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# Central effects of the angiotensin-converting enzyme inhibitor, captopril
# I. Performance and subjective assessments of mood

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**1** Central effects of single doses of captopril (12.5, 25 and 50 mg) were studied in fourteen healthy male subjects. Two placebos and an active control drug, oxazepam (15 mg), were included, together with a single dose of atenolol (100 mg). The drugs were administered double-blind at 11.00 h, and performance and subjective feelings were assessed before and from 1.5–2.5 h and 3.5–4.5 h after ingestion.

**2** Performance was assessed using digit symbol substitution, continuous attention, letter cancellation, choice reaction time, finger tapping, immediate and short-term memory, together with critical flicker fusion and two flash fusion. Subjects assessed their mood and well-being on a series of 12 visual analogue scales.

**3** Captopril did not impair performance on any of the tests, but improved short-term memory ($P < 0.05$) and increased the number of letters cancelled ($P < 0.05$). Oxazepam reduced the number of substitutions completed in the digit symbol test ($P < 0.01$), accuracy on continuous attention ($P < 0.05$), number of letters cancelled ($P < 0.05$), and rate of finger tapping ($P < 0.05$), and increased choice reaction time ($P < 0.001$). Atenolol reduced the rate of finger tapping ($P < 0.05$), but increased the number of letters cancelled ($P < 0.05$).

**4** No effects on mood or on subjective feelings were evident with captopril. Oxazepam reduced subjective alertness ($P < 0.05$), and atenolol increased feelings of sleepiness ($P < 0.05$)

**5** Although these observations suggest that central effects may exist with captopril, no adverse consequences have been established on performance or on subjective assessment of mood. Captopril may, therefore, be an appropriate drug for hypertensive patients engaged in skilled activity.

**Keywords** captopril performance mood

## Introduction

Hypertension is associated with increased risks of disability and death from coronary heart disease and stroke, but treatment with drugs often leads to adverse effects. These effects may be particularly significant to those involved in skilled work, but little comparative information exists on the effects of various anti-hypertensive medications on performance. To decide the most appropriate therapy a variety of approaches is needed from studies on their central effects to

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epidemiological studies on so-called quality of life. Indeed, such epidemiological studies have suggested that work performance is related to the nature of treatment (Croog *et al.*, 1986), and it was in this context that in previous studies (Currie *et al.*, 1988; Nicholson *et al.*, 1988) we looked at the central effects of β-adrenoceptor antagonists. In the present study we extend these assessments to an angiotensin-converting enzyme (ACE) inhibitor.

## Methods

### *Subjects and restrictions*

The subjects were fourteen healthy male volunteers aged between 20 and 33 (mean 25 years). The study was approved by the Hospital Ethics Committee, and possible subjects with history of cardiorespiratory disease, evidence of renal impairment or electrolyte imbalance were excluded. Each participant received a test dose of captopril (50 mg) before starting the study, and was withdrawn if mean arterial blood pressure decreased by more than 20 mm Hg. None was taking any concurrent medication.

The subjects were asked to abstain from alcohol for 24 h before each experimental period, and no caffeine-containing beverages were allowed during the day of the experiment.

### *Experimental design*

Each subject ingested single doses of captopril (12.5, 25 and 50 mg), and oxazepam (15 mg) as an active control and two inactive placebos. Atenolol (100 mg) was included in the design in order to substantiate our previous findings (Currie *et al.*, 1988). The drugs were administered double-blind according to a multiple Latin square design, with one placebo included in each half of the study. Treatments were separated by at least 1 week. The drugs were taken orally at 11.00 h with 100 ml of water, and performance and physiological parameters tested 1 h before (10.00 h) and from 1.5–2.5 h and from 3.5–4.5 h after ingestion. At each time, a venous blood sample was taken to measure drug plasma concentration.

Each test session lasted approximately 1 h and consisted of several aspects of performance, critical flicker fusion and two-flash fusion, subjective assessment of well-being and recordings of body sway and the waking electroencephalogram (EEG). This experimental design has been used previously (Currie *et al.*, 1988; Nicholson *et al.*, 1988) to assess central effects of β-adrenoceptor antagonists, and the techniques have been shown to be sensitive to the effects of centrally-acting drugs.

