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Tacrine in Alzheimer's Disease

Time Course of Changes in Cognitive Function and Practice Effects

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This paper concerns certain questions which arose during the analysis of a trial showing positive effects of tacrine in Alzheimer's disease. Cognitive improvement occurred during the first two weeks, reached a maximum at one month and was maintained during the rest of the three-month treatment period. Rebound effects were not detected in any of the key outcome variables, but were suggested by one of the supporting cognitive tests and other measures. Practice effects occurred on tests which were repeated at short intervals or too frequently. The paper discusses the significance of these findings for the interpretation of other trials and for practical management.

Improvement in cognitive function on tacrine (tetrahydroaminoacridine, or THA) in patients with Alzheimer's disease (AD) was first claimed by Summers *et al* (1986) in a much-criticised paper. Subsequent negative studies (Chatellier & Lacomblez, 1990; Gauthier *et al*, 1990; Molloy *et al*, 1991) led to increased scepticism about the supposed effect. However, these studies have been flawed owing, among other things, (a) to the use of a cross-over design with an insufficiently long or totally absent wash-out period and (b) to the repeated use of tests at short time intervals, thus introducing practice effects during the placebo phase which may well have masked any drug effects.

On the basis of results of our own seven-month study in which 89 patients were entered, we believe that we have demonstrated a definite beneficial effect of THA (Eagger *et al*, 1991). The study was completed by 65 patients and there were highly significant differences between drug and placebo phases on the Mini-Mental State Examination (MMSE; Folstein *et al*, 1975) and the Abbreviated Mental Test Score (AMTS; Hodkinson, 1972). When patients were on active treatment, 45% showed an improvement of three or more points on the MMSE, compared with 11% when on placebo. In view of the current criticism of trials using cross-over designs (Food and Drug Administration, 1990) in patients with AD, we also looked at the first three months as a parallel group study and found significant advantages of drug over placebo on the MMSE ($P=0.0006$). We have argued that the improvement is roughly equivalent to the deterioration which might be expected over 6–12 months (but in the opposite direction).

A number of important practical questions remain with regard to efficacy. How quickly does the improvement take to emerge? How enduring is the effect? Bearing in mind that some patients have to be withdrawn due to adverse events, is there a rebound effect? Is there a practice effect and if so of what order of magnitude is it?

Method

Patients were selected from men and women of any age or race, who met National Institute of Neurological and Communicative Disorders and Stroke criteria for a diagnosis of probable AD (McKhann *et al*, 1985). They had a standardised physical and psychiatric evaluation, which included a computerised tomography (CT) scan and relevant laboratory investigations, to exclude patients with evidence of any other significant illnesses. Details are given elsewhere (Eagger *et al*, 1991).

This was a randomised, double-blind placebo-controlled cross-over study. There were two 13-week treatment periods separated by a 4-week wash-out. Subjects were randomly assigned to one of two groups. Patients in group A received active THA and active lecithin followed by placebo THA and placebo lecithin, and those in group B received treatment in the reverse order. The first week of each treatment phase was on active or placebo lecithin alone.

During the active treatment phase, THA was given in the form of 25 mg capsules (equivalent to 20 mg THA base). The dose was gradually increased from 50 mg to 150 mg daily over four weeks. If it was tolerated, patients remained on this dose for the further eight weeks. Even though the patients were concomitantly given lecithin to replicate the original study (Summers *et al*, 1986), it was of such low purity that it failed to make any significant impact on choline blood levels. We have, therefore, discounted its effect in this study.

The primary outcome variables were the MMSE (selected because of its simplicity, its wide use and the availability of long-term data), the AMTS and a scale for Activities of Daily Living (ADL; Lawton & Brody, 1969). Of our three outcome measures, two (MMSE, AMTS) showed significant treatment effects. Of the supporting measures included in

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order to document treatment effects in greater detail (Eagger *et al*, 1991), two components of the Attention Battery of the Cambridge Neuropsychological Test Automated Battery (CANTAB; Sahakian *et al*, 1990) also demonstrated significant treatment effects. These were a test of following a simple rule and its reversal, and a reaction-time task. As these were the tests that revealed treatment effects, they were used to answer questions regarding the time course of these effects and any rebound phenomena. Two other observer rating scales, the Blessed dementia rating scale (Blessed *et al*, 1968) and the Rosen Alzheimer's Disease Assessment Scale: Non-Cognitive Subscale (Rosen *et al*, 1984), although not showing any significant treatment effects, did demonstrate carry-over effects and are relevant to the discussion of rebound phenomena.

