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The effects of anti-hypertensive medication on learning and memory

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1 The aim of the study was to investigate whether there were differential effects of three different anti-hypertensive medications (cilazapril, atenolol, nifedipine) on cognitive function.
2 A sub-group of patients participating in a large clinical trial of these three drugs, randomly allocated between the three drug conditions, received cognitive assessment at two points before the commencement of treatment and then after 12 and 24 weeks of treatment. Seventy-six patients began treatment, and 55 completed the full course.
3 Tests of learning and memory were designed specially for the study, with a different but comparable version administered on each assessment occasion, in a fixed order.
4 No significant differences between drug groups were found in any index of learning or memory, at any testing occasion. The results were the same whether or not treatment non-completers were included in the analysis.

Keywords atenolol cilazapril nifedipine hypertension learning memory

Introduction

An adequate evaluation of any pharmacological treatment must include assessment of so-called 'adverse effects' as well as of efficacy in ameliorating the condition. The potential psychoactive effects, including alterations in both emotional state and in cognitive functioning, clearly warrant careful investigation, since adverse changes here might, from the patient's perspective at least, outweigh other symptomatic improvements. Likewise, where several drugs are known to achieve comparable amelioration of the presenting complaint, awareness of more subtle differences between them in their psychoactive effects could, and should, provide a basis for discrimination in prescribing. The present paper describes a comparative study of the effects of three types of anti-hypertensive medication on learning and memory.

There exists a wide range of pharmacological routes to the treatment of essential hypertension. The older agents, including diuretics and β-adrenoceptor blockers, are very effective in reducing blood pressure but they also cause many adverse effects, including unwanted metabolic changes (Ames, 1986a,b; Kaplan, 1986; Knochil, 1984; Murphy *et al.*, 1982); these are, however dose-dependent and are difficult to demonstrate after 1 year. Whilst the more recently introduced agents, which include calcium antagonists and angiotensin-converting enzyme (ACE) inhibitors, are no more effective than the older drugs, there is some evidence that they lack the adverse metabolic effects (Hedner *et al.*, 1987; Pollare *et al.*, 1989). In cases of mild to moderate hypertension, treatment is initiated in patients who are otherwise symptom-free, and in recent years attempts to discriminate between the different classes of drug have therefore focused on more subjective factors, collectively termed 'Quality of Life'. One such factor which has thus far received little attention is the effect of medication on learning and memory. In the literature which does exist on this subject, the evidence is inconclusive. On the one hand, a few studies have reported impairments with β-adrenoceptor blockers, particularly in verbal memory (see Richardson & Wyke, 1988, for a review), with drug-related decrements in performance among hypertensive patients found in both between-subject designs (Hartley *et al.*, 1983; Solomon *et al.*, 1983) and within-subject designs (e.g. Lichter *et al.*, 1986; Steiner *et al.*, 1990). On the other hand, a recent double-blind study by Skinner *et al.* (1992) which used a crossover design to evaluate the effects of the β-adrenoceptor blocker, atenolol, and the calcium antagonist, nifedipine, on memory and other cognitive functions in elderly hypertensive subjects, found no adverse effects of atenolol. Nifedipine, by contrast, was associated with mild impairments on tests which involved learning. Deary *et al.*

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(1991) conducted a similar study, comparing the effects of atenolol and captopril treatment in a sample of hypertensive adults, again using a double-blind crossover design. Patients were assessed with an extensive battery of standard tests of memory and information-processing ability at baseline and after 6 weeks on each medication. No differences were found between the atenolol and captopril conditions.

The study by Lichter *et al.* (1986) evaluated the effects of an ACE inhibitor, enalapril, and found that it was not associated with alterations in performance on any of the memory tests used, contrasting with the results for the β-adrenoceptor blocker atenolol. In the absence of many other carefully designed studies exploring the effects of ACE inhibitors on memory functions, this finding must be treated tentatively. One other investigation which has included an index of memory was conducted by Croog *et al.* (1986): here, neither captopril (an ACE inhibitor) nor propranolol (a β-adrenoceptor blocker) were associated with any change in visual memory test scores. However, as Richardson & Wyke (1988) point out, this single index of memory may well have lacked sensitivity to possible subtle changes in functioning.

It should be noted, however, that the majority of the above clinical studies have either not been adequately controlled or have had rather small sample sizes. Further rigorously designed studies with larger samples are therefore essential in order to clarify the reasons for the apparently conflicting results. In general, the within-subjects experimental design is to be preferred, since it measures change over time directly, with each subject serving as his/her own control, and thus overcomes the difficulties inherent in matching separate treated and control groups.

Other relevant lines of evidence come from experimental studies exploring the cognitive effects of the various classes of drugs in animals and in non-hypertensive human subjects. Costall *et al.* (1989) were able to demonstrate that two ACE inhibitors (captopril and SQ29,852) not only produced pronounced improvements in the rate with which rats learned several behavioural responses but also reversed scopolamine-induced impairments on the same tasks. It is of interest that SQ29,852 was markedly more effective than captopril, and that it worked best within a restricted dose range. Two studies with healthy human volunteers have found enalapril to be associated with an enhancement of tapping rate (Frcka & Lader, 1988; Olajide & Lader, 1985), although the latter study also found that, relative to placebo, enalapril and propranolol were associated with *impaired* ability to recall a word list both immediately after presentation and after a 10 min delay. Currie *et al.* (1989), by contrast, comparing the effects of single doses of captopril, atenolol and oxazepam with a control condition, found captopril to enhance recall of photographic stimuli but to have no effect on tapping rate. The effects observed in human studies so far are thus inconsistent, and certainly not as striking as the animal data reported by Costall *et al.* (1989). It may be that the drug effects are species-specific, but it also possible that the effects are only seen at critical dose levels or are sensitive to variations in testing procedures. With respect to the cognitive effects of calcium antagonists in non-hypertensive volunteers, McDevitt *et al.* (1991) employed a double-blind comparison of nifedipine and oxazepam with placebo in 14 healthy men, and found no acute effects of a single dose of nifedipine on tests of attention, memory or other psychomotor functions.

