(A)DME of the Dopamine Agonist Rotigotine in Man — Administration by Intravenous Infusion or Transdermal Delivery

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Abbreviations: ADME, absorption, disposition, metabolic fate and elimination; A_{ef}, amount excreted into feces; A_{ur}, amount excreted into urine; AUC, area under the plasma concentration-time curve; CL_{f}, fecal clearance; CL_{ren}, renal clearance; C_{max}, maximum plasma concentration; E_{f,max}, maximum fecal excretion rate; E_{r,max}, maximum renal excretion rate; HPLC, high performance liquid chromatography; LC-MS/MS, liquid chromatography with tandem mass spectrometry; LC-RAD-MS, liquid chromatography-radiochemical detection-mass spectrometry; LOQ, lower limit of quantification; PD, Parkinson’s disease; t_{1/2}, terminal phase half-life; T_{max}, time to reach maximum plasma concentration; λ_{z}, terminal rate constant
Abstract

The dopamine agonist rotigotine was developed for the treatment of Parkinson's disease and restless legs syndrome. Disposition, metabolism, elimination, and absolute bioavailability of rotigotine were determined in six healthy male subjects using two different administration forms in a randomized sequence with a cross-over design. Treatment A (continuous infusion) consisted of a single radiolabelled 12 h-intravenous infusion of 1.2 mg rotigotine (0.6 mg $^{14}$C and 0.6 mg unlabelled; 3.7 MBq) solution. Treatment B (transdermal application) was a single 10 cm$^2$ patch containing 4.5 mg unlabelled rotigotine with a patch-on period of 24 h. During the 12 h-infusion, total radioactivity concentration rapidly increased within 2 h; there was a slight further increase towards the end of infusion. Plasma concentrations of total radioactivity declined by 75% within 12 h after completion of infusion. More than 94% of the radioactivity was excreted 216 h after start of infusion, 71% by the kidneys and 23% by feces. Renal elimination of the parent compound was <1%. Systemically absorbed rotigotine was rapidly metabolized. The major rotigotine biotransformation pathway was conjugation of the parent compound, mainly by sulfation; a second pathway was the formation of phase 1 metabolites (N-desalkylation) with subsequent conjugation. Plasma concentration-time profiles of unchanged rotigotine during and after infusion and during and after patch administration were comparable. Absolute bioavailability of transdermally applied rotigotine was 37%.
Introduction

Although levodopa remains the gold standard in the treatment of Parkinson’s disease (PD), its long-term use is often associated with the development of motor complications (Poewe et al., 1986; Rascol et al., 2000; Lees et al., 2001). Abnormal pulsatile stimulation of striatal dopamine receptors owing to intermittent administration of agents with short half-lives such as levodopa is thought to be a major factor for these complications (Olanow et al., 2000). Current strategies for more continuous dopaminergic stimulation to the brain include treatment with dopamine agonists, either as adjunct to levodopa or as monotherapy in early PD treatment (Olanow, 2002).

Rotigotine, (-)-5,6,7,8-tetrahydro-6-[propyl-[2-thienyl]ethyl]amino]-1-naphthalenol hydrochloride, is a unique non-ergoline dopamine agonist with activity across D1 through D5 receptors as well as select adrenergic and serotonergic sites which has been formulated for convenient once-daily administration in a silicone-based matrix for transdermal delivery (Jenner, 2005). This ensures a continuous drug release providing stable plasma concentrations over a period of 24 h (Braun et al., 2005). Clinical studies with rotigotine transdermal patch have shown efficacy and safety in the treatment of early and advanced PD (Watts et al., 2007; Poewe et al., 2007) and moderate to severe restless legs syndrome (Oertel et al., 2008; Trenkwalder et al., 2008).

