Differential effects of atenolol and enalapril on memory during treatment for essential hypertension

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1 A randomized single-blind study was designed to compare the performance on memory tests requiring recall of information relevant to everyday life of two groups of hypertensive patients.

2 One group of 13 patients were taking a β -adrenoceptor blocker (atenolol) and the other group of 12 patients received the angiotensin-converting enzyme inhibitor (enalapril).

3 The results suggested that when compared with placebo the group of patients treated with enalapril showed no changes in memory function, whilst there was a mild, but consistent deficit in the group taking atenolol.

Keywords atenolol enalapril hypertension memory

Introduction

The treatment of essential hypertension is of necessity life-long, and a wide variety of anti-hypertensive drugs are available. Among the most widely used drugs are the β -adrenoceptor blockers. Apart from blockade of peripheral β -adrenergic receptors, they also act on the central nervous system and several reports have described effects attributable to their central action. These include depression (Waal-Manning, 1967), sleep disturbance (Betts & Alford, 1982) and psychosis (Fraser & Carr, 1976). There have also been reports describing deficits in cognitive function (Patel & Turner, 1981; Salem & McDevitt, 1983) including memory (Solomon *et al.*, 1983; Hartley *et al.*, 1983). Angiotensin-converting enzyme inhibitors like enalapril reduce blood pressure by a mechanism unrelated to that of β -adrenoceptor blockers. The possible central effects of these drugs have not yet been evaluated, although in a recent study it was found that they enhanced attention and alertness (Olajide & Lader, 1985).

Methods

Subjects

The subjects were drawn from a hypertension clinic where they were taking part in a multi-centre trial evaluating the antihypertensive effect of atenolol *vs* enalapril. A condition for inclusion was a supine diastolic blood pressure > 100 mmHg during the placebo period. All patients gave their informed consent to the study. Patients were excluded if they were receiving psychotropic medication, had secondary or malignant hypertension, or had had a cerebro-vascular accident or hypertensive encephalopathy within the past year.

Twenty-five patients (15 men and 10 women) took part in the present study, mean age 55.7 years (range 37–72 years) and all had moderate to severe hypertension, defined as a documented supine diastolic blood pressure of 100–130 mmHg. Mean ages, sex and blood pressure readings are shown in Table 1.

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Table 1 Demographic and blood pressure data for atenolol and enalapril treatment groups

Group	n	Mean age (years)	Mean BP (mmHg)		Mean BP fall (mmHg) between Week 0 and Week 16	
			Systolic Week 0	Diastolic Week 16	Systolic	Diastolic
Atenolol	13 (9M 4F)	55.8	189/115	163/91	26.2	23.8
Enalapril	12 (6M 6F)	55.6	196/115	149/89	46.7*	26.5

* $P < 0.05$ (between group difference)

Patients were randomly assigned to two groups: one received placebo followed by atenolol 50 mg and the other placebo followed by enalapril 20 mg daily. After 4 weeks on active treatment, patients whose diastolic blood pressure was > 90 mmHg were tritrated to atenolol 100 mg or enalapril 40 mg. If a diastolic blood pressure of 90 mmHg was not reached within 8 weeks, hydrochlorothiazide 25–50 mg was added.

The first assessment of memory function was carried out at the end of a 2 week drug washout period while the patients were taking a placebo (week –2–0) and the second assessment at 16 weeks, the end of the active treatment period (week 0–16). Memory function was assessed using two alternative versions of a memory test (Form A and Form B). The choice of whether a particular individual should start with Form A followed by Form B or vice versa, was randomly varied, also the four tests were given in a random order. All testing was carried out by an observer (I.L.) who was not aware of the treatment allocations.

Memory tests

The tasks were designed to test the ability of subjects to acquire and retain various items of information which have meaning in everyday life. Although the test material was constructed specifically for this study, the general design of the memory tests followed the outline proposed by Randt *et al.* (1980) and used in a similar manner in one of our previous studies (Cull & Wyke, 1984). The complete evaluation of memory required seven trials for each test, five learning trials (trial 1–5), one 'short-term' memory trial (trial 6) and one 'long-term' memory trial (trial 7) (see Figure 1). These estimates of memory function therefore yield measures of immediate recall (trial 1), learning ability (trial 5), 'short-term' recall (trial 6) and 'long-term' recall (trial 7). In short there were four tests or tasks each one presented on seven separate occasions (i.e. seven trials).

