Absorption, Disposition, Metabolic Fate, and Elimination of the Dopamine Agonist Rotigotine in Man: Administration by Intravenous Infusion or Transdermal Delivery

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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 by using two different forms of administration in a randomized sequence with a crossover design. Treatment A (continuous infusion) consisted of a single radiolabeled 12-h intravenous infusion of 1.2 mg of rotigotine (0.6 mg of [14C] and 0.6 mg of unlabeled rotigotine, 3.7 MBq) solution. Treatment B (transdermal application) consisted of a single 10-cm² patch containing 4.5 mg of unlabeled 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 additional increase toward 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 the 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%.

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 due 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 an adjunct to levodopa or as monotherapy in early PD (Olanow, 2002).

Rotigotine, (65)-6-{propyl[2-(2-thienyl)ethyl]amino}-5,6,7,8-tetrahydro-1-naphthalenol hydrochloride, is a unique nonergoline dopamine agonist with activity across D1 through D5 receptors as well as select adrenergic and serotoninergic sites, which has been formulated for convenient once-daily administration in a silicone-based matrix for transdermal delivery (Jenner, 2005). This process ensures a continuous drug release by providing stable plasma concentrations over a period of 24 h (Braun et al., 2005). Clinical studies with the rotigotine transdermal patch have shown efficacy and safety in the treatment of early and advanced PD (Poewe et al., 2007; Watts 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 an N-despropyl and an N-desthienylethyl rotigotine metabolite; these metabolites were rapidly conjugated to glucurononides 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 of the administered medication is essential for a risk-benefit evaluation of the treatment. The mass balance of radiolabeled 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...
Subjects and Methods

Study Medication. [14C]rotigotine [radiochemical purity 98.7% (high-performance liquid chromatography; HPLC); specific activity 2.11 GBq/mmol] was synthesized by Nycomed Amersham (Little Chalfont, UK) (Fig. 1). The final solution for administration as a continuous 12-h i.v. infusion contained 1.2 mg of rotigotine (0.6 mg of [14C] labeled and 0.6 mg of unlabeled rotigotine, 3.7 MBq) in 480 ml of sterile 0.9% saline solution. Transdermal 10-cm² patches contained 4.5 mg of unlabeled rotigotine (Schwarz Biosciences GmbH, UCB Group, Monheim am Rhein, 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 white males between 18 and 50 years of age 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 the start of study, and antipsychotic drugs, antiemetic drugs, monoamine oxidase inhibitors, or antihypertensive drugs were not permitted within 30 days before the first medication administration. Other exclusion criteria consisted of any current medical or psychiatric illness that might affect the study outcome, any skin disease that might influence the absorption of transdermally administered rotigotine, suspicious un-diagnosed skin lesions, >10 cigarettes/day, >600 mg of caffeine/day, and >40 g of alcohol/day, and participation in a study involving administration of a radiolabeled test substance within the previous year. No concomitant medication except paracetamol (2 × 1000 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 crossover 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 radiolabeled 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 four calibrated infusion pumps. Because the expected apparent dose of a 10-cm² patch containing 4.5 mg of rotigotine was ~50% (2.25 mg), the infusion was planned to contain 1.2 mg rotigotine/12 h (corresponding to 2.4 mg/h or 53% of the amount in the patch). Treatment B (4 days) consisted of a single 10-cm² patch containing 4.5 mg of unlabeled 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 (intravenous 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 the start of infusion. One milliliter 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 before dosing, in the intervals of 0 to 6, 6 to 12, 12 to 24 h, and thereafter in 24-h intervals up to 216 h after the 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 were 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 (GE Healthcare, Little Chalfont, Buckinghamshire, UK). Before scintillation counting, whole blood and feces were first combusted using an OX-500 Biological Material Oxidizer (Harvey Instrument Corporation, Hillsdale, NJ); the radioactive CO₂ gas was trapped in scintillation fluid (Oxisolve-C-400; Zinsser Analytic). To determine concentrations of unconjugated and total rotigotine and its metabolites in plasma, urine, and feces samples, an HPLC-UV-radiochromatography method was performed.

