The Development of the Rotigotine Transdermal Patch
A Historical Perspective

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INTRODUCTION

The motor deficits associated with Parkinson’s disease (PD) result from the progressive loss of dopaminergic neurons in the substantia nigra pars compacta.1,2 Dopaminergic replacement (levodopa) and dopaminergic stimulation (dopamine receptor agonists) are consequently central to the treatment of the motor deficits that typify PD.2–4 Levodopa is the gold standard for dopaminergic therapy in PD; however, its long-term use is complicated by the development of motor complications including dyskinesias and the end-of-dose deterioration known as wearing off.3,5,6 These motor complications increase functional disability and severely affect patients’ quality of life.7,8 Wearing-off effects are thought to indicate a shortening of the effectiveness window for levodopa, as a result of the progressive loss of nigrostriatal dopamine.6 Although the pathogenesis is still not fully understood, preclinical and clinical findings suggest that the development of levodopa-induced dyskinesias is related to its short duration of action, which results in pulsatile stimulation of striatal dopamine receptors.

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and altered basal ganglia output. Normal striatal dopamine receptor stimulation is thought to be continuous; therefore, continuous, rather than pulsatile, dopaminergic drug delivery, which is based on the tonic/phasic hypothesis of dopamine release, may more closely mimic physiologic dopaminergic stimulation. This possibility is supported by various animal studies (reviewed in detail by Jenner elsewhere in this issue) in which continuous dopaminergic delivery has been shown to substantially improve mobility and reduce the incidence of dyskinesias.

The rotigotine transdermal system (Neupro) is a dopamine receptor agonist that is delivered over a 24-hour period. It is approved for idiopathic PD and restless legs syndrome (RLS) in the United States and European Union.

This article reviews the development of the rotigotine transdermal system for the treatment of PD, and the clinical pharmacology of rotigotine. The results of several phase III clinical studies have been published that support the efficacy of the rotigotine patch for the treatment of early and advanced PD. However, this article focuses on the development of the medication from a pharmacokinetic point of view. A detailed review discussing the results of the clinical studies can be found in the article by Lyons and Pahwa elsewhere in this issue.

RESULTS OF PRECLINICAL STUDIES: THE PHARMACOLOGIC PROFILE OF ROTIGOTINE

Rotigotine: the Active Compound

Rotigotine is the (–)-enantiomer of the aminotetralin derivative, 2-(N-propyl-N-2-thienylethylamino)-5-hydroxytetralin; (originally termed N-0437), and is structurally similar to dopamine. Early preclinical in vitro binding studies and in vivo studies investigating the anti-Parkinson’s potential of N-0437 were performed on the (±) enantiomeric mixture of N-0437. However, it was found after separation of the enantiomers that the (+) and (–) enantiomers of N-0437 showed marked differences in their pharmacologic action; although both have been shown to act as agonists in presynaptic models of dopaminergic receptor activity (induction of hypomotility in mice), only the (–) enantiomer (–)-N-0437 was effective in postsynaptic models (rotation in 6-hydroxydopamine-lesioned rats). Although administration of the (–) enantiomer improved locomotor activity in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-lesioned primates, there was no activity following administration of the (+) enantiomer. Preclinical studies such as these led to the development of the (–) enantiomer of N-0437 (rotigotine) for the treatment of PD [which later was also used under the code N-0923, whereas the (+) enantiomer was termed N-0924].

