Studia Universitatis "Vasile Goldiş", Seria Ştiinţele Vieţii
Vol. 22, issue 4, 2012, pp. 537-541
© 2012 Vasile Goldis University Press (www.studiauniversitatis.ro)

THE EFFICIENCY OF ADMINISTERING DRUGS TROUGH TRANSDERMIC SYSTEMS

Robert DUKA[1*], Melania MUNTEANU[2]
[1]"Vasile Goldiş" Western University Arad, Faculty of Medicine, Department of Pharmacy
[2]"Vasile Goldiş" Western University Arad, Faculty of Medicine, Department of Pharmacy

ABSTRACT. Transdermal delivery systems have become more increasingly important for treating neurologic and psychiatric disorders. Cholinesterase inhibitors have all been available in oral formulations but the rivastigmine patch was the first patch to be approved to treat Alzheimer's disease (AD). The goal was to review the available pharmacokinetic data that supported the rationale behind the development of the rivastigmine transdermal patch and its clinical effects in Alzheimer's disease. The 9.5 mg/24 h rivastigmine patch was shown to provide comparable exposure to the highest recommended doses of capsules (12 mg/day) with significantly lower maximum plasma concentration (Cmax 8.7 vs. 21.6 ng/ml) and slower absorption rate (tmax 8.1 vs. 1.4 h). In a clinical trial of 1195 AD patients, this translated into similar efficacy with three times fewer reports of nausea and vomiting (7.2% vs. 23.1%, and 6.2% vs. 17.0% respectively). Consequently, more patients in the 9.5 mg/24 h patch group achieved their target therapeutic dose at the end of the study, compared with those in the 12 mg/day capsule group (95.9% vs. 64.4%). This treatment is well tolerated by patients because drug delivery is even and continuous, reducing fluctuation in drug plasma level, and attenuating the development of centrally mediated cholinergic side effects. Improved compliance with a subsequent drug administration may contribute to better clinical efficacy, reduce caregiver burden, result in a slower rate of institutionalization, and lead to a decrease in healthcare and medical costs. Because of these advantages, the rivastigmine patch has enabled great progress in treatment of AD, and may allow patients to achieve optimal therapeutic doses and to benefit from a longer duration of treatment.

Keywords: patch, transdermal delivery system, Alzheimer's disease, rivastigmine, dementia

INTRODUCTION

The first transdermal delivery system (TDS) , a patch to treat sea sickness based on the agent scopolamine was approved in the 1970s. To date, various trandermal patches to treat neurological and psychiatric diseases have been approved, including methylphenidate to treat attention deficit hyperactivity disorder, rotigotine to treat Parkinson's disease, selegiline to treat depression, and fentanyl for pain. Cholinesterase inhibitors are widely used in the symptomatic treatment of Alzheimer's disease (AD) in clinical practice. They act by inhibiting one or both of the enzymes responsible for the hydrolysis of acetylcholine in the synaptic cleft [acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE)], thereby increasing available acetylcholine levels and improving neurotransmission. Three cholinesterase inhibitors are commonly used to treat cognitive symptoms in mild-to-moderate AD: rivastigmine (Exelon®; Novartis, Basel, Switzerland), donepezil (Aricept®; Pfizer, New York, NY, USA) and galantamine (Reminyl®/Razadyne®; Johnson & Johnson, New Brunswick, NJ, USA).

