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Psychotropic effects of repeated doses of enalapril, propranolol and atenolol in normal subjects

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1 Enalapril 20 mg, propranolol 160 mg, atenolol 50 mg and placebo each were given once a day for 8 days to 12 normal volunteers, using a Latin-square design and double-blind procedures. A battery of tests was applied before, 2 and 4 h after the dose on day 1 and 8.
2 EEG effects were detected on day 8 with propranolol but not consistently after atenolol or enalapril.
3 Reaction-time, symbol copying and memory were impaired with propranolol; only memory was marginally affected by atenolol. Enalapril impaired memory but improved tapping ability.
4 Subjectively, propranolol was associated with drowsiness, enalapril with calmness and perhaps contentedness. Ratings of headache were increased with enalapril.
5 It is concluded that the apparent beneficial subjective effects of enalapril in clinical practice are attributable partly to intrinsic central effects but mainly to the contrast with β-adrenoceptor blockers such as propranolol.

Keywords enalapril propranolol atenolol psychotropic effects in normal subjects

Introduction

Many drugs used to treat hypertension have been reported to cause a variety of psychological changes ranging from impaired motor performance and feelings of general lethargy to frank psychotic disorders. Whilst such reactions are more commonly seen with centrally acting drugs this is by no means exclusively the case.

Enalapril is an angiotensin converting enzyme inhibitor which has been extensively studied in normal volunteers (Hodsman *et al.*, 1984) and in patients with hypertension and/or cardiac failure (e.g. Chrysant *et al.*, 1983; Webster *et al.*, 1986; Zezulka *et al.*, 1987). Enalapril is administered orally, is itself inactive and undergoes hepatic deesterification to enalaprilat. Peak concentrations of enalaprilat occur 3–4 h after single oral dosing with enalapril. Neither enalapril nor its metabolite cross the blood brain barrier to any significant extent (Todd & Heel, 1986).

Anecdotal reports from studies of enalapril give the impression of mood enhancement (From our files, 1984) though it is not clear whether this is a true mood elevating effect or merely the lack of the general subjective mood depressant effect that is so commonly seen with many antihypertensive drugs, notably the β-adrenoceptor antagonists. A recent study of ours indicated that enalapril given in repeated doses to normal volunteers had no effect on mood although tapping rate was enhanced (Olajide & Lader, 1985). We wished, however, to compare enalapril with β-adrenoceptor blockers to test the second of the two hypotheses above. Two β-adrenoceptor blockers were studied, propranolol (as an example of a lipophilic agent) and atenolol (a hydrophilic compound less likely to exhibit central effects) (Neil-Dwyer *et al.*, 1981); the effects of repeated doses were compared with those of placebo in normal healthy volunteer subjects.

Methods

Subjects

Twelve healthy volunteers, six male and six female, were selected for the study. Their ages ranged from 20 to 48 years (mean 34.3). Subjects were asked not to drink alcohol in the period starting 24 h prior to each treatment period and up to the end of each 8-day session, and to abstain from all CNS drugs. Subjects were advised not to drive during each treatment period. Female subjects were not pregnant and had to use an effective contraceptive. Approval was obtained from the Ethics Committee (Research) of the Institute of Psychiatry and each subject gave written informed consent before the study.

Drug supply

A double-dummy procedure was used. Tablets of enalapril, specially-prepared capsules of propranolol, and atenolol and matching placebos were supplied by Merck Sharp & Dohme. Subjects were instructed to take their daily dose (1 capsule and 1 tablet) at a fixed time in the morning.

Experimental design

Each subject was given each of the following four treatments, enalapril 20 mg, propranolol 160 mg, atenolol 50 mg or placebo, each treatment sequence lasting for 8 days. The four treatment occasions were assigned to the 12 subjects according to a balanced Latin-square design under double-blind conditions. At least 14 days were left between the 8-day treatments to ensure wash-out of the study medication.

Assessment

During each treatment period the full battery of tests was administered to subjects on day 1 and day 8 pre-drug level, 2 h after and 4 h after the morning dose. Thus, each subject was tested six times during each treatment period.