The Receptor Profile of Rotigotine

Dopamine receptor activity

The affinity and functional activities of rotigotine have been determined at a broad range of cloned human receptors in vitro. Conventional binding assays have shown that, of the dopamine receptors, rotigotine binds with the highest affinity to the D3 receptor (inhibition constant [Kᵢ] value of 0.71 nM), whereas its affinity is approximately 20-fold weaker at the D2 receptor (Kᵢ value = 13.5 nM), and approximately 100-fold weaker at the D1 receptor (Kᵢ value of 83 nM). Rotigotine also binds to the D4 (Kᵢ of 3.9 nM at D4.2, 5.9 nM at D4.7, 15 nM at D4.4) and D5 (Kᵢ of 5.4 nM) receptors. Functional assays, measuring intrinsic activity, have confirmed that rotigotine behaves as a potent agonist at all five dopamine receptors; its potency at the D3 and D2 receptors is 2600 and 53 times higher than that of dopamine, whereas it is similar to that of dopamine at the D1 receptor. Activation of the D1 receptor is unique to rotigotine among the non–ergot-derived dopamine receptor agonists; for example, pramipexole and
Ropinirole have been shown to act at the D2 and D3 receptors, but exhibit little or no affinity at the D1 receptor. The ergot-derived dopamine receptor agonist, pergolide, does have D1 receptor properties, but is not widely available.

The dopamine receptor-binding and activation profile of rotigotine is clearly key to its role in PD. The role of D3, D2, and D1 receptors in the control of normal motor activity by dopamine, and their activation in the treatment of PD, are well recognized. Anatomic and neurochemical studies reveal that the D3 receptor is presynaptically localized in the substantia nigra pars compacta and seems to play a role in modulating dopamine release. The D2 receptor is abundant in the caudate-putamen of the dorsal striatum; stimulation is thought to increase locomotion. The D1 receptor is the most widespread dopamine receptor in the central nervous system and is highly expressed in the striatum. Evidence suggests a synergistic interaction between D1 and D2 receptors; in the MPTP-lesioned monkey model of PD, a high-efficacy D1 receptor agonist acted synergistically with a D2 receptor agonist to prolong the motor stimulation induced by each drug alone.

**Nondopamine receptor activity**

Among nondopaminergic sites, rotigotine also binds to serotonergic 5-hydroxytryptamine (5-HT)1A and alpha2B-adrenergic receptors, at concentrations similar to those at the D1 and D2 receptors (K_i = 30 nM and 27 nM). Rotigotine acts as an agonist at the 5-HT1A receptor, but as an antagonist at the alpha2B receptor, and this may also play a role in its efficacy profile.

Although PD is primarily a disorder of the nigrostriatal dopaminergic pathway, dysfunction of nondopaminergic systems, including serotoninergic and norepinephrinergic pathways, may contribute to the development of both motor and nonmotor symptoms. For example, depression is a common nonmotor symptom in patients with PD and has been linked to low serotonin levels; imaging studies have reported reduced 5-HT1A receptor binding in patients with major depressive disorders compared with normal controls, and reductions in serotonin levels of approximately 50% have been reported in the cortex and basal ganglia of patients with PD. Furthermore, alpha2-adrenoceptors located within the striatum may modulate gamma-aminobutyric acid–ergic function and contribute to the generation of dyskinesias in PD. Activation of 5-HT1A receptors and inhibition of alpha2-adrenergic receptors have therefore been identified as potential therapeutic strategies for the treatment of motor symptoms of PD as well as certain nonmotor symptoms, such as anxiety and depression. In experimental studies, specific alpha-adrenergic receptor antagonists, when combined with levodopa, have been shown to reduce the incidence of dyskinesias and prolong the antiparkinsonian effect of levodopa, whereas the alpha2-adrenergic receptor antagonist mirtazapine, which also acts at several 5-HT receptor subtypes, has been shown to improve depressive symptoms and sleep parameters. Thus, agents that target the serotoninergic and norepinephrinergic pathways, in addition to the classic dopaminergic system, may prove useful in the treatment of PD.