The MMSE was administered at the beginning and end of each treatment period and the AMTS every two weeks, along with liver function tests. The other tests were given at the beginning, middle and end of each treatment period, that is, at 6 and 12 weeks after the start of active or placebo drug.

Statistical analysis

A sample size of 65 out of an intent-to-treat population of 89 was analysed by use of a two-stage procedure for the analysis of cross-over trials (Hills & Armitage, 1979). A 2×2 analysis of variance was performed on the two groups by the change during the two treatment periods. As generally recommended, we used a conservative significance level of 0.1 to detect carry-over effects. If these were detected, a one-way analysis of variance on the change during the first treatment only was performed.

Results

Results are set out in the form of answers to questions which have arisen in the course of the analysis.

How rapid and enduring is the response to THA?

Three variables which were previously demonstrated to be significantly affected by THA were analysed: (a) AMTS; (b) 'following a simple rule and its reversal'; and (c) the dot-localisation task. (The latter two are both subtests of the CANTAB Attentional Battery.) For all of these variables, period by treatment interactions (carry-over effects) had previously been ruled out. The following analyses were, therefore, conducted on the results of the two periods of the trial taken together, with each subject given a score on both drug and on placebo.

For the AMTS (measured seven times in each treatment period) a two-way analysis of variance revealed a significant interaction between stage of treatment and drug effect ($P<0.0001$). In order to determine when this effect occurred, a *post hoc* analysis using baseline scores as a covariate was performed. When this was done the interaction disappeared, suggesting that the effect of THA occurred in the first two

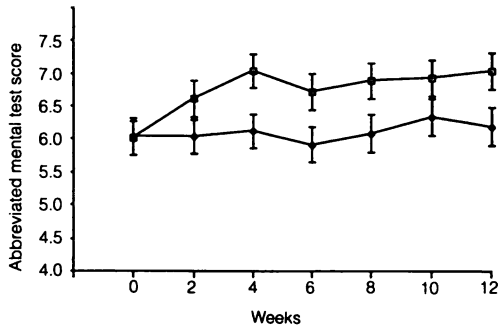

Fig. 1 Mean AMTS scores over time; error bars show s.e. (—⊡— THA, -●- placebo).

weeks of treatment (the dose increase during this period is from 50 mg to 100 mg a day). Although the drug effect continued to increase between weeks 2 and 4, this further increase was not statistically significant, whereas the increase between baseline and week 2 was (Fig. 1).

Analyses of variance for 'following a simple rule and its reversal' and the dot-localisation task revealed drug by stage of treatment interactions significant at $P=0.06$ and $P=0.006$ respectively. In an attempt to establish exactly where these effects occurred, two *post hoc* contrasts were conducted. The first of these, comparing the mean of scores obtained after 6 and 12 weeks of treatment with baseline scores, revealed a significant improvement in the first 6 weeks on THA but not on placebo ($P=0.032$ and $P<0.001$ for the two tasks respectively). Non-significant results were obtained for both variables in a second contrast, comparing scores at week 6 with those at week 12, confirming that the effect of THA occurred in the early stages of treatment (Figs 2, 3).

Following the initial improvement, the effects of THA were relatively enduring. Scores did not continue to improve but remained consistently raised throughout the rest of the treatment period (Figs 1–3).

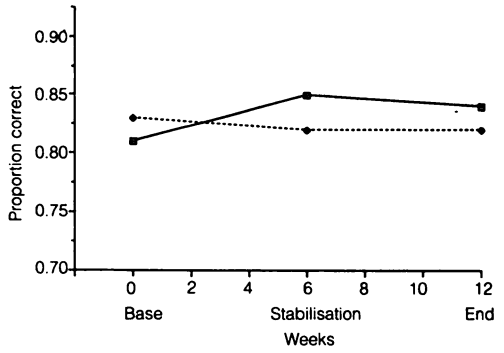

Fig. 2 Dot-localisation scores over time (—⊡— tacrine, ---●--- placebo).

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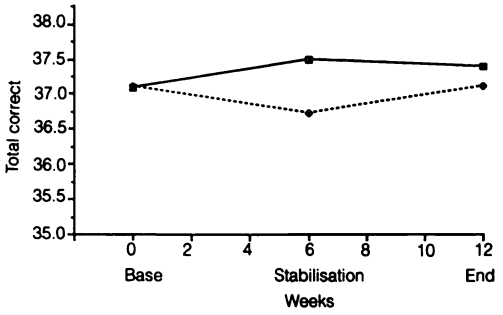

Fig. 3 'Following a simple rule and its reversal' scores over time (—⊡— tacrine, ---●--- placebo).