Although the evidence discussed above is somewhat equivocal with respect to the existence of pharmacologically-induced memory deficits, it is clear that any impairment on routine laboratory tests is likely to be slight. In all of the tests employed to date, subjects are explicitly told what they are to attempt to remember, and thus are given every encouragement to exert appropriate mnemonic strategies. Another aspect of memory, however, which is central to everyday functioning is recall of adventitious information which the individual has not been specifically directed to learn. A loss in abilty to recall '*incidental*' information (e.g. the locations/general appearance of objects) might be affected independently of the ability to commit material to memory deliberately, for instance via impairments of normal attentional processes. A deficit in this aspect of cognition, hitherto unevaluated, could be highly detrimental to quality of life. The investigation reported here, which formed part of a larger evaluation of the effects of anti-hypertensive medication on various aspects of quality of life (Fletcher *et al.*, 1992) has therefore included specially developed assessments of both explicit and incidental memory. The study is a controlled double-blind parallel group design, permitting within- and between-subject comparisons, and evaluates the effects on learning and memory of three anti-hypertensive medications: cilazapril, an ACE inhibitor; atenolol, a β-adrenoceptor blocker; and nifedipine, a calcium antagonist.

Methods

Subjects

The subjects were a small group of hypertensive patients participating in a larger multi-centre comparison of the effects of cilazapril, atenolol, and nifedipine on quality of life, in terms both of physical and of psychosocial well-being (see Fletcher *et al.*, 1992, for a detailed description). The cognitive assessments described here were added to the other quality of life assessments for all those subjects recruited through three of the centres. In the present study, criteria for inclusion were identical with those in the larger study, i.e.: age between 35 and 69 years, with women of childbearing potential excluded; a sitting diastolic blood pressure (SDBP) between 95 and 115 mm Hg (the mean of two readings) during the third and fourth week of a placebo 'run-in' period; literacy; no history of heart failure, cerebrovascular accident, psychiatric illness, or drug/alcohol dependence; free of clinically significant neurological, respiratory, hepatic, gastro-intestinal, haematologic, autoimmune, renal and endocrine disease other than non-insulin dependent diabetes controlled by diet; no evidence of atrioventricular block (1° or greater) in the prestudy ECG, nor a haemodynamically relevant heart rhythm disturbance, nor angina pectoris; and no myocardial infarctions in the preceding 6 months. Subjects were not permitted

Table 1 Demographic characteristics (by drug group)

	Age (years) Mean (s.d.)	n	*Sex ratio (M:F)*
Cilazapril	56.4 (8.8)	22	10:12
Atenolol	56.1 (8.6)	18	6:12
Nifedipine	58.7 (7.8)	15	10:5

to take psychotropic or sedative drugs during the course of the study.

All subjects in the memory study were patients of three GPs in Kent, and the study protocol was approved by their local Ethics Committee. Seventy-six subjects entered the study. Two did not complete any follow-up memory assessment and could not therefore be included in any analysis of drug effects. Of the remaining 74 patients, 35 were men, and mean age was 56.8 years (range 34 to 69 years). The average SDBP at randomisation was 100 mm Hg (range 95 to 115 mm Hg). Nineteen of the 74 subjects withdrew prior to the end of the 24-week treatment period: 4 of 26 (15%) in the cilazapril group, 7 of 25 (28%) in the atenolol group, and 8 of 23 (35%) in the nifedipine group. In total, 55 patients completed the study, and demographic information for these subjects is summarised in Table 1, by treatment group. Results have been analysed both for the incomplete data from the full 'intention to treat' sample ($n = 74$) and for the complete data from the treatment 'completers' ($n = 55$). As there was no difference in the outcome and the interpretation of results is more straightforward for 'completers', the remainder of this report concentrates on their data.

Design

Patients who were already receiving anti-hypertensive medication had this withdrawn prior to study entry. Subjects were informed that they would receive one of three anti-hypertensive medications, but that at some point during the study they would be given placebo for 4 weeks. For all patients, this in fact occurred prior to the commencement of active treatment; the 'run-in' period. The active treatment period lasted 24 weeks, during which time blood pressure was measured every 4 weeks. If mean SDBP remained higher than 90 mm Hg (2–8 h post-dose) during the first 12 weeks of the study, the dose was doubled; if it continued to remain higher than this level between weeks 12 and 24, hydrochlorothiazide (HCTZ) was prescribed from week 16 onwards, initially in a dose of 12.5 mg and increasing to 25 mg.

Patients were randomly allocated to receive either cilazapril (2.5 mg once daily), atenolol (50 mg once daily), or nifedipine retard (20 mg twice daily). The patients, prescribing GPs, and psychologists conducting the assessments were all blind to the treatment condition. To achieve this, patients in all three groups were given capsules identical in appearance, two to be taken in the morning and one in the evening throughout the study period. GPs were not blind to the addition of HCTZ or to dose titration, but psychologists remained blind throughout the study.

Memory assessments were conducted at the beginning and end of the run-in period (weeks −4 and 0), and then after 12 and 24 weeks of active therapy. A battery of tests was designed specifically for the study, with four versions (Forms A to D) which were found in a pilot study to be of approximately equivalent difficulty. Test versions were given in a fixed order, with Form A at week −4, From B at week 0, Form C at week 12, and From D at week 24 or at the time of premature withdrawal from the study.

