Efficacy of tacrine and lecithin in mild to moderate Alzheimer's disease: double blind trial

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Abstract

Objective—To assess the efficacy of tacrine and lecithin in treating Alzheimer's disease over nine months.

Design—Double blind randomised controlled trial.

Setting—Outpatients clinic of university department of geriatric medicine.

Subjects—53 subjects (26 women, 27 men) with probable Alzheimer's disease. 41 completed the dose finding phase and were randomised to treatment. 32 (14 tacrine, 18 placebo) completed nine months' treatment.

Interventions—Lecithin and tacrine or lecithin and placebo for 36 weeks.

Main outcome measures—Scores on neuropsychological tests sensitive to deficits in the cholinergic system; mini-mental state score; behaviour change; mood; functional state; and stress in carers.

Results—The tacrine and placebo groups were similar except that the tacrine group had a longer duration of disease (mean 5.4 v 2.5 years in placebo group; $P=0.003$). Only 17 of the 32 patients could tolerate the maximum dose of tacrine (100 mg). No significant difference was found between the groups for any of the tests after nine months' treatment except for the digit backwards test, which is insensitive to cholinergic deficit. Analysis of subjects taking the maximum dose of tacrine and of subjects with mild dementia also found no differences.

Conclusions—Tacrine produces no clinically relevant improvement over 36 weeks at the doses tolerated by these patients.

Introduction

One of the most consistently reported brain deficits in Alzheimer's disease is in the cholinergic system. Consequently many treatment regimens have aimed at enhancing cholinergic transmission.¹

The acetylcholine precursors (lecithin and choline) and cholinergic receptor agonists (for example, arecoline and bethanechol) have been shown to have no significant effect on the course of Alzheimer's disease.²⁻⁸ A limited effect has been shown, however, with physostigmine,⁸⁻¹⁰ and substantial improvement has been reported with tacrine (1,2,3,4-tetrahydroaminoacridine),¹¹ a less potent but longer acting cholinesterase inhibitor. The trial of tacrine has been criticised,¹²⁻¹⁵ but at least one better designed trial also found improvement on some measures.¹⁶ Recent trials have been criticised for their short treatment period, poor design,^{11 17-20} poor patient selection,¹¹⁻¹⁹ small numbers,^{19 21-23} rapid dose titration, and the absence of washout during crossover.^{11 19 20 23} Taking these

criticisms into account, we report a randomised double blind trial aimed at determining the longer term effects of tacrine used with lecithin in treating dementia of the Alzheimer type.

Subjects and methods

Fifty three subjects (26 women and 27 men) participated in the study. They were recruited from referring neurologists, psychiatrists, and other physicians. All subjects fulfilled the criteria for dementia in the *Diagnostic and Statistical Manual of Mental Disorders*, third edition, revised (DSM-III-R)²⁴ and the criteria for probable Alzheimer's disease of the National Institute of Neurological and Communicative Disorders and Stroke.²⁵ All the subjects lived at home and had a carer willing to complete questionnaires. Exclusion criteria were concurrent terminal illness or end organ failure, inability to speak English or to comprehend the instructions for the verbal selective reminding task,²⁶ which was used to assess efficacy. Carers and, whenever possible, the patients gave informed written consent.

All patients initially underwent a dose finding phase with tacrine. Memory performance, liver enzyme concentrations, and carers' assessment of functioning were recorded at baseline and after two weeks of treatment with lecithin alone (9 x 1200 mg capsules daily). Subjects were then given tacrine, starting at 25 mg daily; doses were increased by 25 mg every two weeks to a maximum daily dose of 100 mg if there were no side effects and liver enzyme concentrations were not raised. Doses are expressed in terms of the hydrochloride salt of tacrine; an equivalent maximum dose of the base of tacrine is 80 mg daily. We defined a best dose of tacrine as either the highest tolerated dose or the tolerated dose at which performance on memory tests was at least 50% better than at baseline.

After a four week wash out period on lecithin alone, 41 subjects who could tolerate at least 25 mg tacrine daily were randomly assigned to one of two treatment groups for the nine month double blind phase: placebo plus lecithin or tacrine plus lecithin. Subjects took their own best dose and were assessed monthly for drug efficacy and safety.

ASSESSMENT

We assessed memory using verbal and visual selective reminding tasks consisting of lists of 10 words or seven objects respectively.^{26 27} Subjects were given 10 attempts to learn the lists. Multiple forms of the verbal and visuospatial tests were available so that different lists were presented to the patient at each test, thus minimising practice effects.

