Captopril Suppression Tests in Normotensive Individuals

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Abstract

Objective : We aimed to measure the serial (time related) concentrations of aldosterone and renin after a single dose of 25 mg of captopril in normotensive individuals. With these results, we aim to ascertain the best sampling times for future tests.

Design : Six normotensive subjects were studied under two different conditions- once in a supine position and once under normal (erect-position) activity. Each subject was given 25 mg of captopril and his serum aldosterone and renin concentrations measured at half hourly intervals for four hours. Simultaneous half hourly blood pressure measurements were also noted.

Results : All subjects showed suppression of aldosterone levels with ingestion of captopril, and in the supine position maximal suppression was consistently observed from the 3rd to the 4th hour after ingestion. When studied in the erect posture, although there was significant suppression, this was not sustained, and a paradoxical rise of aldosterone levels was seen after 2 hours. Renin activity measured during this study showed no consistent patterns. The renin levels were unchanged in almost 40 per cent of cases, and raised in about 60 per cent of cases.

None of the subjects had symptomatic postural hypotension after 25 mg of captopril.

Conclusions : The captopril suppression test is safe and effective in assessing the suppressibility of aldosterone and the period of maximal suppression is from the 3rd to the 4th hour after oral ingestion of captopril.

Key word : Angiotensin-Converting, Enzyme Inhibitors, Renin, Aldosterone

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The renin-angiotensin system plays a pivotal role in normal blood pressure and fluid and electrolyte regulation. Angiotensin II (AII), has been shown to play an important role in the pathogenesis of several common causes of hypertension, which include essential hypertension, renal and renovas-

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cular hypertension, and less commonly primary hyperaldosteronism. Angiotensin converting enzyme (ACE) inhibitors, by blocking the formation of AII, have been used widely in the treatment of hypertension, and have now been included as first line treatment[1,2]. Also, as AII has been shown to be important in the pathophysiology of congestive cardiac failure, myocardial necrosis and remodeling, and in renal diseases associated with albuminuria, blockade of its formation with the use of ACE inhibitors has been extremely effective in the management of the above conditions[3-5].

Besides the therapeutic roles of ACE inhibitors, drugs like captopril have been used as a helpful tool in the diagnosis of secondary hypertension due to renovascular causes and primary hyperaldosteronism. A single dose of captopril to stimulate renin secretion has been suggested as an inexpensive, noninvasive way to accurately detect patients with renovascular hypertension[6]. In primary hyperaldosteronism, the lack of suppression of aldosterone levels, and the absence of a significance rise in renin activity after a single dose of captopril ingestion, is highly supportive of its diagnosis[7].

The captopril suppression test has been suggested as being particularly useful in the above cases of secondary hypertension. In a review paper[6], where 16 studies of the captopril test were analysed, the authors concluded that although the data support the usefulness of this test, specific clinical recommendations could not be made until further studies define cutoff points and identify patients who are most likely to benefit from the test.

The two main objectives of our study were:

a) to measure the serial concentrations of aldosterone and renin activity after a single dose of 25 mg of captopril in the normotensive individuals.

b) to identify the best sampling times to asses suppressibility of aldosterone, a test helpful in the evaluation of hypertensive individuals suspected to have primary hyperaldosteronism.

Subjects and methodology

We studied 6 normotensive and consenting subjects with no previous medical problems. They were fasted overnigh prior to the test. On the morning of the test they were to arrive at 0700 hours and after emptying their bladder, were to lie flat till 12 noon.

At 0730 hours, an intrvenous cannula was inserted for blood sampling purposes. A 25 mg tablet of captopril was ingested at 0800 hours with 50 ml of plain water.

Serial blood pressure recordings were taken with an electronic blood pressure monitoring device. Blood samples were taken at T_{-20} minutes, T_0 (0800 hours) and half hourly for the next four hours. This test was performed with the volunteers remaining supine throughout. A similar test was performed on another day, this time with the volunteers instructed to remain in the erect posture for the 4 hours following the ingestion of 25 mg of captopril, with blood pressure monitoring and blood sampling done at corresponding times. The subjects were allowed to continue their usual daily activities for this second test.

Blood for aldosterone was collected in plain tubes, allowed to clot at room temperature, centrifuged for 10 minutes and the serum collected and stored at -70°C. Blood for renin activity was collected into prerefrigerated EDTA tubes, kept in ice bath till the tests was completed. The samples were then centrifuged at 2000 rpm at 4°C to separate the plasma which was then collected in aliquot and stored at -70°C till the assays were performed within 2 weeks of sample collection.

Aldosterone assays were done using the Coat-A-Count® kit by Diagnostic Products Corporation. This assay has a sensitivity of 16 pg/ml, and very high specificity, and extremely low crossreactivity to other compounds that might be found in the patient samples. Renin activity was assayed using the Magnetic Antibody Immunoassay Method (MAIA) by Serono Diagnostics. This had a sensitivity of being able to detect the smallest endogenous Angiotensin I value of 0.1 ng/ml, and a specificity of 100 per cent.