Venous blood was taken at 2 and 4 h after ingestion for measurement of plasma concentration, and the samples spun and stored at −20° C until analysis. Captopril concentrations were determined by radioimmunoassay, where captopril is first transformed to a stable *N*-ethylmaleimide (G. Clarke, personal communication). Atenolol was assayed using high performance liquid chromatography (Rosseel *et al.*, 1982; Winkler *et al.*, 1982).

### *Performance testing and physiological procedures*

Before the study began the subjects were trained to plateau level at each performance test, and spent at least 1 day in the laboratory to become familiar with the schedule and physiological procedures. Performance and the EEG were recorded in individual cubicles, and critical flicker fusion and two-flash fusion tested in a room with controlled lighting to allow dark adaptation. All measures other than memory were completed on three occasions each day.

*Digit symbol substitution test (DSST)* Two sheets each containing 200 randomised digits and a code relating each digit to a symbol were presented to the subjects. For each sheet, they were given 2 min to complete as many substitutions as possible, and the total number of substitutions recorded.

*Six-letter cancellation* Subjects were presented with a single sheet containing 1200 randomised letters arranged in 40 columns, with 6 target letters printed at the top. They were required to cancel as many target letters as possible in 5 min, and the number of letters correctly cancelled, attempted and errors were recorded.

*Continuous attention* A randomised series of letters generated by microcomputer was presented on individual TV monitors at a rate of one per second, and a 'critical stimulus' consisting of two letters displayed continuously on the screen. Subjects were required to press a key within 750 ms when the second letter followed the first in the random series. The test lasted 15 min, and the number of correct responses and errors were recorded.

*Choice reaction time (CRT)* Subjects pressed a key corresponding to one of four light emitting diodes illuminated in a random sequence of 30

presentations. Mean reaction time to the last 20 responses was measured.

*Short term memory* Immediately before drug ingestion, the subjects were presented with a set of twelve photographs of unrelated objects and given 1 min to memorise them. Four hours after drug ingestion they were allowed 1 min to recall and write down as many objects as possible.

*Immediate recall memory* Two hours after ingestion, immediate recall was tested by presenting a list of 16 unrelated words (two syllable nouns). These were generated by microcomputer and displayed on TV monitors at a rate of one word every 3 s. Immediately after the presentations subjects were allowed 45 s to write down all words recalled.

*Finger tapping* Subjects tapped a pressure-sensitive transducer as rapidly as possible for 1 min, and the total number of taps and of involuntary rest pauses exceeding 200 ms were recorded.

*Critical flicker fusion* Flicker fusion threshold was measured using a central flickering source, with the initial frequency chosen randomly between 15 and 20 Hz. Frequency then increased or decreased by 4 Hz depending on whether the subject perceived a flickering or fused source. Subsequent changes in response halved the stepsize until steps of 0.25 Hz were reached. Each stimulus was presented for 2 s and fusion threshold defined as a mean of the last 20 presentations of stepsize 0.25 Hz.

*Two-flash fusion* Pairs of 10 ms flashes of light separated by a period between 12 and 120 ms were presented, and the subjects required to report whether the light sources appeared as two separate flashes or were fused. Initial separation was between 50 and 63 ms, with subsequent increases or decreases of 8 ms depending on the subject's response. The stepsize was then halved until steps of 1 ms were reached. Flash fusion point was defined as a mean of the last 20 responses of 1 ms stepsize.

*Heart rate and blood pressure* Resting heart rate and systolic and diastolic blood pressure were recorded.

*Subjective assessments*

Subjects assessed their mood and well-being on a series of twelve 100 mm visual analogue scales (0–100) presented on a single sheet, with scores toward 100 representing favourable subjective feelings. The assessments were: A: I am, extremely sleepy (0) – extremely wide awake (100); B: I am, extremely tense (0) – absolutely relaxed (100); C: I am, extremely agitated (0) – absolutely calm (100); D: I am, extremely lethargic (0) – extremely energetic (100); E: I am, mentally very dulled (0) – extremely alert (100); F: I have, no ability to concentrate (0) – complete ability to concentrate (100); G: with regard to carrying out general duties I feel that I am, absolutely useless (0) – extremely efficient (100); H: I am, extremely irritable (0) – not at all irritable (100); I: I am, extremely aggressive (0) – extremely passive (100); J: I feel, extremely withdrawn (0) – extremely sociable (100); K: I am, in the depths of depression (0) – ecstatically happy (100); L: I feel, extremely anxious (0) – absolutely carefree (100).

