

## 알쯔하이머병과 소혈관성 치매에서 Donepezil 복용 후 K-MMSE의 변화와 의미 있는 K-MMSE 변화를 보이는 알쯔하이머병 환자의 특징

곽용태\*† · 한일우\*\* · 김 준\*\*\* · 이유상\*\*\*

### The Change of K-MMSE Following Donepezil Medication in Patients with Alzheimer's Disease and Small Vessel Dementia, and the Characteristics of Alzheimer's Disease with Meaningful K-MMSE Change

Yong Tae Kwak, M.D.,\*† Il-Woo Han, M.D.,\*\* June Kim, M.D.,\*\*\* Yu-Sang Lee, M.D.\*\*\*

#### ABSTRACT

**O**bjectives : Donepezil is a widely used drug for the treatment of patients with Alzheimer's disease(AD). The aim of the present study was to clarify the efficacy and the characteristics of responders to donepezil.

**Methods** : Patients with probable AD(n=80 ; 75.7 years) and small vessel dementia(SVD)(n=18 ; 77.8 years) who received donepezil were retrospectively analyzed using Alzheimer's registry, and three questions were asked : 1) Does donepezil therapy improves cognitive symptoms in patients with dementia? 2) If donepezil improves cognitive symptoms, which items of the K - MMSE are improved? 3) What are the characteristics of responder to donepezil medication?

**Results** : 1) After donepezil medication, cognitive function measured by the K - MMSE was significantly improved in both types of dementia(AD and SVD), However, statistical differences were not found between these groups. 2) In a clinical trial of donepezil, the patients performed better than before mediation on K - MMSE items assessing orientation, recall, construction, concentration, calculation. 3) In AD, the K - MMSE score before medication was closely related with response of donepezil.

**Conclusion** : This study suggests that donepezil improves various cognitive functions in both types of dementia, and the responsive group had significantly lower K - MMSE scores than the non - responsive group before medication.

**KEY WORDS** : Donepezil · Alzheimer's disease · Small vessel dementia · K - MMSE · Responsive group.

\* Department of Neurology, Hyoja Geriatric Hospita, Yongin, Korea

\*\* Department of Psychiatry, Hyoja Geriatric Hospital, Yongin, Korea

\*\*\* Department of Psychiatry, Yong-In Mental Hospital, Yongin, Korea

†교신저자 : , 449 - 910 33  
) (031) 288 - 0602, ) (031) 288 - 0539 E - mail) ytkwak@drkwak.com

서 론

가 <sup>12)</sup>

(basal forebrain)  
 가 <sup>1)</sup>  
 (nucleus basalis)  
 (presynaptic)  
<sup>2)3)</sup>

donepezil

<sup>3)</sup>  
 Donepezil  
 가 piperidine <sup>4)</sup>  
 , 가 가 70  
 acridine 가 tacrine

(FDA) 가  
 (core manife-  
 stations of dementia) 가  
<sup>13)</sup> The Alzheimer's Disease Assess-  
 ment Scale - Cognitive portion(ADAS - Cog)<sup>14)</sup> Cli-  
 nical Interview - Based Impression of Change with  
 caregiver input(CIBIC - plus)<sup>15)</sup>가 가

<sup>5)</sup>  
 donepezil  
<sup>6)7)</sup> donepezil  
 가  
 25%(low - dose rivastigmine)  
 50%(high - dose tacrine and donepezil)  
 34% <sup>8)</sup> done-  
 pezil 30~50%  
<sup>6)</sup> donepezil

Korean Mini - Mental State Exami-  
 nation(K - MMSE)  
 3  
 donepezil K - MMSE가  
 K - MMSE

방 법

1. 연구 대상군과 임상척도

가 Donepezil

1 , 3 , 6

K - MMSE  
 (registry)  
 1997 11 2004  
 donepezil  
 9  
 80

donepezil 가 <sup>9)</sup>  
<sup>10)11)</sup>

(small vessel dementia)

18 National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association(NINCDS - ADLDA)<sup>16)</sup> probable

Erkinjuntti<sup>17)</sup>

가

Clinical Dementia Rating Scale(CDR)<sup>18)</sup> CDR 1, CDR 2, CDR 3 가 Korean Mini - Mental State Examination(K - MMSE)<sup>19)</sup> (MRI) (CT) 1가

