

A Review of the First Transdermal Treatment for Alzheimer's Disease – The Rivastigmine Patch

a report by

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Currently, cholinesterase inhibitors are the mainstay in clinical practice of symptomatic treatment for Alzheimer's disease (AD). They are believed to act by inhibiting one or both of the enzymes that degrade acetylcholine in the synaptic cleft, i.e. acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE), thereby putatively improving neuronal transmission.¹ An association of AChE and BuChE with the underlying AD pathology has also been reported;^{2,3} however, the long-term clinical impact of these effects, and of targeting one versus both of these enzymes, is still being elucidated.^{1,4}

Currently, there are three cholinesterase inhibitors widely used to treat AD patients: rivastigmine, donepezil and galantamine. Rivastigmine provides sustained inhibition of AChE and BuChE, while donepezil and galantamine are selective AChE inhibitors.⁵ In 2005, rivastigmine became the first approved treatment for mild to moderate Parkinson's disease dementia (PDD). All cholinesterase inhibitors have been available in oral formulations. Recently, a transdermal rivastigmine patch has been developed, and is approved in many countries worldwide (including the US, Latin America, Europe and Asia) for the treatment of AD. The rivastigmine patch has also been approved for the treatment of PDD in the US, Latin America and Asia.

A transdermal drug delivery system has the potential to change the treatment paradigm for many AD patients.⁶ This article reviews the clinical and pharmacokinetic data that supported the development of the rivastigmine patch, and discusses the ways in which the use of a transdermal patch may improve the management of dementia patients in a real-life setting.

Rationale for the Development of a Transdermal Treatment for Alzheimer's Disease

Cholinesterase inhibitors have been shown to exhibit dose–response relationships,^{7–9} with higher plasma levels of the drug corresponding to higher levels of enzyme inhibition. However, the incidence of adverse events

(AEs) also increases with higher oral doses, particularly gastrointestinal occurrences such as nausea and vomiting.¹⁰ Consequently, not all patients in clinical practice are able to achieve and maintain the recommended therapeutic doses of conventional oral cholinesterase inhibitors.^{11,12}

Cholinergic side effects are thought to be the result of high peak plasma concentrations of the drug (C_{max}), rapid absorption into the bloodstream resulting in a short time to C_{max} (t_{max}), and the frequency and magnitude of the resulting fluctuations in drug plasma level.¹⁰ A transdermal patch can provide smooth and continuous delivery of the drug, reducing C_{max} and prolonging t_{max} while maintaining drug exposure.¹³ This pharmacokinetic profile has the potential to reduce the incidence of cholinergic side effects, allowing patients easier access to optimum therapeutic doses, thus improving the effectiveness of treatment over oral administration.¹³ Additional benefits of transdermal administration, including a simplified treatment regimen, convenience and ease of use, are discussed by Bernabei and Martinez-Lage elsewhere in this issue.⁶

The Rivastigmine Transdermal Patch

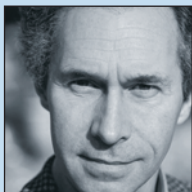
Rivastigmine is chemically well-suited to transdermal delivery. As a small (<500Da) lipophilic and hydrophilic molecule, it passes rapidly through the skin and into the bloodstream, and is therefore considered a viable patch medication.¹⁴ Moreover, rivastigmine is a potent cholinesterase inhibitor, requiring only small doses of the drug for effective treatment.¹⁵ This enables the patches to be small and discreet, thereby improving adhesion and reducing the risk of frequent adverse skin reactions.

Patch Technology

The rivastigmine patch uses modern matrix technology, combining the drug, antioxidants, a polymer mixture (to control the drug delivery rate) and a silicon matrix adhesive into a single layer through which the drug diffuses. Unlike early transdermal patches, there is no 'reservoir' of the drug within the patch or adjunct (such as ethanol) to facilitate diffusion of rivastigmine through the skin. Matrix technology enables the rivastigmine patch to be smaller and thinner than a conventional reservoir patch, demonstrate greater adhesion to the skin and provide a more consistent delivery of the drug.¹⁴ The absence of an adjunct also reduces the potential for frequent adverse skin reactions. The starting-dose (4.6mg/24-hour) rivastigmine patch has a surface area of 5cm² and a diameter of 2.5cm, and the target-dose (9.5mg/24-hour) patch has a surface area of 10cm² and a diameter of 3.5cm.

Pharmacokinetics

The rate and efficiency of rivastigmine absorption through the skin and into the bloodstream can vary with the site of patch application. The ideal site would offer optimal rivastigmine exposure, be easily accessible and avoid areas where adhesion or skin tolerability may be a concern,



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e.g. hairy or sensitive areas. In a recent open-label application study of 40 healthy men and women 40–80 years of age, the pharmacokinetics, adhesion and skin tolerability of the rivastigmine patch were assessed at five suitable application sites: upper back, upper arm, chest, abdomen and thigh. Optimal rivastigmine exposure (greatest AUC_{24h}) was shown to occur when the patch was applied to the upper back, upper arm or chest (122, 116 and 123ng-hour/ml, respectively).¹⁶ The t_{max} remained slow (over eight hours) irrespective of the application site investigated. The overall skin tolerability was good during this study. Based on these findings, it is recommended that the rivastigmine patch be applied to clean, dry, hairless skin on the upper back, upper arm or chest.