A battery of psychometric tests aimed at the specific cholinergic effects of tacrine was completed at baseline and after three and six months of treatment. The tests

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were selected on the basis of reported effects in healthy volunteers given the cholinergic blocking drug hyoscine. The battery included cholinergic sensitive tests (that is, hyoscine impairs test performance) and cholinergic insensitive tests. Further details have been reported.²⁸

A clinical examination, including a standardised neurological examination and the mini-mental state examination,²⁹ was repeated every three months. We calculated the extrapyramidal score taking into account resting tremor, glabella tap, rigidity of upper or lower limbs, nuchal rigidity, cogwheeling, fine finger movement, postural flexion, arm swing, and bradykinesia. Each measure was scored on a scale of 0 (normal) to 3 (severe defect), and the scores were summed.

Carers rated the patient's functioning and mood using the London psychogeriatric rating scale³⁰ and a profile of mood states scale³¹ modified for use by carers. They assessed the patients' instrumental activities of daily living³² and their own symptoms of stress (using a 30 item general health questionnaire³³) every three months.

We used standardised neurological tests to assess patients before inclusion in the trial and after the nine month double blind phase. Based on the neuropsychological approach of Walsh,³⁴ the tests assessed language, attention, memory and learning, visuospatial and constructional skills, frontal or executive function, visual agnosia, and apraxia. In addition the national adult reading test³⁵ and geriatric depression scale were administered.³⁶

SIDE EFFECTS

Carers reported side effects by completing a monthly checklist of 20 symptoms of cholinergic and liver dysfunction. Side effects were regarded as present if they were noted at least once by a carer during three months and had not been noted at baseline.

We tested liver function monthly. If enzyme concentrations were raised, they were measured weekly; if the rise continued or worsened the dose of tacrine (or placebo) was reduced. Treatment was stopped if concentrations reached three times the upper limit of normal.

TABLE I—Baseline characteristics of patients randomised to placebo and tacrine treatment groups who completed 36 weeks of treatment. Figures are means (ranges)

	Tacrine (n=14)	Placebo (n=18)
Sex (M:F)	8:6	9:9
Age (years)	66.5 (52-80)	71.1 (52-84)
Best tacrine dose (mg/day)	80.4 (25-100)	75.0 (25-100)
Duration of Alzheimer's disease (years)*	5.4 (1-11)	2.5 (<1-7)
Mini mental state score†	16.6 (3-27)	17.3 (4-26)
Carer:		
Spouse	14	13
Children		2
Sister		2
Unrelated		1

*Significant difference by *t* test; *p*=0.003.

†Maximum score 30.

TABLE II—Characteristics of patients who withdrew from double blind phase of study

Sex	Age (years)	Weeks of treatment	Best dose (mg/day)	Reason for withdrawal	Withdrawal related to tacrine
Tacrine:					
M	71	8	75	Aggressive behaviour	Possibly
M	65	19	50	Depression	Possibly
F	74	4	50	Raised liver enzymes	Probably
M	71	1	25	Raised liver enzymes	Probably
M	69	2	75	Joint inflammation	Possibly
F	84	12	50	Raised liver enzymes	Probably
Placebo:					
F	71	16	100	Travel intolerable	No
F	57	4	50	Refused medication	No
F	81	4	75	Carer unavailable	No

STATISTICAL ANALYSIS

For the verbal selective reminding task, total words recalled over 10 trials (maximum 100) were scored as outlined by Buschke *et al.*²⁶ A similar scoring system was used for the visuospatial selective reminding task (maximum 70). The total London psychogeriatric rating score and subscores of mental disorganisation (confusion), physical disability, socially irritating behaviour, and disengagement were calculated according to standard scoring procedures.³⁰ Scores of fatigue (worn out, fatigued, weary), vigour (alert, lively, vigorous), depression (sad, miserable, gloomy), and confusion (confused, forgetful, unable to concentrate) were calculated from the modified profile of mood states.³¹

For measures performed monthly, we averaged the scores over three months to minimise missing data and increase the reliability of the measurement. The baseline score was the average of scores at the pretrial assessment, the lecithin only assessment in the dose finding phase, and the assessment after the wash out phase. Paired *t* tests of the verbal memory test score before dose finding with the score after the wash out phase indicated no significant carry over effect of the drug after the wash out phase (*P*=0.85). We analysed data for patients completing 36 weeks of treatment using repeated measures analysis of variance. Treatment (tacrine *v* placebo) was the independent groups factor and testing occasion (baseline, 1-3 months, 4-6 months, and 7-9 months) the repeated measures factor. We also used repeated measures analysis of variance to compare the results of the neurological tests before and after in the two treatment groups. The *t* test and χ^2 test were used to compare other measures as appropriate.

