Mood Changes During Captopril Therapy for Hypertension
A Double-Blind Pilot Study

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SUMMARY A small double-blind pilot study was carried out to assess whether captopril treatment in hypertension has a euphoriant effect. Eight patients were maintained on constant therapy of atenolol and bendrofluazide for at least 4 weeks before and throughout the study. Captopril 25 mg three times daily or matching placebo was administered double-blind for 6 weeks, with crossover to placebo or captopril from Weeks 7 to 12. Psychiatric assessment was made at Weeks 3, 6, 9, and 12. During the captopril phase, blood pressure was reduced, plasma angiotensin II lowered, and plasma renin raised. Mood was slightly, but significantly, lower during captopril administration; thus, there was no evidence of an euphoriant effect of captopril. This pilot trial also indicates the feasibility of the approach, and such studies of hypertensives under therapy should be usefully extended and refined. (Hypertension 5 (supp III): III-90-III-93, 1983)

KEY WORDS • captopril • hypertension • euphoria • psychiatric assessment

THERE is increasingly clear evidence that the treatment of uncomplicated hypertension can prevent the appearance of a variety of hypertension-related cardiovascular complications. A good case can now be made for preventive antihypertensive therapy in adults with diastolic pressures (Phase V) persistently above 95 mm Hg. This realization has produced a corresponding need for drugs with few side-effects; agents such as guanethidine, reserpine, methyldopa, and clonidine are less readily accepted in this context. Beta-adrenergic blocking agents, thiazide diuretics, prazosin, and hydralazine are generally better tolerated, although not free from unwanted effects.

By contrast, there are several anecdotal reports of spontaneous comments by patients of enhanced sense of well-being when captopril treatment is begun, usually in hypertensives subjected previously to complex drug regimens. While a greater feeling of well-being is an advantage, if captopril had a distinct euphoriant action this might impose limitations to its use. Thus, quantitative assessment is needed to detect mood changes of any nature that might be caused by antihypertensive drugs. The present pilot double-blind trial was designed to address these issues.

Material and Methods

Patients Eight patients with moderately severe hypertension (four women and four men, mean age, 51 years) entered the study after informed consent was obtained. Patients were excluded if there was a history of cerebrovascular accident; evidence of organic brain damage or impairment; a history of schizophrenia or affective psychosis; if they had received any psychotropic medication other than benzodiazepines within 3 months of entry; if they had heart failure; or had severe renal impairment.

Apart from captopril, the only antihypertensive drugs used during the study were atenolol and bendrofluazide. At least 4 weeks before the start of the trial, antihypertensive therapy was standardized and remained fixed for each subject throughout. One patient also received diazepam 5 mg/day for 4 weeks before the start and throughout the study.
Protocol
The study period was 12 weeks, with patients seen at 0, 3, 6, 9 and 12 weeks. At the start (i.e., at least 4 weeks after standardization of atenolol and bendrofluazide doses), patients were randomly allocated to receive captopril 25 mg three times daily or matching placebo for the first 6-week period, with crossover to placebo or captopril respectively for the second 6-week period.

At each visit, supine blood pressure, pulse rate, and serum electrolytes, and full blood count and urine protein were measured. At Weeks 3 and 9, after 30 minutes supine, and 2 hours after dosing, blood was drawn for measurement of plasma active renin concentration and angiotensin II.

Patients and observers remained unaware of the treatment code although this was available in sealed envelopes in the event of an emergency. Observer JC performed a psychological assessment at Weeks 3, 6, 9, and 12, before blood pressure measurements and blood samples were obtained. At these visits a tablet count was made to assess compliance. The physicians were in separate rooms, and there was no exchange of clinical information among them throughout the trial.

Psychological Assessment
Goldberg General Health Questionnaire
The 60-item Goldberg General Health Questionnaire was developed for the detection of psychiatric morbidity in general practice and hospital. Subjects respond to 60 questions by selecting the most appropriate of four possible responses. The test provides a measure of psychological well-being in relation to depression, anxiety, somatic symptoms, and ability to carry out normal functions. It has been used to assess psychiatric morbidity before entry to the large Medical Research Council treatment trial of mild hypertension, and also the effect of participation in the trial on these aspects.

Paced Auditory Serial Addition Task
This is a test of recent memory and of the ability to integrate information quickly. It assesses alertness and concentration with only slight dependence on arithmetical ability and general intelligence.

Rating Scale for Mania
This detects and quantifies hypomanic features.

Results
Three of the eight patients received captopril before placebo; the other five received placebo first. No subject required intervention because of poor blood pressure control. There was no instance of proteinuria, leucopenia, electrolyte disturbance, or skin rash. Taste impairment occurred in one patient at Week 11 while taking captopril.

Tablet counts were correct in all instances. In all patients, plasma renin concentrations were higher and angiotensin II concentrations lower, during the period of captopril therapy. Comparing captopril with placebo overall, mean blood pressures were significantly lower (164/98 mm Hg ± 9/3 SEM vs 176/101 ± 8/2; p < 0.05), plasma active renin concentration was higher (50 ± 19 μU/ml vs 23 ± 7; p < 0.05), and angiotensin II reduced (9.3 ± 1 pg/ml vs 15.1 ± 3; p < 0.05).

