Psychomotor performance and antihypertensive treatment

L. KALRA¹, C. G. SWIFT & S. H. D. JACKSON

Department of Health Care of the Elderly, Kings College School of Medicine and Dentistry, London and ¹Department of Medicine for Elderly People, Orpington Hospital, Bromley Hospitals NHS Trust, Kent

1 The aim of treatment of hypertension is prevention of cardiovascular complications without adverse drug reactions. Psychomotor performance can be measured objectively yet there remains uncertainty concerning the psychomotor effects of antihypertensive drugs during chronic treatment. This uncertainty is partly due to the confounding adverse effects of cerebrovascular disease and hypertension itself. There are as yet insufficient good quality data on psychomotor effects with which to differentiate between the commonly used agents. However, in general, the beneficial effect of lowering blood pressure tends to more than offset any adverse effects of the agent used.

Keywords hypertension psychomotor performance

Introduction

The major goal of drug treatment in hypertension is not to alleviate symptoms, since these may be few or none, but to prevent cardiovascular and cerebrovascular complications [1–5]. Such inherently life-long preventative therapy should, however, aim to achieve its objective at minimal iatrogenic cost. The association of some antihypertensive drugs with changes in psychomotor performance, mood and intellect [6–8] raises a relevant and inadequately researched aspect of the therapeutics of hypertension and is a potentially important consideration in the choice of agent. This may be particularly important in individuals whose occupation is critically dependent on optimal CNS performance and in older hypertensives where there may be reduced CNS functional reserve.

The literature on the effects of antihypertensive therapy on psychomotor performance is conflicting and compounded by failure to take into account the effects of hypertension itself and one of its major complications—cerebrovascular disease. This article will review the literature on psychomotor effects on antihypertensive drugs. Although the precise definition of ‘psychomotor function’ is difficult, it has been used here to refer to measurable psychological and motor processes involved with brain function using psychomotor test batteries. ‘Quality of life’ aspects or other central nervous system (CNS) effects of antihypertensive drugs have not been specifically reviewed, but these areas will be addressed in so far as literature in these areas may aid interpretation of psychomotor performance aspects.

Measurement of CNS performance

The range, precision, sensitivity and reliability of psychomotor tests developed over the last few decades make them valuable tools for investigating minor alterations in intellectual function [9]. Psychomotor tests most commonly assess intellectual functions (in preference to other behavioural aspects) because, in comparison with other aspects, these may be more readily conceptualised, easily measured and have anatomical correlates [9]. Functions assessed include:

- 1) Reception, consisting of sensation and perception, which involve the abilities to acquire, process, classify and integrate information.
- 2) Memory and learning, dealing with information storage and recall.
- 3) Thinking, which concerns mental organisation and reorganisation of information.
- 4) Expression, through which the information is communicated or acted upon.

Psychomotor tests also measure the efficiency of mental processes by measuring 1) attentional activities which include attention and concentration, 2) level of consciousness which ranges over a continuum from full alertness to sedation, and 3) activity rate which refers to both the central processing and motor response speeds. Attention and concentration should be distinguished from sedation in this context. Although sedation will usually impair attentional activities, loss of attention or concentration may not be necessarily associated with sedation. Changes in these variables are the most subtle signs of

brain dysfunction, especially following drug administration, and may be impaired even when intellectual functions, *per se*, are intact [10].

Effects of antihypertensive drugs

There is considerable controversy over the psychomotor effects of antihypertensive treatment (Table 1). Significantly better psychomotor performance scores (e.g. attention, serial reaction times, digit symbol substitution test, memory) have been reported in effectively treated hypertensives when compared with young and middle-aged hypertensive subjects not receiving treatment [11–13]. Improvement on psychomotor tests of attention and speed was also seen in young patients following antihypertensive treatment during a 15 month prospective study [14, 15]. Conversely, antihypertensive treatment was associated with worsening of attention and reaction time measures in hypertensive subjects in other studies [6, 16]. Elsewhere, no differences in psychomotor performance between previously treated and newly diagnosed hypertensive subjects were found [17–23]. There may be several reasons for these conflicting effects

of antihypertensive therapy reported in literature. The major reasons are:

- 1) There are considerable variations in subject selection, methodology and choice of psychomotor tests.
- 2) It was not always possible to separate the direct psychomotor effects of drugs (well known for methyldopa, clonidine and propranolol) from those due to changes in blood pressure.
- 3) The psychomotor effects of individual drugs were not generally investigated.