Results

Twelve of the 53 subjects who began the dose finding phase withdrew before randomisation. Six subjects had raised liver enzyme concentrations and were not rechallenged; two had urticaria; one had partial bowel obstruction; one developed nausea and refused rechallenge; one developed urinary frequency, which caused the carer to withdraw consent; and one died of a myocardial infarction. Forty one patients were randomly assigned to either placebo (21 patients) or tacrine (20 patients) for 36 weeks.

Thirty two patients completed 36 weeks of treatment: 14 in the tacrine group and 18 in the placebo group. Table I gives a profile of the subjects in each treatment group. There was no significant difference between the two groups in age (*P*=0.11), sex (χ^2 =0.161; *P*=0.69), mini-mental state scores (*P*=0.75), or dose of tacrine (*P*=0.60). However, the tacrine group had a significantly longer duration of disease than the placebo group (*P*=0.003).

The repeated measures analysis of variance was done for only these 32 subjects. The nine subjects who did not complete the trial (table II) did not differ from subjects who completed the trial with respect to age (*P*=0.36) or mini-mental score (*P*=0.63). There was, however, a significant difference between the doses of tacrine the groups were taking. The mean daily dose was 55.6 (SD 27.3) mg in subjects who dropped out and 77.3 (27.9) mg in those who completed the trial. When subjects who dropped out are excluded from the analysis, the results should favour a positive effect of tacrine.

Table III summarises the test scores achieved by each treatment group over the 36 weeks of treatment. The only baseline assessment in which there was a significant difference between treatment groups was the instrumental activities of daily living (*P*=0.04). We found no interaction between treatment group and occasion for any of the measures except the digits

TABLE III—Means (SD) values for each test according to treatment group and time of assessment