Rotigotine metabolism was studied in rat, monkey, and human liver microsomes (Swart et al., 1993). The main products of oxidative biotransformation were a N-despropyl and a N-desthienylethyl rotigotine metabolite; these metabolites were rapidly conjugated to glucuronides or sulfates in perfused rat livers (Swart et al., 1994). The pharmacological activity of rotigotine and its metabolites has been tested in in vitro receptor binding assays with human receptor subtypes expressed in cell lines. Whereas rotigotine exhibits its high affinity for the dopamine receptors, in particular for the D3 receptor, the phase 2 conjugates have practically no affinity (data on file). However, the phase 1 metabolites also have a high affinity to some of the dopamine receptors but are hardly detectable in plasma.
Information concerning the absorption, disposition, metabolic fate and elimination (ADME) of the administered medication is essential for a risk-benefit evaluation of the treatment. The mass balance of radiolabelled rotigotine applied transdermally has been previously characterized (Cawello et al., 2007). This study investigated the mass balance of a continuous 12 h rotigotine infusion with focus on detailed evaluation of rotigotine transport and identification of metabolites in man (plasma, urine and feces). Absolute bioavailability of transdermal rotigotine application was also characterized.
Subjects and Methods

**Study Medication.** [14C] rotigotine (radiochemical purity 98.7% [HPLC]; specific activity 2.11 GBq/mmol) was synthesized by Nycomed Amersham, U.K. (Fig. 1). The final solution for administration as a continuous 12 h intravenous infusion contained 1.2 mg rotigotine (0.6 mg [14C] labelled and 0.6 mg unlabelled rotigotine, 3.7 MBq) in 480 mL of sterile 0.9% saline solution. Transdermal 10 cm² patches contained 4.5 mg unlabelled rotigotine (Schwarz Biosciences GmbH, UCB Group, Germany).

**Study Population and Design.** The study was carried out in 2000/2001 in the Czech Republic in accordance with Good Clinical Practice and the Declaration of Helsinki. The study protocol was approved by the Czech Ministry of Health, the State Office for Nuclear Safety and the local Ethics Committee, and written informed consent was obtained from all participating subjects.

Healthy Caucasian males aged between 18 and 50 years with a body weight ± 15% of normal weight and with normal 12-lead ECG recordings were included. Subjects were not to have taken any medication within 14 days of start of study, and antipsychotics, antiemetics, monoamine oxidase inhibitors or antihypertensives were not permitted within 30 days prior to first medication administration. Other exclusion criteria consisted of any current medical or psychiatric illness which might affect the study outcome, any skin disease which might influence the absorption of transdermally administered rotigotine, suspicious undiagnosed skin lesions, >10 cigarettes/day, >600 mg caffeine/day and >40 g of alcohol/day, and participation in a study involving administration of a radiolabelled test substance within the previous year. No concomitant medication except paracetamol (2 x1000 mg) was allowed during the study.

After screening (medical history, complete physical examination, vital signs, 12-lead ECG, safety laboratory parameters, and alcohol and drug test), eligible subjects entered the cross-over study consisting of two treatment periods (A and B) separated by a wash-out
phase of at least 2 weeks. Allocation to the sequence of administration was random. Treatment A (10 days) consisted of a continuous radiolabelled rotigotine intravenous infusion over a period of 12 h on Day 1 of the treatment period. An infusion was chosen to simulate a comparable drug input as expected during a patch administration. For practical reasons, the treatment was limited to 12 h and was performed by means of 4 calibrated infusion pumps. As the expected apparent dose of a 10 cm² patch containing 4.5 mg rotigotine was ~50% (2.25 mg), the infusion was planned to contain 1.2 mg rotigotine/12 h (corresponding to 2.4 mg/24 h or 53% of the amount in the patch). Treatment B (4 days) was a single 10 cm² patch containing 4.5 mg unlabelled rotigotine applied to the upper abdomen on Day 1 of the treatment period with a patch-on period of 24 h (corresponding to a nominal dose of 2 mg/24 h delivered to the skin). Subjects remained under permanent supervision until the end of infusion and until patch removal, respectively. They were hospitalized for the duration of treatment A and for 48 h after patch application. A safety follow-up examination was conducted within 14 days of completion of both treatments.