These visual analogue scales have been used in a number of recent studies concerning the effects of drugs on performance in man (Bradley & Nicholson, 1986, 1987; Currie *et al.*, 1988) and have been found to be sensitive to perceived changes in mood and well-being associated with centrally-acting drugs.

*Statistical analysis*

All data were analysed using analysis of variance (ANOVA), with the factors drugs, times and subjects specified in the model. Drugs and times were fixed effects and subjects a random effect. The assumptions of ANOVA—homogeneity of variance, normality and independence—were examined for each variable, and transformations of the data selected where appropriate using the method of maximum likelihood of Box & Cox (1964). In the case of one variable, systolic blood pressure, no suitable transformation was possible, and the data were analysed using normal scores.

The pre-ingestion sessions were screened for homogeneity, and where no influential differences were found, direct comparisons of mean drug and placebo values after ingestion were made. Where differences at pre-ingestion time occurred, changes from pre-ingestion level were used to compare drug responses with placebo at each post-ingestion time. Based on this criterion, direct comparisons of drugs with placebo were made for all performance tests other than DSST, where changes from pre-ingestion time for the drug and placebo treatments were compared.

The effect of single doses of captopril and the mean response over dose, together with oxazepam and the single dose of atenolol were

**Table 1** Effects of captopril and atenolol on performance—means over post-ingestion times (means for 14 subjects)

| | *Placebo* | *Oxazepam 15 mg* | *Atenolol 100 mg* | *Captopril 15.5 mg* | *Captopril 25 mg* | *Captopril 50 mg* | *Mean for 12.5–50 mg* | *#Standard error* |
|---|---|---|---|---|---|---|---|---|
| DSST | 161.6 | 152.6** | 168.4 | 158.2 | 164.1 | 161.6 | 161.3 | 1.536 |
| Cancellation (number correct) | 90.4 | 82.3* | 97.8* | 91.5 | 98.8* | 91.7 | 94.0 | 2.729 |
| Attention (% correct) | 96.5 | 95.0* | 97.4 | 96.6 | 97.5 | 97.1 | 97.0 | 0.103 |
| Attention (number of errors) | 1.27 | 1.77** | 1.09 | 1.31 | 1.05 | 1.13 | 1.16 | 0.008 |
| Choice reaction time (ms) | 350.5 | 372.8*** | 360.7 | 361.2 | 357.3 | 349.4 | 356.0 | 2.060 |
| [I]Short term memory | 7.34 | 7.28 | 7.27 | 8.25 | 8.65* | 7.86 | 8.26* | 0.389 |
| | (7.11 | 7.43 | 7.49 | 8.36* | 8.64** | 7.87 | 8.29**) | |
| [I]Immediate recall memory | 10.50 | 9.71 | 9.56 | 9.64 | 10.14 | 10.44 | 10.08 | 0.445 |
| Tapping (number) | 401.6 | 392.0* | 392.6* | 395.3 | 398.0 | 399.8 | 397.7 | 3.422 |
| Tapping (involuntary rest pauses) | 145.5 | 151.7* | 149.5 | 149.0 | 145.6 | 146.9 | 147.2 | 2.551 |
| Critical flicker fusion (Hz) | 37.1 | 35.9 | 38.4 | 36.1 | 36.7 | 36.6 | 36.4 | 0.963 |
| Two flash fusion (Hz) | 38.5 | 38.4 | 35.2 | 37.0 | 37.6 | 38.3 | 37.6 | 1.455 |

[I]Immediate recall and short-term memory were each tested in a single session only at 2 and 4 h respectively after drug ingestion. Values for short-term memory are means for 12 subjects because data for two subjects were of doubtful validity. Mean values over 14 subjects in short-term memory are shown in brackets on the line below.