In july 2007 the rivastgmine patch was approved to treat mild to moderate AD and Parkinson-associated dementia (US Food and Drug Administration 2008). TDS has several advantages. Continuous release, for example, enables a constant drug plasma level, which may a benefit when treating Parkinson's disease, assuming that a brief stimulation of the dopamine receptor in particular is responsible for the development of L-Dopa-associated motor complications (Fabbrini et al 2007). Because the drug absorption is independent of ingestion and gastrointestinal interactions, the incidence of adverse gastrointestinal effects may be reduced. The first-pass effect can be circumvented (Oertel et al 2007). Some cholinesterase inhibitors exhibit a dose–response relationship, with higher drug doses correlating with greater enzyme inhibition. As AD is a progressive, neurodegenerative disorder where patients deteriorate over time, one goal in clinical practice is to achieve higher doses that maximise the effectiveness of treatment. However, the incidence of adverse events (AEs) associated with oral cholinesterase inhibitors, particularly nausea and vomiting, also increases with higher doses . Consequently, achieving and maintaining high therapeutic doses in clinical practice may be difficult.

Furthermore, transdermal administration allows the application of drugs with a short half-life and a low therapeutic index. And in case of an accidental overdose, an effective disruption of transdermal administration is possible.

The easy employment of patches, with usually only a once-daily change, increases patient compliance. Furthermore, the caregivers can inspect the application of the patch. Improved compliance of the patient, and thus intake of the agent, is a significant benefit in the treatment of AD (Small et al 2005; Oertel et al 2007). One

***Correspondence:** Duka Robert, "Vasile Goldiş" Western University Arad, Faculty of Medicine, Department of Pharmacy, Romania, Tel: 0726 257108, email: rob_footprint@yahoo.com

disadvantage of the TDS is a possible skin reaction. In one clinical trial the applicationof of the rigotine patch caused local skin reactions in 44% of patients, although only 5% interrupted the treatment because of the side effect (Watts et al 2007).

MATERIALS AND METHODS

Patch structure

A transdermal patch or skin patch is a patch that is placed on the to deliver a specific of medication through the skin and into the . Often, this promotes healing to an injured area of the body. An advantage of a transdermal drug delivery route over other types such as oral, topical, etc is that it provides a controlled release of the medicament into the patient. A disadvantage to development however, stems from the fact that the skin is a very effective barrier. A wide variety of pharmaceuticals can be delivered by transdermal patches.

Rivastigmine is a 2.6-dioxo-4-phenyl-piperidine-3-carbonitrile (Fig.1). The small molecular weight of 250.34 Da, the lipophil, and the hydrophil characteristics, along with the potent effect of even very small portions, established the explicit aptitude of the drug for application with TDS.

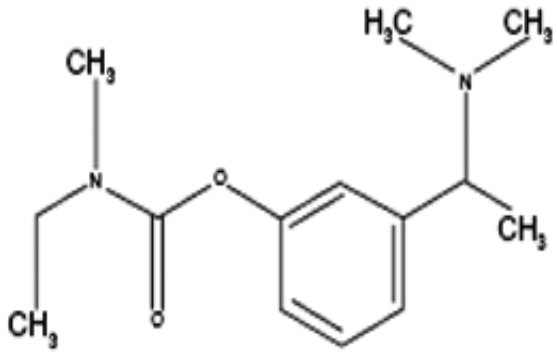

Fig. 1 Chemical structure of rivastigmine (adapted from Cummings and Winblad 2007)

The rivastgmine patch is composed of four layers (Fig.2). The highest layer, the backing film is colored and has a protective function against mechanical, extraneous causes. In the second layer, the drug is incorporated into an acrylic matrix, which ensures effective storage of rivastgimine (Oertel et al 2007). The next coating, a silicone matrix layer with silicone polymer, provides good adhesion of the patch to the skin. Directly on the skin, a release liner guarantees continuous dispensing of the drug through the skin, providing smooth delivery into the bloodstream. This layer also minimizes skin reactions.

