# USE OF A RIVASTIGMINE TRANSDERMIC PATCH IN ALZHEIMER'S DISEASE AND PARKINSON'S DISEASE DEMENTIA

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**ABSTRACT**

Alzheimer's disease and Parkinson's disease dementia are becoming a public health issue. Given the therapeutic pitfalls in the elderly, there is a need of effective therapies. Rivastigmine, a cholinesterase inhibitor, emerges as an important agent in the symptomatic treatment of dementia. The efficacy of this drug has been shown in several studies, being now included in the guidelines for dementia management. The new matrix rivastigmine patch represents a step forward in managing the elderly patient with dementia. The IDEAL (Investigation of Transdermal Exelon in Alzheimer's disease) study demonstrates the superiority of the transdermal rivastigmine patch over capsules, proving an increased tolerability and compliance for the 9.5 mg/24 h rivastigmine patch in patients with Alzheimer's disease. The transdermal patch with rivastigmine may offer additional therapeutic benefits and may prove to be the best delivery system for this drug to treat Alzheimer's disease. The benefits of rivastigmine in dementia associated with Parkinson's disease have been shown by a smaller study, using the oral formula, but a study using rivastigmine patch is still lacking. The new technological developments in drug delivery may change our view in managing patients, improving their adherence to therapy and better results.

**Key words:** Alzeimer's disease, Parkinson's disease dementia, rivastigmine, transdermal patch.

## INTRODUCTION

As life expectancy increases and the elderly population grows in number, so does the risk of neurodegenerative disorders. Of this group of neurological disorders, Alzheimer's disease (AD) and Parkinson's disease (PD) are the most common. AD is characterized by a progressive loss of memory and cognitive functions, resulting in an impaired ability to perform activities of daily living. It is the most commnon form of dementia in older adults, accounting for 60-70% of all cases (1). The hallmark of PD is damage of the motor system, causing tremor, rigidity, and slowness of movement. But cognitive symptoms are frequently present at the time of diagnosis, contribute heavily to disability, and progress to dementia at an alarming rate. Dementia will develop in 40-70% of patients with PD during the course of their illness. The term "Parkinson's disease dementia" (PDD) refers to dementia that develops at least two years after the diagnosis of PD (2). The presence of dementia represents a burden for caregivers, including families and the medical system, involving huge costs for the society. On the other hand, the old patient has reduced compliance to any treatment. Dementia, mainly of the AD and PDD type, has developed to an important public health issue in the modern world.

Until now, the therapy for dementia was limited, the backbone being symptomatic therapy, in an attempt to slow the progression of the disease. Disease modifying treatment is only experimental, none being approved for human use. Two classes of drugs are approved for the simptomatic treatment of AD: the cholinesterase inhibitors (ChEI) – rivastigmine (Exelon®), donezepil (Aricept®) and galantamine (Razadine®) – and the NMDA receptor

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modulators – memantine (Nameda®) (3). Of these drugs, only rivastigmine has been approved in the USA for the treatment of PDD (3).

There are some particular aspects in the pharmacotherapy of the elderly patient, and, chiefly, of the demented patient. The elder patient has a modified metabolism of drugs and the doses have to be adequately formulated, but not always in the efficient range. The tolerance is reduced and the risk of adverse effects rises, most of the discontinuation of treatments being the effect of intolerable side effects. The older patient, and mostly the demented patient forgets to take the medication and caregivers are not always around. This is true for most drugs, and the empiric administration of prescribed drugs may lead to an increased risk of overdoses, or, on the other hand, to false negative therapeutic results, due to gaps in therapy (4).

Until recently, all pharmacological treatments for dementia were delivered orally, exposing the patients to the aforementioned pitfalls. The ChEI are the mainstay of therapy for the symptoms of AD and the recent guidelines of the American Academy of Neurology (AAN) recommend that the ChEI should be considered in patients with mild-to-moderate AD (5). There is a medical need for effective, well-tolerated treatment options that have the potential to enhance compliance and improve treatment outcome in patients with dementia.

Rivastigmine patch is the first transdermal treatment approved for AD and PDD (3). The advantages of this type of therapy over conventional oral therapy are: smooth drug delivery with reduced side effects; avoidance of the gastointestinal tract; independence of food intake; avoidance of the first pass effect; access to higher doses with concomitant therapeutic effect; a simple treatment option for patients on multiple medications; and enhanced compliance (3,6,7).

