

Neupro® – A New Alternative to Conventional Parkinson's Therapy

a report by

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The first and only transdermal patch for the monotherapy of Parkinson's disease (PD) is now available.

Optimal symptom control is the goal of Parkinson's therapy. A novel alternative to the existing conventional therapies is now available. Schwarz Pharma has launched the first ever Parkinson's patch, Neupro®, which is indicated as monotherapy for the treatment of early-stage PD. Application for market authorisation in Europe for the treatment of advanced PD in combination with Levodopa (L-dopa) has been filed. Neupro contains the non-ergolinic dopamine agonist rotigotine, a molecule suited for transdermal application. Patients treated with Neupro could benefit from the constant release of rotigotine, leading to stable plasma levels and symptom improvement over 24 hours. Approval for combination therapy with L-dopa is expected in 2007.

What is the rationale of a transdermal Parkinson's therapy? Due to the chronic-progressive development of PD, a lifelong therapy is needed. The choice of therapy should be based on the type and intensity of symptoms, the age of the patient, as well as possible co-morbidities. Recently, complications in late stages of the disease, such as dyskinesia, or 'on-off' fluctuations, have become a particular focus. To prevent the development of such complications, continuous dopaminergic stimulation (CDS) is thought to be the key.

Oral medication that is usually taken several times a day causes peaks and troughs in drug plasma levels. After each intake of a tablet, plasma levels rise, reach a peak and finally decrease again until it is time for the next intake. Not only during low plasma levels but also at the peaks, Parkinson's symptoms can be present. These fluctuating plasma levels are thought to translate into pulsatile dopaminergic stimulation, which is also considered to contribute to the long-term development of dyskinesia.¹

This background sets the stage for the research of the

neupro therapy, which offers stable plasma levels, whilst being convenient to use. Applied once a day, Neupro releases rotigotine continuously over the next 24 hours and therefore leads to stable rotigotine plasma levels. A study showed clinically relevant improvements, with rotigotine treatment in early morning motor abilities 12 to 24 hours after last-patch application, as well as improvement in nocturnal akinesia, dystonia and cramps, and a reduction in the number of nocturias.²

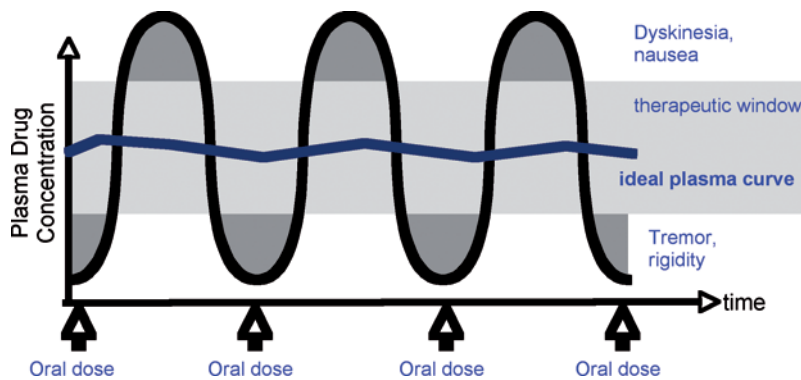
"So what's exciting here," says Dr Peter LeWitt, Professor of Neurology at Wayne State University, Detroit, US, "is that I think that we have the potential for smoothing out dopaminergic stimulation, from day one of treatment, if Neupro is used initially and gives patients continued relief, much like their physiological state before they had Parkinson's".

Rotigotine, a Novel Non-ergolinic Dopamine Agonist

Rotigotine is a novel non-ergolinic D3/D2/D1 dopamine receptor agonist developed for patch application. Analysis of the receptor profile of rotigotine showed agonistic activity at all dopamine receptor subtypes, with a pronounced preference towards the D3 receptor. The affinity to the D3 receptor is approximately 10 – 20 - fold higher than to the D2 receptor and about 100 – fold higher than the D1 receptor. Rotigotine also has agonistic activity on serotonergic 5-HT1A receptor and adrenergic alpha2B receptor. The effect of rotigotine via D3, D2 and D1 receptors, are thought to improve the motor symptoms in the treatment of PD. Current scientific opinion is that the activity on 5-HT1A and alpha2B receptors, could mediate antidepressive and neuroprotective activity. Its molecular structure largely resembles that of the natural transmitter dopamine.³

Rotigotine does not stimulate the 5HT2B receptor. The 5HT2B receptor is thought to mediate fibrotic complications, as seen with ergolinic dopamine agonists.⁴

Figure 1: Variable Versus Stable Plasma Levels of Dopaminergic Treatment in Parkinson's Disease, Schematic Description



Improvement of Unified Parkinson Disease Rating Scale (UPDRS) score

In more than 15 studies with approximately 1,500 patients, efficacy of Neupro has been proven. Neupro is the first dopamine agonist to get approval-granted as monotherapy for early-stage PD, before receiving the advanced licence. Treatment with the Neupro patch using dosages of 6mg/24h and 8mg/24h rotigotine resulted in a significant improvement of the UPDRS subscales II and III.⁶

As adjunct therapy, the rotigotine transdermal patch reduces 'off' times significantly and increases 'on' times without troublesome dyskinesia.⁷ Application for market authorisation in Europe, for the treatment of advanced PD in combination with L-dopa, has already been filed with the European Medicine Agency (EMA).

Neupro is Generally Well Tolerated

The safety and tolerability profile of Neupro, was tested in a comprehensive clinical trial programme in patients with PD.