Figure 1 Example of a sequence in which the memory tests were administered.

Test 1 (shopping list) was a task which required memorising a 10 item list. Each item was printed on a separate card (e.g. 3 lb FLOUR, 2 lb RICE) shown for 6 s, and read aloud to the subject, who was then asked to recall the items in any order. Two points were given when an item was correctly recalled; one point was gained if only part of the information was recalled. The score was the total number of correct responses (maximum 20 points). A total of five learning trials was given to each subject.

Test II required memorising five black and white photographs of men's faces, paired with first names and surnames printed on a card. The first names were taken from a book of common English names. All the surnames occurred with approximately the same frequency in the London Telephone Directory (covering one page). The

five cards and matching photographs were shown to the subjects for 6 s each and the names were read aloud, then each photograph was presented in random order and the subject was asked to give the appropriate name and surname. Two points were given when the first name and surname corresponded to the photograph; one point when only the first name of the surname were correct. The score was the total number of correct responses (maximum 10 points). A total of five trials was given to each subject. After completing this test, the subjects were asked to recall the items of Test I (shopping list).

After this, Test III (telephone extension numbers) was given. This task required memorising six telephone extension numbers paired with the names of various departments of a general store. Each item of information was printed on a separate card (e.g. BOOKS $\times$ 74; SHOES $\times$ 63). The cards were shown for 6 s each and the information also read aloud to the subject, who was then asked to recall the list in any order. Two points were given when the two items of information were correctly recalled; one point if only one of the items was remembered. The score was the total number of correct responses (maximum score 12 points). A total of five trials was given to each subject. The subjects were then asked to recall the items of the Faces task (Test II).

After this, Test IV (Logos) was given. This required memorising six simple drawings or logos paired with business classifications in the London Yellow Pages Telephone Directory (e.g. 'Plumbers', 'Engineers'). Each classification and logo was printed on a separate card. The cards were shown for 6 s each and the business classifications read aloud to the subject. Each logo was then presented in random order, and the subject was asked to recall the corresponding classification. One point was given when the absent item was correctly recalled. The score was the number of correct responses (maximum score 6 points). A total of five trials was given. When the Logos test was completed, the subjects were asked to recall Test III (telephone extension numbers) followed by the recall of Test IV (Logos). After the tests were completed (approximately 45 min), subjects were asked to recall the four tests.

Patients were also asked to rate their memory function subjectively (Asberg *et al.*, 1978). The following ratings were used: 0, memory as usual; 1, occasional increased lapses of memory; 2, reports of socially inconvenient or disturbing loss of memory; 3, complaints of complete inability to remember.

Controls

A control group of nine subjects drawn from patients' relatives and normal volunteers matched for age, sex and years of education, was tested at the same interval as the patient group. The purpose of the matched control group was two-fold. Firstly, to establish that the two Forms (A and B) were equivalent and therefore could be considered analogous for the purpose of the present study; secondly to establish whether there were practice effects at the second testing session. The control group's performance on Forms A and B showed no significant differences in any of the trials in the four tests. In addition the coefficient of correlation between Form A and Form B was high ($r > 0.8$ for the four tests). There was, however, a small but not significant effect between the two sessions, in the shopping list and faces tests, but due to the balanced design of this study, this would not affect the results.

Results

There was no significant difference in the ages of subjects in the atenolol group compared with the enalapril group. The fall in diastolic pressure was the same in both groups (see Table 1). Systolic pressure however, was more markedly reduced in the enalapril group ($t = 2.53$, $P < 0.05$), as has previously been reported (Arr *et al.*, 1984).