The psychomotor effects of β -adrenoceptor blockers have been most extensively examined, whereas there are few reports on diuretics, calcium channel antagonists or ACE inhibitors (Table 1).

Diuretics

The psychomotor effects of diuretics have received little attention in double-blind controlled studies. Indirect evidence suggests that there may be psychomotor consequences of chronic diuretic use. Headache, dizziness and drowsiness have been reported with spironolactone

Table 1 Studies assessing the psychomotor effects of antihypertensive treatment

Reference	Study design	Tests	Treatment	Findings
11	Open comparison, 30 untreated HT, 30 treated controls	DSST, TMT, 10-choice RT	not stated	Treated HT performed better than untreated HT
16	Open comparison, 22 treated HT, 17 untreated HT and 15 NT	CST, WAIS, Progressive matrices, Benton	thiazide, reserpine, propranolol	Increased impairment with treatment
37	Open study, 33 treated HT, 8 NT	WMS	thiazide, propranolol, methyldopa	Poorer memory in propranolol and methyldopa group
14	Open study, 15 month period, 21 treated HT, 13 untreated HT and NT controls	15 test battery	thiazide, propranolol, methyldopa	Improved performances in treated group
40	2 week double-blind, randomised, placebo controlled parallel group study; 26 HT subjects	Memory-search paradigm	atenolol or propranolol	No adverse effects due to β -adrenoceptor blockers
53	16 week single-blind, randomised, placebo controlled parallel group study, 25 HT subjects	Memory tests for recall	atenolol, enalapril	Cognitive impairment with atenolol but not with enalapril
25	24 week double-blind, randomised, parallel group study; multicentre; 626 HT men	TMT, Visual recognition (WMS)	methyldopa, propranolol, captopril and diuretic	Best performance scores with captopril, worst with methyldopa; deterioration on addition of diuretic
19	Longitudinal study, 5–6 years follow-up, 30 HT on treatment and 24 NT subjects	WAIS battery	not specified	HT on treatment worse than NT; no progression in either group
20	Longitudinal (third point), 10–12 years follow-up, 22 HT on treatment and 20 NT subjects	WAIS battery	not specified	No further changes; no antihypertensive drug effects

Table 1 (continued)