A patch has the potential to minimize drug level fluctuation in the blood by maintaining the plasmatic level within the "therapeutic window", and thus, avoiding variation in plasma drug levels which, subsequently, will decrease the side effects and will increase the efficacy.

## OVERVIEW OF RIVASTIGMINE

Rivastigmine is an established dementia therapy. It was first introduced in Switzerland in 1997. Deterioration in cholinergic neuronal pathways has been associated with cognitive decline in patients with AD. It seems that ChEI may be of benefit by prolonging the activity of ACh in the neuronal synapse by preventing the breakdown of Ach (3). Patients with PDD have a greater cholinergic deficit than those with AD, and the extent of the deficit correlates with the severity of cognitive symptoms; patients with PDD have less devastation in the number of neocortical neurons, which can benefit from cholinergic repletion (2). Treatment with these agents has demonstrated its efficacy in cognition, functional activity and behavioural symptoms (3).

Rivastigmine is available in oral administration forms, either capsules or liquid, and in the new transdermal patch developed by Novartis – Exelon® (2,3). The latter form has an improved tolerability and releases the drug more slowly and gradually than the oral formulation.

A number of properties make rivastigmine well suited for transdermal delivery. Its low molecular weight and amphipathic nature, having both lipophilic and hydrophilic properties, allow rivastigmine to pass easily through the skin into the bloodstream. In addition, the potency of rivastigmine allows patches to be discreetly small (3,6,7,8,9).

Rivastigmine is embedded in a new transdermal patch utilizing matrix technology. Matrix patches comprise four main components: a colored, protective backing layer; an acrylic matrix layer in which the drug substance is stored along with an acrylic polymer; a silicone matrix layer; and the release TTliner, which facilitates skin absorbtion and minimizes skin reactions. In addition to rivastigmine base, the patch contains vitamine E, as antioxidant, poly-butylmethacrylate, methyl-methacrylate, acrylic copolimer, all as coating and agents with mecanical properties, and, finally, silicone oil, included in the adhesive matrix (3,6).

## PHARMACODYNAMICS AND PHARMACOKINETICS

Rivastigmine is a carbamate compound. The precise mechanism of action is unknown, although it is thought to be due to the enhancement of cholinergic function. It acts as a selective, reversible inhibitor of acetylcholinesterase (AchE) and butyrylcholinesterase (BuChE), with a stronger effect on BuChE than on AchE (11). Because the duration of the inhibition is longer than its elimination half-life, rivastigmine can be classified as a pseudo-irreversible cholinesterase inhibitor (11). The result of this inhibition is the accumulation

of ACh in the neural synapse and a longer Ach effect. Also, it inhibits BuChE and AchE in plaques and tangles, being quite likely that rivastigmine interfere with the disease progression (11). Rivastigmine is selective for central versus peripheral AchE, the therapy being more targeted, with less systemic effects (3,11). Furthermore, since the rivastigmine patch delivers less drug than the oral formula, but with constant concentration in time, it has even milder secondary effects.

Rivastigmine is an amphypathic agent with a good absorbtion level through the intact skin, being well suited for transdermal use. After the first application, the lag time for absorbtion is about 0.5-1 hour. After the absorbtion, the drug reaches the peak value ($C_{max}$) in a median time of 8 hours ($t_{max}$), after which the concentration decreases slowly, maintaining a constant plasmatic level until the next adminstration 24 hours later (6). At steady state, through levels are approximately 60-80% of peak level (6,12). Fluctuation, between $C_{max}$ and $C_{min}$ is lower in the patch than in the oral formulation. Exposure to rivastigmine was highest when the patch was applied to the upper back, chest, or upper arm (9,12). Other areas were also used (abdomen and thigh) but the plasma exposure to rivastigmine was 20-30% lower (13).

Rivastigmine is weakly bound to plasma proteins over the therapeutic range. It crosses the blood brain-barrier reaching cerebrospinal fluid (CSF) peak concentration in 1.4-2.6 hours (6).