RESULTS

All 6 subjects studied were males. The mean age was 36 years (range of 30 to 53). The volunteers were all of normal weight with a mean body mass index of 22.8 (sd. 1.09). All were normotensive, with a mean basal systolic blood pressure of 110 mmHg (sd. 10.9) and a mean basal diastolic blood pressure of 70.2 mmHg (sd. 8.7).

After ingestion of captopril 25 mg, the lowest blood pressure reached in the supine position was 90/50 mmHg, and that in the erect posture

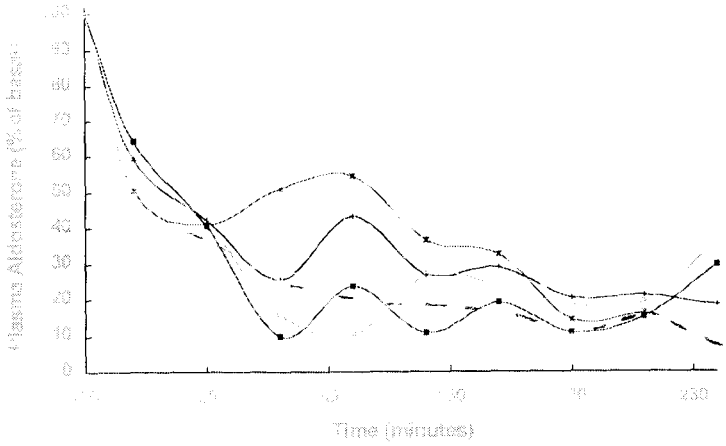

Fig. 1. **Effect of a single dose of 25 mg captopril on plasma aldosterone levels in the supine position.**

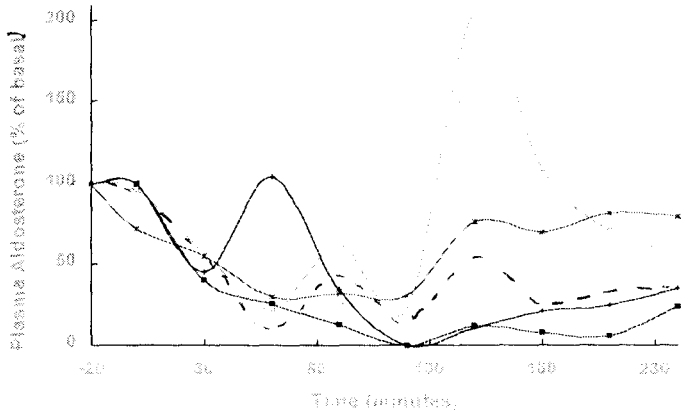

Fig. 2. **Effect of a single dose of 25 mg captopril on plasma aldosterone levels in the erect position.**

was 90/60 mmHg. The average drop in systolic blood pressure post captopril was 13.5 mmHg (range of 10 to 20 mmHg). The maximal drop in blood pressure was observed after 2 hours in all volunteers, and all had their blood pressures returning to baseline levels within 4 hours. All the volunteers remained asymptomatic throughout the tests. Patterns of renin activity measured during this study showed no consistent pattern, rising with captopril in some, being suppressed in some, and yet in others remaining at about the same baseline levels. As the subjects studied were very few, no statistically valid conclusion could be drawn from these renin results.

Fig. 1 and Fig. 2 show the aldosterone measurements in the erect and supine positions respectively at baseline and after ingestion of 25 mg of captopril.

As seen in Fig. 1, the study of aldosterone patterns showed a much more consistent pattern, with a general suppression after ingestion of captopril. This was well maintained in the supine position, with marked suppression from the second hour, and maximal between the third and fourth hour; thereafter, there was a rise in supine aldosterone levels towards the baseline levels. In the erect posture however, although there was an initial suppres-

sion in aldosterone levels, a rebound increase in was observed even as early as in the second hour after ingestion of captopril.

DISCUSSION

The renin-angiotensin hormone cascade plays a major role in normal blood pressure and fluid and electrolyte regulation. Angiotensin converting enzyme (ACE) inhibitors, primarily by blocking the formation of AII, have been used widely in the treatment of hypertension, congestive cardiac failure, and in renal diseases associated with albuminuria.

