Effect of tetrahydroaminoacridine on cognition, function and behaviour in Alzheimer's disease

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Objective: To determine the efficacy of tetrahydroaminoacridine (THA) in Alzheimer's disease.
Design: Randomized, double-blind, multiple crossover trial with three treatment periods, each consisting of 3 weeks of active drug therapy and 3 weeks of placebo administration.
Setting: Referral-based geriatric practice in a community hospital.
Patients: Thirty-four patients with moderate to severe Alzheimer's disease. Subjects were included if they had stage 3 to 6 disease (as determined by the Reisberg scale) and had not been taking psychotropic drugs for at least 1 month and if informed consent had been obtained from the patients and their next of kin.
Interventions: Fifty to 100 mg of THA daily and matched placebo.
Results: Of the initial 34 patients 14 experienced liver toxicity and 3 gastrointestinal side effects during the study; however, all 22 who completed the study were able to tolerate at least the minimum dose. For the 22 patients there was no clinically or statistically significant effect of THA on cognition, functional status or behaviour. The results for individual patients showed no subgroup of THA-responsive patients.
Conclusion: THA has no clinically important benefits in Alzheimer's disease and is associated with appreciable toxic effects.

Objectif : Déterminer l'efficacité de la tétrahydroaminoacridine (THA) dans les cas de maladie d'Alzheimer.
Conception : Essai aléatoire, à double insu et croisé multiple comportant trois périodes de traitement constituées, dans chaque cas, d'une thérapie médicamenteuse active durant 3 semaines et de l'administration de placebo durant 3 autres semaines.
Contexte : Pratique gériatrique sur présentation dans un hôpital communautaire.
Patients : Trente-quatre sujets atteints de la maladie d'Alzheimer à un stade intermédiaire ou avancé. Les sujets choisis devaient avoir atteint les stades 3 à 6 de la maladie (selon l'échelle de Reisberg) et ne pas avoir pris de psychotrope durant au moins 1 mois. Il fallait aussi avoir obtenu le consentement avisé des sujets et de leurs proches.
Interventions : Cinquante à 100 mg de THA par jour et placebo correspondant.
Résultats : Chez les 34 sujets du début, 14 ont souffert de toxicose hépatique et 3, d'effets secondaires gastrointestinaux au cours de l'étude. Cependant, les 22 sujets qui ont terminé l'essai ont pu tolérer au moins la dose minimale. Chez les 22 sujets, on n'a constaté aucun effet cliniquement ou statistiquement important de la THA sur la cognition, l'état fonctionnel ou le comportement. Les résultats particuliers à chaque sujet n'ont indiqué aucun sous-groupe de sujets sensibles à la THA.
Conclusion : La THA n'offre aucun avantage cliniquement important dans les cas de maladie d'Alzheimer, et elle a des effets toxiques importants.

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Neuropathologic studies have reported a decrease in the number of neurons in the cholinergic nuclei of patients with Alzheimer's disease.[1,2] The level of choline acetyltransferase, which synthesizes acetylcholine, is lower in patients with this disease than in age-matched control subjects.[3,4] Cholinergic cell loss and neuropathologic abnormalities have been positively correlated with cognitive impairment.[5] Neuropharmacologic studies have demonstrated that anticholinergic drugs produce short-term memory deficits similar to those found in patients with Alzheimer's disease.[6,7] Thus, there may be a deficit in cholinergic neurotransmission in people with Alzheimer's disease, and augmentation of cholinergic neurotransmission could improve cognition.

In a review of 31 randomized trials of the effects of cholinergic drugs on cognitive function in patients with Alzheimer's disease the results were found to be conflicting;[8] however, they provided some support for the hypothesis that cholinergic drugs improve cognition in such patients. One of the agents, tetrahydroaminoacridine (THA), is a centrally acting anticholinesterase and cerebral stimulant that selectively blocks potassium channels,[9] alters the function of M_1 muscarinic receptors[10] and blocks presynaptic and postsynaptic nicotinic and muscarinic receptors at high doses.[11]

THA has been tested in several clinical trials. Kaye and associates[12] reported a modest benefit when THA was combined with lecithin. Studies published in 1981 and 1986 showed a dramatic clinical improvement with THA.[13,14] Most recently Gauthier and collaborators[15] reported improvement in cognition and activities of daily living in 19 patients given THA.

We conducted a multiple crossover randomized trial to examine the effects of THA on cognition, function in routine and instrumental daily activities, and behaviour of patients with Alzheimer's disease. This disease may not be homogeneous, and only a portion of patients may respond to any particular therapy. Therefore, our study design allowed strong inferences about the degree to which each patient benefited from THA.[16]

Methods

Approval for the study was obtained from the institutional ethics committee.