	Months of treatment								P value
	Placebo				Tacrine				
	0	3	6	9	0	3	6	9	
Selective reminding tests:									
Verbal (total words)	35.5 (15.9)	37.0 (15.8)	37.5 (16.0)	34.6 (16.3)	34.9 (15.1)	37.8 (17.8)	38.7 (16.5)	38.5 (16.3)	0.200
Visual (total objects)	36.8 (21.2)	32.6 (20.3)	32.8 (22.8)	30.8 (22.7)	30.7 (13.3)	30.4 (20.2)	31.4 (18.1)	26.2 (16.9)	0.359
Cholinergic insensitive tests:									
Digit forward	5.9 (2.7)	5.1 (2.6)	5.2 (2.6)		6.1 (2.8)	5.5 (2.1)	5.9 (2.4)		0.723
Digit backwards	4.2 (2.6)	4.7 (2.6)	3.5 (2.1)		3.4 (1.9)	3.1 (2.2)	3.2 (2.0)		0.035
Verbal fluency	22.4 (13.2)	20.5 (13.1)	19.8 (11.8)		23.1 (15.0)	22.6 (14.9)	24.3 (14.8)		0.198
Similarities	9.4 (6.8)	8.7 (6.8)	7.5 (6.5)		12.6 (6.9)	12.6 (7.9)	12.9 (7.0)		0.197
Word stem completion	2.2 (2.7)	2.3 (1.9)	2.0 (1.4)		1.7 (1.8)	1.5 (1.7)	2.4 (1.9)		0.360
Homophone spelling	1.6 (1.7)	1.0 (1.3)	1.7 (1.7)		1.4 (1.3)	0.9 (1.6)	1.3 (1.3)		0.889
Cholinergic sensitive tests:									
Face recognition	3.8 (1.4)	3.7 (1.3)	3.4 (1.8)		3.9 (2.0)	3.4 (1.1)	3.4 (1.2)		0.651
Word recognition	5.3 (2.9)	5.5 (4.4)	4.1 (4.3)		4.4 (3.5)	3.93 (4.6)	2.6 (4.9)		0.913
Word recall	1.1 (1.0)	1.3 (1.0)	1.0 (0.8)		1.4 (1.3)	1.4 (1.8)	1.3 (0.7)		0.932
Symbol digit modalities	10.9 (9.7)	11.7 (10.8)	10.6 (9.6)		8.5 (9.5)	9.1 (10.3)	8.1 (9.1)		0.981
Neurological assessment:									
Mini-mental state	17.3 (6.7)	17.2 (6.8)	16.4 (6.8)	15.2 (8.0)	16.6 (6.8)	16.8 (6.6)	16.1 (6.5)	14.4 (6.7)	0.944
Extrapyramidal score	1.9 (3.0)	2.0 (2.8)	2.7 (3.4)	1.9 (2.5)	2.7 (2.3)	2.9 (2.9)	3.2 (3.1)	2.3 (3.3)	0.899
Mean blood pressure (mm Hg)	104.6 (12.7)	104.6 (11.8)	105.3 (14.9)	101.8 (14.8)	103.1 (13.8)	99.6 (17.8)	95.2 (10.4)	97.3 (11.0)	0.423
Carer assessments:									
London	14.1 (7.7)	14.7 (9.3)	15.7 (10.9)	18.9 (12.1)	15.2 (6.5)	16.9 (6.9)	18.2 (9.6)	19.5 (10.9)	0.638
Modified profile of mood states									
Fatigue	5.5 (2.1)	5.2 (2.1)	5.3 (2.4)	5.7 (2.5)	5.8 (2.0)	5.3 (2.1)	5.3 (2.0)	5.9 (2.2)	0.951
Vigour	8.7 (2.1)	9.0 (2.2)	9.4 (2.3)	8.6 (1.9)	8.9 (1.9)	8.9 (2.0)	9.0 (2.4)	8.9 (2.3)	0.571
Depression	4.2 (1.4)	4.0 (1.4)	4.2 (1.8)	4.8 (2.3)	4.8 (2.0)	4.8 (2.4)	4.6 (2.2)	4.6 (1.7)	0.316
Confusion	8.6 (2.4)	8.8 (2.2)	9.0 (2.6)	9.4 (2.8)	8.9 (1.7)	8.8 (2.6)	8.7 (2.9)	8.6 (2.6)	0.281
Instrumental activities of daily living	10.3 (2.6)	9.8 (2.5)	9.5 (2.6)	9.6 (2.7)	8.5 (2.5)	8.1 (3.0)	8.3 (2.8)	7.6 (3.4)	0.622
Carer stress assessment:									
General health questionnaire	2.4 (4.4)	1.6 (2.7)	2.6 (4.9)	2.2 (3.9)	4.0 (6.3)	4.4 (6.9)	2.0 (2.2)	3.1 (4.8)	0.397

* Repeated measures analysis of variance.

backwards test. Performance on the digits backwards deteriorated in the placebo group but not in the tacrine group. This test is cholinergic insensitive so tacrine would not be expected to have affected the results.

One year after the first neuropsychological assessment—that is, two months in the dose finding phase, one month wash out, and nine months of double blind treatment—only two out of the 22 tests showed any treatment effect: the colour form sorting test ($P=0.002$)³⁷ and similarities test ($P=0.04$).³⁸ The tacrine group improved on both tests. The placebo treated group improved on the similarities test but to a lesser extent.

There was no significant interaction between the treatment group and the total number of side effects reported. Three subjects withdrew because of raised liver enzyme concentrations (more than three times normal). Four subjects (two in the tacrine group and two in the placebo group) developed raised alanine aminotransferase concentrations less than three times the upper limit of normal; this resolved without reducing the dose in all but one case (placebo group).

To check the possibility that the dose was inadequate, 17 subjects with complete data who were taking tacrine or placebo at the 100 mg dose (10 placebo, seven tacrine) were analysed separately. No improvement was found in mini-mental state score or in the tests in the cholinergic battery compared with the placebo group. We also analysed separately data on a subgroup of patients with milder disease with mini-mental state scores above 20 (eight placebo, six tacrine). These subjects might be expected to have a purely cholinergic deficit and therefore be more responsive to treatment. No treatment effect of tacrine was observed in any of the tests.