Metabolite identification. Radioactive plasma, urine, and feces samples were also evaluated by liquid chromatography-radiochemical detection-mass spectrometry for identification of rotigotine metabolites. Samples were pooled across time points for each subject to yield sufficient radioactivity: in plasma samples, the time intervals were 0 to 4, 6 to 12, and 14 to 24 h; in urine samples, the time intervals were 0 to 12 and 12 to 48 h; and in feces samples, the time intervals were 0 to 72 h. Sample extracts were loaded onto a Hypersil BDS C18 5-µm column (Thermo Fisher Scientific, Waltham, MA) 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 min and from 70 to 100% B in 2 min using a flow of 1 ml/min. No special precautions were taken to avoid degradation of metabolites. However, a degradation 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 several 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 Reeves radiochromatographic monitor 9701 (liquid scintillator; Reeve Analytical, Glasgow, UK) and ionized using a Finnigan MAT TSQ 700 mass spectrometer (Thermo Fisher Scientific) (column effluent split was 200 µl to radioactivity counter and 400 µl to mass spectrometer). Difficulties were encountered during mass spectral analysis due to very low substance levels in the samples. Therefore, identification of compounds in plasma and feces samples was based on coelution with reference standards. To facilitate identification in urine samples, samples were over spiked 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 before dosing and in intervals of 0 to 6, 6 to 12, 12 to 24, and 24 to 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 performed on a Finnigan MAT LCQ (Thermo Fisher Scientific) with either oxybutynine hydrochloride (LCG 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, LOQ for unconjugated N-desethyl rotigotine was 0.25 ng/ml, LOQ for unconjugated N-despropyl rotigotine was 0.1 ng/ml, and LOQ for total rotigotine and total N-desalkyl metabolites was 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 radiolabeled rotigotine. Radioactivity levels in blood were expressed as nanogram- or microgram-equivalent per gram of whole blood or plasma. Pharmacokinetic parameters were the maximum plasma concentration (Cmax) and the area under the concentration-time curve (AUC0-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 radiolabeled rotigotine. Other pharmacoki-

FIG. 1. Structure and labeling position of [14C]rotigotine [IUPAC: (6S)-6-(propyl(2-thiophen-2-yl)amino)-5,6,7,8-tetrahydronaphthalen-1-ol].
Table 1 shows pharmacokinetic parameters after a 12-h radioactive intravenous infusion of 1.2 mg of rotigotine (data are pooled from all subjects).

**Table 1**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Total Radioactivity</th>
<th>Unconjugated Rotigotine</th>
<th>Rotigotine Sulfate</th>
<th>Rotigotine Glucuronide</th>
<th>N-Despropyl Rotigotine Sulfate</th>
<th>N-Dethiennethyl Rotigotine Sulfate and Other Conjugates</th>
</tr>
</thead>
<tbody>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (ng/ml)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>4.160 (600)</td>
<td>0.509</td>
<td>1.479</td>
<td>0.410</td>
<td>0.621</td>
<td>0.287</td>
</tr>
<tr>
<td>T&lt;sub&gt;max&lt;/sub&gt; (h)</td>
<td>10.3 (1.5)</td>
<td>8</td>
<td>8</td>
<td>10</td>
<td>10</td>
<td>6</td>
</tr>
<tr>
<td>t&lt;sub&gt;1/2&lt;/sub&gt; (h)</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>AUC&lt;sub&gt;12-h&lt;/sub&gt; (h · ng/ml)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>65.57 (12.34)</td>
<td>5.972</td>
<td>17.381</td>
<td>3.360</td>
<td>6.908</td>
<td>3.985</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;12-h&lt;/sub&gt; (h · ng/ml)&lt;sup&gt;c&lt;/sup&gt;</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>
</tr>
<tr>
<td>λ&lt;sub&gt;d&lt;/sub&gt; (1/h)</td>
<td>0.06 (0.02)</td>
<td>0.28</td>
<td>0.18</td>
<td>0.28</td>
<td>0.22</td>
<td>0.07</td>
</tr>
<tr>
<td>CL&lt;sub&gt;r&lt;/sub&gt; (L/h)&lt;sup&gt;d&lt;/sup&gt;</td>
<td>12.3</td>
<td>9.3</td>
<td>31.6</td>
<td>14.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CL&lt;sub&gt;f&lt;/sub&gt; (L/h)&lt;sup&gt;d&lt;/sup&gt;</td>
<td>4.0</td>
<td></td>
<td></td>
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</table>

<sup>a</sup> Mean (S.D.), per gram of plasma  
<sup>b</sup> Not calculated (n.c.) because the extrapolated area beyond the last quantified sample would have exceeded 20% of the total AUC.  
<sup>c</sup>Approximated by the quotient of mean amount excreted and AUC<sub>12-h</sub>.  
<sup>d</sup> ng, ng-equivalent.