Blood pressure and heart rate were measured at the start of each testing session while subjects were sitting. The test battery as described below comprised physiological measures, psychomotor tasks, cognitive tasks, and self-rating scales of mood and side effects. In addition, a sleep questionnaire was completed in the first session of each testing day.

Physiological and psychomotor tests

Electroencephalogram The EEG was recorded from the vertex and the left side of the head (Cz and C3 in the 10–20 system), referenced to an ear clip earth. Amplifier half amplitude lower and upper cut off frequencies were set at 1 Hz and 30 kHz respectively. The amplified EEG signal was fed into an analogue to digital converter channel of a Research Machine 380Z microcomputer and approximately 98 s of artifact free EEG were digitised for each eyes open and eyes closed conditions. Each epoch was transformed into a power spectrum, which was then condensed into four bands, being 2.0 Hz to 4.0 Hz ('delta'), 4.5 Hz to 7.5 Hz ('theta'), 8.0 to 13.0 Hz ('alpha') and 13.5 to 26.0 Hz ('beta').

Auditory reaction time Auditory reaction time to 32 clicks of moderate intensity (70 db) was measured; the mean reciprocal value was calculated (reaction speed).

Tapping interval The subject tapped a morse key with his preferred hand as quickly as possible for 60 s. The intertap interval was computed to measure motor speed.

Critical flicker fusion threshold (c.f.f.) The subject viewed a flickering light through one eye (the same throughout the trial). Flicker frequency was increased until the subject reported that the flicker disappeared. The frequency was then decreased until the subject reported detecting the flicker again. Two repeats of this cycle yielded three measures of the rising frequency and three of the falling frequency. The mean of the six values was calculated.

Cognitive tests

Digit symbol substitution test (D.S.S.T) The D.S.S.T. is a sub-test of the Wechsler Adult Intelligence Schedule involving coding skills (symbols are substituted for numbers). The score was the number of items correctly completed in 90 s.

Symbol copying test (SCT) This test measured the motor component of the D.S.S.T. The same symbols are used but the subject only has to copy them. The score was the number of items correctly completed in 90 s.

Memory test Subjects were shown 10 mono- and bisyllabic words for 20 s and asked to recall them immediately and then again after approximately 10 min. The two scores were the number of words correctly remembered each time.

Self rating scales

Mood rating scales These consisted of 16 visual analogue scales of 100 mm in length. A principal component analysis of these scales has yielded three factors: alertness which is made up of nine scales: alert–drowsy, strong–feeble, muzzy–clear-headed, well coordinated–clumsy, lethargic–energetic, mentally slow–quickwitted, attentive–dreamy, incompetent–proficient and interested–bored. The second factor, contentedness, is made up of five scales: contented–discontented, troubled–tranquil, happy–sad, antagonistic–amicable and withdrawn–gregarious. The third factor is calmness and consists of two scales: calm–excited and tense–relaxed. Subjects rated their mood on each scale by placing a vertical mark across the 100 mm line. The score was measured in mm from the left end of the line to the mark and ranged from zero to 100.

Side effect rating scales A similar set of scales was constructed to measure bodily symptoms consisting of 100 mm visual analogue scales. Zero indicated the absence of a symptom and 100 the presence of the symptom to a very severe degree. Side effects listed were those reported for β-adrenoceptor blockers or for enalapril: dizziness, headache, physical tiredness, weakness, nausea or sickness, looseness of bowels, muscle cramps, alteration of taste, anxiety and depression.

Sleep questionnaire The sleep questionnaire had the following 5 100 mm dimensions: quality of sleep (good–bad), onset of sleep (abrupt–slow), speed of awakening (slow–fast), feeling on awakening (alert–sleepy) and dreaming (vivid–no dreams).

Statistical analysis Effects of the study drugs were evaluated by analysis of variance with three between subject factors (subjects, occasions and drugs) and two within subject factors (days and times) as the main sources of variation. Only significant main effects of drugs, times and days and their relevant interactions will be reported. Change scores were used for all figures.