Discussion

This randomised double blind trial was designed to determine the longer term effect of treatment with tacrine and lecithin on the dementing process of Alzheimer's disease. Measures of efficacy included repeated psychometric testing, neurological

examinations, and assessments of carers of patients' functioning. Thirty two of the 41 subjects with mild to moderate Alzheimer's disease who were randomised completed 36 weeks of double blind treatment: 14 in the tacrine treatment group and 18 in the placebo treatment group. Significant treatment effects were detected in no more of the efficacy measures than would be predicted by chance. Although the number of patients completing the trial was not large, neither was the difference in response to treatment between active and placebo groups. This study had a 90% chance of detecting a difference between groups in cognitive performance of three mini-mental state points or six Buschke words over 36 weeks.³⁹

The trial measured the effects of tacrine on top of any effects of lecithin. Lecithin alone could affect cholinergic transmission by saturating the metabolic enzymes and thus promoting synthesis of acetylcholine in the brain. Previous research has found little evidence of any effect of lecithin on the course of Alzheimer's disease,⁸ but there is theoretical evidence that lecithin could prevent damage from tacrine by loading the brain with choline. Cholinesterase inhibitors have been suggested to cause cell suicide by promoting breakdown of membranes containing phosphatidylcholine in order to obtain choline.⁴⁰

Many of the tests that we used to assess drug efficacy have been used in previous trials of cholinergic agonists^{9 41-43} or to assess the progression of Alzheimer's disease.^{32 36 44} The tests are reproducible and sensitive to change and despite the power of the study to detect clinically significant changes we found no effect of tacrine. It is unlikely that all the instruments used were consistently insensitive to an effect by tacrine. The doses of tacrine administered may, however, have been subtherapeutic or only a subgroup of patients may have been responsive to the treatment.

DOSES ADMINISTERED

No studies since that of Summers *et al*¹¹ have reported clinically relevant results of treatment with tacrine. Chatellier *et al*, Molloy *et al*, and Wilcock *et al* were unable to detect any significant effect of tacrine.^{17 23 45} Two studies reported that tacrine pro-

duced significant changes in mini-mental state score but not in other measures after 13 and four weeks of treatment,^{16,46} and Davis *et al* noted marginal improvements over six weeks of treatment.²⁰

The most important factor limiting the tolerated dose of tacrine was liver toxicity. Raised liver enzyme concentrations have often been reported, ranging in incidence from 13% to 42%.^{20,22} In this trial 14 of the 53 patients (26%) given tacrine in the dose finding phase had liver enzyme concentrations three times the upper limit of normal. Although there are no reported incidents of permanent damage and all our subjects had normal concentrations within a month of withdrawing the drug, biopsies of patients with raised liver function test results have reported damage ranging from focal inflammatory infiltration to extensive hepatocellular necrosis.⁴⁶⁻⁴⁹ We therefore decided to restrict doses to 100 mg daily. The trials which found a noticeable effect of tacrine used doses up to 150 mg and 200 mg daily.^{11,16}

We used a dose finding phase before randomisation to determine personal best doses for each subject, largely on the basis of the subject's highest tolerated dose. The mean best dose of tacrine was 72.6 (SD 28.94) mg daily. Therapeutic serum concentrations of tacrine four hours after the last dose are suggested to be 7 to 20 µg/l.⁴⁶ We did not always collect blood exactly four hours after the last dose and the methods did not take into account the metabolites of tacrine or differential protein binding. The plasma concentrations can therefore be considered only a rough estimate. However, in the dose finding phase the mean concentration of tacrine when patients were taking their best dose was 13.3 µg/l (SE 1.91; range 0 to 49.64). This is potentially a therapeutic dose.

We found a marginally significant correlation between memory (selective reminding task scores) and blood tacrine concentrations ($R=0.33$; $P=0.04$). This seems to support the argument that higher doses of tacrine are needed for a cognitive effect. Analysis of the subgroup of patients whose 'best dose' for the trial was 100 mg daily, however, showed no evidence of a long term treatment effect on the mini-mental state score. Because of liver toxicity, higher doses could be used only in selected patients and would require conservative titration and frequent monitoring.

Compliance may be a problem in subjects with dementia, but all our subjects had a carer who took responsibility for ensuring drugs were taken. General inquiry by the neurologists at three monthly assessments suggested that compliance was excellent, but this was not assessed independently.

RESPONSIVE SUBGROUPS

Eagger *et al* suggested that some patients respond better than others to tacrine.¹⁶ If tacrine is an effective centrally acting cholinergic agonist it might be expected to be most effective in mild Alzheimer's disease, when the deficits are predominantly cholinergic. We carried out a sub analysis on a group of patients with mild Alzheimer's disease who had a pattern of cognitive performance consistent with a purely cholinergic deficit.²⁸ However, we found no difference between the tacrine and placebo treatments.