**In Vivo Effects of Continuous Administration of Rotigotine**

In rats, a single subcutaneous injection of the slow-release rotigotine preparation resulted in a constant level of extracellular striatal rotigotine for up to 48 hours and a concomitant sustained decrease in extracellular dopamine as measured using a microdialysis probe inserted into the striatum. In 6-hydroxydopamine–lesioned rats, Schmidt and colleagues (2008) showed that subcutaneous administration of slow-release rotigotine nearly abolished the induction of dyskinetic movement...
compared with pulsatile administration of rotigotine (once-daily or twice-daily intra-peritoneal injection) or pulsatile levodopa. In MPTP-lesioned marmosets, continuous rotigotine infusion (delivered via osmotic pump) reduced the expression of dyskinesias compared with pulsatile administration (Fig. 1). Although both continuous and pulsatile administration of rotigotine improved motor deficits and normalized motor function, animals receiving pulsatile rotigotine eventually reverted to a parkinsonian state during the trough of the plasma levels and were unresponsive to external stimuli during that period. In contrast, animals receiving continuous rotigotine performed their normal diurnal activities, and continued to remain responsive to external stimuli during that period.

Rotigotine Toxicology

The toxicology of rotigotine has been evaluated in several preclinical studies and results are available in summary in the prescribing information for rotigotine and presented in detail in the marketing-authorization scientific discussion. To summarize, retinal degeneration has been observed in a 3-month study of rats receiving rotigotine; however, it has not been observed in routine histopathologic observation of other species, and the relevance to humans is unknown. Moreover, the dose used in this study was equivalent to 5.6 times the maximum human recommended dose. In carcinogenicity studies in male and female rats receiving rotigotine, Leydig cell hyperplasia and testicular and uterine tumors were observed following administration of medium to high doses; these tumor types are related to the well-known effect in rats on decreased prolactin levels by dopamine agonists such as rotigotine. The accumulated information of compounds in this class has led to the conclusion that rotigotine does not seem to pose a carcinogenic risk for humans. At high doses, rotigotine has been shown to reduce the motility of spermatozoa in male rats, but to have no effect on fertility. However, fertility was reduced in female rats. The implication of these effects for humans is not known. No clinically relevant changes in clinical laboratory values, vital signs, physical examinations, or electrocardiogram results that indicate toxicity have been reported in any of the human clinical studies conducted to date.

Fig. 1. Continuous subcutaneous application of rotigotine resulted in increased duration of locomotor activity, increased reversal of motor disability, and shorter duration of dyskinesias, compared with pulsatile rotigotine delivery in MPTP-lesioned marmosets. Black bars, continuous subcutaneous application of rotigotine; white bars, pulsatile rotigotine delivery. (Data from Stockwell KA, Scheller D, Rose S, et al. Continuous administration of rotigotine to MPTP-treated common marmosets enhances anti-parkinsonian activity and reduces dyskinesia induction. Exp Neurol 2009;219(2):533–42.)
PROPERTIES OF THE ROTIGOTINE TRANSDERMAL SYSTEM

Rotigotine is highly lipid soluble, and therefore appropriate for transdermal administration, whereas oral formulations of rotigotine undergo extensive first-pass gastrointestinal (GI) metabolism. In a study in MPTP-lesioned marmosets, topical application of an alcohol-based rotigotine solution improved locomotor activity for up to 48 hours, whereas the duration of action of the intraperitoneal and oral formulations was approximately 2 hours. Thus, these data support the administration of rotigotine via the transdermal route. The transdermal delivery system consists of a thin, silicone-based, matrix-type patch composed of 3 layers (Fig. 2) as follows:

- A flexible backing film that provides structural support and protects the drug-loaded layer from the environment
- A self-adhesive drug matrix layer that contains the active component rotigotine and inactive components
- A transparent polymer liner that protects the adhesive layer during storage and is removed before application.

Rotigotine drug delivery has been shown to be proportional to patch size. Hence, increasing the surface area of the patch allows the dose to be increased. For the treatment of PD, patches are available in several sizes: 10 cm², 20 cm², 30 cm², and 40 cm²; it has been estimated that the release of rotigotine from the patch is 0.2 mg/cm² over a 24-hour period. Thus, the apparent dosage of rotigotine ranges from 2 mg/24 h for a 10-cm² patch containing 4.5 mg to 8 mg/24 h for a 40-cm² patch containing 18 mg.