Patient selection

We recruited patients referred to the Division of Geriatric Medicine, McMaster University, Hamilton, Ont., from October 1987 to August 1989. Referrals were made by family physicians, internists, neurologists, psychiatrists and geriatricians. All patients underwent a standard investigation, including comprehensive history-taking, physical examination, hematologic and biochemical screening, computed tomography of the head, electroencephalography, electrocardiography and chest radiography. Patients were then entered into the study if they had probable Alzheimer's disease (as determined by the National Institute of Neurological and Communicative Disorders and Stroke criteria[17]), had stage 3 to 6 dementia (as determined by the Reisberg scale[18]) and had not been taking psychotropic drugs for at least 1 month and if informed consent had been obtained from them and their next of kin. All of the subjects were living at home with a competent, reliable caregiver who supervised their compliance with medications and who was willing to bring the patient for each study visit.

Patients were excluded if their liver or renal function was abnormal, if their score on the Hachinski scale[19] was 4 or more or if their score on the Geriatric Depression Scale[20] was 7 or greater. A concomitant medical illness, such as angina, arthritis or chronic bronchitis, that could interfere with cognitive function or performance of daily activities was another exclusion factor.

Study design

There were two phases: a nonblind dose-finding phase and a double-blind, multiple crossover phase. Each patient received 10 g/d of lecithin throughout the study.

In the first phase the patients received labelled THA in doses of 50, 75 and 100 mg, each for 2 weeks. The highest tolerated dose was then administered in nonblind fashion for 3 more weeks. The duration of this phase was chosen to ensure that drug toxicity was excluded before the second phase. There was a 2-week washout period before the double-blind phase.

In the second phase all of the patients underwent three treatment sessions, each of which consisted of 3 weeks of THA therapy and 3 weeks of placebo administration. There were eight possible orders of drug and placebo administration across the three sessions. The patients were randomly assigned to receive one of the orders, so that after each group of eight patients had been randomly selected, all eight orders had been used. The patients, the caregivers and the study personnel were blind to treatment allocation; the code was held by the pharmacy.

The patients and their caregivers were asked to return for assessment at the end of each 3-week period. Cognitive function was assessed with the use of the Standardized Mini-Mental State Examination,[21] the Mental Status Questionnaire,[22] the Word

Fluency Test,[23,24] the Paired Words Test,[25] the Digit Span Test and the Logical Memory Test from the Weschler Adult Intelligence Scale,[26] the Colour Slide Test,[27,28] the Block Design Test[29] and the Benton Visual Retention Test.[29] We measured function using the Barthel Index,[30] the Blessed-Roth Scale[31] and the Lawton Scale.[32] Behaviour was measured with the use of the Blessed-Roth Scale[31] and the Behavioral Problem Checklist.[33] As an additional measure of behaviour we asked each caregiver to complete a questionnaire about the five most important functional or behavioural problems he or she had as a result of the patient's dementia. The severity of each problem was monitored at every visit.

Toxic effects

In both phases of the study blood samples were collected weekly from the patients to monitor their liver function through the serum levels of alanine and aspartate aminotransferase, alkaline phosphatase, γ-glutamyl transferase and bilirubin. The patients were telephoned weekly and asked about commonly reported side effects of THA, particularly gastrointestinal ones. Severe liver toxicity was defined as a level of liver enzymes greater than twice the upper limit of normal for two variables or greater than three times the upper limit of normal for one. In patients with these abnormalities the THA was stopped and a lower dose subsequently tried. Elevations in the enzyme concentrations below those levels did not necessitate withdrawal of the drug.

Statistical analysis

The sample size was chosen so that differences of less than one standard deviation in each outcome measure would be detected. The analysis of crossover trials is usually completely valid only if no effects from one treatment period are carried over to the next. We therefore began our analysis by examining for such effects. First, we analysed the results of the first treatment session for an interaction between treatment effect and order of administration of THA and placebo. We then repeated this analysis in each of the next two sessions using both the order of the previous session and the order of the current session as factors. This allowed us to examine the possibility of the effect's being enhanced if, for instance, two active treatments were given consecutively. Having excluded order effects we conducted a repeated measures analysis of variance, the two factors being treatment and time.

Individual results from the double-blind phase were analysed as follows. For each primary outcome the differences between scores during active drug therapy and placebo therapy were calculated for each treatment session. We compared the differences for each patient using a paired *t*-test with two degrees of freedom. This simple approach to analysis of data from randomized trials in individual patients has been described previously,[34] and it has been shown that *p* values often reach conventional levels of statistical significance in trials with positive results.[35] Because of the limited power of our trial (only three treatment sessions) and the desire not to miss a subgroup of responders we considered *p* values of 0.1 or less to be significant.