Although patients were randomly assigned to treatment groups, patients treated with tacrine had a longer duration of disease than those treated with placebo. Our results could be falsely negative if subjects with a short duration of disease respond better to treatment. However, within the tacrine treated group there was no correlation between response to tacrine (as measured by the mini-mental state examination) and duration of disease ($P=0.50$), and analysis of the whole group showed no correlation between duration of disease and

Clinical implications

- Patients with Alzheimer's disease are thought to have deficits in the cholinergic system
- Patients have been treated with the cholinesterase inhibitor tacrine to enhance cholinergic transmission
- In this study no clinically relevant effect of tacrine was found over nine months of treatment, and nine of the 53 subjects withdrew because of liver toxicity
- Tacrine is not clinically useful for patients with Alzheimer's disease

baseline mini-mental state score ($R=0.25$) or verbal memory ($P=0.21$).

CONCLUSION

We found no evidence of any effect of treatment with tacrine on Alzheimer's disease. Although the doses administered may have been too low to be effective, fewer than half our subjects were able to tolerate the maximum 100 mg dose, and we believe that trials at higher doses would not find clinically relevant improvement.

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- 1 Hollander E, Mohs RC, Davis KL. Cholinergic approaches to the treatment of Alzheimer's disease. *Br Med Bull* 1986;42:97-100.
- 2 Barus RT, Dean RL, Beer B, Lippa AS. The cholinergic hypothesis of geriatric memory dysfunction. *Science* 1982;217:408-17.
- 3 Bruno G, Mohr E, Gillespie M, Fedio P, Chase TN. Muscarinic agonist therapy of Alzheimer's disease. *Arch Neurol* 1986;43:659-61.
- 4 Mouradian MM, Mohr E, Williams JA, Chase TN. No response to high-dose muscarinic agonist therapy in Alzheimer's disease. *Neurology* 1988;38:606-8.
- 5 Tariot PM, Cohen RM, Welkowitz JA, Sunderland T, Newhouse PA, Murphy DL, *et al*. Multiple dose arecoline infusions of Alzheimer's disease. *Arch Gen Psychiatry* 1988;45:901-5.
- 6 Penn RD, Martin EM, Wilson RS, Fox JH, Savoy SM. Intraventricular bethanechol infusion for Alzheimer's disease: results of a double-blind and escalating-dose trial. *Neurology* 1988;38:219-22.
- 7 Little A, Levy R, Chauagui-Kidd P, Hand D. A double-blind, placebo controlled trial of high-dose lecithin in Alzheimer's disease. *J Neurol Neurosurg Psychiatry* 1985;48:736-42.
- 8 Jorm AF. Effects of cholinergic enhancement therapies on memory function in Alzheimer's disease: a meta-analysis of the literature. *Aust NZ J Psychiatry* 1986;20:237-40.
- 9 Davis KL, Mohs RC. Enhancement of memory processes in Alzheimer's disease with multiple-dose intravenous physostigmine. *Am J Psychiatry* 1982;139:1421-4.
- 10 Stern Y, Sano M, Mayeux R. Long-term administration of oral physostigmine in Alzheimer's disease. *Neurology* 1988;38:1837-41.
- 11 Summers WK, Majovski LV, Marsh GM, Tachiki K, Kling A. Oral tetrahydroaminoacridine in long-term treatment of senile dementia, Alzheimer type. *N Engl J Med* 1986;315:1241-5.
- 12 Relman AS. Special report: tacrine as a treatment for Alzheimer's disease. *N Engl J Med* 1991;324:349.
- 13 Pirozzolo FJ, Baskin DS, Swihart AA, Appel SH. Oral tetrahydroaminoacridine in the treatment of senile dementia, Alzheimer type. *N Engl J Med* 1987;316:1603.
- 14 Hayward L, Brodaty H. THA and Alzheimer's disease. *Aust NZ J Psychiatry* 1987;21:618-24.
- 15 Levy R. Tetrahydroaminoacridine and Alzheimer's disease. *Lancet* 1987;i:139-41.
- 16 Eagger SA, Levy R, Sahakian BJ. Tacrine in Alzheimer's disease. *Lancet* 1991;337:989-92.
- 17 Molloy DW, Guyatt GH, Wilson DB, Duke R, Rees L, Singer J. Effect of tetrahydroaminoacridine on cognition, function and behavior in Alzheimer's disease. *Can Med Assoc J* 1991;144:29-34.
- 18 Kaye WH, Sitaram N, Weingartner H, Ebert MH, Smallberg S, Gillin JC. Modest facilitation of memory in dementia with combined lecithin and anticholinesterase treatment. *Biol Psychiatry* 1982;17:275-9.
- 19 Fitten LJ, Perryman KM, Gros PL, Fine H, Cummins J, Marshall C. Treatment of AD with short- and long-term oral THA and lecithin: a double-blind study. *Am J Psychiatry* 1990;147:239-42.
- 20 Davis KL, Thal LJ, Gamzu ER, Davis CS, Woolson RF, Gracon SI, *et al*. A double-blind, placebo-controlled multicenter study of tacrine for Alzheimer's disease. *N Engl J Med* 1992;327:1253-9.
- 21 Davies B, Andrewes D, Staggart R, Ames D, Tuckwell V, Davis S.