Memory tests

The performance of the three groups was scored in terms of items recalled in each trial. Figure 2 shows the performance scores for the four memory tests and the seven trials. Comparisons between the placebo and treatment session (atenolol or enalapril) were carried out using *t*-tests for related means. The results show that in the atenolol group, performance scores were lower during the active treatment phase compared with placebo (nine out of 28 trials reaching statistical significance). By contrast, there was no significant difference in the performance of the enalapril group; the results were similar to the control group. In both of these groups there was a small practice effect between the two sessions in the shopping list and faces tests. Results on item 17 of the Comprehensive Psychopathological Rating Scale showed that most patients did not report any subjective changes in memory function. One patient in the atenolol group thought that his memory function had

Figure 2 Performance scores for enalapril and atenolol treatment groups in the two testing sessions. Scores across the seven trials of the four memory tests are expressed as mean number of correct responses. ● Placebo, ○ atenolol, (Δ) enalapril, ○—○ placebo, ○---○ atenolol (in upper graphs), ○---○ enalapril (in lower graphs). Differences between the two testing sessions: atenolol group: $P < 0.05$: trials 1 & 6 (shopping list test), trial 4 (Logos) $P < 0.01$: trials 2–7 (Telephone Extension numbers). Enalapril group: Not significant.

deteriorated slightly from week 0 (self-rating 0) to week 16 (self-rating 1). Two patients in the atenolol group and one patient in the enalapril group thought that their memory function had improved slightly from week 0 (self-rating 1) to week 16 (self-rating 0).

Discussion

The main finding of this study is the mild but consistent impairment in memory function in the group of patients treated with atenolol. This deficit was found in all aspects of memory tested i.e. acquisition, short-term and long-term recall. The results are consistent with a recent study which demonstrated verbal memory impairment in subjects taking methyldopa or propranolol (Solomon *et al.*, 1983).

Whilst it is recognised that hypertension may give rise to memory impairment, it is not felt that the slightly greater systolic fall in the enalapril treated group would be sufficient to account for changes observed. Furthermore since the patients acted as their own controls, differences in the ages of the patients is not relevant.

During an active treatment phase, only one subject in the atenolol group reported memory difficulties. This patient was engaged in full-time work requiring careful attention to detail and therefore may have been more aware of his impairment. This is consistent with the observations of Solomon *et al.* (1983) who found that most of the subjects who had memory deficits while on β -adrenoceptor blocker therapy were unaware of their impairment.

It is unlikely that the addition of hydrochlorothiazide during the active treatment phase could have affected the results. Solomon *et al.* (1983) provided evidence that diuretics did not produce memory impairment; furthermore, an equal number of patients in both of our treatment groups received hydrochlorothiazide.

The mechanism of atenolol's central action is not well understood. Atenolol has low lipid-solubility, reaching a brain/plasma ratio of only 0.054 (Day *et al.*, 1977), therefore it is not distributed in the brain as readily as highly lipid-soluble β -adrenoceptor blockers like propranolol (Day *et al.*, 1977). Nonetheless, the mild deficit of memory function seen in patients taking atenolol suggests that low lipid-solubility

may not fully protect against the central effects of atenolol. Furthermore, in a study carried out on rats, the highest concentration of a β -adrenoceptor blocker (propranolol) was reached in the hippocampus (Garvey & Ram, 1975). This finding is particularly interesting as it is well known that the hippocampus plays an important role in the organisation of memory function (Milner *et al.*, 1970). It is also worth noting that atenolol may exert an influence on systems other than those involving β -adrenoceptors, as it has been demonstrated that in rats, β -adrenoceptor blockers bind to serotonin receptors in the brain (Middlemiss *et al.*, 1977). By contrast, angiotensin-converting enzyme inhibitors do not appear to cross the blood-brain barrier readily (Heald &

Ita, 1977), and this might explain why the patients taking enalapril showed no impaired performance on memory tests.

Whilst this preliminary study may suggest differences between atenolol and enalapril, this can only be confirmed by a randomised double-blind cross-over study. However, we believe the results are important, as even a mild memory deficit can affect the lives of some patients taking β -adrenoceptor blocking drugs for long periods of time.

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