The memory tests

The battery comprised three sub-tests, given in a fixed order. Each incorporated a number of components, described below, which were designed to evaluate several aspects of memory performance. The first sub-test, 'Faces', required patients to associate faces with three pieces of personal information; the second, 'Objects', required them to memorise a list of common objects; and the third, 'Stories', tested the ability to recall a spoken prose passage. Details of the materials and procedures are given below. Patients received three learning trials for each sub-test in turn, with recall measured after each trial; delayed recall testing and incidental memory (IM) questions (i.e related to the memory which occurs in the absence of formal instruction) were administered at the end of the session. The procedure was fully explained to subjects, with the exception that they were not forewarned of the IM questions. Figure 1 shows the test protocol schematically.

A number of indices were extracted for each test. Scores on the first trial of each sub-test served as a measure of initial acquisition, influenced considerably by short-term (primary) memory processes; scores on trial 3 provided a broad index of cumulative learning; and scores on trial 4 (delayed reall); served as a measure of long-term (secondary) memory, with the level of learning achieved by trial 3 taken into account. A single score for incidental memory (defined earlier) was computed by simply adding the scores achieved on the relevant questions from all three sub-tests.

The 'Faces' sub-test comprised six close-up photographs of unfamiliar faces, each set against a distinctive background. In two test versions, women's faces were used, and in the other two versions the faces were male. Each photograph was exposed for approximately 4 s, while the experimenter recited the first name, occupation and home town of the depicted person (e.g. 'this is Simon, a waiter, from Sheffield'). Subjects were instructed to

'Faces'	Trial 1	(presentation and recall)
	Trial 2	(presentation and recall)
	Trial 3	(presentation and recall)
'Objects'	Trial 1	(presentation and recall)
	Trial 2	(presentation and recall)
	Trial 3	(presentation and recall)
'Stories'	Trial 1	(presentation and recall)
	Trial 2	(presentation and recall)
	Trial 3	(presentation and recall)
'Faces'	Trial 4	(Delayed recall)
	Incidental memory questions	
'Objects'	Trial 4	(Delayed recall)
	Incidental memory questions	
'Stories'	Trial 4	(Delayed recall)
	Incidental memory questions	

Figure 1 Testing protocol.

memorise this information as best they could. Immediately following such a learning trial, the photographs were shuffled and then re-presented to the subject in a random order. One point was awarded for each piece of information correctly associated with each face, yielding a maximum score of 18 on each recall trial. Prior to each trial (i.e. presentation followed by recall), the photographs were shuffled so that the order of presentation varied. The test of delayed recall differed only in that it was not preceded by a learning presentation. Two IM questions were asked for each photograph, with the pictures concealed from view, and concerned visual details (e.g. 'What was Simon wearing'?, 'Where was Mary standing'?). The maximum IM score possible was therefore 12.

The 'Objects' sub-test comprised a set of 12 colour photographs of common objects, which were exposed consecutively for approximately 1 s each while the experimenter named them aloud. Immediately following presentation of the complete set, the subject was required to recall as many as possible in his/her own time. The maximum score was therefore 12 in each recall trial. The pictures were shuffled prior to each trial so that the order of presentation varied. As with the 'Faces' sub-test, the delayed recall test did not include a separate learning presentation. For the IM test, two forced-choice questions concerning visual details were asked for each of six photographs selected at random and concealed from view (e.g. 'Was there one bicycle or two?', 'Did the clock say 12.00 or 3.00?'. The maximum IM score was again 12.

The 'Stories' sub-test comprised a short prose passage containing 24 simple items of information, and was illustrated by a colour picture which was shown to the subject whilst the story was read aloud by the experimenter. Recall of the story was then required, the picture remaining visible as a cue. Each correctly remembered item scored one point, giving a maximum of 24 for each trial. As with the other two sub-tests, the delayed recall test was not preceded by a learning presentation, and the picture was simply handed to the subject to prompt recall. Following this, the picture was concealed, and the experimenter asked four IM questions concerning pictorial details (e.g. 'What was Mrs Appleby wearing?', 'What was under the bed?'). Maximum IM score here was thus 4.

Results

Subject characteristics

Ages and sex distributions are shown for each group separately in Table 1, and sitting diastolic and systolic blood pressures at each testing occasion in Table 2. One-way ANOVA confirmed that the groups did not differ significantly in age ($F2,52 = 0.47$, NS); but as can be seen, the sex ratios did differ, with the nifedipine group having a higher proportion of men. This uneven distribution reflected the fact that more of the subjects who withdrew from nifedipine prematurely were women: there were originally 12 women and 11 men in this group.

Repeated measures ANOVAs were used to analyse the blood pressure data, with one between-subjects factor, drug group (DRUG), and one within-subjects factor, testing occasion (OCCASION). This revealed highly significant effects of OCCASION for both SSBP ($F3,51 = 26$, $P < 0.0001$) and SDBP ($F3,51 = 161$, $P < 0.0001$), and as can be seen from inspection of Table 2, this reflects a striking decrease following the introduction of medication at week 0. There were, however no effects of DRUG ($F2,52 < 1$, NS, for both SSBP and SDBP) nor any OCCASION × DRUG interactions ($F6,48 < 1$, NS, for both SSBP and SDBP). Thus, for these subjects the drugs exerted comparable effects on both systolic and diastolic blood pressure.