Rivastigmine is metabolized by AchE and BuChE-mediated hydrolisis to the decarbamylated compound NAP226-90, a metabolite with low in vitro inhibition activity (6). The metabolism of the drug occurs to a lesser extent after patch administration than after oral administration. The excretion of rivastigmine metabolites occurs mainly trough the renal route, with the majority being eliminated in the first 24 hours. The plasmatic half-life is about 3 hours. Rivastigmine's half life in the brain, about 8 hours, is substantially longer than its plasma half-life (6,12).

The rivastigmine 9.5 mg/24h patch provides comparable exposure to the highest capsule dose (12 mg/day), but with prolonged time to $C_{max}$ and lower peaks (3).

There were no significant drug-drug interactions of rivastigmine with other drugs (e.g. antihypertensives, α-blockers, calcium channels blockers, antidiabetic agents, NSAIDs, etc.) and there was no need of dosage adjustment in patients with hepatic or renal impairment. The only patient group that requires additional monitoring are the patients with low body weight of <50 kg, who may experience a higher incidence of adverse events (6,10,12).

The most frequent adverse reactions of rivastigmine are nausea and vomiting, followed by dizziness, headache, asthenia, diarrhea and loss of weight. The first two were reported in almost 1 of 5 treated patients, and they are the two leading causes of treatment discontinuation (3,6,14). To avoid acute and severe reactions, the rivastigmine dose has to be slowly increased, namely titrated. The oral treatment begins with a small dose, generally, 3 mg/day and then, in terms of tolerability, the dose is increased to a maximum of 12 mg/day in a stepwise manner by 1.5 mg every 4 – 8 weeks, or, if adverse reactions occur, the dose is maintainted at the maximum tolerated dose (9,12). Using the patch, the treatment begins with a small patch 5 $cm^2$ realeasing 4.6 mg/24 h, and then after 4 weeks continuing with the 10 $cm^2$ releasing 9.5 mg/24 h, which is the therapeutic dose, equivalent to the 12 mg/24 h regimen (6,9). This single-step dose titration represents a great advantage of the patch therapy.

Patients treated with Exelon capsules or oral solution may be switched to Exelon Patch as follows: a patient who is on a total daily dose of <6 mg of oral rivastigmine can be switched to Exelon Patch 4.6 mg/24 hours. A patient who is on a total daily dose of 6-12 mg of oral rivastigmine may be directly switched to Exelon Patch 9.5 mg/24 hours. It is recommended to apply the first patch on the day following the last oral dose.

## CLINICAL TRIAL RESULTS

The Investigation of Transdermal Exelon in Alzheimer's Disease (IDEAL) study was a 24-week, multicentric, double-blind, double-dummy, placebo- and active-controlled study comparing the efficacy, safety and tolerability of the rivastigmine patch with conventional rivastigmine capsules and placebo. In total, 1,195 patients with mild-to-moderate AD, both men and women, with a mean age of 73 years, were randomized to one of four treatment groups: rivastigmine 9.5 mg/24 h patch (n=293), rivastgmine 17.4 mg/24 h patch (n=303), rivastigmine 12 mg/day capsules (n=297) or placebo (n=302). Primary efficacy measures were the Alzheimer's Disease Assessement Scale – Cognitive subscale (ADAS-Cog) and Alzheimer's Disease Cooperative Study – Clinical Global Impression of Change (ADCS-CGIC). Secondary

outcome measures assessed a range of domains, including behaviour, cognitive performance, attention, executive functions, and activities of daily living. These included the Alzheimer's Disease Cooperative Study – Activities of Daily Living (ADCS-ADL), Mini-Mental State Examination (MMSE), Neuropsychiatric Inventory (NPI), Ten Point Clock-drawing Test and Trail-making Test part A. Also, adverse events and vital signs were monitorized and recorded. Patch adesion was evaluated by caregivers, troughout the study (14,15).

This study showed significant improvement in all primary efficacy measures and, also, in the secondary measures in all rivastimine treated groups over placebo (15), indicating once again that rivastigmine is an efficient symptomatic treatment of AD, with the capacity of slowing the mental decline. It is well established that higher doses of rivastigmine are associated with greater efficacy. In the IDEAL study, this dose dependent relationship was apparent on the ADAS-Cog (14). The 10 $cm^2$ patch releasing 9.5 mg/24 h showed the same efficacy as the maximum addmited oral dose 12 mg/24 h, with a substantially lower incidence of the side effect associated with capsules (14). The 20 $cm^2$ patch was associated with much higher levels of exposure than the highest oral daily dose of rivastigmine, being equivalent to 18 – 20 mg/24 h, yet it was tolerated equally as well as the capsule (14).