Reference	Study design	Tests	Treatment	Findings
57, 59	Longitudinal, 11 HT, 10 NT, 10–12 years; on antihypertensive treatment	H-R battery	not specified	Poorer performances in HT; no decline with time; no antihypertensive drug effect
47	Population based study, open comparison, 488 men; 96 HT	Purdue Pegboard, WAIS	methyldopa, propranolol	Better performances with propranolol, worse with methyldopa
26	Isolated systolic hypertension, placebo controlled open study; <i>n</i> = 443 HT	SHORT-CARE instrument, DSST, TMT	chlorthalidone	No significant impact on cognitive function
45	2 week placebo controlled study, double-blind, <i>n</i> = 26M; DBP: 90–110 mm Hg	Memory-search paradigm	atenolol, propranolol	Improvement in memory with propranolol
46	30 HT, uncontrolled on diuretics	WAIS	atenolol, enalapril (both with diuretics)	Impaired digit span (backward) on atenolol; enalapril: no change
32	Acute single dose, double-blind study; <i>n</i> = 14 healthy young NT subjects	DSST, CAT, letter cancellation, CRT, CFFT, two flash fusion, finger tapping, memory	captopril, atenolol, placebo	Improved short-term memory and cancellation speed with captopril; sedation, reduced finger tapping but improved letter cancellation with atenolol
42	Double-blind, crossover 8 week treatment, <i>n</i> = 42 HT, aged 35–64; DBP = 90–110 mm Hg	H-R battery	atenolol, propranolol	No impairment with either drug
23	Subjects aged 60+, 1 year study; double-blind parallel group study; <i>n</i> = 74 HT	Psychomotor battery to assess cognition, motor skills and memory	thiazide, methyldopa, reserpine, hydralazine, metoprolol	No adverse effects of any antihypertensive treatment in elderly subjects. Control of HT must have had a beneficial effect if methyldopa did not impair it
13	4 week randomised, double-blind parallel study after dose titration, <i>n</i> = 360 HT men	Psychometric questionnaire	atenolol, propranolol, captopril, enalapril	Controlled HT, propranolol associated with worsening, improvement with others
43	Multicentre, randomised, double-blind study; 6 months; <i>n</i> = 540 HT; mean age 54 years	Reitan TMT-B	cilazapril, atenolol, nifedipine	Mean BP fall = 15 mm Hg; no significant psychomotor differences between drug groups
44	4 week randomised, double-blind cross-over; <i>n</i> = 25 HT; aged 60–81 years	Buschke selective reminding test (verbal learning and memory)	nifedipine, atenolol	Poorer performance in nifedipine group compared with placebo; no change with atenolol
27	Single dose study, 12 male volunteers, double-blind, randomised cross-over study	DSST, CAT, CRT, CFFT, two flash fusion, body sway, visual analogue scale	atenolol (AT), bendrofluazide (BFZ), AT+BFZ	No changes with AT or BFZ alone, significant impairment with AT+BFZ, no change in visual analogue scale
60	4 week, randomised, single-blind, placebo controlled parallel study, <i>n</i> = 25 HT; aged 60–80 years	Automated psychomotor test battery	diuretic, atenolol, nifedipine, captopril	improvement in psychomotor speed and memory with captopril
60	Double-blind, crossover study with intervening placebo washout, 2 week each limb, <i>n</i> = 13	Automated psychomotor test battery	nifedipine, captopril	Significant and comparable improvement on several tests with both drugs

WAIS, Wechsler Adult Intelligence Scale; DSST, Digit Symbol Substitution Test; TMT, Trail Making Test; RT, Reaction Time; WMS, Wechsler Memory Scale; CST, Card Sorting Test; CAT, Continuous Attention Test; HT, Hypertensive subjects; NT, Normotensive subjects.

and triamterene [7]. There is a report of depression and cognitive impairment following long-term diuretic use in elderly people which has been attributed to sub-clinical dehydration and electrolyte imbalance although psychomotor performance was not measured [24]. Hypertensive subjects treated with a single intravenous dose of frusemide half an hour before psychomotor testing showed significantly poorer performance on subtests of the Wechsler Adult Intelligence Scale (WAIS) and Halstead-Reitan battery compared with matched normotensive controls. [17, 18]. However, this was considered to be an effect of hypertension *per se* rather than due to frusemide. Impaired performance due to a diuretic is not surprising because of fluid-electrolyte shifts, as well as anxiety and discomfort associated with diuresis. Poorer performance on trail-making test A and visual memory assessment (Wechsler Memory Scale) was seen in hypertensive men when diuretics were added to other antihypertensive drugs to control their hypertension [25] (Table 1). It is, however, not clear whether this was due to the addition of the diuretic or because of severity of hypertension which required additional treatment with diuretics. In a study of 443 elderly subjects (aged over 60 years) with isolated systolic hypertension treated with chlorthalidone, Gurland *et al.* [26] found no significant deterioration in psychomotor performance compared with baseline assessment despite a significant fall in systolic blood pressure to target level of less than 165 mm Hg (Table 1). Goldstein *et al.* [23] found that antihypertensive treatment with diuretics alone or in combination with other agents was not associated with deterioration in psychomotor performance compared with the untreated baseline assessment (Table 1). However, it is possible that the variability in performance due to test conditions and the interval between assessments (24 weeks in Croog *et al.* [25] and 1 year in Goldstein *et al.* [23]) affected the ability of the psychomotor instrument to detect minor drug related changes due to a trade-off between stability and sensitivity in psychomotor tests. In addition, both systolic and diastolic hypertension may have been associated with impairment in baseline assessments which was not controlled by the inclusion of normotensive subjects.