Significance levels: $*P < 0.05$; $**P < 0.01$; $***P < 0.001$.

#The standard errors are pooled estimates taken from the analysis of variance based on all treatments. Where data were transformed, the standard error relates to the transformed value, and applies to the following variables: Attention (% correct): log (1.01−x); Attention (number of errors): $\sin^{-1}(\sqrt{x})$.

examined at 2 and 4 h after ingestion, and for the mean post-ingestion response of each drug. Significance levels for all comparisons were adjusted to allow for multiple simultaneous comparisons using the appropriate Bonferroni bound (Miller, 1966).

Principal components analysis was used to analyse mood assessments, and component weightings tested for drug effects using ANOVA and subsequent individual comparisons. Individual assessments were examined but are reported only where additional explanation of effects is provided.

## Results

The results relating to performance, subjective assessments of mood, heart rate and blood pressure values are shown in Tables 1, 2 and 3. Findings from the electroencephalograms and body sway are reported elsewhere (Nicholson *et al.*, 1990).

### *Performance tests*

Captopril did not impair performance at any of the skills tested either at individual doses or when meaned over dose and post-ingestion time. Captopril (25 mg) increased the number of letters cancelled ($P < 0.05$), and captopril meaned over dose improved short-term memory ($P < 0.05$), although only the 25 mg dose alone achieved statistical significance ($P < 0.05$). Values for short term memory in Table 1 are based on 12 subjects only because data for two individuals were of doubtful validity, with one subject having constant values for all drugs, and the second omitted because one placebo was very low. However the results including all subjects are shown in brackets.

Oxazepam reduced the number of substitutions completed on the digit symbol test ($P < 0.01$), number of letters cancelled ($P < 0.05$), accuracy at continuous attention ($P < 0.05$) and rate of finger tapping ($P < 0.05$), and increased choice reaction time ($P < 0.001$). It did not affect short term memory or immediate recall, critical flicker fusion or two-flash fusion.

Atenolol reduced the rate of finger tapping ($P < 0.05$) but increased the number of letters cancelled ($P < 0.05$).

### *Subjective assessments*

Three principal components derived from the 12 assessments explained 63% of the total variance. Each scale was included in one of the three independent vectors: assessments A, D, E, F and G comprised the first component (26% of the variance) and reflected feelings of alertness. Scales B, C, H, I and L were represented by the second component and J and K by the third (22 and 15% of the variance respectively). These latter two derived variables were interpreted as mood related to tension and anxiety (second component) and feelings of happiness and sociability (third component).

ANOVA identified a drug effect on alertness, although captopril did not affect this component at any dose. Oxazepam reduced alertness ($P < 0.05$) 1.5 to 2.5 h after ingestion compared with placebo ($P < 0.05$), while atenolol increased feelings of sleepiness (scale A) when meaned over post-ingestion times ($P < 0.05$). The component loadings and inspection of the data indicated that reduced alertness was mainly attributable to scales A—awake/sleepy—and to G—ability to perform general duties.

No drug effect was present with the second and third principal components related to 'mood', and ANOVA of the individual assessments represented by these components gave no additional information.

### *Heart rate and blood pressure*

Captopril meaned over dose reduced diastolic blood pressure (DBP) ($P < 0.05$), with the effect occurring at both 25 and 50 mg while atenolol reduced heart rate ($P < 0.001$) and systolic blood pressure ($P < 0.001$).

### *Plasma concentrations*

Plasma concentrations for captopril and atenolol are given in Table 4.

## Discussion

The present study shows that the angiotensin-converting enzyme inhibitor, captopril, is without adverse effects on performance or on subjective alertness and mood over the dose range 12.5–50 mg. Indeed, short-term memory and performance at letter cancellation were improved.