Cognitive tests

Results will be presented for (a) immediate recall, (b) learning, (c) delayed recall, and (d) incidental memory, with the relevant data from all three sub-tests considered under each heading. In each case a repeated measures ANOVA with the between-subjects factor of DRUG and the within-subjects factor of OCCASION has been conducted. (In all cases, Huynh-Feldt corrections for non-homogeneity of variance were applied, and in no case did they materially alter the significance levels obtained.) Univariate contrast analyses were conducted where appropriate to localise any significant differences. Specifically, scores at each testing occasion were compared with the average of scores across all subsequent testing occasions.

Table 2 Sitting blood pressure at each assessment by drug group

		Diastolic (mm Hg)				*Systolic (mm Hg)*			
		−4	*0*	*12*	*24*	*−4*	*0*	*12*	*24*
Cilazapril	Mean	100.7	99.2	85.9	85.1	158.0	154.4	142.9	140.0
	s.d.	4.6	2.2	8.1	6.7	9.9	12.4	21.5	14.3
Atenolol	Mean	100.6	100.3	86.6	83.3	155.3	151.3	144.7	140.7
	s.d.	3.1	3.6	8.4	7.5	11.3	11.6	18.6	16.1
Nifedipine	Mean	101.6	99.9	85.3	82.9	157.7	155.9	141.7	139.5
	s.d.	4.1	3.3	6.7	5.8	11.7	12.5	17.6	13.7

N.B. −4, 0, 12 and 24 refer to weeks at which assessments were conducted.

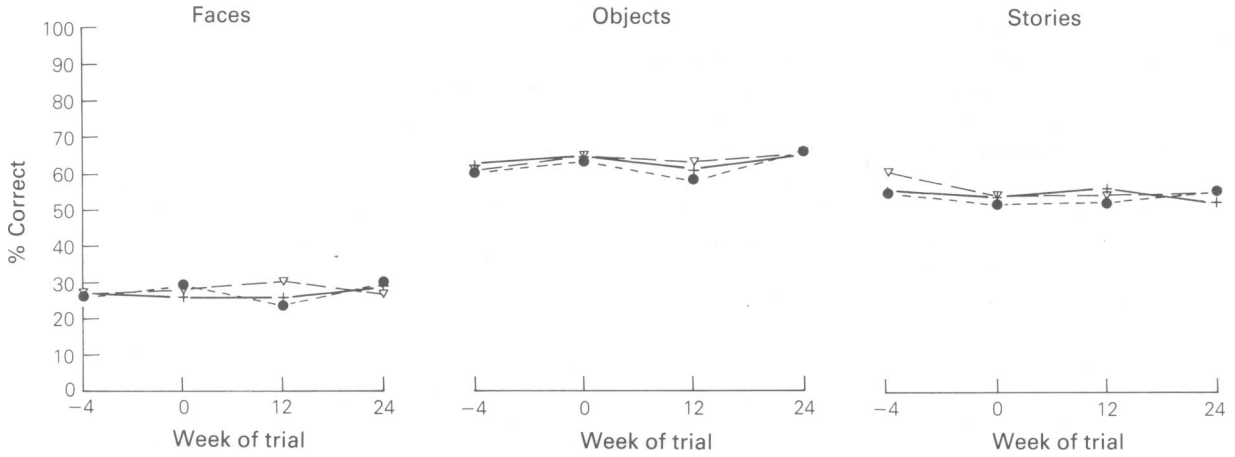

Figure 2 Immediate recall (trial 1) scores for each sub-test, by group (cilazapril, +; nifedipine, •; atenolol, ▽).

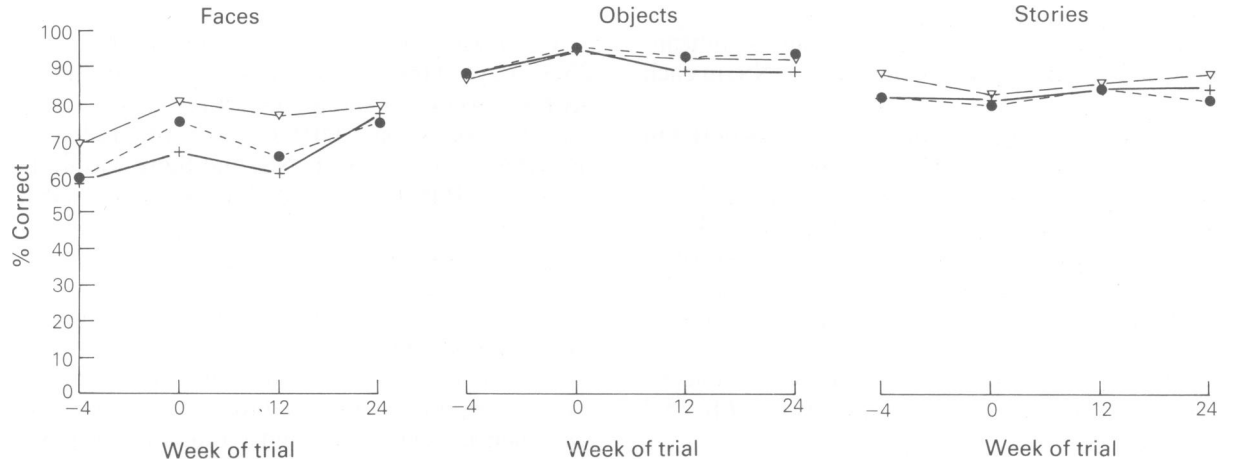

Figure 3 Learning (trial 3) scores for each sub-test, by group (cilazapril, +; nifedipine, •; atenolol, ▽).