- Tetrahydroaminoacridine in Alzheimer's disease. *Int J Geriatr Psychiatry* 1990;5:317-21.
- 22 Forsyth DR, Surman DJ, Morgan RA, Wilcox GK. Clinical experience with and side effects of tacrine hydrochloride in Alzheimer's disease: a pilot study. *Age Aging* 1989;18:223-9.
 - 23 Chatellier G, Lacomblez L, on behalf of Groupe Français d'Etude de la Tetrahydroaminoacridine. Tacrine (tetrahydroaminoacridine; THA) and lecithin in senile dementia of the Alzheimer type: a multicentre trial. *BMJ* 1990;300:495-9.
 - 24 American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 3rd ed, revised. Washington, DC: American Psychiatric Association, 1987.
 - 25 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 the auspices of the Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology* 1985;34:939-44.
 - 26 Buschke H, Fuld PA. Evaluating storage, retention and retrieval in disordered memory and learning. *Neurology* 1974;24:1019-25.
 - 27 Muramoto O. Selective reminding in normal and demented aged people: auditory verbal versus visual spatial task. *Cortex* 1984;20:461-78.
 - 28 Christensen H, Maltby N, Jorm AF, Creasey H, Broe GA. Cholinergic blockade as a model of the cognitive deficits in Alzheimer's disease. *Brain* 1992;115:1681-99.
 - 29 Folstein MF, Folstein SE, McHugh PR. Mini-mental state: a practical guide for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 1985;12:189-98.
 - 30 Hersch EI, Kral VA, Palmer RB. Clinical value of the London psychogeriatric rating scale. *J Am Geriatr Soc* 1978;26:348-54.
 - 31 McNair DM, Lorr M, Droppleman L. *Manual for the profile of mood states*. San Diego: Educational and Industrial Testing Service, 1978.
 - 32 Lawton MP, Brody EM. Assessment of older people: self-maintaining and instrumental activities of daily living. *Gerontologist* 1969;9:179-86.
 - 33 Goldberg D. *Manual of the general health questionnaire*. Windsor: NFER-Nelson, 1978.
 - 34 Walsh KW. *Neuropsychology: a clinical approach*. Edinburgh: Churchill Livingstone, 1978.
 - 35 Nelson HE. *National adult reading test (NART) test manual*. Windsor: NFER-Nelson, 1982.
 - 36 Brink TL, Yesavage JA, Lum O, Heersema P, Adey M, Rose TL. Screening tests for geriatric depression. *Clinical Gerontologist* 1982;1:37-43.
 - 37 Weigl E. On the psychology of so-called processes of abstraction. *Journal of Abnormal and Social Psychology* 1941;36:3-33.
 - 38 Wechsler D. *Wechsler adult intelligence scale-revised*. New York: Psychological Corporation, 1981.
 - 39 Cohen J. *Statistical power analysis of the behavioural sciences*. Revised edition. New York: Academic Press, 1977.
 - 40 Wurtman RJ, Blusztajn JK, Growdon JH, Ulus IH. Cholinesterase inhibitors increase the brain's need for free choline. In: Giacobini E, Becker R, eds. *Current research in Alzheimer therapy*. New York: Taylor and Francis, 1988.
 - 41 Beller SA, Overall JE, Rhoades HM, Swann AC. Long-term outpatient treatment of senile dementia with oral physostigmine. *J Clin Psychiatry* 1988;49:400-4.
 - 42 Peters BH, Levin HS. Effects of physostigmine and lecithin on memory in Alzheimer's disease. *Ann Neurol* 1978;6:219-21.
 - 43 Kraemer HC, Peabody CA, Tinklenberg JR, Yesavage JA. Mathematical and empirical development of a test of memory for clinical and research use. *Psychol Bull* 1983;94:367-80.
 - 44 Applegate WB, Blass JP, Williams TF. Instruments for the functional assessment of older patients. *N Engl J Med* 1990;322:1207-14.
 - 45 Wilcock GK, Surman DJ, Scott M, Boyle M, Mulligan K, Neubauer KA, et al. An evaluation of the efficacy and safety of tetrahydroaminoacridine (THA) without lecithin in the treatment of Alzheimer's disease. *Age and Aging* 1993;22:316-24.
 - 46 Gauthier S, Bouchard R, Lamontagne A, Bailey P, Bergman H, Ratner J, et al. Tetrahydroaminoacridine-lecithin combination treatment in patients with intermediate-stage Alzheimer's disease. *N Engl J Med* 1990;322:1272-6.
 - 47 Summers WK, Tachiki KH, Kling A. Tacrine in the treatment of Alzheimer's disease. *Eur Neurol* 1989;29:28-32.
 - 48 Ames DJ, Fraser JRE, Bhatthal PS, Gibson PR, Davies BM, Roberts S. Heterogeneity of adverse hepatic reactions to tetrahydroaminoacridine. *Aust NZ J Medicine* 1990;20:193-5.
 - 49 Hammel P, Larrey D, Bernuau J, Kalafat M, Freneaux E, Babany G, et al. Acute hepatitis after tetrahydroaminoacridine administration for Alzheimer's disease. *J Clin Gastroenterol* 1990;12:329-31.