It is therefore of interest that the behavioural effects of ACE inhibitors have become the subject of a number of recent studies, both in healthy individuals and in patients. Olajide & Lader (1985) examined the effects of enalapril over a period of 15 days in healthy volunteers. Rate of finger tapping increased and there were no adverse effects on critical flicker fusion, digit

**Table 2** Effects of captopril and atenolol on subjective assessments (means for 14 subjects)

| | *Time after ingestion (h)* | *Placebo* | *Oxazepam 15 mg* | *Atenolol 100 mg* | *15.5 mg* | *Captopril 25 mg* | *50 mg* | *Mean for 12.5–50 mg* | | *#Standard error* |
|---|---|---|---|---|---|---|---|---|---|---|
| PC1 | 2 | −0.065 | −0.682* | −0.330 | 0.228 | −0.120 | 0.188 | 0.119 | } | 0.232 |
| | 4 | 0.113 | 0.262 | −0.359 | 0.005 | 0.187 | 0.548 | 0.247 | } | |
| | Mean 2, 4 | 0.024 | −0.210 | −0.344 | 0.147 | 0.033 | 0.368 | 0.183 | | 0.188 |
| PC2 | 2 | 0.012 | 0.063 | 0.291 | 0.245 | −0.241 | 0.108 | 0.037 | } | 0.219 |
| | 4 | −0.024 | 0.106 | −0.132 | −0.007 | −0.341 | −0.305 | −0.218 | } | |
| | Mean 2, 4 | −0.006 | 0.084 | 0.079 | 0.119 | −0.291 | −0.099 | −0.090 | | 0.174 |
| PC3 | 2 | 0.253 | 0.271 | −0.218 | 0.039 | 0.202 | 0.162 | 0.134 | } | 0.230 |
| | 4 | 0.001 | 0.040 | 0.079 | −0.261 | 0.047 | 0.136 | −0.026 | } | |
| | Mean 2, 4 | 0.127 | 0.156 | −0.069 | −0.111 | 0.124 | 0.149 | 0.054 | | 0.169 |
| A | 2 | 48.9 | 42.8 | 43.2 | 53.4 | 48.4 | 51.8 | 51.2 | } | 2.691 |
| | 4 | 50.0 | 51.0 | 45.9 | 48.1 | 48.6 | 53.4 | 50.0 | } | |
| | Mean 2, 4 | 49.4 | 46.9 | 44.6* | 50.8 | 48.5 | 52.6 | 50.6 | | 2.049 |
| G | 2 | 51.3 | 46.1 | 50.4 | 51.4 | 52.1 | 51.4 | 51.6 | } | 2.032 |
| | 4 | 52.6 | 54.7 | 48.4 | 51.0 | 53.4 | 54.6 | 53.0 | } | |
| | Mean 2, 4 | 52.0 | 50.4 | 49.4 | 51.2 | 52.8 | 53.0 | 52.3 | | 1.567 |

PC1 = score on component representing assessments A, D, E, F, G (alertness)
PC2 = score on component representing assessments B, C, H, I, L (mood)
PC3 = score on component representing assessments J, K (happy/sociable)
A: analogue scales assessing sleepiness.
G: assessment of ability to carry out general duties.
Significance levels: $*P < 0.05$.
#The standard errors are pooled estimates taken from the analysis of variance based on all treatments.

**Table 3** Effect of captopril and atenolol on blood pressure and heart rate (means for 14 subjects)

| | *Time after ingestion (h)* | *Placebo* | *Oxazepam 15 mg* | *Atenolol 100 mg* | *Captopril 15.5 mg* | *Captopril 25 mg* | *Captopril 50 mg* | *Mean for 12.5–50 mg* | *#Standard error* |
|---|---|---|---|---|---|---|---|---|---|
| Diastolic blood pressure (mm Hg) | 2 | 68.9 | 70.1 | 64.7 | 66.4 | 61.9* | 61.7* | 63.3* | |
| | 4 | 69.1 | 71.8 | 67.0 | 70.1 | 65.8 | 66.7 | 67.5 | |
| Systolic blood pressure (mm Hg) | 2 | 120.1 | 116.9 | 108.1*** | 118.6 | 117.2 | 116.7 | 117.5 | |
| | 4 | 113.6 | 117.3 | 108.1** | 117.5 | 116.1 | 115.8 | 116.5 | |
| Heart rate (beats $min^{-1}$) | 2 | 63.4 | 65.3 | 53.6*** | 67.7 | 62.1 | 67.4 | 65.7 | |
| | 4 | 64.3 | 63.3 | 53.7*** | 63.9 | 65.4 | 64.3 | 64.5 | |

Significance levels: $*P < 0.05$; $**P < 0.01$; $***P < 0.001$.
For each variable the pooled estimates for standard error were: diastolic blood pressure: 1.953; systolic blood pressure 0.2259 (based on normal scores); heart rate: 1.780.

