Metrifonate, 60–80 mg, led to improvement in cognitive function in mild to moderate Alzheimer's disease

Dubois B, McKeith I, Orgogozo JM, et al, on behalf of the MALT Study Group. A multicentre, randomized, double-blind, placebo-controlled study to evaluate the efficacy, tolerability and safety of two doses of metrifonate in patients with mild-to-moderate Alzheimer's disease: the MALT study. *Int J Geriatr Psychiatry* 1999 Nov;14:973–82.

QUESTION: In patients with mild to moderate Alzheimer's disease (AD), what is the effectiveness of 2 doses of metrifonate compared with placebo for cognitive function and global assessment?

Design

26 week randomised [allocation concealed*]†, blinded (clinicians and patients)*, placebo controlled trial.

Setting

71 study centres in France and the UK.

Patients

605 outpatients who were >45 years of age, met DSM-IV criteria for mild to moderate AD, had a Mini-Mental Status Examination (MMSE) score of 10–26, and a modified Ischaemic Score of <4. Exclusion criteria included coexisting medical conditions, hypersensitivity to cholinesterase inhibitors, and recent use of investigational drugs. 599 patients (99%) (mean age 72 y, 64% women) were included in the safety analysis; 594 (98.5%) were included in the intention to treat analysis.

Intervention

Patients were allocated to metrifonate, 40–50 mg (according to bodyweight: about 0.65 mg/kg/d) (n=200), metrifonate, 60–80 mg (about 1.0 mg/kg/d) (n=197), or placebo (n=208).

Main outcome measures

The primary outcomes were change in cognition (Alzheimer's Disease Assessment Scale - cognitive subscale [ADAS-cog]) and global functioning (Clinician's Interview-Based Impression of Change with Carer Input [CIBIC-plus]). Secondary outcomes included variation in the MMSE, Neuropsychiatric Inventory, and ADAS-noncog (neuropsychiatric measures), and in the Disability Assessment for Dementia (instrumental and basic activities of daily living).

Main results

Greater improvement on the ADAS-cog score was seen with 40–50 mg ($p=0.032$) and 60–80 mg ($p<0.001$) of metrifonate compared with placebo (table). Greater improvement on the CIBIC-plus occurred with 60–80 mg of metrifonate compared with placebo ($p=0.001$); the difference with 40–50 mg did not reach statistical significance ($p=0.052$) (table). Improvement in almost all secondary outcomes occurred with 60–80 mg of metrifonate compared with placebo. 40–50 mg of metrifonate showed improvement in 3 secondary efficacy variables. The groups did not differ for adverse events or for discontinuation caused by adverse events.

Conclusions

In patients with mild to moderate Alzheimer's disease (AD), metrifonate showed improvement in cognitive function, global functioning, and neuropsychiatric dis-

turbances of AD over 6 months. The 60–80 mg dose had the greatest effect.

*See glossary.

†Information provided by author.

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40–50 mg or 60–80 mg of metrifonate v placebo at 26 weeks for mild to moderate Alzheimer's disease†

Scale	Difference in mean score change from baseline	
	Metrifonate, 40–50 mg v placebo	Metrifonate, 60–80 mg v placebo
Alzheimer's Disease Assessment Scale - cognitive subscale	1.30	3.24
Clinician's Interview-Based Impression of Change with Carer Input	0.21§	0.35

‡All differences in score change favour metrifonate. §Not significant.

COMMENTARY

The progressive deterioration in cognitive performance, neuropsychiatric disturbances, physical disabilities, and decrease in global functioning which characterise AD became treatable with a rational therapy only when the acetylcholinesterase inhibitors became available in the early 1990s. Tacrine was the first marketed drug, followed by donepezil, and more recently, rivastigmine.

Dubois *et al* report the results obtained by the latest available acetylcholinesterase inhibitor, metrifonate. The study showed a positive effect of the drug on a wide range of symptoms for the 60–80 mg dose. Previous studies involving the other acetylcholinesterase inhibitors^{1–2} measured the same areas affected by the disease, in most instances with the same scales. All studies measured changes in the ADAS-cog score. It must be remembered that this scale, which assesses cognitive functioning, ranges from 0–70. The benefits of the higher doses shown in the 3 studies were as follows after 6 months of treatment: metrifonate 3.24, donepezil 2.88, and rivastigmine 4.94. Gains in global functioning in 4 areas (general, cognitive, behaviour, and activities of daily living) as measured by the CIBIC-plus (range 0–7) scale, were as follows: metrifonate 0.35, donepezil 0.44, and rivastigmine 0.20. Rivastigmine scored slightly better in terms of ADAS-cog compared with metrifonate and donepezil, while donepezil was superior as measured by CIBIC-plus. If we consider the rate of discontinuation because of adverse events from the acetylcholinesterase inhibition, metrifonate performs better (8% discontinuation compared with 16% with donepezil and 29% with rivastigmine).

The important message of this study is that metrifonate—and acetylcholinesterase inhibitors in general—prevented >1 year of disease progression. Metrifonate offers an alternative to the other acetylcholinesterase inhibitors and has fewer side effects.

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- 1 Rogers SL, Farlow MR, Doody RS, *et al*. A 24-week, double-blind, placebo-controlled trial of donepezil in patients with Alzheimer's disease. Donepezil Study Group. *Neurology* 1998;50:136–45.
- 2 Corey-Bloom J, Anand R, Veatch J. A randomized trial evaluating the efficacy and safety of ENA 713 (rivastigmine tartrate), a new acetylcholinesterase inhibitor, in patients with mild to moderately severe Alzheimer's disease. *Int J Geriatr Psychopharmacol* 1998;1:55–65.