RESULTS OF PRELIMINARY CLINICAL STUDIES

Proof-of-concept Studies of Rotigotine in Patients with PD

Preliminary clinical studies of early formulations of rotigotine in patients with PD suggested that rotigotine was efficacious for the treatment of the motor symptoms of PD. Continuous intravenous infusion of rotigotine over 4.5 hours to 9 patients with moderate to severe PD showed antiparkinsonian effects, as measured by a modified Columbia scale. In a 3-week, phase II, placebo-controlled, dose-finding trial of an early patch formulation of rotigotine in 85 patients with PD, administration of the 2 highest doses of rotigotine enabled the levodopa dose to be reduced (primary outcome). In a 4-week study of 7 patients with advanced PD and on/off fluctuations...
and dyskinesias, transdermal administration of rotigotine allowed a reduction in levodopa dose without loss of antiparkinsonian efficacy. Moreover, there was a dose-response relationship between rotigotine dose and the reduction in levodopa, and most patients experienced less off time and more on time without dyskinesia. In these preliminary studies, rotigotine was also well tolerated. Based on these favorable preliminary findings, studies to evaluate the metabolism and disposition of rotigotine were undertaken.

**Rotigotine Metabolism**

The metabolism of rotigotine has been investigated in vitro in rat, monkey, and human liver microsomes, and perfused rat livers, and in vivo in healthy humans. These studies show that rotigotine is extensively metabolized in vivo, with the major route being conjugation of the parent compound by sulfation. A further metabolic pathway is through cytochrome P450 (CYP)–dependent N-dealkylation to N-despropyl-rotigotine and N-desthienylethyl-rotigotine, which are, in turn, subsequently conjugated with sulfate or glucoronide. The main metabolites of rotigotine are thought to have little pharmacologic activity because plasma concentrations are more than 10 times lower than that of the parent compound. Preclinical studies show that multiple CYP isoforms are able to metabolize rotigotine, suggesting that no specific CYP isoform acts as a rate-limiting factor for rotigotine metabolism. This is relevant when considering potential drug-drug interactions, as discussed later in this article.

Rotigotine metabolites are predominantly excreted by the kidneys (71% in urine) with 23% excreted via the feces, which corresponds with a renal clearance of 12.3 L/h and fecal clearance of 4.0 L/h (Fig. 3). Less than 1% of the parent rotigotine compound is excreted unchanged in the urine. Transdermal delivery of rotigotine is unaffected by food, gastric emptying or impaired gastric motility, or first-pass metabolism.

**Steady-state Pharmacokinetics of Rotigotine**

In vitro studies conducted on excised human skin have shown linear drug permeation of rotigotine over the intended application time of 24 hours with the rotigotine patch. Approximately 95% of the rotigotine in a 10-cm² patch (containing 4.5 mg rotigotine) is recovered within 96 hours of patch application, inclusive of the residual rotigotine in

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**Fig. 3.** Most radiolabeled rotigotine is excreted by the kidneys. (From Cawello W, Wolff HM, Meuling WJ, et al. Transdermal administration of radiolabelled [14C]rotigotine by a patch formulation: a mass balance trial. Clin Pharm 2007;46(10):851–7; with permission.)
the patch. In healthy volunteers or patients with early-stage PD, once-daily application of the rotigotine patch provided stable, dose-dependent, steady-state plasma concentrations over the 24-hour patch application period. Moreover, mean plasma concentrations of rotigotine were similar for different patch application sites. The absolute bioavailability of rotigotine after patch application is approximately 37% to 46% of the applied dose (>60% of the drug delivered to the skin). Rotigotine plasma concentrations increase over time, reaching maximum levels between 12 and 24 hours after first patch application in healthy human subjects, and they decrease quickly, with an elimination half-life of 5.3 hours, after patch removal. A slight transient dip in mean rotigotine plasma concentrations has been observed over the 1 to 4 hours following the application of a new patch, but this is consistent with a lag time for absorption with a new patch. Overall, plasma levels of rotigotine generally remain stable throughout long-term treatment. It is thought that the negligible changes during periods of patch removal and replacement are unlikely to have any clinically relevant impact on motor performance.