Immediate recall The data from Trial 1 are represented graphically for each sub-test in Figure 2. There was a significant effect of OCCASION for the 'Objects' sub-test ($F[3,156] = 2.7$, $P < 0.05$), which univariate contrasts revealed to reflect higher scores at week 24. There was no effect of OCCASION for either the 'Faces' ($F[3,153] < 1$, NS or 'Stories' ($F[3,153] = 1.3$, NS). However, the factor of DRUG did not exert an effect on any of the three sub-tests ($F < 1$, NS, in each case), and there were no significant DRUG × OCCASION interactions ('Faces': $F[6,153] = 1.1$; 'Objects': $F[6,156] < 1$; 'Stories': $F[6,153] = 0.6$; all NS).

Rate of learning Since there were no differences between the three drug groups on Trial 1 for any of the sub-tests, scores on Trial 3 could be taken as straightforward indices of rate of learning over the three trials, with no need to engage a statistical correction for level of initial acquisition. The data from Trial 3 are shown in Figure 3.

All three sub-tests showed a main effect of OCCASION ('Faces', $F[3,156] = 13.4$, $P < 0.0001$; 'Objects', $F[3,156] = 8.2$, $P < 0.001$; 'Stories', $F[3,156] = 3.1$, $P < 0.05$). Univariate contrasts showed that for 'Faces', scores were significantly lower at week −4 relative to the other occasions, and higher at week 24; for 'Objects', scores at week −4 were lower than at the other occasions, and were highest at week 0; finally, for 'Stories', scores were significantly lower at week 0.

There was no main effect of DRUG for any of the sub-tests ('Faces', $F[2,52] = 1.7$, NS; 'Objects', $F[2,52] < 1$, NS; 'Stories', $F[2,52] = 1.3$, NS); nor did any of the interactions between DRUG and OCCASION reach significance ($F < 1$, NS, for all sub-tests).

Delayed recall Scores on Trial 4 are represented in Figure 4, for each group separately. Again, there were significant main effects of OCCASION for all three sub-tests ('Faces', $F[3,153] = 14.3$, $P < 0.0001$; 'Objects', $F[3,150] = 8.6$, $P < 0.0001$; 'Stories', $F[3,156] = 5.2$, $P < 0.005$). Univariate contrasts showed this to reflect higher scores at weeks 0 and 24 for 'Faces'; whilst for 'Objects', significantly higher scores were achieved at week 0 than on the other three occasions. Finally, for 'Stories', scores at week 0 were significantly worse than on the other occasions.

There was again no effect of DRUG for any of the three sub-tests ('Faces', $F[2,51] = 1.1$; 'Objects', $F[2,50]$

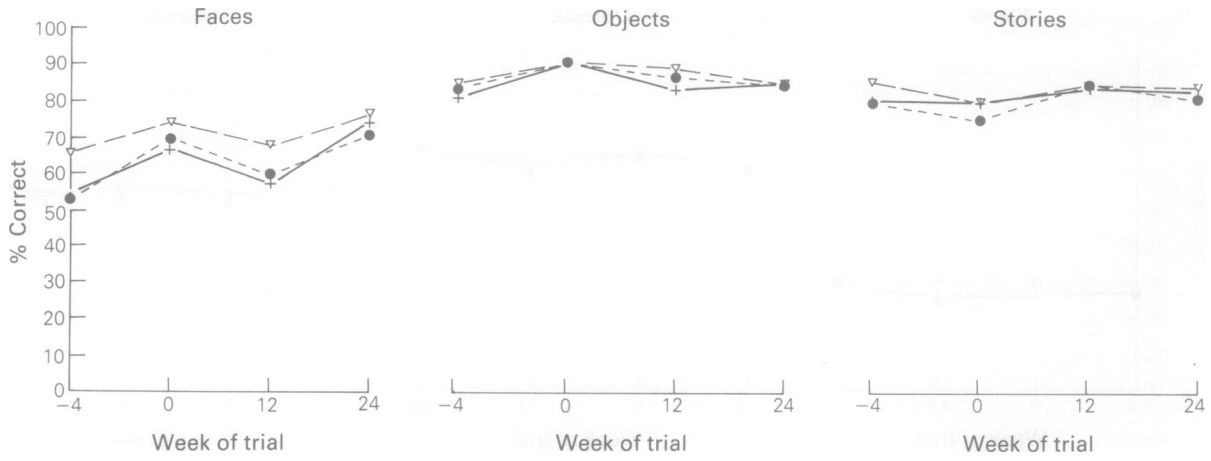

Figure 4 Delayed recall (trial 4) scores for each sub-test, by group (cilazapril, +; nifedipine, •; atenolol, ▽).

< 1; 'Stories', $F[2,52] < 1$; all NS), nor any significant DRUG × OCCASION interactions ($F < 1$, NS, in each case).

Delayed recall scores were additionally considered in relation to initial learning, by computing trial 4 scores as a proportion of trial 3 scores (i.e. Trial 4/Trial 3). These derived scores showed no main effect of either DRUG ('Faces', $F[2,51] < 1$; 'Objects', $F[2,50] < 1$; 'Stories', $F[2,52] < 1$; all NS) or OCCASION ('Faces', $F[3,153] = 1.1$; 'Objects', $F[3,150] = 1.4$; 'Stories', $F[3,156] < 1$; all NS). The DRUG × OCCASION interaction also failed to reach significance for all sub-tests ('Faces', $F[6,153] = 1.1$; 'Objects', $F[6,150] < 1$; 'Stories', $F[6,156] < 1$).

Incidental memory A single incidental memory score was derived for each testing occasion, namely the total of IM scores from the three sub-tests combined. These data are shown in Figure 5.