In a more recent double-blind crossover placebo controlled study in 12 normal male volunteers [27], a single dose of either bendrofluazide 5 mg or atenolol 100 mg was associated with no significant change in psychomotor performance over 4 h (Table 1). A significantly greater impairment in performance was seen when the drugs were used in combination even in the absence of changes in subjective awareness. The clinical implications of these observations are speculative as the subjects were young and normotensive and only the acute effects of a single dose studied.

β -adrenoceptor blocking agents

Normotensive volunteers Impairment in complex tasks requiring attention, discrimination and accuracy has been described in normal volunteers [7, 28–33]. The degree of impairment seems to depend upon:

- a) dosage,
- b) β -adrenoceptor selectivity,

- c) peripheral effects (e.g. on skeletal muscles) which may modify the expression of central effects, and
- d) lipid solubility, hence penetration of the blood-brain barrier, although the difference between lipid soluble and hydrophilic agents may be one of degree.

Hypertensive patients The findings of studies on the effects of β -adrenoceptor blockade in hypertensives are conflicting. Impairment in immediate and delayed memory recall on the Wechsler Memory Scale was seen in hypertensive subjects treated with propranolol ($n = 11$) when compared with those treated with a diuretic ($n = 12$) (Table 1). However, the hypertensives were treated in an open fashion with propranolol only after treatment with diuretics had failed and it is possible that these subjects had more severe hypertension which may have contributed to the observed psychomotor deficit. In addition, the control group size was inadequate. A mild but consistent deficit in short and long term memory was also reported in hypertensive subjects ($n = 13$) treated with atenolol in a 12 week prospective double-blind study comparing atenolol with enalapril [38].

In contrast, a double-blind prospective study using a memory-search paradigm [39] showed no significant change in the memory processes of 26 hypertensives (age range 27–54 years) treated with atenolol ($n = 8$), propranolol ($n = 9$) or placebo ($n = 9$) (Table 1). However, the memory-search paradigm is prolonged in untreated hypertensive subjects [41] and it is possible that any improvement in memory search speed due to control of hypertension may have been offset by slowing due to β -adrenoceptor blockade. In a more recent study, the same group found impairment in short-term memory on the digit (backward) span associated with treatment with atenolol [46] (Table 1). These conflicting observations make their findings difficult to interpret. Palac *et al.* [42] studied 42 male hypertensive subjects (aged 35–64 years) treated with propranolol or atenolol for 8 weeks (Table 1). Repeated measures analysis of variance did not show any deterioration following β -adrenoceptor blockade on seven of the nine tests in the battery. Performance on digit cancellation test was impaired with enhanced performance on trail making test. There were no differences between the two drugs. Their conclusion was that neither drug impaired psychomotor performance. In a prospective one year study comparing antihypertensive treatment in elderly people using diuretics or combination treatment with several drugs including metoprolol (Table 1), Goldstein *et al.* [23] found no deterioration in psychomotor performance using a range of tests. However, metoprolol was not studied independently. More importantly, performance improved in both the control and the study group suggesting practice effects. More recent studies have also shown that antihypertensive treatment with atenolol may not be associated with adverse psychomotor effects either in young or elderly patients [43, 44] (Table 1). More recently, Gerrard *et al.* [27] have shown that although acute administration of atenolol in healthy volunteers did not result in significant psychomotor impairment, combination with bendrofluazide resulted in significant psychomotor impairment, as referred to previously.