**Table 4** Plasma concentrations (ng $ml^{-1}$) of captopril and atenolol (means for 14 subjects)

| | *Dose (mg)* | *Time after ingestion (h)* 2 | 4 |
|---|---|---|---|
| Captopril (mg) | 12.5 | N.D.+ | 28.9 |
| | 25 | 146.4 | 64.9 |
| | 50 | 343.3 | 215.0 |
| Atenolol (mg) | 100 | 579.9 | 491.8 |

+ N.D. Not detected

symbol substitution, reaction time or subjective mood. In a later study finger tapping and symbol copying were increased with enalapril compared with β-adrenoceptor antagonists (Frcka & Lader, 1988), and in the same study feelings of calmness were greater than with the β-adrenoceptor antagonists.

A study which involved a comparison of drug effects in patients has also been carried out by Lichter *et al.* (1986). They showed that over a 16 week ingestion period atenolol impaired memory compared with a pre-drug control period, but that there were no changes with enalapril. Further, a study with patients which compared the effects of captopril, propranolol or methyldopa (Croog *et al.*, 1986, 1987) over a 6 month period indicated that captopril enhanced self-assessed work performance compared with propranolol and methyldopa, and improved cognitive function compared with methyldopa. In addition to quantitative behavioural studies, the effects of ACE inhibitors and other antihypertensive drugs have been studied on quality of life and well-being in patients. Improved general well-being and a reduced withdrawal rate due to adverse effects (Croog *et al.*, 1986) were observed in patients receiving captopril compared with methyldopa or propranolol, and there were fewer complaints of sexual dysfunction (Croog *et al.*, 1988) reported with captopril than with propranolol. Captopril was also associated with fewer side effects and complaints than nadolol or methyldopa and, compared with oxprenolol, tended to reduce feelings of depression (Hill *et al.*, 1985; Pupita *et al.*, 1987). However, though individual case reports (Zubenko & Nixon, 1984) and studies with multiple drug therapies (Callender *et al.*, 1983) suggest altered mood, such changes are difficult to evaluate objectively.

Although many of the clinical studies have inherent uncertainties, including confounding factors such as concomitant or previous medication, lack of adequate placebo control and failure to account for natural changes over time,

they nevertheless suggest that, in contrast with other antihypertensive drugs, ACE inhibitors at least may have a less adverse influence on the quality of life. It is therefore of interest that the present study in healthy volunteers has failed to demonstrate sedation or impaired performance with captopril, and, indeed, some aspects of performance were improved.

In contrast with clinical reports of improved well-being we have, however, been unable to demonstrate analogous changes in subjective feelings in healthy volunteers. It could well be that the reported improvements with ACE inhibitors arise because they do not have the adverse effects on well-being found with other antihypertensive drugs such as β-adrenoceptors and methyldopa. Alternatively, such effects may only become evident after several months, thus explaining the lack of effect with single ingestions.

The influence of captopril on memory suggests that such drugs may have a central effect. Although the effect occurred at the 25 mg dose, it is unlikely that this is a dose-related effect, since the 12.5, 25 and 50 mg doses did not differ statistically, and furthermore the mean value over the three doses demonstrated an improvement in memory. The way in which ACE inhibitors may influence neurotransmission is not fully understood, but the potential role of a renin-angiotensin system has been discussed in a number of studies (Ganten & Speck, 1978; Phillips, 1978; Ramsay, 1979). Early autoradiographic studies indicated that captopril administered systemically did not readily enter the brain (Heald & Ita, 1977), but inhibition of brain angiotensin-converting enzyme has been reported (Cohen & Kurz, 1983; Evered *et al.*, 1980). Indeed, it would appear that captopril can modify the permeability of the blood-brain barrier and cerebral blood flow in animals (Sharma, 1987), and so enter areas of the brain where the barrier is less complete. Sharma (1987) has suggested that angiotensin-converting enzymes may be important in maintaining the integrity of the blood-brain barrier, and it is therefore possible that ACE inhibition may modulate brain function and metabolism.