**Sample Collection and Analytical Methods (continuous 12 h infusion).** Blood samples were collected during treatment A (i.v. infusion) into lithium-heparinized tubes at predose, 0.25, 0.5, 1, 1.5, 2, 4, 6, 8, 10, 12 (before end of infusion), 14, 16, 20, 24, 30, 36 and 48 h, and then every 24 h up to 216 h after start of infusion. One mL from each blood sample was retained for determination of total radioactivity in whole blood; plasma was collected from the remainder of the sample. Urine samples were collected for 12 h prior to dosing, in the intervals of 0-6, 6-12, 12-24 h, and thereafter in 24 h intervals up to 216 h after start of infusion. Feces were collected in the 12 h period before dosing and then in 24 h intervals up to 216 h; samples were homogenized mechanically with 100 mL of water and 10 mL aliquots retained for analysis. All samples were stored at -20°C.

**Total Radioactivity.** Total radioactivity in plasma and urine was measured by scintillation counting; samples were mixed with Aquasafe 500™ (Zinsser Analytic, Maidenhead, UK) and counted in an LKB 1219 Spectral Liquid Scintillation Counter RACK BETA (LKB Wallace, Turku, Finland). Before scintillation counting, whole blood and feces were first combusted.
using an OX-500 Biological Material Oxidiser (Harvey Instrument Corporation, Hillsdale N.J., USA); the radioactive CO₂ gas was trapped in scintillation fluid (Oxisolve-C-400™, Zinsser Analytic, Maidenhead, UK). For the determination of concentrations of unconjugated and total rotigotine and its metabolites in plasma, urine and feces samples, an HPLC-UV-radio chromatography method was performed.

**Metabolite Identification.** Radioactive plasma, urine and feces samples were also evaluated by liquid chromatography-radiochemical detection-mass spectrometry (LC-RAD-MS) for identification of rotigotine metabolites. Samples were pooled across time points for each subject in order to yield sufficient radioactivity; in plasma samples the time intervals were 0-4, 6-12, and 14-48 h, in urine samples 0-12 and 12-48 h and in feces samples 0-72 h. Sample extracts were loaded onto a Hypersil BDS C18 5 µm column and eluted at ambient temperature with a shallow gradient using 0.1% formic acid (solvent A) and 0.1% formic acid in methanol (solvent B). Starting with 90% A and 10% B, the methanol was linearly increased to 70% B in 45 minutes and from 70% to 100% in 2 minutes using a flow of 1 mL/min. No special precautions were taken to avoid degradation of metabolites. However, it could be shown in the assay development for conjugated rotigotine metabolites and desalkylated metabolites that both types of compounds were stable in spiked frozen samples. Reference standards for a number of postulated desalkylated and glucuronidated rotigotine metabolites were available as synthesized compounds (Schwarz Biosciences) when the study was performed.

The column eluate was monitored with a Reeve radiochemical monitor 9701 (liquid scintillant; Reeve Analytical, Glasgow, UK) and ionized using a Finnigan MAT TSQ 700 mass spectrometer (Thermo Finnigan MAT, Bremen, Germany) (column effluent split was 200 µl to radioactivity counter and 400 µl to mass spectrometer). Difficulties were encountered during mass spectral analysis owing to very low substance levels in the samples. Identification of compounds in plasma and feces samples was therefore based on co-elution with reference standards. To facilitate identification in urine samples, samples were overspiked with an extract of monkey urine obtained from a previous rotigotine study (data on file).
Sample Collection and Analytical Methods (transdermal application). Blood samples during treatment B (patch) were taken predose, 1, 2, 4, 6, 8, 10, 12, 16, 24 (before patch removal), 25, 26, 28, 32, 36, and 48 h after patch application and then centrifuged for collection of plasma. Urine samples were collected for 12 h prior to dosing and in the intervals of 0-6, 6-12, 12-24, and 24-48 h after patch application. Concentrations of unconjugated and total rotigotine and its N-desalkyl metabolites in plasma and urine samples were determined by liquid chromatography with tandem mass spectrometry (LC-MS/MS) performed on a Finnigan MAT LCQ (Thermo Finnigan MAT, Bremen, Germany) with either oxybutynine hydrochloride (LGC Promochem, Chessington, UK) or fentanyl citrate (Sigma-Aldrich, Munich, Germany) as internal standard. All standard curves were linear over their respective calibration ranges with overall accuracy and precision within or better than 15%. The lower limit of quantification (LOQ) for unconjugated rotigotine in plasma was 0.01 ng/mL; in urine, LOQ for unconjugated rotigotine was 0.05 ng/mL, for unconjugated N-desethenyl rotigotine 0.25 ng/mL, for unconjugated N-despropyl rotigotine 0.1 ng/mL and for total rotigotine and total N-desalkyl metabolites 0.5 ng/mL.

