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한국인 치매환자에서의 리바스티그민 패취 사용 경험; 예비 연구

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Clinical Experience of the Transdermal Patch of Rivastigmine in Korean Patients with Dementia; Preliminary Study

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While rivastigmine transdermal patch has consistently demonstrated better tolerability and similar efficacy compared to conventional rivastigmine capsules in clinical studies; it has not been specifically evaluated in Korean dementia patients. From February to November 2008, 94 patients with dementia and mild cognitive impairment (MCI) were treated with rivastigmine transdermal patch at Konkuk University Hospital and Bobath Memorial Hospital. To evaluate the safety and tolerability in Korean patients with dementia and MCI, we reviewed the clinical data of the patients. The participating subjects were diagnosed as Alzheimer's disease (n=34), mild cognitive impairment (n=5), vascular dementia (n=26), Parkinson's disease dementia (n=13), dementia with Lewy body (n=3), frontotemporal dementia (n=2) and other types of dementia (n=11). All of the patients were followed within 3 months (90±14 days), in terms of evaluating adverse events. Adverse events occurred in 11 cases (11.7%) and adherence of the patch was good in 91 cases (96.8%). Most of the participants showed clinical improvement similar to other acetylcholinesterase inhibitors (AchEIs). The most common adverse effects were skin-related problems including simple skin irritation, itching sensation, erythematous lesion, patch marks (contact dermatitis) and even severe symptoms mixed with all of the above (allergic contact dermatitis), occurred in eight cases (8.5%). Gastrointestinal (GI) discomfort was reported in two cases (2.1%). Among patients who stopped rivastigmine transdermal patch, six patients (6.3%) withdrew due to adverse events. Rivastigmine transdermal patch provides a good tolerability profile in treating Korean patients with the various subtypes of dementia and may be effective for the improvement of cognitive function in Korean patients with Alzheimer's disease.

Key Words: *Rivastigmine transdermal patch, Dementia, Tolerability*

INTRODUCTION

Rivastigmine inhibits acetylcholinesterase and butyrylcholinesterase and is currently widely approved for the treatment of mild to moderate Alzheimer's disease (AD) and mild to moderate Parkinson's disease dementia [1-12]. A transdermal patch of rivastigmine (Exelon®) has recently been developed. Rivastigmine is a small, potent molecule that has both lipophilic and hydrophilic-properties that make it well suited to transdermal therapy [1].

There are several reports regarding the causes of dementia patients not receiving enough efficacy from acetylcholinesterase inhibitors (AchEIs). The reasons can be summarized into two points. The first is the suboptimal dosing of the AchEIs due to cholinergic Gastrointestinal (GI) side effects, particularly in titration phase [13], and the second is the treatment non-compliance due to multiple medications, a serious issue in 75% of older patients [14, 15].

A transdermal patch formulation may offer improved tolerability, convenience and therapeutic advantages for this

AchEIs treated patient population [16-18]. By providing continuous delivery of drug with reduced fluctuation levels in the plasma, transdermal administration may improve tolerability and make optimal doses easier to achieve and lessen the number of drug of one patient [16-18].

Rivastigmine transdermal patch was approved for use in Korea in July in 2007; however, it was not approved by the Korean National Health Insurance Corporation until December 2008. Therefore, until now, there have been no reports about the clinical experiences in Korean dementia patients. The current objective is to review the clinical data about safety and tolerability of two rivastigmine patch sizes among Korean patients with dementia.

MATERIALS AND METHODS

We reviewed the clinical data of the recruited 94 patients with dementia and multiple etiologies; those were prescribed rivastigmine transdermal patch between January and November 2008 (Fig. 1).

Before and after using rivastigmine transdermal patch for 3 months, the Korean version of Mini-Mental Examination (K-MMSE), the Clinical Dementia Rating (CDR) scale, the Global deterioration scale (GDS), the Barthel Activities of Daily Living (B-ADL), and the Korean Instrumental Activities of Daily Living (K-IADL) were checked, however, not in all the participants [19-25].

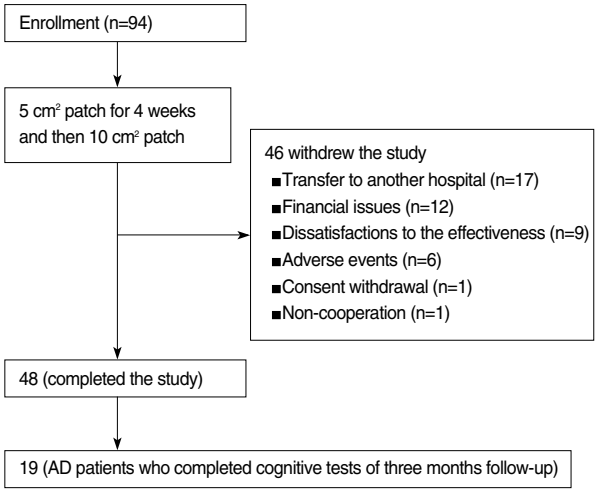

Fig. 1. Disposition of the patients.