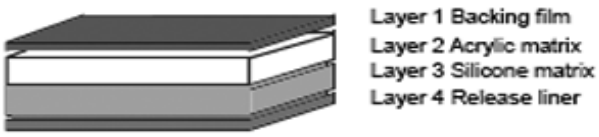

Fig. 2 Patch structure

Dosage and patch application

To provide the necessary concentration gradient to drive the diffusion process through the skin, all rivastigmine transdermal patches are loaded with a greater amount of rivastigmine than will be absorbed into the bloodstream. In a study of 51 AD patients, the average amount of rivastigmine absorbed from a patch over a 24-h application period was approximately 50% of the total loading dose. The 5 cm2 patch released 4.6 mg (51% of 9 mg), the 10 cm2 patch released 9.5 mg (53% of 18 mg), the 15 cm2 patch released 13.3 mg (49% of 27 mg) and the 20 cm2 patch released 17.4 mg (48% of 36 mg). Absorption of any remaining rivastigmine following the 24-h application period was shown to occur very slowly. Patients should therefore not be at risk of toxic exposure should a new patch be mistakenly applied without prior removal of the previous patch. Once removed, the short elimination half-life (t1/2) of rivastigmine (capsule doses = 1.3–1.9 h; 17.4 mg/24 h patch = 3.4 h) ensures the rapid reduction of drug levels in the plasma. As a result, even with the continuous delivery provided with the rivastigmine patch, there is little potential for accumulation in the body.

The pharmacokinetic parameters of transdermal drug delivery can vary between patch application sites. The optimal position would offer maximum drug exposure, be easily accessible and avoid adhesion or tolerability issues (e.g. areas of hairy or sensitive skin).

In a recent single-centre, single-dose, open-label, randomised-sequence, application study in 40 healthy men or women aged 40–80 years, the pharmacokinetics, adhesion and skin tolerability of the rivastigmine patch were assessed . A 9.5 mg/24 h (10 cm2) patch was applied to one of the following five sites and worn for 24 h: upper back, chest, thigh, abdomen and upper arm. Each participant underwent five 24-h applications, one for each application site, which were separated by a 72-h washout period.

Exposure levels (AUC24 h) and Cmax were shown to be the greatest when the patch was applied to the chest, upper back and upper arm. Because of the small molecular size and lipophilic nature of rivastigmine, the minimal skin thickness and subcutaneous body fat at these sites may have contributed to this finding. The degree or level of adhesion was only shown to have a significant effect on AUC24 h and Cmax when the patch was applied to the chest ($p = 0.014$ and 0.022 respectively). At all application sites, tmax was very slow (16–22 h) indicating smooth and controlled release of rivastigmine into the bloodstream.

Erythema was the only type of skin reaction reported during the study and was least likely to occur when the patch was applied to the upper arm, chest and upper back.

It is therefore recommended that the patch be applied to clean and dry skin on the back, upper arm or chest to obtain maximum rivastigmine exposure with minimal risk of skin reactions.

To further reduce the potential for skin irritation, the patch should be alternated daily between sites on the right and the left side of the body.

Studia Universitatis "Vasile Goldiş", Seria Ştiinţele Vieţii
Vol. 22, issue 4, 2012, pp. 537-541
© 2012 Vasile Goldis University Press (www.studiauniversitatis.ro)

Pharmacokinetic profile

The results from an open-label study of 51 AD patients randomised to rivastigmine patch (4.6–17.4 mg/24 h; 5–20 cm2), or capsules (3–12 mg/day), were used in a compartmental analysis to model rivastigmine plasma levels over a 24-h application period. Drug exposure was assessed by measuring the area under the curve over a 24-h treatment period (AUC24 h), using a specific power model.

The 4.6 mg/24 h patch was shown to provide comparable rivastigmine exposure to a 6 mg/day capsule dose [AUC24 h = 64 and 60 ng·h/ml (p = ns) respectively] and the 9.5 mg/24 h patch comparable exposure to the highest recommended capsule dose [12 mg/day; AUC24 h = 166 and 207 ng·h/ml (p = ns) respectively]. The 13.3 mg/24 h and 17.4 mg/24 h patches provide greater rivastigmine exposure than any approved oral dose (AUC24 h = 312 and 474 ng·h/ml).