Pharmacokinetic Parameters. One study objective was the determination of total radioactivity in whole blood, plasma, urine and feces samples after continuous 12 h infusion of radiolabelled rotigotine. Radioactivity levels in blood were expressed as ng or µg-equivalent per g whole blood or plasma. Pharmacokinetic parameters were the maximum plasma concentration ($C_{\text{max}}$) and the area under the concentration-time curve (AUC(0-t)) calculated by the linear trapezoidal rule up to the last time point $t$ with a concentration greater than LOQ for rotigotine and its main metabolites after continuous 12 h infusion of radiolabelled rotigotine. Other pharmacokinetic parameters included: pharmacokinetic parameters after patch administration $C_{\text{max}}$, AUC(0-t), AUC(0-$\infty$) (not reported if the extrapolated area beyond the last quantified sample was greater than 20% of the total AUC(0-$\infty$)), time to reach maximum plasma concentrations ($T_{\text{max}}$), terminal phase half-life ($t_{1/2}$, calculated from the terminal rate constant ($\lambda_z$) which was derived by log-linear regression) and the total amount of rotigotine and metabolites excreted into urine ($A_{\text{er}}$); $T_{\text{max}}$, $t_{1/2}$, $A_{\text{er}}$ and $A_{\text{ef}}$ (the
amount excreted into feces) of rotigotine and metabolites after 12 h intravenous infusion; maximum renal and fecal excretion rate (E_{r,max} and E_{f,max}); renal and faecal clearance, calculated as the quotient A_{er(ef)}/AUC_{(0-t)} (CL_{ren} and CL_{fa}, respectively). For determination of the absolute bioavailability of the parent compound from transdermal administration, an intraindividual comparison of the two treatments regarding pharmacokinetic profiles of rotigotine was carried out. Values of dose normalized AUC_{(0-t)} were therefore chosen to characterize the extent of rotigotine in the central circulation.

Calculation of parameters of pharmacokinetics and descriptive statistics of these parameters were performed using the softwares Kinetica (Thermo Scientific, Philadelphia, PA, USA, version 4) and SAS (SAS Institute, Cary, NC, USA, version 6.1).

Apparent dose. The apparent dose is an estimate of the drug delivered to the skin over 24 hours; it was calculated by the difference of the total drug content and the residual drug amount in the used patches after removal.

Safety. Safety was monitored by 12-lead ECG, vital signs and safety laboratory parameters. Adverse events were recorded throughout the study and skin tolerability of the transdermal patch was assessed at the end of the 24 h patch-on period.
Results

Both treatments were well tolerated and no drug-related changes were observed in any of the investigated safety parameters. Coughing of mild intensity was reported for one subject (relationship not assessable), no other adverse events were reported. All subjects completed the study; no protocol violations were reported. Mean age of the male Caucasian volunteers was 28.8 ± 4.6 years, mean body weight was 83.8 ± 8.2 kg.

Continuous 12 h Infusion.

Mass Balance of Total Radioactivity. During a 12 h intravenous $[^{14}C]$ rotigotine infusion, the total radioactivity increased to 3.90 ± 0.62 ng-equivalent/g (mean ± SD) in plasma followed by a decrease to 0.82 ± 0.36 ng-equivalent/g within 12 h after the end of the infusion. Low concentrations of total radioactivity were determined up to 72 h after start of infusion in all subjects. The concentration at that time point was 0.18 ± 0.10 ng-equivalent/g. Mean individual $C_{\text{max}}$ of the sum of unconjugated rotigotine and all potential metabolites (total radioactivity) was 4.16 ng-equivalent/g plasma with a mean $t_{\text{max}}$ of 10.3 h; AUC$_{(0-\infty)}$ was 69.7 h·ng-equivalent/g plasma (Table 1). 216 h after start of the infusion, 71.3% of the total administered radioactivity was excreted by the kidneys and 23.4% were eliminated by feces. Fig. 2A illustrates the excretion profile. The total amount excreted corresponds to a renal clearance of 12.3 L/h and a fecal clearance of 4.0 L/h.