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Chest pain in women: clinical, investigative, and prognostic features

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Abstract

Objective—To characterise clinical, investigative, and prognostic features of women referred with chest pain who subsequently underwent coronary angiography.

Design—Analysis of all women with angina referred to one consultant during 1987-91 who subsequently underwent coronary angiography, with follow up to present day.

Setting—Cardiothoracic centre.

Subjects—Women with normal coronary arteries; women with coronary artery disease shown on angiography; men with coronary artery disease matched for age; men referred with chest pain during the same period subsequently found to have normal coronary arteries.

Main outcome measures—Risk factor analysis; results of exercise testing and coronary angiography; intervention; morbidity and mortality.

Results—Women comprised 23% (202/886) of patients referred with chest pain who subsequently underwent angiography. 83/202 women had normal coronary angiograms compared with 55/684 men (41% v 8%, $P < 0.001$). Diabetes mellitus was the only risk factor more frequently encountered in women with coronary artery disease ($P = 0.001$). The specificity and positive predictive value of exercise testing before angiography were significantly lower in women than men (71% v 93%, $P < 0.001$ and 76% v 95%, $P < 0.001$, respectively). Revascularisation procedures were as common in women with coronary artery disease as in men (81 (68%) v 70 (59%)), and there was no difference in event rate during follow up. Many patients with normal coronary arteries, irrespective of sex, had symptoms during follow up (61 (73%) women, 36 (65%) men) and continued to take antianginal drugs (27 (33%) women, 14 (28%) men); 14 (17%) women and six

(11%) men required hospital readmission for severe symptoms.

Conclusions—In this series, although women comprised the minority of patients referred with chest pain, a diagnosis of normal coronary arteries was five times more common in women than men. Risk factor analysis and exercise testing were of limited value in predicting coronary artery disease in women. There was no sex bias regarding revascularisation procedures, and outcome was similar. A diagnosis of non-cardiac chest pain in patients with normal coronary arteries was of little benefit to the patient with regard to morbidity.

Introduction

Chest pain in women is a commonly encountered condition which accounts for an appreciable number of referrals to cardiologists for further evaluation.¹ The symptom of chest pain has many causes which may or may not be cardiac in origin, and difficulty arises in establishing whether or not the patient's symptoms can be ascribed to reversible myocardial ischaemia. Coronary angiography is the criterion for establishing a diagnosis of coronary artery disease.

The reasons for referral for cardiac investigation are multifactorial and generally take into account the severity of the symptoms and the perceived likelihood of coronary artery disease. For example, increasing age and the presence of several recognised risk factors for coronary artery disease would tend to lower the threshold for referral. Patients with positive results on an exercise test are more likely to be further investigated, but ST segment shift with exercise is a less specific marker of coronary artery disease in women.^{2,4} Many patients referred with chest pain for investigation undergo coronary angiography. However, coronary angiography carries a small but well docu-

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