2. 연구 방법

1) 알츠하이머병 환자에서 동일 검사자에 의한 K-MMSE 재검사의 신뢰성

30 가 4 2 가 K - MMSE

2) Donepezil 투약 전후의 신경심리 검사

1, 3, 6 K - MMSE, CDR

3) 인지 기능 변화에 대한 정의

1, 3 K - MMSE 가 4 가 CDR 가

(small

가

4) 부분별 인지기능의 변화

Donepezil K - MMSE (orientation), (registration), (recall), (language), (visual construction), (attention and calculation) 6

5) Donepezil 복용 후 인지기능의 호전을 보이는 환자와 관계되는 요소

Donepezil ( ApoE4 allele 3, CDR, NICE guideline<sup>20)</sup> K - MMSE(0~9, 10~18. 19~30)

6. 통계 처리

SPSS 11.5 repeated measure of GLM (multinomial logistic regression analysis), chi square test donepezil

결 과

1. 성별 및 연령 분포

Donepezil 89 4 5 80 18

Barthel

75.7, K - MMSE 13.5 77.8, K - MMSE 15.3

가 ( 1).

2. 알츠하이머병 환자에서 K-MMSE 재검사의 신뢰도와  
유익한 점수차이에 대한 정의  
K - MMSE

30  
가 4  
2  
가  
( 0.58 )

(correlation)  
Kendall's index of concordance가  
가(intra-rater reliability)  
K - MMSE 가 1.97

2 4  
( 2).

**Table 1.** Demographic data between patients of Alzheimer's disease and small vessel dementia(mean ± standard deviation)

|                            | Alzheimer's disease | Small vessel dementia | p-value* |
|----------------------------|---------------------|-----------------------|----------|
| Numbers                    | 80                  | 18                    |          |
| Sex                        |                     |                       | NS       |
| Male                       | 22                  | 6                     |          |
| Female                     | 58                  | 12                    |          |
| Age (year)                 | 75.7 ± 8.3          | 77.8 ± 7.2            | NS       |
| Onset age (year)           | 72.5 ± 8.8          | 76.8 ± 7.3            | 0.15     |
| Duration (month)           | 37.8 ± 26.4         | 19.9 ± 17.2           | 0.05     |
| Education                  | 7.4 ± 5.7           | 7.0 ± 5.0             | NS       |
| K-MMSE                     | 13.1 ± 5.8          | 15.3 ± 5.4            | NS       |
| CDR                        |                     |                       | NS       |
| 1                          | 27                  | 5                     |          |
| 2                          | 33                  | 9                     |          |
| 3                          | 20                  | 4                     |          |
| GDS                        | 17.3 ± 6.5          | 16.5 ± 8.8            | NS       |
| Barthel index              | 17.8 ± 4.7          | 13.4 ± 7.2            | 0.04     |
| Donepezil (mg)             | 5.5 ± 1.5           | 5.8 ± 1.9             | NS       |
| Follow up duration (month) | 9.2 ± 9.16          | 5.4 ± 5.3             | NS       |

\* : Independent T-test, Chi-square test was done.  
K-MMSE : Korean Mini-Mental State Examination,  
CDR : Clinical dementia rating scale,  
GDS : Geriatric depression scale

**Table 2.** The K-MMSE values after test-retest trials and reliability test\*

|                            | 1st test   | 2nd test   | Mean 1st-2nd | SD of Mean |
|----------------------------|------------|------------|--------------|------------|
| Alzheimer's disease (n=30) | 17.8 ± 7.1 | 18.3 ± 7.0 | - 0.58       | 1.97       |

\* : Pearson correlation ; 0.967(p<0.001) between 1st and 2nd test.  
Kendall's index ; 0.844(p<0.001) between 1st and 2nd test, SD : standard deviation

**Table 3.** Change of K-MMSE after donepezil treatment

|                               | 0 week     | 4 week     | 12 week    | 24 week    |
|-------------------------------|------------|------------|------------|------------|
| Alzheimer's disease(N=80)*    | 13.0 ± 5.7 | 14.2 ± 5.7 | 15.0 ± 6.1 | 14.1 ± 7.4 |
| Small vessel dementia(N=18) † | 13.7 ± 5.3 | 15.0 ± 5.1 | 14.7 ± 5.4 | 15.0 ± 5.7 |

Repeated measure of ANOVA test ; p-values within subjects were 0.00 and between subjects were 0.401.

\* : Statistical significance was found between 0 week and 4, 12 week(p<0.05),

† : Statistical significance was found between 0 week and 4, 12, 24 week(p<0.05),

After 12 weeks, number of Alzheimer's disease n : 40 and small vessel n : 14

3. Donepezil 투약 후 K-MMSE 점수의 변화  
Donepezil

K - MMSE 가  
donepezil 12

가  
4  
가  
24  
(  
40 , 14 )  
( 3).