Rivastigmine transdermal patch was applied by caregivers to clean, dry, hairless skin on the patient's back upper back or lower back or chest or upper arm every morning and worn for 24 hr, during which normal activities including bathing were allowed. To minimize possible skin irritation, patch placement was alternated, daily and in the same site, patch was not placed for two weeks. Patients were titrated to their target dose in 4-week steps over 8 weeks, followed by an 8-week maintenance phase. Patients were titrated from a 5 cm^2 starting dose to a size of 10 cm^2.

The participant were diagnosed as AD, mild cognitive impairment (MCI), Vascular disease (VaD), Parkinson's disease dementia (PDD), dementia with Lewy body (DLB), frontotemporal dementia (FTD), and others, based on the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) criteria for dementia, the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria for AD, Petersen's criteria for MCI, the National Institute of Neurological Disorders and Stroke and the Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN) criteria for VaD, report of the consortium on DLB international workshop for DLB, DSM IV criteria for PDD, and revised Neary's criteria for FTD [26-32]. Discontinuation rate, and reasons for discontinuation as well as adverse events were studied.

Safety evaluations included recordings all adverse events, which were coded using a standard glossary. Vital signs and body weight were recorded. Routine laboratory tests were performed at baseline; post-baseline laboratory tests were not routinely collected but done if any abnormal clinical laboratory findings developed and induced clinical signs or symptoms were considered clinically significant or required therapy, they were recorded as adverse events (AEs). Skin irritation was evaluated at every visit by the clinician based on inspection of the skin at the site of application. Changes in K-MMSE, CDR, GDS, K-IADL, and B-ADL scores from baseline were assessed by paired t test. Statistical analyses were performed using SPSS version 17.0 software.

RESULTS

The clinical features of the 94 patients included in the study are listed in Table 1.

Thirty-four patients were diagnosed as AD, five as MCI, 26 were as VaD, 13 as PDD, three as DLB, two as FTD, and 11 were diagnosed as others.

All of the patients included were followed up for three months, a mean duration of 90±14 days. However, 46 (48.9%) patients withdrew from the medication, and the reasons for discontinuation were as follows in order; those included transfers to another hospital (n=17), financial issues (n=12), dissatisfaction to the effectiveness (n=9), adverse events (n=6), consent withdrawal (n=1), and non-cooperation (n=1).

Nineteen patients with AD, those had three months follow-up data showed improvement in their MMSE scores from 13.7 points to 16.9 points (p<0.05). However, three cases of the patients who had experienced severe AEs such as nausea and vomiting even to minimal dosage of any oral AchEI showed significant cognitive improvement. The K-MMSE score changed from 11 to 15 during three months follow-up in one patient. One severe stage dementia patient who was nearly mutic and abulic began speaking and responded to simple commands, and showed an improvement of K-MMSE score from 0 to 5.

The rate of adverse events related to the study drug was 11.7% (11/94). Most of the AEs were mild to moderate in intensity and transient in duration. The most common AEs in these patients were skin lesions and gastrointestinal disorders, followed by nervous system disorders. No unexpected safety issues emerge (Table 2).

The adverse skin events that were most frequently assessed as moderate or severe intensity were redness (erythema) 6.3%

Table 1. Subject characteristics at baseline (n=94)

Characteristics	
Age (yr); mean±SD (range, median)	74.92±9.76 (32-95, 76)
Male:female	39:55
K-MMSE, mean±SD (range, median)	12.01±9.13 (0-30, 10.00)
CDR, number of subjects (n=73), 0.5:1:2:more	9:16:22:22:4
CDR, mean±SD (range, median)	2.04±1.12 (0.5-6, 2.0)
GDS, number of subjects (n=73), 3:4:5:6:7	3:12:22:25:1
GDS, mean±SD (range, median)	5.26±0.90 (3.0-7.0, 5.0)
K-IADL, mean±SD (range, median)	4.39±1.07 (0.73-32.00, 2.67)
B-ADL: 18.0±1.47	10.39±7.58 (0-20, 10.0)

K-MMSE, Korean version of Mini-mental status examination; CDR, Clinical Dementia Rating; GDS, Global Deterioration Scale; K-IADL, Korean Instrumental Activities of Daily Living; B-ADL, Barthel Activities of Daily Living.