The transdermal application of rotigotine was generally well tolerated. Most adverse events were typical of those observed with other dopaminergic agents, such as nausea, vomiting, somnolence and dizziness. As compared to other dopamine agonists, relatively low rates of adverse events like orthostatic hypotension, leg oedema and psychiatric side effects like hallucinations were observed. Application site reactions were the only adverse event specific for Neupro, which was usually mild to moderate in intensity and caused 5% of the patients to stop treatment. Overall, 6% of placebo-treated patients, compared to 14% in the active group, discontinued due to adverse events.⁸

Neupro Offers Additional Benefits

Although PD is often considered a movement disorder, it is now known that patients are suffering not only from motor symptoms, but also from non-motor symptoms. Among those non-motor symptoms are sleep disturbances, which may be as debilitating for patients as the motor symptoms. So far, treating sleep problems with PD medication has been limited, due to the wearing-off of conventional anti-Parkinsonian therapies at night. Now Neupro may offer relief to these patients because its patch formulation releases the dopamine agonist rotigotine 24 hours, day and night.

There can be many causes of Parkinson-associated sleep disturbances. Painful cramps, rigidity in the limbs, but also urges to go to the bathroom, can trigger patients to wake up each night. Eventually, sleep problems may lead to decreased vigilance during the day and, thus, these problems may have an impact on the patient's quality of life. Conventional oral medication usually has to be taken several times a day, although it can wear off at night, causing some patients to get up to take pills in the middle of the night. With the launch of Neupro, the first Parkinson's Patch, a medication is now available that offers a once-a-day application.

In an exploratory, open-label study, Neupro showed a clinically relevant improvement in early-morning motor impairment, measured as a decrease on the UPDRS I, II and III. Also, improvement has been found in the Nocturnal Akinesia, Dystonia and Cramps Score (NADCS) that measures Parkinson's related night-time symptoms. The average number of nocturias was also reduced by the rotigotine treatment.⁹ "The above observations suggest that the rotigotine transdermal patch may improve sleep quality in PD patients by improving PD symptoms at night and reducing the numbers of nocturias" says Dr Nir Giladi from the Tel Aviv Sourasky Medical Center in Israel. These findings will have to be confirmed in a well-designed, placebo-controlled study.

Patient Survey Reveals Need for Help in Daily Life

Fifty-one per cent of Parkinson's patients ask for a new therapy with fewer tablet administrations, according to a survey involving 250 patients with early-stage PD, and 250 patients with late-stage PD across six countries.¹⁰ Among the early-stage patients, 7% had already experienced swallowing difficulties due to their disease. In the early stages of the disease, tablets have to be taken up to three times per day. In later stages, 20 tablets and more per day is not an unusual medication schedule. Improving motor symptoms is the second most

frequent requirement of patients (28%), followed by improved tolerability of medication (7%).

Impairments were evaluated that develop during the early stages of PD. Patients suffered from early morning motor impairment (33%), pain (33%), restless legs syndrome (22%) and dyskinesias (16%). At night, patients complained of nocturias (30%), as well as decreased sleep quality (28%) and sleep quantity (26%).

Thirty-four per cent of patients with early-stage PD complained that with conventional therapy, early-morning akinesia is not treated because the effect of medication wears off ('wearing-off phenomenon'). In conclusion, 27% of patients do not generally consider the currently available therapies suitable to support an independent life. Fifty-one per cent of all patients wish for a new therapy with less tablet intakes.

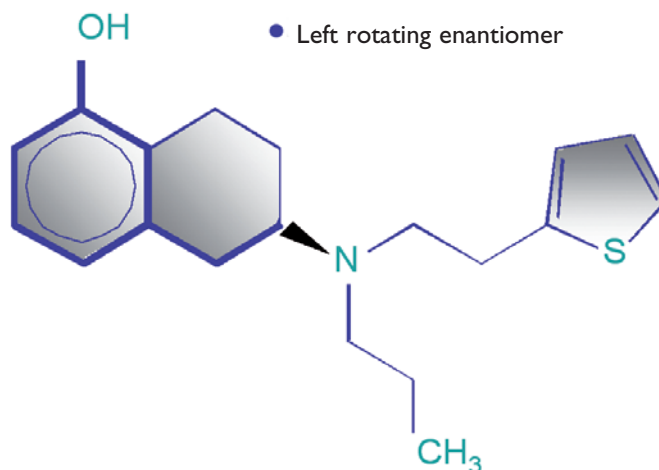
Compliance Rate Improves with Transdermal Rotigotine

A survey of patients receiving transdermal rotigotine showed an improved self-reported compliance with the patch, compared to their former oral therapy, which continued to be the case in long-term use.¹¹ Additionally, studies are available providing evidence that the compliance rate for oral therapies, especially for complicated dose schedules, can be as low as 50%.¹²

Conclusion

Neupro is available in four patch sizes, translating

Figure 2: Rotigotine Structure⁵



into four different strengths. Dosages available are: 2mg/24 h, 4mg/24h, 6mg/24h and 8mg/24h. A single daily dose should be initiated at 2mg/24h, and then increased in weekly increments of 2mg/24h to an effective dose up to a maximal dose of 8mg/24h.

Neupro is an innovative alternative to oral Parkinson's therapy. With Neupro, patients will benefit from stable plasma levels, as well as the non-ergolinic structure of rotigotine.

Neupro may also offer additional benefits, such as improved early-morning motor and night-time Parkinson's symptoms. Once-daily application and ease of use may be the reason for improved compliance with the patch as reported by patients. ■

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