Determination of Rotigotine and Metabolites in Plasma. For quantitative analyses by HPLC-UV radiochromatography, plasma samples from all six subjects had to be pooled, as radioactivity in plasma was low. Fig. 2B shows the cumulative concentration-time profiles of unconjugated rotigotine and its metabolites in plasma during the first 24 h after start of infusion. Table 1 provides the corresponding pharmacokinetic parameters. The concentration of unconjugated rotigotine steadily increased after the start of infusion with a $C_{\text{max}}$ of 0.509 ng-equivalent/mL after 8 h. There was a rapid decline after the end of infusion with a terminal half-life of 2.5 h. Comparison of the AUC$_{(0-\infty)}$ of 6.1 h·ng-eq/mL with the AUC$_{(0-\infty)}$ for total radioactivity suggests that the metabolites contributed negligibly to the total radioactivity. The radiochromatograms of plasma samples from one subject are shown in Fig. 2B. The chromatograms demonstrate the presence of several metabolites, which are likely to be further unidentified conjugates.
radioactivity in plasma (69.7 h·ng-eq/g) shows that less than 8.8% can be attributed to the unchanged parent compound. The main metabolite in plasma (25.4% of the total radioactivity measured by HPLC) was rotigotine sulfate (AUC$_{[0-\infty]}$ 17.7 h·ng-eq/mL); its concentration increased rapidly in the first 2 h. Rotigotine glucuronide contributed 4.9% to the total radioactivity; its concentration-time profile followed a 2h-pattern of increasing and declining values in contrast to the smoother profiles for unconjugated rotigotine and the other metabolites. N-despropyl rotigotine sulfate and N-desthienylethyl rotigotine sulfate (including other conjugates) contributed 10.2% and 5.7% of total radioactivity, respectively. The AUC for N-desthienylethyl rotigotine sulfate reflects the AUC up to the last measured time point as extrapolation to infinity would have exceeded 20%. Other metabolites such as unconjugated N-despropyl or N-desthienylethyl rotigotine could not be detected or were below LOQ. Terminal half-life of the metabolites was short (2.5-3.8 h) except for N-desthienylethyl rotigotine sulfate (10.3 h). A comparison of the total radioactivity of identified compounds in plasma as detected by HPLC (AUC$_{[0-\infty]}$ 38.4 h·ng-eq/mL) and the total radioactivity in plasma measured for mass balance (69.7 h·ng-eq/g) showed that 55% can be attributed to the parent compound and the described metabolites. There was a number of additional small peaks (<5% of radioactivity) but no evidence for any further major metabolite.

**Determination of Rotigotine and Metabolites in Urine and Feces.** Rotigotine sulfate was the main metabolite excreted into urine (13.1% of applied dose) followed by rotigotine glucuronide (8.7%) and N-despropyl rotigotine sulfate (7.6%). Less than 1% was eliminated as N-despropyl rotigotine glucuronide and concentrations of unconjugated rotigotine, N-despropyl and N-desthienylethyl rotigotine were below LOQ (300 dpm/mL). More than half of the radioactivity eliminated renally (38.4%) could not be attributed to known compounds. Maximum renal elimination was reached 9 h after the start of infusion for all substances. HPLC-detected radioactivity in feces was low and did not permit any identification of the composition.