Results

Physiological and psychomotor measures

Systolic blood pressure (SBP) Figure 1 shows drug effects graphically. SBP was lowered effectively by all three drugs, subjects on placebo having higher SBP at all times. The unexpected sharp drop at time 0 on day 8 of placebo subjects must be considered an artefact. On average SBP was lower on day 8 compared with day 1 but whereas SBP was higher at pre-drug times than post-drug times on day 1 this was not so on day 8.

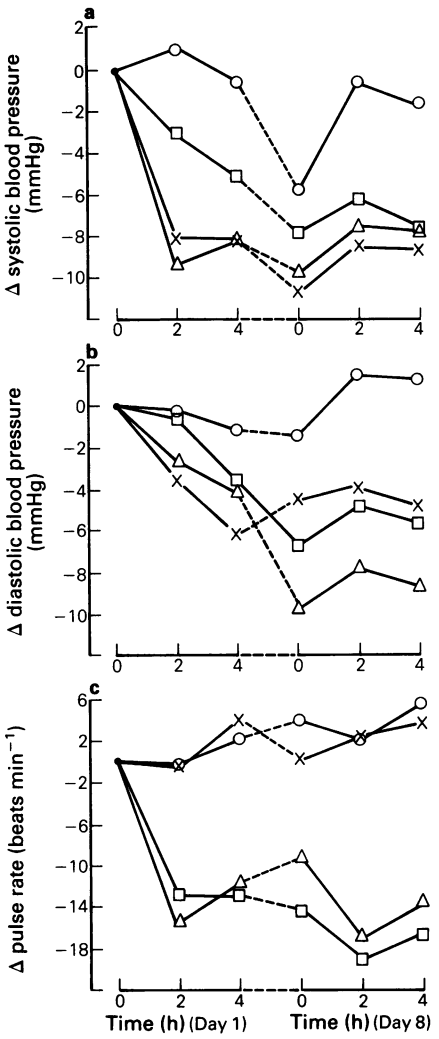

Figure 1 a) Mean change in systolic blood pressure, b) mean change in diastolic blood pressure and c) mean change in pulse rate after enalapril (×), propranolol (□), atenolol (△) and placebo (○).

No main effect of drugs was observed on this variable but the overall difference between placebo and active drugs was significant ($F = 4.92$; $P<0.03$). A significant D × T interaction ($F = 3.77$, $P<0.003$) resided in the average difference between placebo and active drugs ($F = 11.15$, $P<0.0003$) as well as in the difference between these drugs at pre-drug and post-drug times ($F = 21.56$, $P<0.0001$).

Diastolic blood pressure (DBP) On average DBP was lower during day 8 than day 1 due to the fall in DBP of subjects on active drugs on both days (Figure 1b). Enalapril lowered the blood pressure more than the two β-adrenoceptor blockers on day 1 but this order was reversed on day 8. A main effect of drugs ($F = 5.28$, $P < 0.005$) comprised a significant difference between placebo and active drugs ($F = 10.78$, $P < 0.03$) plus a difference between enalapril and the β-adrenoceptor blockers ($F = 4.44$, $P < 0.04$).

Pulse rate (PR) As Figure 1c shows, only the two β-adrenoceptor blockers lowered PR; the difference between subjects on those drugs and when on enalapril and placebo occurred as early as 2 h after the first morning dose. The drop in pulse rate with the β-adrenoceptor blockers was maximal at 2 h. A highly significant main effect of drugs ($F = 43.98$, $P < 0.0001$) was mainly due to the difference between enalapril and the two β-adrenoceptor blockers ($F = 93.83$, $P < 0.0001$). Similarly, the difference in pulse rate between days 1 and 8 ($F = 4.96$, $P < 0.03$) was mainly accounted for by the difference between enalapril and the β-adrenoceptor blockers ($F = 9.47$, $P < 0.0045$).

Electroencephalogram Activity in the 2–4 Hz waveband showed no consistent drug effects. The activity in the 4–7.5 Hz waveband (eyes open) was increased post-drug especially with propranolol (Figure 2a) ($F = 12.03$, $P < 0.002$). The pattern with eyes closed was similar.