4. 알츠하이머병 환자에서 donepezil 사용 후 K-MMSE  
점수 각 영역별 변화

donepezil K - MMSE

, , ,  
12  
4 가



- 가 가 Donepezil <sup>10)11)</sup>  
 , me-  
 MMSE K-MMSE, MMSE - K, MMSE -  
 mantine study<sup>34)</sup>  
 KR, MMSE - CK  
 K-MMSE가 - donepezil 가  
 가 memantine 가 가  
 가  
 4  
 2 K-MMSE  
 K-MMSE - donepezil  
 Kendall 's index of concordance donepezil <sup>10)11)</sup> 가 MMSE  
 - 95% 가 .  
 23) K-MMSE가  
 3 4  
 4 K- 가  
 MMSE donepezil 가  
 Donepezil  
 12 가 , tacrine , , ,  
 4 12 donepezil 가 3 nition), , , , (recog-  
 12 가 28) K-MMSE  
 가 5) , , , ,  
 가 가 가 가  
 4  
 25) 가  
 basal forebrain 가 . K-  
 cholinergic nuclei가 MMSE 가 가  
 (0 1 ),  
 26) 가 (ceiling effects)가 가  
 .  
 20) NICE  
 MMSE MMSE가  
 가 가



중심 단어 : Donepezil

K - MMSE

---

## 참고문헌

---

1. Whitehouse PJ, Price DL, Struble RG, Clark AW, Coyle JT. Alzheimer's disease and senile dementia: loss of neurons in the basal forebrain. *Science* 1982;215:1237-1239.
2. Davies P, Maloney AJ. Selective loss of central cholinergic neurons in Alzheimer's disease. *Lancet* 1976;2:1403.
3. Davis RE, Doyle PD, Carroll RT, Emmerling MR, Jaen J. Cholinergic therapies for Alzheimer's disease. *Arzneimittelforschung Drug Res* 1995;45:425-431.
4. Cardozo MG, Iimura Y, Sugimoto H, Yamanishi Y, Hopfinger AJ. QSAR analysis of the substituted indanone and benzylpiperidine rings of a series of indanone-benzylpiperidine inhibitors of acetylcholinesterase. *J Med Chem* 1992;35:584-589.
5. Rogers SL, Friedhoff LT, the Donepezil Study Group. The efficacy and safety of donepezil in patients with Alzheimer's disease: results of a US multicenter, randomized, double-blind, placebo-controlled trial. *Dementia* 1996;7:293-303.
6. Rogers SL, Doody RS, Mohs RC, Friedhoff LT. Donepezil Improves Cognition and Global Function in Alzheimer Disease: A 15-Week, Double-blind, Placebo-Controlled Study. *Arch Int Med* 1998;158:1021-1031.
7. Rogers SL, Farlow MR, Doody RS, Mohs RC, Friedhoff LT. A 24-week, double-blind, placebo-controlled trial of donepezil in patients with Alzheimer's disease. *Neurology* 1998;50:136-145.
8. Giacobini E. Cholinesterase Inhibitor Therapy Stabilizes Symptoms of Alzheimer Disease. *Alz Dis and Ass Disor* 2000;14:S3-S10.
9. Cummings JL. Use of cholinesterase inhibitors in clinical practice: evidence-based recommendations. *Am J Geriatr Psychiatry* 2003 Mar-Apr;11:131-145.
10. Black S, Roman GC, Geldmacher DS, Salloway S, Hecker J, Burns A, et al. Group. Efficacy and tolerability of donepezil in vascular dementia: positive results of a 24-week, multicenter, international, randomized, placebo-controlled clinical trial. *Stroke* 2003;34:2323-2332.
11. Wilkinson D, Doody R, Helme R, Taubman K, Minzer J, Kertesz A, et al. Donepezil in vascular dementia: a randomized, placebo-controlled study. *Neurology* 2003;61:479-486.
12. Gottfries CG, Blennow K, Karlsson I, Wallin A. The neurochemistry of vascular dementia. *Dementia* 1994;5:163-167.
13. Leber P. Guidance for the clinical evaluation of anti-dementia drugs. First draft. Rockville, MD: US Food and Drug Administration;1990.
14. Rosen WG, Mohs RC, Davis K. A new rating scale for Alzheimer's disease. *Am J Psychiatry* 1984;141:1356-1364.
15. Schneider LS, Olin JT, Doody RS, Clark CM, Morris JC, Reisberg B. Validity and reliability of the Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change. *AD Assoc Dis* 1997;11 (suppl 2):S22-32.
16. McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under Auspices of Department of Health and Human Services Task Force on Alzheimer's disease. *Neurology* 1984;34:939-44.
17. Erkinjuntti T, Inzitari D, Pantoni L, Wallin A, Scheltens P, Rockwood K, et al. Research criteria for subcortical vascular dementia in clinical trials. *J Neural Transm Suppl* 2000;59:23-30.
18. Hughes CP, Berg L, Danziger WL, Coben LA, Martin RL. A new clinical scale for the staging of dementia. *Br J Psychiatry* 1982;140:566-572.
19. Kang Y, Na DL, Hahn S. A validity study on the Korean Mini-Mental State Examination(K-MMSE) in dementia patients. *J Korean Neurol Assoc* 1997;15:300-308.
20. National Institute for Clinical Excellence. Guidance on the Use of Donepezil, Rivastigmine, and Galantamine for the treatment of Alzheimer's Disease. London: NICE; 2001.
21. Galasko D, Abramson I, Corey-Bloom J, Thal LJ. Repeated exposure to the Mini-Mental State Examination and the Information-Memory-Concentration Test results in a practice effect in Alzheimer's disease. *Neurology* 1993;43:1559-1563.
22. Morris JC, Edland S, Clark C, Galasko D, Koss E, Mohs R, et al. The consortium to establish a registry for Alzheimer's disease(CERAD). Part IV. Rates of cognitive change in the longitudinal assessment of probable Alzheimer's disease. *Neurology* 1993;43:2457-2465.
23. Clark CM, Sheppard L, Fillenbaum GG, Galasko D, Morris JC, Koss E, et al. Variability in annual Mini-Mental State Examination score in patients with probable Alzheimer disease: a clinical perspective of data from the Consortium to Establish a Registry for Alzheimer's Disease. *Arch Neurol* 1999;56:857-862.
24. Folstein MF, Folstein SE, McHugh PR. 'Mini-mental state': a practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 1975;12:189-198.
25. Wilkinson D, Doody R, Helme R, Taubman K, Mintzer J, Kertesz A, et al. Donepezil 308 Study Group. Donepezil in vascular dementia: a randomized, placebo-controlled study. *Neurology* 2003;61:479-486.
26. Vinters HV, Ellis WG, Zarow C, Zaias BW, Jagust WJ,