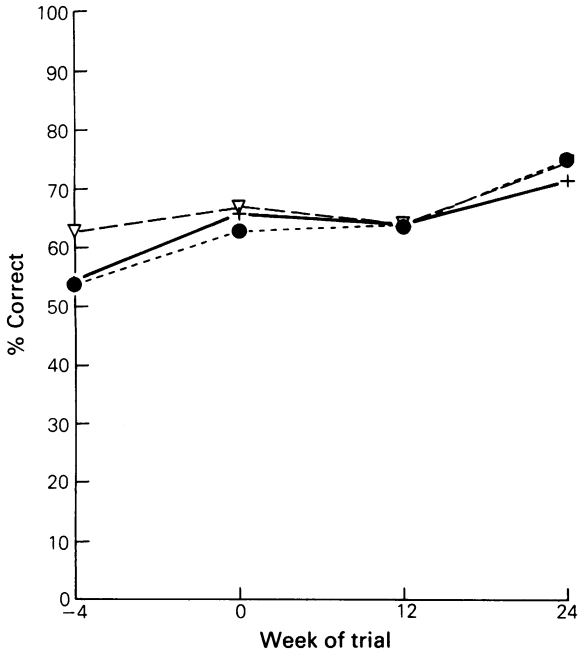

Figure 5 Incidental memory scores, by group (cilazapril, +; nifedipine, •; atenolol, ▽).

There was a main effect of OCCASION ($F[3,144] = 25.3$, $P < 0.001$), attributable to significantly lower scores at week −4 and higher scores at week 24 than on the other occasions. DRUG, however, failed to exert any effect ($F[2,48]) < 1$, NS, and there was no DRUG × OCCASION interaction ($F[6,144] = 1.4$, NS).

Sensitivity of memory tests

It is important to explore whether the learning and memory tests designed to test the hypotheses of this study were in fact sensitive to sources of variation which would normally be expected to affect memory abilities. One such influence is age, and a comparison was therefore made between the scores achieved by the 74 patients who participated in this study (mean age = 56.8 years, s.d. = 8.2 years) and the scores achieved by the 20 subjects on whom the four test versions were piloted (mean age = 30 years, s.d. = 10.7 years).

The pilot study was a partially balanced design in which each subject received two of the four test versions, and confirmed that the four parallel forms were of equivalent difficulty. For the present purpose, scores on their second test version are compared with patients' scores at the second assessment (week 0), when they had been drug-free for at least 4 weeks: this comparison equates the two groups for familiarity with the testing procedure and minimises any effects of recent drug withdrawal.

Table 3 shows the mean percentage accuracy for both hypertensive and pilot subjects on each of the sub-tests. One-tailed *t*-tests were used to test the hypothesis in each case that the younger pilot subjects would achieve higher scores than the hypertensive patients, and it is apparent from Table 3 that this was strongly supported for all indices relating to the 'Faces' and 'Stories' sub-tests as well as for incidental memory. The 'Objects' sub-test discriminated less clearly, superiority for the pilot subjects failing to be seen for either immediate recall or for delayed recall.

Data from the 'Faces' sub-test have been explored in more detail in connection with another study, and within the present sample of 55 hypertensive patients who completed all four test versions a highly significant

Table 3 Comparison of test scores (percentage accuracy) achieved by hypertensive patients (n = 74) with scores achieved by pilot subjects (n = 20)

	Faces		*Objects*		*Story*		*Incidental*	
	Patients Mean % (s.d. %)	*Pilots Mean % (s.d. %)*	*Patients Mean % (s.d. %)*	*Pilots Mean % (s.d. %)*	*Patients Mean % (s.d. %)*	*Pilots Mean % (s.d. %)*	*Patients Mean % (s.d. %)*	*Pilots Mean % (s.d. %)*
Immediate recall (Trial 1)	27.7 (15.5)	39.7*** (12.5)	65.9 (14.6)	66.3 (14.9)	53.5 (14.3)	66.4*** (10.2)	65.6 (11.8)	72.7** (10.8)
Learning (Trial 3)	73.8 (21.9)	86.4** (15.0)	87.3 (11.3)	92.5* (6.6)	81.3 (12.4)	88.2*** (6.9)		
Delayed recall (Trial 4)	69.8 (23.7)	86.1*** (13.6)	89.8 (11.4)	84.2 (13.3)	78.7 (15.0)	86.6*** (7.2)		

N.B. One-tailed t-tests compared the two groups: $*P < 0.05$, $**P < 0.01$, $***P < 0.005$.

negative correlation was found with age ($r = -0.38$, $P < 0.005$), further confirming sensitivity of the test to this source of variation. The 'Faces' sub-test was also administered to a separate group of 30 elderly subjects (Pickering & Hogg, unpublished), and scores were found to be significantly positively correlated with scores on the Vocabulary sub-test of the Wechsler Adult Intelligence Scale—Revised ($r > 0.43$, $P < 0.01$, for all recall trials). It thus appears that the test is also sensitive to variations in general intellectual ability.

Discussion

There is no evidence, in the present study, for any differential effects of cilazapril, atenolol and nifedipine on learning and memory in hypertensive patients. A comparison of test scores at baseline (week 0) with scores after 12 and 24 weeks of experimental treatment indicates a mixed pattern of change: immediate recall (Trial 1) scores tended to improve or stay the same; rate of learning (Trial 3) improved for 'Faces' and 'Stories' but became slightly worse for 'Objects'; and delayed recall (Trial 4) worsened for 'Objects', improved for 'Stories', and showed no clear pattern for 'Faces'. When delayed recall was considered in relation to the amount of information acquired by trial 3, however, (by looking at the ratio between recall in trials 3 and 4), there were no effects of either group or session, indicating that delayed recall was a simple function of acquisition, unaffected by duration or class of medication.