ACE inhibitors, like captopril, have been used as a helpful tool in the diagnosis of secondary hypertension due to renovascular causes and primary hyperaldosteronism. The physiological response to captopril suppression will be the suppression of aldosterone levels and a corresponding rise in renin activity. In patients with primary hyperaldosteronism, the aldosterone secretion is autonomous and unsuppressible. This fact has been used to help screen for primary hyperaldosteronism in hypertensives. In hypertensives, if the ratio of supine aldosterone/renin activity is greater than 1,400 pmol/l/per μg/l/h, the patients is likely to have primary hyperaldosteronism, the accuracy of this prediction having a sensitivity of 100 per cent and specificity of 75 per cent. If this ratio after 60 minutes of captopril 25 mg ingestion remains greater than 1,400, the diagnosis of primary hyperaldosteronism can be now made with a higher specificity of 83 per cent[8]. We compared our data on aldosterone suppression, with that in a study Hollenberg et al[9]. This study included 9 healthy men who had their aldosterone levels measured after the ingestion of captopril 25 mg. There was a 70 per cent drop in aldosterone levels 90 minutes after captopril ingestion in our group of volunteers as compared to an only 51 per cent drop in the study by the latter Boston group. The most likely reason for the greater response in our volunteers is the fact that Asians are generally of a smaller body stature, (average body weight of 60 kg in our volunteers) as compared to the Westerners (average body weight of 72.9 kg in the Boston group's study subjects). Thus although both groups received the same dose of 25 mg, our group received a higher dose when compared to dose per kg body weight, and hence a greater degree of aldosterone suppression.

In our study on normotensive individuals, it was noted that captopril was safe and all patients were asymptomatic throughout. As the effect on aldosterone suppression did not last more than 4 hours, one might question whether captopril should be given more frequently as compared to its usual three times daily recommendations. However, it is well known that the antihypertensive effect of ACE inhibitors is not solely due to serum aldosterone suppression; a rise in bradykinin levels and also the local action in endothelial tissues play important roles in the long-term control of blood pressure by ACE inhibitors[10]. Hence, the frequency of dosing should be based on the overall duration of blood pressure control in the long-term, rather than that over a single morning as in our study.

It is noted that in the supine position, blood pressure suppression with captopril was for a longer duration than that in the erect position. It took 4 hours for the blood pressures to return to baseline in the supine position as compared to 2 hours in the erect position. This observation may have clinical implications in that bedridden patients may either need a lower dose or less frequent dosing of ACE inhibitors in contrast to the mobile ambulant hypertensive. As our study was done only in normotensive individuals, this postulate needs to be tested on hypertensive patients.

SUMMARY

From our limited study on 6 normotensive volunteers, we have the following conclusions:

1. Captopril was safe for use in experimental studies in normotensive subjects and no significant side effects were noted. However in practice, as it is well known that the elderly do respond more markedly to captopril, caution needs to be exercised in selecting patients.

2. The effect of captopril in terms of aldosterone suppression was marked in the second hour after ingestion of captopril 25 mg, and maximal between the third and fourth hour. The best sampling times to assess aldosterone suppressibility appears to be at 90 minutes and 120 minutes as seen from the graph in Fig. 1.

3. Captopril seems more effective at aldosterone suppression in the supine rather than erect posture. As there are a number of confounding variables which affect blood pressure in the erect posture, captopril suppression tests are best done with patients in the supine posture.

This study also reminds us that measurements of hormone levels such as aldosterone and

renin may be confounded by many factors like physiological factors, pharmacological factors, and also importantly the laboratory factors. Performance of tests and interpretation of results would have to take these into account.

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REFERENCES

1. The Fifth Report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure. Arch Intern Med 1993; 153: 154-83.
2. Materson BJ, Preston RA. Angiotensin-converting enzyme inhibitors in hypertension. Arch Intern Med 1994; 154: 513-23.
3. Groden DL. Vasodilator therapy for congestive heart failure. Arch Intern Med 1993; 153: 445-54.
4. Cody RJ. Comparing angiotensin-converting enzyme inhibitor trial results in patients with acute myocardial infarction. Arch Intern Med 1994; 154: 2029-36.
5. Hollenberg NK, Raij L. Angiotensin-converting enzyme inhibitors and renal protection. Arch Intern Med 1993; 153: 2426-35.
6. Gaul MK, Linn WD, Mulrow CD. Captopril-stimulated renin secretion in the diagnosis of renovascular hypertension. Am J Hypertension 1989; 2: 335-40.
7. Lyons DF, Kem DC, Brown RD, Hanson CS, Carollo ML. Single dose captopril as a diagnostic test for primary hyperaldosteronism. Journal of Clinical Endocrinology and Metabolism 1983; 57: 892-6.
8. Hambling C, Jung RT, Gunn A, Browning MCK, Bartlett WA. Re-evaluation of the captopril test for the diagnosis of primary hyperaldosteronism. Clinical Endocrinology 1992; 36: 499-503.
9. Fisher NDL, Allan D, Kifor I, et al. Responses to converting enzyme and renin inhibition. Hypertension 1994; 23: 44-51.
10. Katzung BG. Basic and Clinical Pharmacology, 2nd edition 1984/5. p 123.