As with all transdermal medications, a concentration gradient is required to drive the diffusion of rivastigmine through the skin and into the bloodstream. Therefore, it is necessary to load the patch with more than the required dose. In a study of 51 healthy men and women, both recommended sizes of rivastigmine patch released approximately 50% of their total drug load over a 24-hour period (5cm² patch released 4.6mg [51%]; 10cm² patch released 9.5mg [53%]).¹⁷

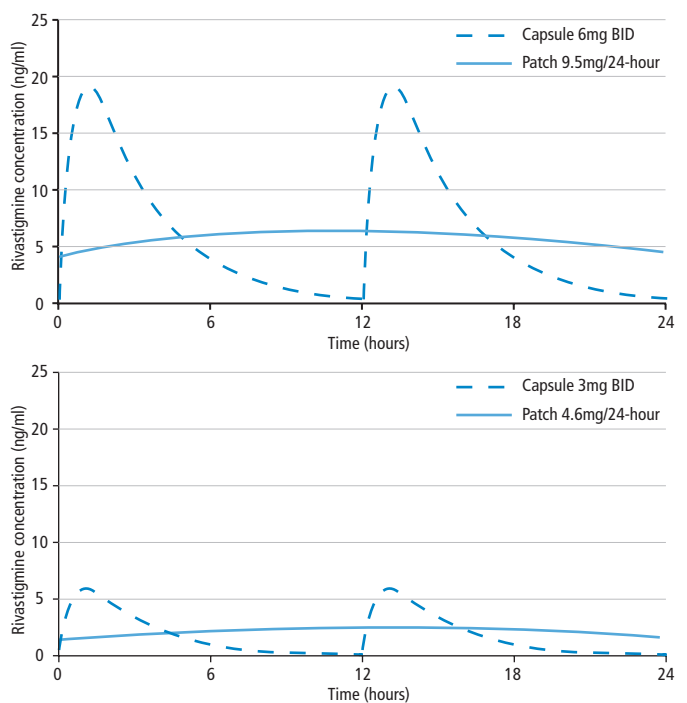
The results from an open-label study of 51 AD patients randomised to a rivastigmine patch (4.6–17.4mg/24-hour) or capsules (3–12mg/day)¹⁷ were used in a compartmental modelling analysis to predict rivastigmine exposures over a single 24-hour application period (see Figure 1).¹⁸ This analysis incorporated adjustments for baseline demographic differences such as bodyweight and gender, and demonstrated that the target-dose (9.5mg/24-hour) patch provides comparable drug exposure to the highest recommended dose of capsules (12mg/day).¹⁸ Since drug exposure corresponds to efficacy, these data predict similar efficacy for the target-dose rivastigmine patch and 12mg/day capsules. The 4.6mg/24-hour rivastigmine patch was shown to provide similar exposure to 6mg/day capsules, which is considered to be an effective therapeutic dose.^{19–21} These results suggest that patients undergoing rivastigmine patch therapy are initiated on an effective dose, and then titrated directly to the target dose in a single step. The analysis also demonstrated that the 4.6mg/24-hour patch and the 9.5mg/24-hour patch provided smoother and more continuous delivery of rivastigmine versus doses of capsules with comparable exposure (6 and 12mg/day, respectively).¹⁸ Both patches demonstrated significantly lower C_{max} and longer t_{max} (see Figure 1), substantially reducing rivastigmine plasma fluctuations, thereby predicting an improved tolerability profile versus capsules.

Clinical Data – Efficacy and Tolerability of the Rivastigmine Patch

Clinical evidence for the efficacy and tolerability of the rivastigmine patch was provided by the Investigation of transDermal Exelon in ALzheimer's disease (IDEAL) study. This was a 24-week randomised, double-blind study in 1,195 mild to moderate AD patients from 21 countries, followed by a 28-week open-label extension (n=870). Full details of the IDEAL study have been published previously.^{22–25}

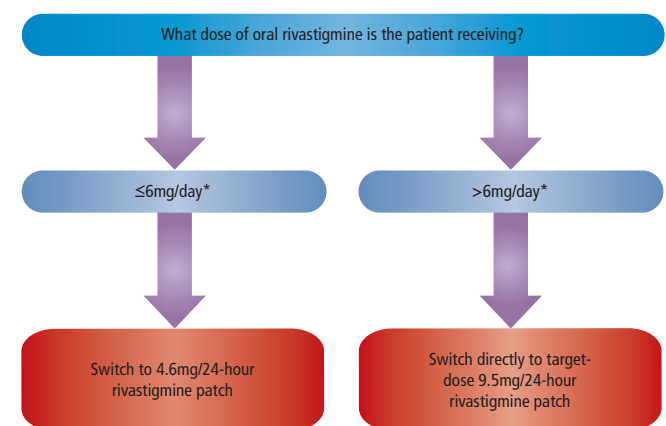
During the double-blind study, the 9.5mg/24-hour rivastigmine patch demonstrated similar efficacy to the highest recommended doses of rivastigmine capsules, with three times fewer reports of nausea or vomiting.²² Nearly all (96%) patients randomised to 9.5mg/24-hour patch treatment reached their target dose compared with 64% of patients in the 12mg/day capsule group.²⁶ Skin tolerability was good, with ≤2.4% of patients in any treatment group discontinuing due to adverse skin

Figure 1: Modelling Analysis Adjusted for Gender and Bodyweight¹⁸



Steady-state rivastigmine plasma levels for a typical patient following application of the 9.5mg/24-hour patch versus 12mg/day capsules, or the 4.6mg/24-hour patch versus 6mg/day capsules.