There is a suggestion that control of hypertension with

β -adrenoceptor blockers may actually improve psychomotor function. Patients in the study of Madden *et al.* [40], underwent a more comprehensive psychomotor assessment (finger tapping, handgrip strength, digit symbol substitution test, paired associate learning, digit span, trail making test and semantic memory). These measures showed a significant improvement in memory and performance tests following treatment with propranolol [45]. However, in a later study comparing atenolol with enalapril, psychomotor performance on most tests remained unchanged and deteriorated on a memory task on treatment with atenolol [46]. Improvement in performance on Reitan trail making test but no change in visual recognition was reported in hypertensive subjects treated with propranolol [25]. The use of just two psychomotor tests in the study of which one improved significantly (trail making test) limits its value in assessing psychomotor consequences of antihypertensive treatment. Psychomotor performance on various tests was better in 48 elderly hypertensives (aged 75–85 years) receiving propranolol compared with those receiving methyl dopa and comparable with that of matched normotensive controls [47] (Table 1). However, these hypertensives formed a small subgroup defined by the type of medication being taken by elderly hypertensives in the Bronx Ageing Study ($n = 487$) and the validity of subgroup analysis is debatable. Methyl dopa is well-known to have CNS side effects and it is not clear whether the differences were due to impairment with methyl dopa or a benefit due to propranolol. The possibility of improved psychomotor functioning following β -adrenergic blockade with atenolol but not with propranolol is also suggested by Steiner *et al.* [13].

Despite the differing findings on the effects of β -adrenoceptor blocker therapy in various studies reviewed, the bulk of evidence would suggest an impairment due to β -adrenoceptor blocker therapy being superimposed on a non-specific beneficial effect of reducing blood pressure.

ACE inhibitors

Normotensive volunteers ACE inhibitors like water soluble β -adrenoceptor blockers, in theory, should not have direct CNS effects, since these drugs do not cross the blood-brain barrier [48]. A study in 12 normal young volunteers using DSST, symbol copying, tapping rate and an auditory reaction time measure showed that enalapril significantly reduced the inter-tap interval [49]. It is possible that these results may have occurred by chance alone, because only one measure (inter-tap interval) showed improvement in a relatively large battery. In contrast, a randomised, double-blind, placebo-controlled, cross-over study in 23 healthy young volunteers failed to show significant changes in several modalities of memory after 8 days of treatment with cilazapril [50]. More recently, a placebo controlled double-blind study in 14 healthy male subjects showed significant improvements in short-term memory and digit cancellation tests after single doses of captopril [51] (Table 1). Although the applicability of these mainly acute drug studies in healthy, frequently young, non-hypertensive volunteers to a hypertensive, generally

elderly, population is limited, they do suggest that these drugs do not have a deleterious effect.

Hypertensive subjects Psychomotor performance using a test of visual memory (Design Reproduction from WMS) and of visual tracking (Trail Making Test) was studied as a part of a more extensive quality of life assessment in a multicentre randomised double-blind trial, conducted in 626 men (aged 21–65 years) with mild to moderate hypertension [25] (Table 1). Patients on captopril scored significantly higher on the trail making test than those on treatment with propranolol or methyl dopa. Improvements were also seen in measures of general well-being and work performance implying a general improvement in psychomotor function. However, the rationale for the choice of only two psychomotor tests (design reproduction from the WMS battery and Reitan trail making test) which are predominantly measures of visual memory and visuomotor coordination was not stated. A more comprehensive psychomotor assessment would have significantly contributed to better understanding of the interaction between hypertension and its treatment. In addition, hypertensive end organ damage was not excluded in the hypertensive group nor their psychomotor performance compared with normotensive subjects prior to antihypertensive treatment. Similar class differences were not seen in a more recent study in 540 middle-aged hypertensive patients using atenolol, nifedipine and cilazapril undertaken by some of the authors of the previous study [43]. The original drugs were not used for comparison and it is difficult to determine whether the previously observed improvement in psychomotor performance was a class effect, a specific drug effect or due to control of hypertension.

In contrast to these studies, no improvement was seen on several memory tasks (based on the outline proposed by Randt *et al.* [52] in 25 hypertensive subjects (age range 37–72 years) treated with enalapril [38, 53]. Again, only the memory aspect of psychomotor performance was measured and the possibility of a type I error cannot be excluded, especially as changes in other measures of psychomotor performance were not assessed.

Calcium-channel antagonists

There is little information on the CNS effects of calcium channel antagonists used in hypertension. The central effects of acute administration of nifedipine have been studied in 14 healthy male subjects using a range of psychomotor tests [54]. No significant effect was seen on digit symbol substitution test, continuous attention test, letter cancellation, choice reaction time, finger tapping, short-term memory and critical flicker fusion frequency suggesting that alertness and performance were not reduced by nifedipine. The limitations of this study are similar to those discussed earlier for a similar study using ACE inhibitors.