**Drug-drug Interactions with Rotigotine**

Drug metabolism via the CYP system is a key source of drug interactions that can result in drug toxicity, reduced efficacy, or an increase in side effects. However, as noted previously, multiple pathways and CYP isoforms seem to be capable of metabolizing rotigotine; thus, if one pathway is inhibited, others can continue to metabolize the drug. In vitro studies with human CYP enzymes have shown that selective inhibition of these CYP isoforms fails to inhibit rotigotine metabolism. Moreover, subcutaneous rotigotine administration did not significantly affect CYP enzyme activity in cynomolgus monkeys. Hence, rotigotine can be expected to have a low risk of drug-drug interactions. Coadministration of rotigotine with domperidone, a dopamine receptor antagonist that undergoes extensive CYP enzymatic metabolism and that is commonly used as an antiemetic in patients treated with levodopa or dopamine agonists, did not change the pharmacokinetic profile or renal elimination of rotigotine in healthy subjects. These data suggest that rotigotine has a low risk of clinically relevant drug-drug interactions related to CYP-450 metabolism. Moreover, in patients with RLS, the mean concentration-time profiles of rotigotine, levodopa, and carbidopa were similar during monotherapy and combination therapy, suggesting a lack of pharmacokinetic interactions between these compounds. However, as would be expected, rotigotine may potentiate the adverse effects of levodopa.

**Pharmacokinetics of Rotigotine in Special Populations**

Because the prevalence of PD increases with age, the effects of impaired hepatic or renal function on the pharmacokinetics of PD drugs must be considered. The pharmacokinetics of rotigotine are similar regardless of age (<65 years and ≥65 years) or gender in patients with early-stage PD, and are similar in healthy Japanese and white subjects administered a single rotigotine transdermal patch. Moreover, moderate hepatic impairment (Child-Pugh class B) does not seem to affect rotigotine pharmacokinetics or the renal clearance of unconjugated rotigotine following repeated patch application. In addition, no differences in bioavailability or total clearance of rotigotine were observed between healthy subjects and symptomatic volunteers with mild to severe chronic renal insufficiency and those requiring hemodialysis; mean plasma concentration-time curves of unconjugated rotigotine and the incidence of adverse events were similar between groups. Taken together, these results suggest that adjustments of rotigotine dose are not required for patients with moderate hepatic impairment or chronic renal insufficiency.
BENEFITS OF TRANSDERMAL DELIVERY VERSUS ORAL ADMINISTRATION

Transdermal administration may be more pharmacologically effective than oral administration for patients with PD. Transdermal administration provides continuous delivery of medication, resulting in constant plasma levels, and therefore avoids the plasma level peaks and troughs associated with more pulsatile oral drug delivery. Moreover, it enables controlled drug delivery over longer periods of time than with oral administration, and administration can be readily discontinued by patch removal.\textsuperscript{62,73} It may improve patient compliance, particularly in patients already receiving multiple oral medications or in patients who may have difficulty swallowing.\textsuperscript{74} Transdermal delivery also avoids hepatic first-pass metabolism and the GI tract. GI disorders, including difficulty swallowing and delayed gastric emptying, are the most commonly observed nonmotor symptoms of PD; the results from a retrospective claims database analysis suggest that around 65\% of patients with PD have a GI disorder 4 years after diagnosis of PD.\textsuperscript{75} Delayed gastric emptying results in increased retention in the stomach, which, in turn, leads to inconsistent intestinal absorption of orally delivered medication. Thus transdermal drug delivery may be preferable to oral administration in patients with PD with altered gastric emptying and other GI disorders.