Does THA accelerate post-treatment deterioration?

In the following analysis, 'rebound' effect was interpreted to imply that at the end of the treatment period patients might be worse off than they would have been had they not had any treatment at all. This latter condition was calculated by means of the expected decline projected from the drop in scores during the placebo phase for those subjects who took placebo first and from the annual rate of decline in MMSE given in previous studies (Salmon *et al*, 1990).

Analyses of variance were conducted comparing the scores at the end of the trial for subjects taking active treatment first with the scores predicted from subjects taking placebo first, using baseline scores as a covariate. The results of these analyses for the three main outcome variables and the two variables from the CANTAB Attention Battery are shown in Table 1.

As the AMTS scores for placebo during the first treatment period showed an increase, presumably due to practice effect (see below), this made them unsuitable for predicting expected decline. Of the four remaining variables, there was evidence of rebound effect on the 'following a rule and its reversal'. No significant differences between predicted and actual scores were found on the other three, suggesting that there were probably no significant rebound effects. Although during the placebo phase following drug treatment scores declined more rapidly than would be expected without drug treatment, by the end of the trial they reached a level comparable with, but not below, that expected with no treatment. This increased rate of decline

Table 1
Tests for rebound effects on variables showing significant effects of THA

MMSE	NS
AMTS	$P=0.016$[1] ($F=6.15$; d.f. = 1)
ADL	NS
Following a rule and its reversal	$P=0.043$[2] ($F=4.23$; d.f. = 1)
5-choice dot-localisation	NS

1. AMTS scores for placebo on the first treatment (used to predict expected decline) show an increase. This is suggestive of practice effects due to frequency of administration, which confound the expected decline.
2. Suggestive of rebound.

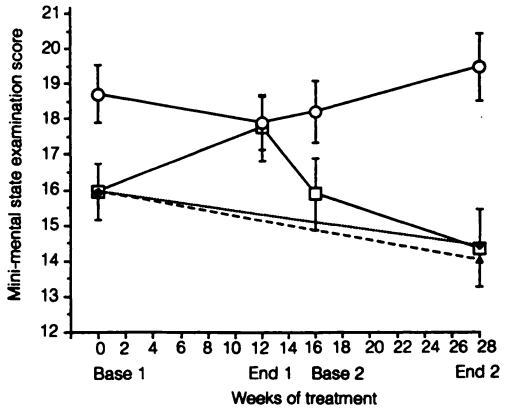

Fig. 4 Actual and predicted mean MMSE scores (error bars show s.e.) over time (—○— group b, receiving THA second; —□— group a, receiving THA first; ---- published rate of decline; ···· predicted rate of decline (see text)).

may in part be explained by cessation of treatment, which is suggested by the more rapid decline on MMSE score during the wash-out period immediately following active treatment (Fig. 4).

A second test for rebound effects was conducted on MMSE scores, for which published rates of decline on similar patient populations exist. Salmon *et al* (1990) reported a deterioration of approximately 3 points on the MMSE over 12 months. This is equivalent to a 1.5 point decline during the period of this trial. Figure 4 shows that this was very similar to the rate predicted from decline of subjects on placebo in the present trial. A paired *t*-test on subjects taking THA first, comparing their MMSE score at the end of the trial with that predicted from their baseline score, revealed no significant differences. This approach showed that there was no evidence of a rebound effect but also none for a continuing improvement.

On two observer rating scales, the Blessed and the Rosen, significant order of treatment effects were detected ($P=0.012$; $P=0.058$) in a direction indicating that patients did worse on these measures during the placebo phase if they had previously been exposed to the drug. However, rebound effects were not seen on the ADL.

Practice effects

The AMTS was administered every two weeks in order to chart the time course of any drug effect. The scores obtained while subjects were on placebo indicated that repeated testing appeared to introduce a practice effect which confounded the expected rate of decline (Fig. 1). This effect was evident from an increase in scores in those subjects who took placebo first (+0.8) but not in those who took it second (−0.6). It was also reflected in the combined scores (+0.15). In all cases the drug effect was still significantly greater than that of placebo. These practice effects did not appear to affect any of the other tests, which were administered less frequently.