Figure 2: The Recommended Procedure for Switching from Oral Rivastigmine to Rivastigmine Patch Treatment



* Regional differences in guidelines apply. The figure above represents the current recommended switching guidelines in Europe (if a dose of 9mg/day is not stable or well tolerated, it is recommended to switch to 4.6mg/24-hour patch).

reactions. No further new or unexpected tolerability or safety concerns were reported.²² Skin adhesion was good, despite normal activities being permitted (including bathing), and some study centres being located in warm climates where perspiration might have been expected such as Chile, Venezuela or Israel. In 96% of the 1,336 evaluations of the 9.5g/24-hour patch, care-givers reported that the patch was completely attached or "had the edges just lifting off" following the 24-hour application period.²²

Results from the 28-week open-label extension study demonstrated the safety and tolerability of the 9.5mg/24-hour rivastigmine patch treatment up to one year, while providing sustained cognitive and functional

benefits.²⁵ Similar to the double-blind study, skin tolerability during the open-label extension was good. Switching directly to the target 9.5mg/24-hour patch upon entering the open-label extension was well-tolerated in patients receiving any form of rivastigmine treatment (capsule or patch) during the double-blind study. During weeks one to four following the switch, $\leq 2.5\%$ of patients reported nausea and $\leq 1.9\%$ reported vomiting.²⁵

Discussion

One of the primary objectives for AD treatment with cholinesterase inhibitors is to improve tolerability. Cholinesterase inhibitors that are administered orally can sometimes lead to gastrointestinal AEs, particularly nausea and vomiting, which may prevent patients from achieving and maintaining optimal therapeutic doses in clinical practice.

As the first transdermal application system for cholinesterase inhibitors, the rivastigmine patch has now been approved for the treatment of AD and PDD in various countries. Modelling analyses of pharmacokinetic data showed that the 9.5mg/24-hour patch provides comparable exposure to the highest doses of rivastigmine capsules (12mg/day) with a slower absorption rate and smoother pharmacokinetic profile,¹⁸ leading to improved tolerability over that possible with oral administration.¹³ Results from the IDEAL study showed that the 9.5mg/24-hour patch provided further clinical evidence for efficacy similar to the highest doses of capsules, with markedly improved gastrointestinal tolerability.²² No unexpected safety or tolerability concerns were reported, resulting in a very favourable risk–benefit profile for the 9.5mg/24-hour rivastigmine patch. Switching directly to 9.5mg/24-hour patch treatment was well tolerated by patients previously receiving oral rivastigmine,²⁵ and cognitive and functional benefits of rivastigmine treatment were maintained for up to one year.²⁵

It is recommended that patients on high rivastigmine capsule doses should be switched directly to the target-dose 9.5mg/24-hour patch as a practical recommendation on how to manage treatment when switching from oral

dosing to patch therapy, whereas *de novo* patients or those on low doses should undergo four weeks of 4.6mg/24-hour patch treatment before increasing to the 9.5mg/24-hour patch (see *Figure 2*).²⁵

Pharmacokinetic studies suggest that the starting-dose 4.6mg/24-hour patch provides similar exposure to 6mg/day capsules.¹⁸ This suggests, for the handling of treatment in clinical practice, that patients undergoing rivastigmine patch therapy are already initiated on an effective dose^{19–21} and need just a single dose-increase step after only four weeks to reach the recommended therapeutic dose. Combined with an improved tolerability profile, these results indicate that the transdermal patch may allow patients easier access to optimal therapeutic doses and potentially improve the effectiveness of treatment compared with oral administration. This was reflected in the fact that almost all patients receiving the 9.5mg/24-hour patch in the double-blind phase of the IDEAL study reached their target dose compared with only two-thirds of patients receiving the comparable capsule dose (12mg/day).²² Easier access to the 9.5mg/24-hour patch dose raises the possibility that higher doses of transdermal rivastigmine could be a viable future option in clinical practice. Studies investigating the comparative efficacy and safety of a 13.3mg/24-hour patch are ongoing.

In summary, the published clinical data support the pharmacokinetic rationale for the rivastigmine patch, indicating that smooth and continuous delivery of rivastigmine translates into an improved tolerability profile versus conventional oral administration, while maintaining clinical effectiveness. This may allow patients easier access to optimal therapeutic doses, potentially improving the effectiveness of treatment. A transdermal patch may be the optimal way of delivering rivastigmine in the pharmacological treatment of AD. ■

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