A retrospective cohort study has shown that patients with PD have significantly longer acute hospital stays and significantly higher in-hospital mortality than individuals without the disease.\textsuperscript{76} Because oral PD medications often require multiple doses throughout the day, many patients with PD undergoing surgical procedures likely miss one or more doses of medication. Thus, the management of PD symptoms in surgical patients is commonly problematic. Issues include postoperative confusion, worsening of PD, off symptoms, and parkinsonism-hyperpyrexia following sudden withdrawal of dopaminergic medication.\textsuperscript{77--79} Transdermal delivery of rotigotine may be of particular value in patients undergoing surgery by potentially reducing the complications associated with disruption of regular medication dosing schedules.\textsuperscript{79,80} In one study, the oral PD medications (levodopa, pramipexole, ropinirole, amantadine, catechol-O-methyl transferase (COMT) inhibitors, rasagiline, and biperidine) of 14 patients with PD receiving general anesthesia\textsuperscript{79} were switched to transdermal rotigotine the evening before surgery, with most patients (64.3\%) able to switch from rotigotine back to prior PD medications within 24 hours following the surgery. Based on a feasibility questionnaire, nearly all neurologists and anesthesiologists (89\% for both), and 100\% of patients, completely agreed (rating of 1) or agreed (rating of 2) that the transdermal rotigotine patch was an easily feasible option for managing perioperative PD symptoms. Of the neurologists, 7 of 9 (78\%) completely agreed (rating of 1) that no unexpected perioperative PD symptoms occurred. These findings are consistent with those of an earlier case study\textsuperscript{80} in which no perioperative worsening of symptoms was noted for 25 patients with PD who had undergone a surgical procedure unrelated to PD and had received rotigotine. A non–clinically important difference of 0.4 (±3.08) points was found between the preoperative and postoperative Unified Parkinson’s Disease Rating Scale (UPDRS) part III score, signifying sustained control of parkinsonian symptoms (a difference of 2.3–2.7 points reflects a minimal clinically important difference on UPDRS part III\textsuperscript{81}).

RESOLVING TRANSDERMAL ROTIGOTINE CRYSTALLIZATION

The formation of rotigotine crystals in the transdermal patch led to the product being withdrawn from the US market in 2008 because of concerns as to the impact on the bioavailability of rotigotine and the subsequent effects on efficacy. The crystallization is caused by the formation of a more stable and less soluble polymorph of pure
rotigotine within the patch. Because only free molecules of rotigotine can cross into the skin, the crystals need to dissolve for rotigotine molecules to be absorbed. Modification of the production process to inhibit the formation of crystals and implementation of a cold chain storage and distribution system in which the patches are refrigerated from the manufacturer to the patient have alleviated these concerns in Europe. However, in the United States, the US Food and Drug Administration (FDA) requested an alternative approach to the cold chain solution, which has led to the development of a novel room-temperature formulation of the rotigotine transdermal patch. The bioavailability of this newer room-temperature formulation is consistent with the previous formulation of the rotigotine patch, thus satisfying the FDA requirements.

SUMMARY

The rotigotine transdermal system provides a continuous mode of delivery, and a convenient once-a-day, nonoral option for treating the signs and symptoms of PD. It is hoped that continuous delivery provides a more physiologic option for treating PD. Pharmacokinetic analysis of the rotigotine transdermal system has shown stable plasma levels of rotigotine within the intended application time of 24 hours, with negligible variation in the periods between patch removal and replacement. Rotigotine has a low risk of drug-drug interactions because its metabolism is independent of a single CYP-450 enzymatic pathway, and dosing adjustments are not required in patients with hepatic or renal insufficiency. Its perioperative use in patients with PD who are undergoing surgical procedures represents a particular advantage for its transdermal mode of delivery.

In conclusion, the preclinical and clinical development of the rotigotine transdermal system has established this system as an effective method for providing continuous delivery of a dopamine agonist across the skin, and may have clinical advantages compared with other agents.

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