**Metabolite Identification.** For further quantification of rotigotine and metabolites in human plasma, urine and feces, samples were also analyzed by HPLC with radiochemical and mass
spectrometric detection. The majority of plasma profiles across subjects and over time contained the same components: N-desthienylethyl rotigotine sulfate, N-despropyl rotigotine sulfate, rotigotine sulfate, and rotigotine glucuronide which were the major components observed in urine samples, and unconjugated rotigotine ([M·H+] \text{316}; mean retention time 42.52 min). The four main components observed in urine profiles, N-desthienylethyl rotigotine sulfate (19.54 min), N-despropyl rotigotine sulfate (30.76 min), rotigotine sulfate (34.57 min) and rotigotine glucuronide (35.96 min) accounted for 10-21%, 14-20%, 16-22% and 11-15% of the administered dose, respectively. Fig. 3 illustrates a typical radio chromatogram with the identified drug molecules in urine. Owing to poor extraction and low recoveries from the feces samples, no single component accounted for >5% of administered radioactivity and poor profiles did not allow any metabolites to be identified from these samples. Using this method, 61% - 82% of the applied radioactivity could be detected in urine within 48h after start of the infusion. 5%-15% of the applied radioactivity could be detected in feces within 72h after start of the infusion.

**Transdermal Delivery.** After administration of a rotigotine patch mean rotigotine plasma concentrations increased to 0.378 ± 0.133 ng/mL within 16 h after patch administration. At the end of the patch-on period of 24 h mean rotigotine plasma concentration was 0.308 ± 0.055 ng/mL. After patch removal mean rotigotine plasma concentration decreased to 0.04 ± 0.013 ng/mL within 12 h. The mean apparent dose (2.9 mg) was 61.4% of the total drug content of the patch. Table 2 summarizes the pharmacokinetic profile of unconjugated rotigotine following application of a 4.5 mg unlabelled rotigotine patch. Fig. 4 compares the plasma concentration-time profiles of the two administration forms.

\text{AUC(0-t)} for unconjugated rotigotine extrapolated to infinity was 8.5 h ng/mL following transdermal application of 4.5 mg rotigotine and 6.1 h ng/mL after continuous 12 h infusion of 1.2 mg of rotigotine. The fraction of the dose systemically available after 24 h transdermal delivery was 0.369 which corresponds to an absolute bioavailability of 37%. With the apparent dose of 61.4% of the dose applied more than 60% of the dose absorbed is bioavailable.
Discussion

Intraindividual comparison of pharmacokinetic parameters following intravenous infusion and transdermal application of rotigotine allowed the evaluation of absolute bioavailability of rotigotine after administration as a patch formulation which was calculated as 37% of the applied dose (>60% of the drug delivered to the skin).

During infusion total radioactivity increased rapidly within two hours. The radioactive dose was almost entirely recovered (95%) within 216 h following infusion. The major elimination route was via the kidneys (71%); 24% was excreted with the feces. These results are in accordance with the findings of a recent mass balance study after transdermal administration of radiolabelled rotigotine where 88% of the radioactive dose was recovered within 96 h after administration, mainly eliminated via the kidneys (66%) and to a lesser extent in feces (22%; Cawello et al., 2007).

Rotigotine was quickly and extensively metabolized; in plasma, less than 8.8% of the total infused radioactivity could be attributed to the unchanged parent compound. Concentrations of the main metabolite rotigotine sulfate increased rapidly in the first 2 h of infusion. Further metabolites were rotigotine glucuronide and the N-desalkylation products N-despropyl and N-desthienylethyl rotigotine sulfate. The main metabolites identified in urine were the conjugates of the parent compound, rotigotine sulfate and rotigotine glucuronide, as well as conjugates of Phase 1 metabolites, N-despropyl rotigotine sulfate and N-desthienylethyl rotigotine sulfate. The concentrations of conjugates of the parent compound were approximately 2 to 4 fold higher compared to conjugated N-desalkyl rotigotine metabolites after iv treatment in plasma and urine, respectively. This suggests conjugation of rotigotine as the main biotransformation pathway with sulfation more prominent than glucuronidation (Fig. 5). Phase I metabolism to the N-desalkyl metabolites N-despropyl and N-desthienylethyl rotigotine which has been characterized in human liver microsomes and hepatocytes (Hansen et al., 2005) was also identified in vivo. Unconjugated N-despropyl and
N-desthienylethyl rotigotine were below the detection limit, indicating a rapid conjugation of both phase 1 metabolites. In a similar fashion to the parent compound, sulfation was more prominent than glucuronidation.