Clearly, then, the general picture is that there is little sign of decreased memory ability after 12 or 24 weeks on the drugs. The changes in rate of learning over sessions cannot be unambiguously attributed to either adverse drug effects or to changes in blood pressure, since different versions of the tests were given (in a fixed order) at each test session. However, a slightly smaller scale pilot study with healthy subjects conducted prior to the present study indicated that the versions were equivalent for all sub-tests across Trials 1 to 3, and it therefore seems unlikely that test differences can account for the observed results. The pilot study likewise revealed no significant practice effects from one assessment to the next for any sub-test. It is difficult, however, to see why medication or changes in blood pressure should exert differential effects on the speed of acquisition of different types of material. There were likewise no differences in the incidental memory scores of patients on each of the three drugs, though again there were differences between test sessions, with a marked improvement from week −4 to week 24. This might either reflect a practice effect, with subjects remembering after the first test session that such questions would be asked, though the pilot study did not find this to be a pronounced effect, or possibly a beneficial effect of decreasing blood pressure.

The higher premature withdrawal from nifedipine than from the other two drugs raises the question of whether an adverse effect was actually obscured by the analysis of data from only study completers. Related to this is the fact that the high drop-out rate led to a disproportionate representation of men in this group, thus confounding the comparison between drugs with a sex difference. However, analysis of the data collected from all subjects indicates that it is unlikely that either of these factors exerted a significant influence. Thus, the three groups initially had very similar sex ratios, and all subjects who withdrew prematurely were given a final cognitive assessment at this point. When these data were included with those of the study completers, the analyses still showed no differential effects of the three drugs.

The absence of any impairments specific to propranolol in the present study is consistent with results from the comparative studies by Deary *et al.* (1991) and Skinner *et al.* (1992), but conflicts with Lichter *et al.*'s (1986) finding that atenolol was associated with impaired learning and memory whilst the ACE inhibitor, enalapril, was not. This raises the possibility that the tests used in the latter study were more sensitive to change than the tests employed here. This suggestion however does not stand up to scrutiny. Firstly, the information to be learned is directly comparable in some of the tests: for example, a shopping list of ten items in Lichter *et al.*'s (1986) study compares with a list of twelve common objects here, and names and towns associated with five faces in the earlier study compares with names, towns and jobs associated with six faces here. Thus if anything the present tests would seem to be somewhat more difficult that those used by Lichter *et al.* (1986), and are hence likely to be more sensitive to subtle deficits. Secondly, comparison of the percentage of correct responses in the two studies again suggests that both batteries of tests are sensitive: subjects tend to score in the middle range, with no floor

or ceiling effects obscuring potential changes. Furthermore, in each case the tests are sensitive enough to reveal some differences, either between drug conditions (Lichter *et al.*, 1986) or between test occasions (the present study). With respect to the present tests, comparison of data from the younger subjects in the pilot study with the data from the hypertensive patients revealed significantly higher scores for the younger subjects, for all indices except those relating to the 'Objects' sub-test. Scores on the 'Faces' sub-test were also found to correlate negatively with age in the hypertensive subjects and positively with verbal ability in a separate group of elderly subjects. These relationships are further confirmation of the sensitivity of the 'Faces' and 'Stories' sub-tests, and of the incidental memory index, to factors which normally influence learning and memory abilities.

Thus, whilst the 'Objects' sub-test may have been insufficiently sensitive to detect drug effects, the other indices are demonstrably sensitive and yet likewise show no differential effect of the various drug classes. Two other possible explanations for the discrepancy with Lichter *et al.*'s (1986) data are apparent. Their study was conducted with a smaller group of subjects (13 on atenolol and 12 on enalapril), comparing with 18 on atenolol and 22 on cilazapril here. It is conceivable, then, that the significant results obtained in the former investigation were an artifact of the small sample size. It is perhaps more likely, however, that differences in blood pressure between subjects in the two studies are a confounding factor. Subjects in the study by Lichter *et al.* (1986) had higher diastolic and systolic blood pressures prior to commencement of active treatment than did subjects in the present study (atenolol groups: 189/115 *vs* 151/100; ACE inhibitors: 196/115 *vs* 154/99). Furthermore, Lichter *et al.* (1986) reported that enalapril produced significantly greater drops in systolic blood pressure than did atenolol, whereas all three classes of drug had virtually identical effects on blood pressure in the present study. It is thus possible, for instance, that adverse effects of medication on cognitive functioning were offset by the beneficial effects on cognition of decreased hypertension in all of the experimental groups but Lichter *et al.*'s (1986) atenolol group. This interpretation is, of course, tentative and needs experimental verification.

Given the finding, discussed earlier, that ACE inhibitors have been found to promote learning in animals (e.g. Costall *et al.*, 1989), it is of particular interest that neither the present study nor those of Lichter *et al.* (1986) or Deary *et al.* (1991) showed any specific benefit of this class of drug in hypertensive patients. However, effects on memory in normal human subjects have not been found consistently (e.g. Currie *et al.*, 1989; Frcka & Lader, 1988), and the failure to find benefits on any of the varied tests used in these studies of hypertensive patients, therefore suggests that ACE inhibitors are of little, if any, effect on human memory. At most, they may exert a subtle effect which is highly sensitive to variations in testing procedures or which, as in animals, is apparent only within a critical dose range.