Results

Of the 34 patients entered into the study 7 did not proceed to the second phase: 2 were unable to tolerate the lowest dose of THA (because of nausea and vomiting in one case and severe liver toxicity in the other), 1 had myocardial infarction during the washout period, and 4 had poor compliance.

Fifteen other patients showed evidence of toxic effects during the dose-finding phase: 13 had severe liver toxicity (9 while receiving 100 mg of THA and 4 while receiving 75 mg), and 2 had nausea, vomiting, flatulence and dyspepsia while taking 100 mg of THA. All were able to begin the second phase on a lower dose.

Of the 27 patients who entered the double-blind phase 12 were given 100 mg of THA daily, 11 were given 75 mg/d, and 4 were given 50 mg/d. Five patients dropped out in this phase, two because of dysfunctional behaviour that required treatment with psychotropic drugs, two because the caregiver became ill and could not continue with the study and one because carcinoma of the bronchus was diagnosed.

Of the 22 patients (14 men) who completed the second phase the women varied in age from 54 to 74 (mean 76) years and the men from 55 to 79 (mean 69) years. The duration of dementia was from 1.5 to 12.0 (mean 3.7) years; the mean Mini Mental State score was 16.1 and the mean Reisberg score 4.

There was no interaction found between order of treatment and magnitude of effect in any analysis. Therefore, order effects were not considered further.

The results of the two simplest and most commonly used cognitive measures, the Standardized Mini-Mental State Examination and the Mental Status Questionnaire, are summarized in Table 1. The differences in effect between THA and placebo were small. The differences in the Mental Status Questionnaire scores reached conventional levels of statistical significance in favour of the placebo. The 16 other tests of cognitive function revealed consistently small differences between THA and placebo as well. None of the *p* values was less than 0.05, and

only three were between 0.05 and 0.1 (two in favour of placebo and one in favour of THA).

The results of the functional and behavioural measures are summarized in Table 1. The mean results are presented for each part of the three treatment sessions. The randomized order of medication within each session was ignored in the format of the table to facilitate understanding and interpretation. The repeated measures analysis of variance showed no clinically or statistically significant differences in effect between THA and placebo.

The overall mean difference in effect between THA and placebo for each major outcome measure, along with the 95% confidence intervals, are shown in Table 2. Invariably the confidence intervals were extremely narrow; thus, it was highly unlikely that a clinically important effect was missed.

Of all the 110 *t*-tests in the analysis of the data for each patient for daily activities and behaviour only 1 gave a *p* value of less than 0.05 (in favour of placebo). None gave a *p* value of 0.05 to 0.1. In addition, there were no substantial or consistent trends in favour of either THA or placebo in any patient.

Of the 396 *t*-tests that measured cognition 19 (in 16 patients) generated a *p* value of less than 0.05; 11 favoured placebo and 8 THA. There were 11 tests (in 10 patients) with a *p* value of 0.05 to 0.1; 9 favoured THA and 2 placebo. In general, the distribution of a *p* value of less than 0.1 in the study populatiuon did not suggest individual drug responders. In one subject the *p* value was less than 0.01 for 1 of the 18 neuropsychologic tests and 0.05 to 0.1 for 2 of the tests; in all three cases placebo was favoured. Overall, however, THA and placebo were favoured in nine tests each.

Discussion

Our data clearly show that THA did not have an overall beneficial effect on cognition, function or behaviour in the study population. Furthermore, in none of the subjects did THA have a clinically important positive effect on any outcome measure. Our findings contradict those of other studies.[12-15]

There are a number of possible explanations for this discrepancy. First, THA may take more than 3

Table 1: Cognition, function and behaviour among 22 patients with Alzheimer's disease given tetrahydroaminoacridine (THA) and placebo for 3 weeks each

	Treatment; mean score						
Outcome measure	Active	Placebo	Active	Placebo	Active	Placebo	*p* value
Cognition							
Standardized Mini-Mental State Examination[21]	16.3	17.3	16.6	16.5	15.4	16.1	0.11
Mental Status Questionnaire[22]	4.5	4.7	4.4	3.9	3.9	4.6	0.07
Function							
Barthel Index[30]	22.9	23.1	22.8	23.0	23.1	22.7	0.84
Blessed–Roth Scale[31]	29.8	30.2	29.7	29.8	29.5	29.4	0.78
Lawton Scale[32]	42.9	43.2	43.0	42.5	42.0	42.7	0.40
Behaviour							
Behavioral Problem Checklist[33]	117.6	116.5	115.9	117.8	116.0	118.1	0.15
Individualized questionnaire	26.2	26.1	26.9	25.8	26.7	27.1	0.34