- Mack WJ, et al. Neuropathologic substrates of ischemic vascular dementia. *J Neuropathol Exp Neurol* 2000; 60:658-659.
27. Orgogozo J-M, Rigaud A-S, Stöfler A, Möbius H-J, Forette F. Efficacy and safety of memantine in patients with mild to moderate vascular dementia: a randomized, placebo-controlled trial (MMM 300). *Stroke*. 2002;33:1834-1839.
28. Farlow MR, Hake A, Messina J, Hartman R, Veach J, Anard R. Response of patients with Alzheimer disease to rivastigmine treatment is predicted by the rate of disease progression. *Arch Neurol* 2001;58:417-422.
29. McLendon BM, Doraiswamy PM. Defining meaningful change in Alzheimer's disease trials: the donepezil experience. *J Geriatr Psychiatry Neurol* 1999;12:39-48.
30. Poirier J, Delisle M-C, Quirion R, Aubert I, Farlow M, Lahiri D, et al. Apolipoprotein E4 allele as a predictor of cholinergic deficits and treatment outcome in Alzheimer's disease. *Proc Natl Acad Sci USA* 1995;92:12260-12264.
31. Rigaud A-S, Traykov L, Latour F. Presence or absence of at least one E4 allele and gender are not predictive for the response to donepezil treatment in Alzheimer's disease. *Pharmacogenetics* 2002;12:415-420.
32. Eagger SA, Levy R. Serum levels of tacrine in relation to clinical response in Alzheimer's disease. *Int J Geriatr Psychiatry* 1992;7:115-119.
33. Homma A, Takeda M, Imai Y, Udaka F, Hasegawa K, Kameyama M, et al. Clinical efficacy and safety of donepezil on cognitive and global function in patients with Alzheimer's disease. A 24-week, multicenter, double-blind, placebo-controlled study in Japan. E2020 Study Group. *Dement Geriatr Cogn Disord*. 2000;11:299-313.