As Figure 2b shows the activity in the 8–13 Hz (eyes open) waveband was elevated with subjects on active drugs ($F = 6.06$; $P < 0.02$). Furthermore, activity at pre-drug times on average was slightly lower than at post-drug times ($F = 4.77$; $P < 0.04$). Eyes closed recordings were similar.

Activity in the 13.5–26 Hz waveband increased from pre- to post-drug times under both eyes open (Figure 2c) and eyes closed condition particularly for subjects on propranolol. A highly significant effect of times ($F = 22.61$, $P < 0.0001$) contained a significant difference between propranolol and atenolol occasions ($F = 5.86$; $P < 0.02$).

Auditory reaction speed Auditory reaction speeds on average were slower post-drug than pre-drug. On placebo, subjects' reaction speeds were quicker than when the subjects were on active drugs ($F = 6.02$; $P < 0.007$).

Subjects on atenolol were faster than when on propranolol ($F = 4.78$; $P < 0.04$).

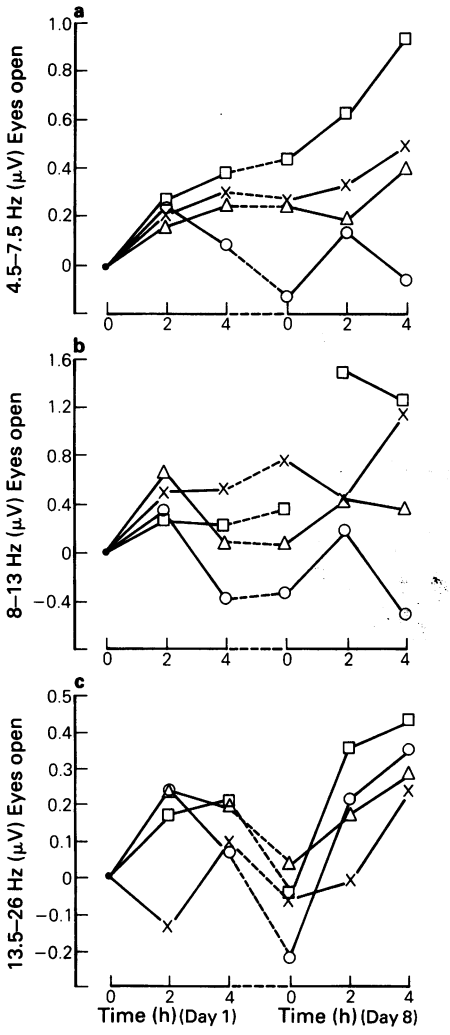

Figure 2 (a) Mean change in the activity of the 4.5–7.5 Hz waveband (eyes open), (b) mean change in the activity of the 8–13 Hz waveband (eyes open) and (c) mean change in the activity of the 13.5–26 Hz waveband (eyes open) after enalapril (×), propranolol (□), atenolol (△) and placebo (○).

Mean c.f.f. threshold No clear drug-related patterns emerged.

Intertap interval As Figure 3a shows, subjects on enalapril progressively shortened their mean intertap interval—they became faster—throughout the week, whereas the intertap interval of subjects on the β-adrenoceptor blockers increased—they became slower, the difference being statistically significant ($F = 3.59$, $P < 0.04$).