Psychological Testing
Goldberg Questionnaire
With this method, a high score indicates psychiatric morbidity and a tendency toward mood diminution and depression.

Overall Score. All except one subject had higher mean overall scores during the captopril than the placebo phase, and this difference was statistically significant (p < 0.05). (fig. 1).

Subdivision of Symptom Scales. Analysis was further pursued by considering separately those items addressing somatic symptoms, anxiety and insomnia, social dysfunction, and severe depression.

In all these subgroups of questions, except those dealing with depression, average scores were higher during the captopril than the placebo phase, although the differences did not achieve conventional levels of statistical significance. Only the subscale of questions dealing with depression appeared to make no substantial contribution to the total.

Paced Auditory Serial Addition Task
This test provided no evidence of any differences between captopril and placebo.

Figure 1. Comparison of scores on the Goldberg General Health Questionnaire (GHQ) (Likert scoring method) during the placebo and captopril phases. A low score indicates mood enhancement. Values given are means of the two assessments made in each phase. In all except one subject, mood was lower during captopril than placebo (p < 0.05).
Mania Rating Scale

No subject at any time had a score on this scale suggestive of hypomanic illness.

Discussion

This small pilot study has provided no evidence of an euphoriant effect of captopril. Indeed, the Goldberg questionnaire revealed a slight but significant lowering of mood when captopril was added to atenolol and bendrofluazide in moderately severe hypertension. Moreover, this pattern was seen with subscales of questions addressing somatic symptoms, anxiety and insomnia, and social dysfunction, but not depression. The paced auditory serial addition task did not discriminate between placebo and captopril; nor did captopril detectably affect the mania rating scale.

Compliance in the trial was satisfactory, assessed by tablet counts, blood pressure reduction, elevation of plasma renin, and lowering of angiotensin II.

Thus, at least in these circumstances, there seems to be no cause for concern about an euphoriant action of captopril, despite evidence from animal experiments that the drug may inhibit the degradation of metenkephalin, substance P, and kinins.16-19

There seems to be a lack of systematic prospective studies of the psychological effects of antihypertensive drugs,20 although the need for such trials is becoming increasingly apparent. Mann,13 using the Goldberg questionnaire of the present study, found that entry to a treatment trial for mild hypertension was accompanied by a lessening of psychiatric symptoms. Snait and McCoubrie21 found no evidence of a relationship between antihypertensive medication and depression using a cross-sectional study of a large patient group. Bulpitt et al.22 administered the Middlesex Hospital Questionnaire to a large number of hypertensive outpatients; this questionnaire was initially developed for the detection of neurotic disorders in psychiatric outpatients. It contains questions that refer to long-standing personality traits as well as neurotic symptoms and is perhaps less sensitive than the Goldberg questionnaire as an indicator of change in mental state related to drug treatment.

Despite the small numbers in the present pilot study, the Goldberg questionnaire was able to detect significant differences between placebo and captopril despite being applied against a background of other antihypertensive therapy. In the U.K., use of captopril is currently restricted to resistant hypertension and that associated with renovascular disease. The present trial has provided evidence that similar quantitative psychological assessments could be useful when small doses of captopril are given alone in mild hypertension.
MOOD CHANGES DURING CAPTOPRIL THERAPY/Callender et al.

Discussion

DISCUSSANTS: J. I. A. S. ROBERTSON
G. MACGREGOR
J. S. CALLENDER
W. VETTER
F. GROSS

MACGREGOR: If you are taking bendroflurazide, which may make you impotent, and atenolol, which may make you feel tired, particularly on exercise, do you really expect another drug to show an effect on top of that? Should you be looking at patients not on other treatment and comparing captopril with placebo or changing from a beta-blocker to captopril? Anecdotal impressions suggest that patients often feel better on captopril than on beta-blockers.

CALLENDER: We were investigating the possibility that captopril was having a direct effect on mood, all other things being held constant. We did show a statistically significant mood effect in patients on captopril in these circumstances.

VETTER: How long were the patients not taking atenolol and diuretic? You had a starting period of 4 weeks?

CALLENDER: The minimum period before the start of the trial was 4 weeks. All the patients had been on a fixed dose of atenolol and bendroflurazide for at least that time and most for much longer than that.

GROSS: You spoke of a possible "euphoriant" action of captopril. I think this is too strong. We associate addiction and euphoria; for example, amphetamines are euphoriant. You demonstrated that there was no "feeling of well-being," which is quoted for patients with heart failure who are given captopril.

CALLENDER: Yes.

ROBERTSON: This is an important issue. There has been a suggestion that there may be a biochemical background for a distinct euphoriant effect. While that would have the benefits referred to by Professor Breckenridge, it would mean that the use of such a drug would be limited if one wished to give it, for example, to airline pilots or heavy goods vehicle drivers. It is an important issue.

GROSS: Do we know if enkephalins have a euphoric action? Substance P may be dysphoric rather than euphoric.

ROBERTSON: Present evidence indicates that, in contradistinction to earlier suggestions, captopril does not inhibit enkephalinase. As our work has not shown any evidence of a euphoriant effect of captopril, speculations on the possible biochemical basis of such an effect are not so relevant.
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