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Discussion

The question of how quickly the improvement emerges is particularly important in designing a trial that is capable of demonstrating any treatment effects. So far, published trials have reported active treatment phases of one hour (Summers *et al*, 1981), three weeks (Summers *et al*, 1986; Molloy *et al*, 1991), four weeks (Chatellier & Lacomblez, 1990), eight weeks (Gauthier *et al*, 1990), and one week in-patient/eight weeks out-patient (Fitten *et al*, 1990). Our analyses suggest that the effects of THA appear relatively early in the course of treatment, that is, in the first six weeks. Analysis of the most frequently measured variable, the AMTS, suggests that effects can occur within two weeks, although more robust measures are needed to confirm this. Certainly, from Fig. 1. it can be seen that, even though significant improvement occurred within the first two weeks, the maximum score was reached at four weeks. That the maximum improvement takes about four weeks to emerge, combined with the fact that THA appears to continue to exert an effect for four weeks after cessation of treatment (Gauthier *et al*, 1989), means that trials of shorter duration (Chatellier & Lacomblez, 1990; Fitten *et al*, 1990; Molloy *et al*, 1991) are not likely to show any clear results, particularly in the case of cross-over trials without an adequate wash-out period. The question of the time course is also important for clinicians wishing to know how long to try the drug in individual patients before deciding on whether a useful effect has been achieved.

The initial improvement in scores was maintained throughout the rest of the treatment period, suggesting that the effects of tacrine are relatively enduring. Our experience with continued open treatment in patients who have elected to go on THA since the cessation of the double-blind trial, and have been followed up for up to three years, suggests that this effect persists for approximately 6–18 months.

The question of 'rebound' is a more contentious one. As patients may have to be withdrawn from the drug if they develop side-effects or fail to improve or be maintained, it is important to know if such patients will be worse off from having been exposed to THA than if they had not. This is how we have defined 'rebound'. In order to exclude this unequivocably, we would have had to use a matched no-treatment group, monitored on all the same measures over the same total period of seven months – an ideal unlikely to gain the co-operation of patients. We have done the next best thing by using two statistical controls, namely the rate of decline in the group receiving placebo first, and the rate of decline reported in the literature. Both assume a linear change, which cannot be proved. We have certainly demonstrated that there is a 'cessation of treatment' effect which is clearly visible on the MMSE, but this is in no sense a true 'rebound' phenomenon. It is entirely predictable and may well give an impression of a more rapid decline when treatment stops. Gauthier *et al* (1989) have commented on a possible worsening after two weeks off THA. They also reported that four weeks were required for patients to return to their baseline scores, which our results also suggest (Fig. 4). They have advised a progressive tailing off rather than abrupt withdrawal in order to lessen this apparent rebound of functional disability. Although advisable, this does not seem essential, since three months after withdrawal from the drug our patients were at a level which was consistent with the expected decline of the cognitive tests predicted in two different ways. The apparent worsening of some non-cognitive measures after treatment, reflected in the Blessed and Rosen scales, is puzzling. Whether it is a true physiological effect or a psychological one reflecting the carers' perceptions after an apparent improvement during the first half of the study is difficult to determine. The lack of change in any direction on the ADL scale is not surprising in view of the scale's insensitivity in this group of patients, on which we have previously commented (Eagger *et al*, 1991).

Practice effects were obvious on the test which was administered most frequently, i.e. every two weeks. This effect is likely to occur early, as it was only seen in those patients who took placebo first. In those taking the drug first, it is likely to have been buried within the treatment effect. The demonstration that patients with AD are able to learn when given frequent reinforcement should be borne in mind in the design of trials to detect changes in cognitive function. In some of the trials mentioned earlier (Gauthier *et al*, 1990; Fitten *et al*, 1990), the MMSE was administered every two weeks, a feature which makes them difficult to interpret. The practice effect can be overcome by administering the relevant test after a reasonably long time interval, avoiding frequent retesting, or devising parallel forms. Other strategies, such as the use of a second 'baseline' after the maximum effects have occurred, and demonstrating a treatment effect over and above this, may also be worth considering.

Conclusion

We have shown that the treatment effects of tacrine appeared within the first two to four weeks of treatment, reaching the maximum effect at four to

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six weeks. The effect was maintained for the rest of the treatment period. After withdrawal, deterioration to a point worse than one would expect was not detected on three out of four cognitive tests or in any of the key outcome measures. Practice effects were seen on tests which were repeated at short intervals, or too frequently, and these may have confounded the results in other trials. Consequently, trials of this and other similar compounds need to allow sufficient treatment time, a suitable interval between tests and an adequate wash-out period. Long-term parallel studies are required in order to make any meaningful statement on the ultimate outcome measures, that is, death or need for institutionalisation.

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