All patch doses provided smoother and more continuous delivery of rivastigmine than oral administration . Both the 4.6 mg/24 h and 9.5 mg/24 h patches provided significantly lower rivastigmine Cmax and longer tmax (all $p < 0.001$) vs. capsule doses of comparable exposure: 6 mg/day (Cmax 3.3 vs. 6.8 ng/ml; tmax 8.2 vs. 1.2 h) and 12 mg/day (Cmax 8.7 vs. 21.6 ng/ml; tmax 8.1 vs. 1.4 h) respectively . These results are supported by a separate, non-compartmental, non-adjusted analysis of the same data. Similarly, a recent study comparing rivastigmine oral solution (3 mg/day) with the 9.5 mg/24 h patch showed the patch to have a 20% lower Cmax and 14-times longer tmax, with five-times the drug exposure of the oral solution (Cmax = 5.8 vs. 7.6 ng/ml; tmax = 14.1 vs. 1.0 h; AUC∞ = 118 vs. 23 ng·h/ml respectively).

By providing similar drug exposure with a lower maximum concentration and slower absorption rate, the rivastigmine patch may provide similar efficacy to orally administered rivastigmine, with a more favourable tolerability profile.

Clinical effects with transdermal dosing

One of the major obstacles to the effective treatment of AD with oral cholinesterase inhibitors has been tolerability, which can prevent many patients from reaching efficacious therapeutic doses in clinical practice. Until recently, all cholinesterase inhibitors were administered orally, but the newly developed rivastigmine patch appears to overcome this tolerability obstacle by employing a different dosing route and may offer a substantial clinical advantage.

Modelling analyses adjusting for baseline demographic factors demonstrated that the 9.5 mg/24 h patch (10 cm2) provides comparable exposure, and therefore potentially similar efficacy, to the highest doses of rivastigmine capsules (12 mg/day). The pharmacokinetic profile, with a reduced Cmax and prolonged tmax, also predicts an improved tolerability profile vs. conventional rivastigmine capsule administration. These hypotheses are supported by results from the landmark Investigation of transDermal Exelon in ALzheimer's disease trial (IDEAL). This was a randomised, double-blind, double-dummy, placebo-controlled trial to investigate the efficacy and tolerability of the rivastigmine patch (4.6–17.4 mg/24 h) vs. capsules (3–12 mg/day) in 1195 AD patients. Patients randomised to patch treatment were started on the 4.6 mg/24 h patch and titrated in a single step to the recommended 9.5 mg/24 h patch. During the 24-h application period, patients were able to pursue all normal activities, including washing and bathing. The trial was also conducted in countries with varying climates, including some hot and humid regions (e.g. Guatemala, Venezuela).

The 9.5 mg/24 h patch provided similar efficacy to the highest doses of capsules (12 mg/day) on various outcome measures , with three times fewer reports of nausea and vomiting (7.2% vs. 23.1% and 6.2% vs. 17.0% respectively. This supports the rationale for the patch that a smoother pharmacokinetic profile would yield fewer cholinergically mediated AEs while maintaining therapeutic concentrations. Similar efficacy between the 9.5 mg/24 h patch and 12 mg/day capsule groups, despite the patch providing slightly less drug, demonstrates the advantage with transdermal delivery of the avoidance of first pass metabolism by peripheral cholinesterases in the gut.

The efficacy of the 4.6 mg/24 h patch was not assessed in the IDEAL trial, however pharmacokinetic data have demonstrated a similar level of exposure to 6 mg/day capsules (64.1 vs. 60.0 ng h/ml respectively), which is considered an effective therapeutic dose. Also, fewer reports of nausea and vomiting were reported with the starting dose 4.6 mg/24 h patch (1.9% and 0.5%, weeks 1–4), than the starting 3 mg/day capsule dose (3.1% and 2.0%; Novartis, data on file). Therefore, in contrast to the conventional capsule regimen (16-week, four-step titration from 3 to 12 mg/day), patients treated with the rivastigmine patch are initiated on an effective dose with improved gastrointestinal tolerability, and can then be titrated in a single step to the recommended therapeutic dose (9.5 mg/24 h patch) after only 4 weeks.