Table 2: Overall mean and confidence intervals (CIs) for each major measure of outcome

Outcome measure	Mean*	95% CI*
Standardized Mini-Mental State Examination[21]	−0.44	−0.87 to 0.03
Mental Status Questionnaire[22]	−0.30	−0.61 to 0.01
Barthel Index[30]	0.03	−0.38 to 0.44
Blessed–Roth Scale[31]	−0.25	−0.88 to 0.38
Lawton Scale[32]	−0.15	−0.65 to 0.35
Behavioral Problem Checklist[33]	−0.94	−2.33 to 0.45
Individualized questionnaire	0.26	−0.45 to 0.97

*Positive values favour THA therapy, and negative values favour placebo.

weeks to work or to stop working. If so, we may have missed an effect because of excessively short treatment periods. This is not likely since we found no evidence of an order effect. The power of our tests for an order effect were limited; however, if THA took several months to work the results would have been negative regardless of the power of the tests. In the other studies the treatment sessions were 18 hours,[12] 1 hour,[13] 3 weeks[14] and 6 weeks;[15] in the last trial the full treatment effect was observed after 2 weeks. Therefore, different durations of treatment cannot explain the discrepant results.

Second, we may have been using inadequate doses. Because of the toxic effects observed at higher doses our maximum dose (100 mg) was only half that used by Summers and colleagues.[14] However, it was greater than that used by Kaye and associates[12] and the same as the maximum dose used by Gauthier and collaborators.[15] None of our 12 patients who tolerated 100 mg of THA daily had any sign of a treatment effect. Perhaps the results in the study by Summers and colleagues were positive because of the patients' ability to tolerate 200 mg/d.

Third, our study may have enrolled patients unresponsive to THA. However, this is unlikely for two reasons. Our criteria for the diagnosis of Alzheimer's disease were standard and similar to those used in other studies,[12,15] and the severity of the dementia in our patients was comparable to that reported in those studies. Furthermore, in examining data from individual subjects, all of whom underwent the three treatment sessions, we found no evidence of apparent responders. Thus, it is unlikely that there was even a small subgroup of patients who had a clinically important response to THA.

Fourth, there may have been inadequacies in our outcome measures that made it impossible to detect treatment effects. This is not likely, because our measurement of cognition, function and behaviour was at least as comprehensive and thorough as the measurement in other studies.[12-15] In addition, we were careful to choose measures that had been reported to show responses previously.[36]

Finally, there may have been methodologic differences. Kaye and associates[12] did not mention whether those who measured outcome were blinded. Because placebo and attention effects are extremely powerful in testing dementia patients, awareness of treatment may have introduced bias. Gauthier and collaborators[15] used an off-on-off design in their dose-finding phase. Such a design is far more open to bias from placebo, attention and natural history effects than is a randomized trial. The study by Summers and colleagues[14] has been criticized for poorly defined inclusion and exclusion criteria, lack of consideration of concomitant use of other medications, failure to report toxic effects and failure to use standard measurements of cognition and behaviour.[37,38] Summers and colleagues[39] have acknowledged the shortcomings in their report and the need for further work in this area.

Our study was randomized and carefully blinded, and standard measurements of outcome were used. Furthermore, the patients were repeatedly exposed to THA and placebo to avoid the identification of "responders" because of a temporary improvement in function that may not have been related to treatment. Therefore, we believe that the most likely explanation of the discrepant results lies in differences in study design and procedures. This conclusion is supported by the results of two other rigorously conducted crossover, randomized trials,[40,41] neither of which showed a clinically important beneficial effect of THA among patients with Alzheimer's disease.

In our study THA was found to be not only ineffective but also associated with appreciable gastrointestinal side effects and liver toxicity. Although Summers and colleagues[14] did not report any toxic effects Gauthier and collaborators[15] reported that 80% of their subjects experienced gastrointestinal problems or other troublesome symptoms and that 34% had reversible elevations in the liver enzyme levels.

Why is a cholinomimetic agent that can cross the blood-brain barrier not effective in Alzheimer's disease? Although the cholinergic deficit has been well documented in Alzheimer's disease there are deficits in other neurotransmitters. Studies have reported deficiencies in somatostatin,[42] serotonin,[43] dopamine[44] and aminobutyric acid.[45] This may explain why treatment with cholinergic drugs alone has not been consistently associated with improvement in function. Replacement of a single neurotransmitter in patients with Alzheimer's disease may not have any clinically important effect on cognition, function or behaviour.

Along with the results of the two other methodologically sound randomized trials[40,41] our data strongly suggest that THA has no role in the treatment of Alzheimer's disease.

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