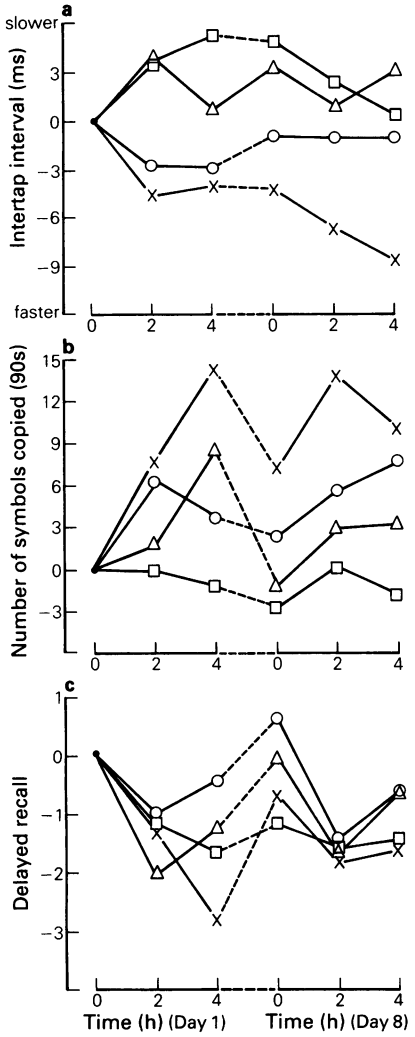

Figure 3 (a) Mean change in intertap interval, (b) mean change in number of symbols copied after the study drugs, and (c) mean change in number of words recalled with delay after enalapril (×), propranolol (□), atenolol (△) and placebo (○).

Symbol copying test Figure 3b shows that the copying capacity of subjects on enalapril was greater than when on atenolol and on propranolol ($F = 5.61$; $P < 0.02$).

Memory tests Subjects on all three active drugs immediately recalled fewer words than when on placebo ($F = 3.04$; $P < 0.04$). Subjects on propranolol recalled fewer words than on atenolol ($F = 6.72$; $P < 0.01$).

Delayed recall Figure 3c shows drug effects on delayed recall. On day 1, 4 h after the morning dose, placebo and atenolol subjects recalled more words than on the other medications; on day 8 all subject groups decreased the number of words recalled from pre-drug to 2 h after the morning dose and increased them from 2 to 4 h. This change was more pronounced for placebo and atenolol subjects. The difference between enalapril and β-adrenoceptor blocker subjects was significant ($F = 3.66$, $P < 0.04$) as was that between propranolol and atenolol subjects ($F = 3.40$, $P < 0.04$).

Self ratings

Mood factors As Figure 4a shows, on placebo subjects felt more alert on day 1 than on day 8; this can be considered a spurious effect. When on the drugs ratings changed less, but with subjects on propranolol reporting themselves more drowsy than when on atenolol ($F = 3.88$; $P < 0.03$). However, complex patterns are seen.

The contentedness–discontentedness factor showed no significant drug effects, although there was a distinct trend for subjects on enalapril to feel more contented.

On the calmness–excitedness factor a significant difference between the ratings of subjects on enalapril and when on the β-adrenoceptor blockers was observed ($F = 4.36$, $P < 0.02$). Figure 4b shows this clearly.

Bodily symptom scale: Headache As can be seen from Figure 4c, enalapril caused an increase in self reported headache, propranolol increased headache on day 8 and atenolol somewhat decreased this complaint. The difference between enalapril and beta blockers was significant ($F = 4.52$, $P < 0.04$) as was that between propranolol and atenolol ($F = 6.71$, $P < 0.01$).

Sleep questionnaire No significant effects were observed.

Discussion

The effects of the drugs on the cardiovascular measures were in line with previous studies in normal volunteers (e.g. Hodsman *et al.*, 1985). Taking both systolic and diastolic blood pressure into account, the three medications were about equi-active producing drops of about 7 mm Hg in the sitting blood pressure. As expected, both the β-adrenoceptor antagonists produced a bradycardia of about 18 beats min^{-1}, whereas enalapril