**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), but no other adverse events were reported. All subjects completed the study, and no protocol violations were reported. The mean age of white male volunteers was 28.8 ± 4.6 years, and mean body weight was 83.8 ± 8.2 kg.

**Continuous 12-h Infusion.** Mass balance of total radioactivity. During a 12-h intravenous [14C]rotigotine infusion, the total radioactivity increased to 3.90 ± 0.62 ng-equivalent/g (mean ± S.D.) 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<sub>max</sub> of the sum of unconjugated rotigotine and all potential metabolites (total radioactivity) was 4.16 ng-equivalent/g plasma with a mean T<sub>max</sub> of 10.3 h; AUC<sub>12-h</sub> was 69.7 h · ng-equivalent/g plasma (Table 1). Two hundred and sixteen hours after start of the infusion, 71.3% of the total administered radioactivity was excreted by the kidneys and 23.4% was eliminated by feces. Figure 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, because radioactivity in plasma was low. Figure 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<sub>max</sub> 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 \cdot ng- eq/ml with the AUC_{0-\infty} for total radioactivity in plasma (69.7 h \cdot 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 \cdot 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 2-h 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 because 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 \cdot ng-eq/ml) and the total radioactivity in plasma measured for mass balance (69.7 h \cdot ng-eq/g) showed that 55% can be attributed to the parent compound and the described metabolites. There were 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/z [M+H]^+ 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 to 21%, 14 to 20%, 16 to 22%, and 11 to 15% of the administered dose, respectively. Figure 3 illustrates a typical radiochromatogram with the identified drug molecules in urine. Due 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, we found that 61 to 82% of the applied radioactivity could be detected in urine within 48 h after start of the infusion. Five to 15% of the applied radioactivity could be detected in feces within 72 h 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 after application of a 4.5-mg unlabeled rotigotine patch. Figure 4 compares the plasma concentration-time profiles of the two administration forms.

AUC_{0-\infty} for unconjugated rotigotine extrapolated to infinity was 8.5 h \cdot ng/ml after transdermal application of 4.5 mg of rotigotine and 6.1 h \cdot 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 after 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 2 h. The radioactive dose was almost entirely recovered (95%) within 216 h after 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 radiolabeled 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. Additional 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 with conjugated N-desalkyl rotigotine metabolites after intravenous treatment in plasma and urine, respectively. This result suggests conjugation of rotigotine as the main biotransformation pathway with sulfation more prominent than glucuronidation (Fig. 5). Phase 1 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 mass spectrometry 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 approximately 42% as conjugates of rotigotine (26% sulfate and 16% glucuronide) and approximately 44% as sulfated N-desalkyl metabolites of rotigotine (22% N-desthienylrotigotine sulfate and 22% N-despropyl rotigotine sulfate).

Comparing the rotigotine plasma concentration profiles during and after infusion to those during and after patch administration, we found that similar levels of maximum rotigotine concentration and a similar decreasing profile of these concentrations after cessation of administration could be seen (Fig. 4). This result suggests a similar pharmacokinetic profile under both routes of administration (intravenous infusion and transdermal administration). The biphasic 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. The difference can be explained by the fact that a lower number of samples with concentrations above LOQ are present after intravenous infusion compared to the concentration after patch removal (Fig. 4). Therefore, the evaluation of the concentration after intravenous infusion reflects the first part of the biphasic course of concentration decrease.

The present article 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, 3 h. 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

TABLE 2

<table>
<thead>
<tr>
<th>Pharmacokinetic parameters following transdermal application of 4.5 mg unlabeled rotigotine (data are arithmetic means ± S.D.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unconjugated Rotigotine</td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (ng/ml)</td>
</tr>
<tr>
<td>T&lt;sub&gt;max&lt;/sub&gt; (h)&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>t&lt;sub&gt;1/2&lt;/sub&gt; (h)</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0→t&lt;/sub&gt; (h·ng/ml)</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0→∞&lt;/sub&gt; (h·ng/ml)</td>
</tr>
</tbody>
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<sup>a</sup> Median (range).
of rotigotine and thus can 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 h 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%. However, the kidneys were the main elimination route for rotigotine metabolites. The total recovery of radioactivity within 216 h after infusion of [14C]rotigotine was 95 and 71% via kidney and 24% via feces.

Acknowledgments. Pharmacon Research GmbH (Berlin, Germany) was the contract research organization 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 rotigotine and total metabolites in urine were carried out by AAIPharma GmbH and Co. KG (Neu-Ulm, Germany). Birgit Brett and Elke Grosselindeman provided editorial assistance and coordination of manuscript development.

References