In addition to the present evidence of improved memory, animal studies with several ACE inhibitors have demonstrated improved learning performance (Costall *et al.*, 1988, 1989). Altered levels of components of the brain renin-angiotensin system have been associated with modified learning and memory in animals. This is a comlex issue, with increased brain renin levels leading to impaired retention (Koller *et al.*, 1979; Sabel *et al.*, 1983), while elevated angiotensin II in the brain may either impair (Morgan & Routtenberg, 1979) or improve memory (Baranowska *et al.*, 1983; Braszko & Wisniewski, 1988), and this raises the possibility of a dose-related effect. It has been suggested that such effects are non-specific to angiotensin II receptors, and involve interaction with central neurotransmitter systems. However, many of the animal studies involved intracerebral injections and clearly the influence of captopril taken orally will be relatively weaker.

Previous studies in patients (Croog *et al.*, 1986; Lichter *et al.*, 1986) did not show changes in memory, though many of the factors relating to these tests, including time of drug ingestion with respect to acquisition and recall, and duration of retention differed. These parameters are extremely important in determining the outcome of memory tests during and after drug administration, since changes in memory involve several processes, including acquisition, consolidation and recall of items. In our short-term memory test pictures were presented immediately before drug ingestion, with recall 4 h later. It is possible therefore that improved performance with captopril could be a specific effect, involving consolidation, retention or recall, since the acquisition phase was not involved, and, in view of the lack of evidence of any change in subjective alertness or performance at tasks involving attention, the effect is unlikely to be related to impaired alertness. In contrast, oxazepam reduced attention and subjective alertness in both the present and previous (Currie *et al.*, 1988) investigations, but did not modify short term memory in either experiment. This result is consistent with the effects of benzodiazepines on memory, where sedation affects the acquisition phase of memory (Curran, 1986) although consolidation processes can also be affected.

In addition to modifying central activity, it would appear that ACE inhibitors may act peripherally and affect tasks involving motor function such as finger tapping (Olajide & Lader, 1985), symbol copying (Frcka & Lader, 1988) and letter cancellation. In the present study, captopril increased the number of cancellations completed without affecting accuracy. These changes, together with modified body sway (Nicholson *et al.*, 1990) could imply that a peripheral component of the nervous system is affected.

With regard to the effect of captopril on blood pressure, a small change in diastolic blood pressure occurred at doses of 25 and 50 mg, while systolic blood pressure was unaffected. This negative finding may have occurred because

the study was done in normotensive volunteers. Captopril reduces blood pressure by blocking the enzyme that converts angiotensin I to angiotensin II, and this mechanism may be active to a lesser degree when blood pressure is normal, while its action is clearly more pronounced in antihypertensive patients. However, the dose range 12.5–50 mg of captopril corresponds to the therapeutically effective level, and therefore our findings with regard to central effects are highly relevant to the clinical situation.

Finally, atenolol led to increased subjective sleepiness in the present study, consistent with our previous findings of reduced alertness and sedation (Currie *et al.*, 1988; Nicholson *et al.*, 1988). The majority of performance skills tested remained unaffected, in contrast with the active control drug, oxazepam, although atenolol decreased the rate of finger tapping, while letter cancellation improved. However, the latter effect involved a change in speed rather than accuracy, and, therefore, a peripheral effect on performance may be present with atenolol.

In summary, the present study suggests that, although effects of both central and peripheral origin may occur with captopril, adverse consequences have not been established. This is in contrast with many studies of β-adrenoceptor antagonists where there is increasing evidence, though not easy to demonstrate, of sedation and impaired performance. In comparison with other antihypertensive drugs ACE inhibitors are more likely to be free of adverse central effects, and so may be more appropriate for individuals who are engaged in occupations where impaired performance could be particularly significant.

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