Table 2. Adverse events (AEs)

Adverse event	Rivastigmine group (n=94)
Any AE	11/94 (11.7%)
Skin lesion	8/94 (8.5%)
Critical skin lesion	3/94 (3.2%)
Erythema	6/94 (6.3%)
Pruritis	5/94 (5.3%)
GI system AE	2/94 (2.1%)
Nausea	1/94 (1.1%)
Vomiting	1/94 (1.1%)
Nervous system	1/94 (1.1%)
Hypersomnia	1/94 (1.1%)

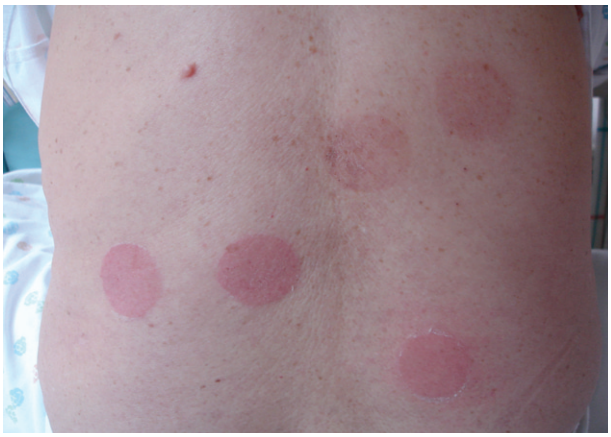

Fig. 2. Well demarcated round erythematous patches on the back.

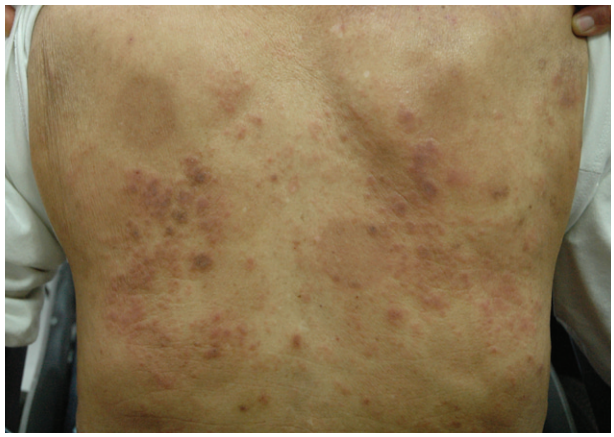

Fig. 3. Relatively well defined multiple dark red colored papules, plaques are distributed on the back.

(6/94) and itchiness (pruritus) 5.3% (5/94). There were overlaps between erythema and pruritis. The lesions from erythema were elevated, and were oval shaped and localized where the patch was applied. This skin reaction was superficial, caused little or no discomfort, and resolved spontaneously within 48 hr after detachment. Those were diagnosed as a result of mild irritant or allergic dermatitis by a dermatologist (Fig. 2). The case with figure 2 was prescribed 5 cm^2 and 10 cm^2 patches. In this case, the skin lesion developed with both patch sizes, faded away within 72 hr and there were many patch marks of different age. However, in three cases, the skin lesions were so severe that the patients discontinued the medication (Fig. 3). In the case with Fig. 3, the skin lesion had developed just after the first application of patch, however, the patient had continued the medication and then he showed serious skin reaction and was diagnosed as allergic dermatitis and he had to discontinue the medication. Patients who discontinued as a result of skin irritation were 3.2% (3/94). The overall adverse skin effect rate was 8.5% (8/94). Similar results were obtained from caregiver assessments of skin tolerability.

Most patches remained adherent to the body over the 24-hr application period. Of the 94 participants, 91 patients (91/94, 96.8%) remained completely attached or had the 'edges just lifting off' after 24 hr, and the patch was described as 'mostly half off', 'just hanging on' or 'completely detached' in three (3/94, 3.2%) of cases. Nausea and vomiting that were most common AE in other study, however, in our study, there were only in two cases (2/94, 2.1%) [1-12].

One patient showed hypersomnolent mental status and discontinued the medication. In 26 patients who had taken rivastigmine transdermal patch and memantine together, no additional adverse effects were reported.

There was one case who showed easy detachment of rivastigmine transdermal patch in the summer after 6 months use and was changed to 9 mg of rivastigmine capsule in a day without escalation schedule, there were no reported AEs.