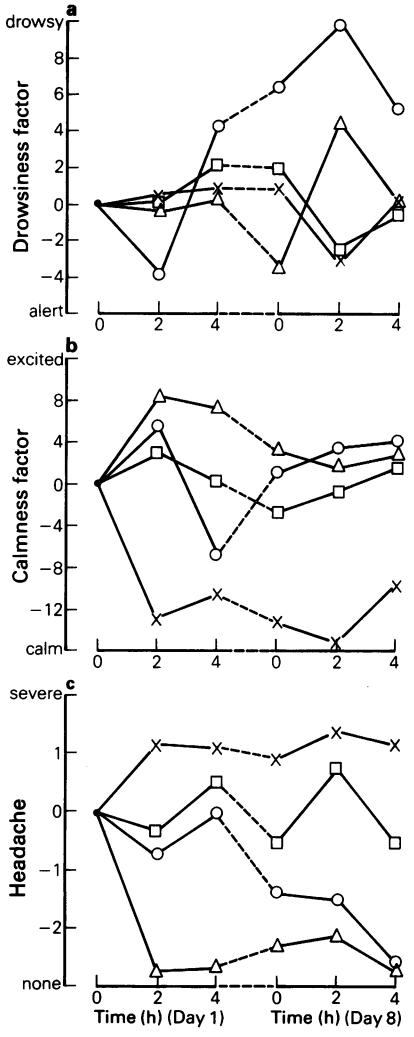

Figure 4 (a) Mean change in the factor of drowsiness derived from the mood rating scales, (b) mean change in the factor of calmness and (c) mean change in self-reported headache after enalapril (×), propranolol (□), atenolol (△) and placebo (○).

had no discernable effect on pulse rate. Thus, the drugs administered exercised their expected cardiovascular effects in normal subjects.

Some EEG effects were detected following the drugs but these were only consistently significant after propranolol, and then only on day 8. This is not inconsistent with the lack of significant EEG effects after the administration of single doses of propranolol (120 mg) or sotalol (240 mg) (Lader & Tyrer, 1972). Enalapril had no EEG effects.

Impairment of psychomotor and cognitive functioning followed the administration of the β-adrenoceptor blockers but was only consistently significant with propranolol. Indeed, for reaction time and delayed recall, a significant difference emerged between these two drugs. The literature concerning central effects of β-adrenoceptor blockers is inconsistent and, indeed, at times even contradictory. Some studies, typically using modest single doses have found no effects (e.g. Tyrer & Lader, 1974; Lader & Tyrer, 1972; Levander & Gillner, 1982). Others have shown impairments, particularly prolonged reaction time and two-flash threshold, with propranolol (Bryan *et al.*, 1974; Ogle *et al.*, 1976) although dose-effect relationships are complex (Salem & McDevitt, 1984). Oxprenolol and atenolol have also been shown to impair various psychological functions (Ogle *et al.*, 1976; Salem & McDevitt, 1983). With repeated dosing in anxious patients, Ghoneim and his colleagues (1984) reported some memory impairment following propranolol but this was greater after diazepam; however, no placebo control was used so the real extent of the impairments is unclear. In hypertensives, atenolol, but not enalapril, was associated with mild but consistent memory deficits (Lichter *et al.*, 1986).

We found a significant speeding of a simple repetitive tapping task in our subjects when on enalapril. This replicated our previous finding (Olajide & Lader, 1985) suggesting that this is a real effect. However, enalapril also impaired delayed recall, implying modest but complex central effects.

Mood effects were reasonably in line with the objective data. Propranolol was associated with drowsiness, atenolol had no consistent effects, and enalapril produced calm and tendency towards contentedness. Again, the literature is inconsistent. Some studies report a decrease in alertness with propranolol (e.g. Salem & McDevitt, 1984), another found mood-elevating and calming effects (Landauer *et al.*, 1979) but most detected no major subjective effects (Webster *et al.*, 1986). Atenolol in high dose (40 mg) exercised a transient calming effect (Salem & McDevitt, 1984).

Overall, enalapril is associated with some central effects, which apart from memory impairment and increased ratings of headache, are positive for subjects. The type of effect, both objective and subjective suggests central mechanisms for these effects despite the low rate of penetration of ACE-inhibitors into the brain. Whether the mechanism in the brain involves enkephalinase inhibition is unknown.

The β-adrenoceptor antagonists varied substantially in their central effects. Propranolol was much more active in this respect than

atenolol, paralleling the pharmacokinetic properties of the two drugs (Neil-Dwyer *et al.*, 1981) and consistent with a wealth of clinical reports on side effects.

Finally, it would appear that the apparent beneficial subjective effects of enalapril in clinical practice are mainly due to the contrast it makes with some β-adrenoceptor blockers such as propranolol but it may also have some positive effects in its own right.

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