The improved tolerability profile of the patch also suggests that it may allow patients an easier path to higher doses, thereby enabling patients to stay on and benefit from effective treatment for longer. This is reflected in the greater proportion of patients who achieved their target therapeutic dose in the 9.5 mg/24 h patch group at the end of the study, compared with the 12 mg/day capsule group (95.9% vs. 64.4% respectively). Further investigations of the efficacy and safety of higher doses of rivastigmine (13.3 mg/24 h, AUC24 h = 312 ng·h/ml) are ongoing.Transdermal administration typically carries with it the risk of additional AEs not associated with oral administration, such as application site skin irritation and sleep disturbances (because of 24-h drug delivery). However, during the IDEAL trial no new safety issues were reported. In addition, the adhesion of the patch was very good, despite patients being permitted to pursue all normal daily activities including bathing and swimming. Skin irritation was actively assessed by the investigator

© 2012 Vasile Goldis University Press (www.studiauniversitatis.ro)

or caregiver, yet most patients experienced 'no, slight, or mild' skin irritation (90–98% across all patch doses), with < 2.5% of patients in any treatment group discontinuing because of adverse skin reactions. Clinical experience suggests that the most common form of skin irritation is erythema caused by removal of the patch, which normally resolves after a short period of time. In the IDEAL trial, the signs or symptoms that were most frequently reported as moderate or severe were erythema (redness; 8% for the 9.5 mg/24 h rivastigmine patch, up to 4% for placebo) and pruritus (itching; 7% for the 9.5 mg/24 h rivastigmine patch, up to 3% for placebo). As stated previously (and in addition to the lower back), Lefèvre et al. demonstrated that the application of the rivastigmine transdermal patch to the upper arm, chest or upper back is least likely to result in the development of erythema. Daily rotation of the application site is recommended in the product label to minimise skin irritation, avoiding the exact same spot for at least 14 days (although consecutive patches may be applied to the same anatomical site).

RESULTS

The 9.5 mg/24 h rivastigmine patch was shown to provide comparable exposure to the highest recommended doses of capsules (12 mg/day) with significantly lower maximum plasma concentration (Cmax 8.7 vs. 21.6 ng/ml) and slower absorption rate (tmax 8.1 vs. 1.4 h). In a clinical trial of 1195 AD patients, this translated into similar efficacy with three times fewer reports of nausea and vomiting (7.2% vs. 23.1%, and 6.2% vs. 17.0% respectively). Consequently, more patients in the 9.5 mg/24 h patch group achieved their target therapeutic dose at the end of the study, compared with those in the 12 mg/day capsule group (95.9% vs. 64.4%).

CONCLUSIONS

Overall, current clinical data support the pharmacokinetic rationale of the rivastigmine patch, demonstrating that the smooth continuous drug delivery provided by transdermal administration translates into comparable efficacy with an improved tolerability profile vs. oral administration. Patients treated with the 10 cm2 patch developed approximately two-thirds fewer gastrointestinal side effects, such as vomiting and nausea, compared with patients treated with rivastigmine capsules (3-12 mg/day). In contrast to the capsules, the incidence of adverse events is not significantly different compared to placebo (Winblad et al 2007a; Winblad et al 2007b).

Compared with the capsules, another advantage of the patch is the easier dosing schedule with ine incrase of the dosage after 4 weeks only. A disadvantage of the rivastigmine patch is higher therapy cost compared to capsules. The rivastigmine patch may be the optimal way to deliver rivastigmine to treat AD because of the good efficacy, rare systemic adverse effects, dynamic skin tolerance, handling ease, and the satisfaction of caregivers, means that the new rivastigmine patch is an important step in the treatment of AD.

