyo, Japan) was used. Acetonitrile/buffer (35/65) was used as a mobile phase at a flow rate of 0.9 ml.min⁻¹. The buffer consisted of 0.1 M NaH2PO4, 0.1 M NaClO3, H2O, 10 mg/l EDTA, pH 4. The voltage of the detector was 0.7 V. The calibration curves for both enantiomers were linear ($r > 0.995$) and the intra- and inter-assay variations were <5% for all concentrations tested (2.5, 12.6 & 25.1 ng.ml⁻¹), (n=5). The detection limit was 0.2 ng.ml⁻¹ for R-apomorphine and 0.6 ng.ml⁻¹ for S-apomorphine at a signal to noise ratio of 3.