The comparability of the three classes of anti-hypertensive drug in relation to learning and memory is consistent with results from the larger study in which it was embedded (Fletcher *et al.*, 1992) indicating no differential drug effects on various 'Quality of Life' indices. These included health status, work satisfaction, psychomotor function, psychological and general well-being, mood, and life satisfaction. There were more physical complaints from subjects on nifedipine, and more subjects in this group dropped out of treatment early; but, as indicated above, when data from these study non-completers were included, there was no evidence that adverse cognitive effects contributed to this drop-out.

In summary, therefore, it seems that the prescription of chronic anti-hypertensive medications can be guided principally by their clinical efficacy in reducing blood pressure taken together with judgments about possible physical adverse effects. On the basis of the present findings it would be inappropriate to select against atenolol on the grounds that it may lead to a disproportionate degree of cognitive impairment; there is little evidence of effects on memory and learning for any of the anti-hypertensive medications tested in the present study.

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References

Ames, R. P. (1986a). The effects of antihypertensive drugs on serum lipids and lipoproteins: I—Diuretics. *Drugs*, **32**, 260–278.

Ames, R. P. (1986b). The effects of antihypertensive drugs on serum lipids and lipoproteins: II—Non-diuretics. *Drugs*, **32**, 335–357.

Costall, B., Coughlan, J., Horovitz, Z. P., Kelly, M. E., Naylor, R. J. & Tomkins, D. M. (1989). The effects of ACE inhibitors captopril and SQ29,852 in rodent tests of cognition. *Pharmac. Biochem. Behav.*, **33**, 573–579.

Croog, S. H., Levine, S., Testa, M., Brown, B., Bulpitt, C. J., Jenkins, C. D., Klerman, G. L. & Williams, G. H. (1986). The effects of antihypertensive therapy on the quality of life. *New Engl. J. Med.*, **314**, 1657–1664.

Currie, D., Lewis, R. & McDevitt, D. G. (1989). Central effects of the angiotensin-converting enzyme inhibitor, captopril, in healthy volunteers. *Br. J. clin. Pharmac.*, **28**, 228P–229P.

Deary, I. J., Capewell, S., Hajducka, C. & Muir, A. L. (1991). The effects of captopril *vs* atenolol on memory, information processing and mood: A double-blind crossover study. *Br. J. clin. Pharmac.*, **32**, 347–353.

Fletcher, A. E., Bulpitt, C. J., Chase, D. M., Collins, W. E., Furberg, C. M., Goggin, T. K., Hewett, A. J., & Neiss, A. M. (1992). Quality of life on three anti-hypertensive treatments: Cilazapril, atenolol, nifedipine. *Hypertension*, **19**, 499–507.

Frcka, G. & Lader, M. (1988). Psychotropic effects of repeated

doses of enalapril, propranolol and atenolol in normal subjects. *Br. J. clin. Pharmac.*, **25**, 67–73.

Hartley, L. R., Ungapen, S., Davie, L. & Spencer, D. J. (1983). The effect of beta-adrenergic blocking drugs on speaker's performance and memory. *Br. J. Psychiat.*, **142**, 512–517.

Hedner, T., Elmfeldt, D., Von Schenck, H., Sjogren, E. & Smith, U. (1987). Glucose tolerance in hypertensive patients during treatment with the calcium antagonist pelodipine. *Br. J. clin. Pharmac.*, **24**, 145–149.

Kaplan, N. H. (1986). Problems with the use of diuretics in the treatment of hypertension. *Am. J. Nephrol.*, **6**, 1–5.

Knochil, J. P. (1984). Diuretic-induced hypokalemia. *Am. J. Med.*, **77**, 18–27.

Lichter, I., Richardson, P. J. & Wyke, M. A. (1986). Differential effects of atenolol and enalapril on memory during treatment for essential hypertension. *Br. J. clin. Pharmac.*, **21**, 641–645.

McDevitt, D. G., Currie, D., Nicholson, A. N., Wright, N. A. & Zetlein, M. B. (1991). Central effects of the calcium antagonist, nifedipine. *Br. J. clin. Pharmac.*, **32**, 541–549.

Murphy, M. B., Lewis, P. J., Kohner, E., Schumer, B. & Dollery, C. T. (1982). Glucose intolerance in hypertensive patients treated with diuretics; a 14 year follow-up. *Lancet*, **ii**, 1293–1295.

Olajide, D. & Lader, M. (1985). Psychotropic effects of enalapril maleate in normal volunteers. *Psychopharmacology*, **86**, 374–376.

Pollare, T., Lithell, H. & Berne, C. (1989). A comparison of the effects of HCTZ and captopril on glucose and lipid metabolism in patients with hypertension. *New Engl. J. Med.*, **321**, 868–873.

Richardson, P. J. & Wyke, M. A. (1988). Memory function—Effects of different antihypertensive drugs. *Drugs*, **35** (suppl. 5), 80–85.

Skinner, M. H., Futterman, A., Morrissette, D., Thompson, L. W., Hoffman, B. B. & Blaschke, T. F. (1992). Atenolol compared with nifedipine: Effect on cognitive function and mood in elderly hypertensive patients. *Ann. Intern. Med.*, **116**, 615–623.

Solomon, S., Hotchkiss, E., Saravay, S. M., Bayer, C., Ramsey, P. & Blum, R. S. (1983). Impairment of memory function by antihypertensive medication. *Arch. gen. psychiat.*, **40**, 1109–1112.

Steiner, S. S., Friedhoff, A. J., Wilson, B. L., Wecker, J. R. & Santo, J. P. (1990). Antihypertensive therapy and quality of life: A comparison of atenolol, captopril, enalapril and propranolol. *J. human Hypertension*, **4**, 217–225.

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