To summarise transdermal drug delivery systems offer several important advantages over more traditional approaches, including: longer duration of action resulting in a reduction in dosing frequency, increased convenience to administer drugs which would otherwise require frequent dosing, improved bioavailability, more uniform plasma levels, reduced side effects and improved therapy due to maintenance of plasma levels up to the end of the dosing interval, flexibility of terminating the drug administration by simply removing the patch from the skin ,improved patient compliance and comfort via non-invasive, painless and simple application.

Transdermal drug delivery is theoretically ideal for many injected and orally delivered drugs, but many drugs cannot pass through the skin because of skin's low permeability.

Pharmaceutical companies develop new adhesives, molecular absorption enhancers, and penetration enhancers that will enhance skin permeability and thus greatly expand the range of drugs that can be delivered transdermally.

REFERENCES

Sorin Leucuta, „Biofarmacie si Farmacocinetica", Editura Dacia, Cluj Napoca 2002 pag 145-159

Rubin C.D. „The primary care of Alzheimer disease". Am J Med Sci 2006 Dec; 332 (6): 314-33.

Fillit H., Cummings J. „Practice guidelines for the diagnosis and treatment of --Alzheimer's disease in a managed care setting: part II. Pharmacologic therapy. -Alzheimer's Disease Managed Care Advisory Council". Manag Care Interface 2000 Jan; -13(1):51-6.

Lyketsos C.G., Colenda C.C., Beck C. et al. „Position statement of the American Association for Geriatric Psychiatry regarding principles of care patients with dementia resulting from Alzheimer disease". Am J Geriatr Psychiatry 2006 Jul; 14 (7):561-73.

Lefevre G., Sedek G., Jhee S.S. et al. „Pharmacokinetics and pharmacodynamics of the novel daily rivastigmine transdermal patch compared with twice-daily capsules in Alzheimer's disease patients".Clin Pharmacol Ther.Epub 2007 May 23

Priano L., Gasco M.R., Mauro „A. Transdermal treatment options for neurological disorders: impact on the elderly". Drugs Aging 2006; 23 (5): 357-75.

Muhlack S., Przuntek H., Muller T. „Transdermal rivastigmine treatment does not worsen impaired performance of complex motion in patients with Alzheimer's disease." Pharmacopsychiatry 2006 Jan; 39 (1): 16-9.

Lefevre G., Sedek G., Huang H.L.A. et al. „Pharmacokinetics of a rivastigmine transdermal patch formulation in healthy volunteers: relative effects of bodz site application". J Clin Pharmacol 2007 Apr; 47 (4): 471-8.

© 2012 Vasile Goldis University Press (www.studiauniversitatis.ro)

Lily Y., Gillian K. „Rivastigmine transdermal patch in the treatment of dementia of Alzheimer's type". CNS Drugs 2007; 21 (11): 957-965.

Winblad B., Cummings J., Andersen N. et al. „A six-month double –blind, randomized, placebo-controlled study of a transdermal patch in Alzheimer's disease: rivastigmine patch versus capsule". Int J Geriatr Psychiatry 2007 May; 22(5): 456-67.

Winbald B., Kawata A.K., Beusterien K.M. et al. „Caregiver preference for rivastigmine patch for rivastigmine patch relative to capsules for treatment of probable Alzheimer's disease". Int J Geriatr Psychiatry 2007 May: 22 (5): 485-91.

„American Psychiatric Association. Diagnostic and statistical manual of mental disorders". 4th ed. Washington, Dc: American Psychiatric Association, 1994.

Berner B, John VA (February 1994). "Pharmacokinetic characterisation of transdermal delivery systems". Clinical pharmacokinetics 26 (2): 121–34

Segal, Marian. "Patches, Pumps and Timed Release: New Ways to Deliver Drugs". Food and Drug Administration. http://www.fda.gov/bbs/topics/consumer/CON00112.html.

© 2012 Vasile Goldis University Press (www.studiauniversitatis.ro)