In the IDEAL study, the rivastigmine 9.5 mg/24 h (10 $cm^2$ patch) emerged as the optimum dose as it was well tolerated with a favorable safety profile in patients with mild-to-moderate AD (3,14,15).

Typical of treatment with any ChEI, the most frequently observed adverse effects were cholinergic in nature. The 10 $cm^2$ rivastigmine patch was associated with two-thirds fewer reports of gastrointestinal side effects compared with capsules. Correspondingly, withdrawals due to gastrointestinal adverse events were reported to be approximately 75% lower in the 10 $cm^2$ patch group than in the capsules group, with no statistically significant differences in nausea and vomiting rates between the 10 $cm^2$ rivastigmine patch group and placebo group (14,15). Good tolerability of the rivastigmine 9.5 mg/24 h patch was also reflected by the fact that the majority of patients in this treatment group attained their target dose (95.9%) (14). No problems with insomnia were reported. The local skin tolerability was very good, and discontinuation due to local skin reactions were rare (14).

Despite higher scores in the ADAS-Cog obtained by patients treated with the 20 $cm^2$ patch, this dose showed no significantly improvement on the other scales, on the one hand, and, on the other hand, it was associated with a higher incidence of adverse effects, comparable to the capsules (14,15).

Adhesion of the rivastigmine patch was very good, with the vast majority (96%) of patches remaining attached to the patient's skin at the end of 24 h, despite their activities or the climate (14).

Caregivers of patients who participated in the IDEAL study expressed a preference for the rivastigmine patch over conventional oral therapy, primarily based on the ease of use and ease of following schedule. These benefits might be expected to improve treatment compliance (14, 15,16).

To conclude, the rivastigmine 10 $cm^2$ patch realeasing 9.5 mg/24 h is an efficient and safe treatment option, and preferred by caregivers in mild-to-moderate AD.

A 24-week randomized, double-blind, placebo-controlled study on oral rivastigmine, conducted on 541 patients with mild-to-moderate PDD, showed a moderate improvement in dementia associated with PD, using the same primary monitoring tools as described in the IDEAL study (2,14,16). As expected, the treatment was associated with adverse effects, predominantly gastrointestinal in nature (nausea and vomiting), leading to discontinuation of therapy, only 55.5% receiving the optimal dose of 12 mg/24 h of rivastigmine (16). It seems that rivastigmine could lead to a worsening of motor symptoms in PD, but an evaluation of the safety profile showed that rivastigmine did not induce clinically significant exacerbation of motor dysfunction in patients with PDD. Rest tremor incidence as an adverse effect was a transient phenomenon during dose titration of rivastigmine (16,17).

This data support the idea of using the rivastigmine patch in the treatment of mild-to-moderate PDD, but at this time, there is no resolute evidence suporting the rivastigmine patch use in PDD.

## CONCLUSIONS

Technology has developed rapidly to provide alternatives to injections and pills, and patches have become more widely used throughout medicine in the past decade (7).

A major barrier to the effective treatment of chronic conditions such as AD and PDD is poor

treatment compliance. Managing medications is complex for patients and their caregivers (3,4).

The Rivastigmine patch is a viable treatment option combining the favorable effects of its base compound, and the new matrix patch technology, targeting not only the symptomatic relief, but also the compliance of the patient for a maximum efficacy. It is a fact that the rivastigmine patch has demonstrated favorable efficacy and tolerability profiles that provide "proof of concept" for the pharmacokinetic rationale underlying its development (3). The patch provides smooth, continuous delivery of the drug, providing a reduced $C_{max}$ and delayed $t_{max}$, with more stable exposure over 24 h. Improved compliance and one-step titration will help caregivers to provide optimal dosing of rivastigmine.

The rivastigmine patch represents a step forward in the management of dementia.

However, cholinesterase inhibitors represent for AD and PDD a symptomatic treatment rather than a pathogenetic one. Several agents that target the underlying disease mechanisms are in development and may offer substantial disease modification.

In the future, it will be ideal to combine the symptomatic therapy with disease modifying drugs for the best outcome for these categories of patients.

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