DISCUSSION

This study is the first study of rivastigmine transdermal patch treatment in Korean patients with dementia. Rivastigmine transdermal patch was launched at Konkuk University Hospital and Bobath Memorial Hospital in January 2008. In our clinical practice, we used rivastigmine transdermal patch in patients with all types of dementia, all age groups and all stages of dementia regardless of the national health insurance coverage. This was made possible because of the patients' ability to pay for their own treatment.

In our experience, we assumed the effectiveness of rivastigmine transdermal patch in three aspects. First, rivastigmine transdermal patch might strengthen the effect of acetylcholine with reduced troublesome AEs as compared to conventional AchEIs. It was effective in three patients who could not take AchEIs because of serious AE effect with currently available oral AchEIs at minimal dosages and who were not taking AchEIs because they were in severe stage dementia.

Second, it was effective in lowering drug interaction in patients on multiple drug medications. We recruited 13 PDD patients, who were on medications, especially dopaminergic agents. Approximately, half (46.2%, 6/13) did not take maximal dosages of AchEIs, because they experienced AEs such as nausea, GI discomfort and were afraid of not being able to take sufficient doses of antiparkinsonian drugs. In those cases rivastigmine transdermal patch was effective in maximizing the effects of the AchEI without any GI AE or lowering the dosage of antiparkinsonian drugs.

Lastly, we experienced various types of dementia patients who showed cognitive dysfunction, AchEIs could be another promising treatment. Because this study was done regardless of medical insurance coverage, we could glean the clinical application of AchEI in various patients with hemorrhagic stroke, traumatic brain injury, even hypoxic brain damage and others. Because of small number of cases, we could not statistically prove the efficacy of rivastigmine transdermal patch, however, we observed some cognitive improvement and caregiver's satisfaction. Rivastigmine transdermal patch might be effective in the patients who are assumed to have dysfunction in cholingergic pathways as hypothesized in previous studies.

The AE profile was compatible with cholinergic stimulation. Acute cholinergic side effects, such as nausea and vom-

iting, have been associated with high maximum plasma concentrations (Cmax) and short times to Cmax (tmax) following oral administration. Transdermal administration prolongs tmax and lowers Cmax for equivalent exposure. Furthermore, transdermal delivery reduces fluctuations of plasma drug levels and allows more continuous drug delivery over a 24-hr period [16-18]. Consistent with these observations, the side effect profile of patch was much improved, compared with the previous data with capsules [1]. Thus, these patients were receiving the equivalent of the highest optimal oral daily dose of rivastigmine, while experiencing relatively few side effects.

Overall, the safety and tolerability profile of the treatment in this study was better than previously reported data in patients with AD (11.7% [11/94]: 50.5% [147/291]) [1]. However, AEs profile was quite different from the previous study. The most common AEs in these patients were skin lesions, not gastrointestinal disorders. The rate of GI adverse events was lower than the previous study (2.1% [2/94]: 19.6% [57/291]) [1]. We assumed the reason for better safety and tolerability profile of this study in three points. First, the short duration of follow-up in this study might be the one reason and the second is that the participating patients of this study were in more severe stage of dementia comparing with the previous study [1] and they might not be able to specifically express mild symptoms. Lastly, minor symptoms such as mild dizziness, asthenia and others might not be precisely checked in this analysis.

Rivastigmine transdermal patch demonstrated good skin tolerability and good adhesion in Korean patient with dementia. The incidence of skin lesion was similar to other reports [1]. This skin reaction was superficial, caused little or no discomfort, and resolved spontaneously within 48 hr. Therefore, rotating the application site of the patch over 14 days should be sufficient to minimize irritation. As with irritant dermatitis, these typically manifested as erythema with no additional signs or symptoms. Allergic dermatitis was suspected with rivastigmine transdermal patch only in a few cases. Allergic dermatitis didn't usually require any intervention, and dissipated in several days. Serious skin effects did not cause discontinuation of medication. However, when it occurred, it caused the clinicians to be disconcerted. The period of this study was from spring to fall. Humidity during this period is relatively higher than that of winter, so we canexclude possibility of increasing AE related to skin problem owing to low humidity and concurrently dry skin.

This study was limited because: 1) this is a restrospective study reviewing the clinical data of the patient; 2) the study participants had a heterogeneous nature of disease 3) there was no regular or a significant duration of follow-up to be able to check for specific AEs, and 4) there was a limited number of cases (total number of patients=94, and the number of AD patients who completed cognitive tests for the three months of follow-up duration=19).

In summary, rivastigmine transdermal patch was safe and may be effective for the improvement of cognitive function in Korean patients with dementia. Further studies that define the responses and long-term adverse effects of rivastigmine patch are needed to confirm our observations.

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