The extensive additional analytical evaluation of the pooled urine samples using MS detection after radiochromatography has resulted in a clear picture of the molecules eliminated by the kidneys. The composition of the radioactivity eliminated into urine was identified by 87% with about 42% as conjugates of rotigotine (26% sulfate and 16% glucuronide) and about 44% as sulfated N-desalkyl metabolites of rotigotine (22% N-desthienyl rotigotine sulfate and 22% N-despropyl rotigotine sulfate).

Comparing the rotigotine plasma concentration profiles during and after infusion to during and after patch administration, the similar levels of maximum rotigotine concentration and a similar decreasing profile of these concentrations after cessation of administration could be seen (Fig. 4). This suggests a similar pharmacokinetic profile under both routes of administration (iv infusion and transdermal administration). The bi-phasic decrease of rotigotine concentrations after cessation of administration compares very well to other data reported for the pharmacokinetics of rotigotine after patch removal (Cawello et al., 2006). Whereas the terminal half life for rotigotine after completion of infusion was 2.5 h, the corresponding half life after patch removal was 5.3 h. This nominal difference can be explained by the fact that the samples after iv infusion were pooled for each time point over all 6 subjects and reflect more the first part of the bi-phasic course of concentration decrease.

The present paper describes for the first time details of the pharmacokinetics of rotigotine metabolites in human subjects. The results illustrate that the terminal half-lives of the rotigotine conjugates are similar to the half-life of unconjugated rotigotine, 3h. The decrease in plasma concentrations for conjugated N-desalkylated rotigotine metabolites can be characterized by a terminal half life of 10 h for N-desthienylethyl rotigotine sulfate and 3 h for N-despropyl rotigotine sulfate.
The main metabolites (rotigotine conjugates) can be considered as having no pharmacological activity in patients. Although the phase 1 metabolites have a considerable affinity to the dopamine receptors, their plasma concentrations are more than 10 times lower than those of rotigotine and can thus also be regarded as having no pharmacological activity.

The structure of rotigotine is based on 5-hydroxy-di-n-propyl-tetralin. A literature research did not identify any publications reporting on the metabolism of similar compounds.

In conclusion, more than 60% of rotigotine delivered to the skin within 24 hours was systemically available. The compound was extensively metabolized by conjugation, N-desalkylation and subsequent conjugation. Conjugation of the parent compound was the main biotransformation pathway. Renal elimination of the unchanged parent compound was below 1%. The kidneys were, however, the main elimination route for rotigotine metabolites. The total recovery of radioactivity within 216h following infusion of $^{14}$C-rotigotine was 95%, 71% via kidney and 24% via feces.
Acknowledgements

Pharmacon Research GmbH Berlin, Germany was the contract research organisation of the study. The Institute for Clinical and Experimental Medicine Praha, Czech Republic conducted the clinical part of the study and the measurement of total radioactivity. Quintiles Limited Research Edinburgh UK was responsible for the identification of the rotigotine metabolites in urine, plasma and feces by HPLC with radiochemical and mass spectrometric detection. Quantification of unconjugated rotigotine in plasma and quantification of unconjugated and total rotigotine and total metabolites in urine was carried out by AAIPharma GmbH & Co. KG, Neu-Ulm, Germany.
References


Footnotes

The study was sponsored by SCHWARZ BIOSCIENCES GmbH, UCB Group.

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Figure Legends

**Fig. 1** Structure and labelling position of \([^{14}C]\) rotigotine (IUPAC: (6S)-6-[propyl(2-thiophen-2-ylyethyl)amino]-5,6,7,8-tetrahydronaphthalen-1-ol)

**Fig. 2A.** Elimination profile of radioactivity in urine and feces during and after a 12 h infusion of 1.2 mg rotigotine (arithmetic mean ± SD)

**Fig. 2B.** Cumulative plasma concentration of unconjugated rotigotine and metabolites during and after a 12 h infusion of 1.2 mg rotigotine (data are pooled from all six subjects)

**Fig. 3.** Radiochemical profile of pooled urine extracts obtained following iv administration of rotigotine (subject 8002, samples 0-12 h)