Skinner *et al.* [44] have compared atenolol with nifedipine in treating hypertension in elderly people (Table 1). The psychomotor performance of 25 elderly hypertensives treated with both drugs following placebo washout in a cross-over study was assessed using a psychomotor battery. There were no significant differences in memory recall between active treatment and

placebo when atenolol was used as the first drug. However, memory recall deteriorated significantly compared with placebo when nifedipine was used as the first drug. There also was a significant deterioration in performance on the digit symbol substitution test when nifedipine was used as the first drug. No differences were seen on other measures of attention, motor performance, verbal fluency or abstract reasoning. The significance of impairment in one of several measures of psychomotor performance is debatable. In addition, the differences observed were in groups first treated with nifedipine or atenolol and the differences in drug groups as a whole (first and second limb) have not been discussed. The results may also have been influenced by the reduced sample size for first usage of each drug in this study.

Our own study [60] comparing nifedipine with captopril in 13 elderly hypertensive patients, who did not have evidence of target organ damage and who were not on any other medication, showed a significant rapid and comparable improvement in several measures of psychomotor performance following control of hypertension (Table 1). The improvement in psychomotor performance was independent of order of administration of the drug.

Other antihypertensive drugs

Drugs acting wholly or partially on the central nervous system such as methyldopa, reserpine and clonidine can cause sedation, drowsiness, depression and have a significant effect on psychomotor performance [8, 23, 25, 37, 47, 53]. Indoramin and prazosin, the most commonly used α -adrenoceptor blocking agents in the treatment of hypertension, have been associated (particularly indoramin) with sedation in 6–55% of the patients, and dizziness in up to 18% of patients in different trials [7]. This will inevitably affect psychomotor performance particularly in tests measuring attention and concentration. There are no data on the effects of these drugs or newer agents (doxazosin, terazosin) on psychomotor function in normotensive or hypertensive subjects.

Conclusions

Studies on the effect of treatment of hypertension on psychomotor performance have, in general, investigated either the psychomotor effects of lowering blood pressure regardless of type of treatment, or investigated the overall CNS effects of antihypertensive drugs without differentiating between direct drug effects and those due to lowering of blood pressure. It is difficult to determine from the literature whether reducing blood pressure reverses the psychomotor impairment observed in untreated hypertensive subjects [18–20, 56–60] and to what extent the choice of individual drugs determines any change in psychomotor performance. Experimental data on psychomotor performance in normal volunteers are available for some antihypertensive agents but these may be misleading particularly if the effects differ from those in hypertensive patients. The observed effects of single doses may also differ from those resulting from chronic use. In addition, most volunteer studies have been conducted in young adults rather than in middle

aged or older subjects, the age groups most likely to be affected by hypertension.

If, as the evidence suggests, hypertension itself in the absence of structural target organ damage results in sub-optimal psychomotor performance, it is possible that this may be reversible with drugs which do not themselves impair CNS function. Another consideration is that even minor degrees of drug-induced interference with levels of function in occupational or recreational activities may have a negative impact on the all-important long-term compliance with medication required to prevent cardiac or cerebrovascular consequences of uncontrolled hypertension. Although there is some evidence in the literature on the lack of psychomotor disadvantages of pharmacological treatment of hypertension, evidence for improvement in psychomotor performance or for superiority of one drug group over others is equivocal. The balance of evidence suggests that most of the commonly used antihypertensive agents, with the exception of centrally-acting drugs, are safe (in a psychomotor context) for most patients with normal occupational or recreational requirements. Lowering of blood pressure to normal levels is associated with a beneficial psychomotor effect which is modified by the psychomotor effect of the drug itself and the net psychomotor effect may vary with individual compounds. Literature on β -adrenoceptor blockers and ACE inhibitors suggests that any intrinsic detrimental effect of the drugs is sufficiently small to be partially or totally offset by the beneficial effect of blood pressure reduction. The failure to demonstrate a similar positive effect with calcium channel antagonists could be the result of fewer studies with these agents and further carefully designed studies using sensitive measures are needed in this area.

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