**Fig. 4.** Plasma concentration-time profile of unconjugated rotigotine following start of infusion (●) and patch application (▲)

**Fig. 5.** Metabolic pathway of rotigotine in man
TABLE 1

Pharmacokinetic parameters following a 12 h radioactive intravenous infusion of 1.2 mg rotigotine (data are pooled from all subjects)

<table>
<thead>
<tr>
<th></th>
<th>Total radioactivity&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Unconjugated rotigotine</th>
<th>Rotigotine sulfate</th>
<th>Rotigotine glucuronide</th>
<th>N-despropyl rotigotine sulfate</th>
<th>N-desthienylethyl rotigotine sulfate and other conjugates</th>
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</thead>
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<td><strong>C&lt;sub&gt;max&lt;/sub&gt; (ng/mL)&lt;sup&gt;a&lt;/sup&gt;</strong></td>
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<td>1.479</td>
<td>0.410</td>
<td>0.621</td>
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<td>8</td>
<td>10</td>
<td>10</td>
<td>6</td>
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<tr>
<td><strong>t&lt;sub&gt;1/2&lt;/sub&gt; (h)</strong></td>
<td>12.8 (5.8)</td>
<td>2.5</td>
<td>3.8</td>
<td>2.5</td>
<td>3.1</td>
<td>10.3</td>
</tr>
<tr>
<td><strong>AUC&lt;sub&gt;(0-t)&lt;/sub&gt; (h·ng/mL)&lt;sup&gt;a&lt;/sup&gt;</strong></td>
<td>65.37 (12.34)</td>
<td>5.972</td>
<td>17.381</td>
<td>3.360</td>
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<tr>
<td><strong>AUC&lt;sub&gt;(0-∞)&lt;/sub&gt; (h·ng/mL)&lt;sup&gt;a&lt;/sup&gt;</strong></td>
<td>69.72 (13.3)</td>
<td>6.126</td>
<td>17.696</td>
<td>3.428</td>
<td>7.146</td>
<td>n.c.</td>
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<tr>
<td><strong>λ&lt;sub&gt;z&lt;/sub&gt; (1/h)</strong></td>
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<td>12.3</td>
<td>-</td>
<td>9.3</td>
<td>31.6</td>
<td>14.5</td>
<td>-</td>
</tr>
<tr>
<td><strong>CL&lt;sub&gt;f&lt;/sub&gt; (L/h)</strong></td>
<td>4.0</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

<sup>a</sup> ng = ng-equivalent; <sup>b</sup> mean (SD), per g plasma; <sup>c</sup> not calculated as the extrapolated area beyond the last quantified sample would have exceeded 20% of the total AUC;

<sup>d</sup> approximated by the quotient of mean amount excreted and AUC<sub>(0-∞)</sub>
TABLE 2

Pharmacokinetic parameters following transdermal application of 4.5 mg unlabelled rotigotine
(data are arithmetic means ± SD)

<table>
<thead>
<tr>
<th>Metric</th>
<th>Unconjugated rotigotine</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{\text{max}}$ (ng/mL)</td>
<td>0.471 ± 0.114</td>
</tr>
<tr>
<td>$T_{\text{max}}$ (h)$^a$</td>
<td>14.0 (12-25)</td>
</tr>
<tr>
<td>$t_{1/2}$ (h)</td>
<td>5.4 ± 1.3</td>
</tr>
<tr>
<td>$\text{AUC}_{(0-t)}$ (h·ng/mL)</td>
<td>8.305 ± 1.971</td>
</tr>
<tr>
<td>$\text{AUC}_{(0-\infty)}$ (h·ng/mL)</td>
<td>8.477 ± 2.029</td>
</tr>
</tbody>
</table>

$^a$ median (range)
Figure 3

- N-desthienylethyl rotigotine sulfate
- N-despropyl rotigotine sulfate
- Rotigotine sulfate
- Rotigotine glucuronide

Retention time (min): 4.29, 6.83, 8.14, 11.98, 18.90, 20.86, 28.08, 30.55, 33.88, 35.40, 37.42, 47.61

Intensity of signal (%): 0, 20, 40, 60, 80, 100
Figure 5