The captopril test: an aid to investigation of hypertension

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SUMMARY Twenty three children aged from 5 to 16 with mild to moderate hypertension were investigated using the orally active angiotensin converting enzyme inhibitor captopril. Falls in both systolic and diastolic blood pressure after a single dose of captopril were significantly correlated with initial plasma renin activity. In addition, some information about the aetiology of hypertension was deduced from the renin response to captopril. The blood pressure response to captopril is a useful screening test for renin dependent hypertension in childhood.

Hypertension is an important cause of morbidity and mortality in adults and probably has its origin in childhood. Awareness of this has led to more frequent recording of blood pressure in children and adolescents and the realisation that in up to 3% blood pressure is raised compared with the normal population.¹ Most children with mildly raised blood pressure probably represent an early presentation of essential hypertension,² whereas moderate to severe hypertension is often secondary. Though controversy exists about whether treatment of mild hypertension will affect later morbidity,³ severe untreated hypertension results in serious illness. Identification of an underlying cause for the rise in blood pressure may permit definitive surgical cure⁴⁻⁶ and hence obviate the need for lifelong antihypertensive treatment.

Secondary hypertension in children is often the result of renal parenchymal or renovascular disease, and is thus potentially surgically curable. Primary or essential hypertension, however, is not curable by surgical intervention and remains a diagnosis of exclusion. There are therefore considerable advantages in identifying those children with secondary hypertension. Renovascular or renal parenchymal hypertension are usually associated with activation of the renin-angiotensin system, and measurement of renin (as plasma renin activity) may therefore help diagnosis. This is, however, a difficult and time consuming assay and only a few centres have an established normal range for children.⁷

Blood pressure changes resulting from pharmacological manipulation of the renin-angiotensin pathway could aid in the identification of renin dependent

hypertension without the need for measurement of plasma renin activity. To date most studies have examined the use of the angiotensin II analogue, saralasin.⁸ This, however, requires a continuous, carefully graded infusion and has been associated with profound falls in blood pressure in some patients. The test has not always been definitive, especially in children.⁹

The advent of the orally active angiotensin converting enzyme inhibitor captopril¹⁰ prompted consideration of its use as a diagnostic agent. Early reports suggested a greater hypotensive response after captopril in patients known to have high plasma renin activity,¹¹ although the association between the fall in blood pressure and initial plasma renin activity has not previously been quantified. Published studies of the hypotensive response to captopril have centred on the identification of renovascular as opposed to essential hypertension in adults.¹²

Case *et al*¹³ also investigated the renin response to captopril and showed a more pronounced increase in plasma renin activity after captopril in patients with known renovascular disease compared with patients with essential hypertension. Variable responses were noted with a tendency for overlap between diagnostic groups. Only limited studies in childhood have been reported.¹⁴

The aim of this study was to evaluate the use of the hypotensive response to captopril as an aid to the identification of renin dependent hypertension in childhood. In addition, data about the renin response to captopril was examined to see if it cast light on the underlying aetiology of hypertension.

Patients and methods

PATIENTS

Twenty three patients aged from 5 to 16 with mild to moderate hypertension (greater than the 95th centile for age¹⁵) were studied. Twenty were newly diagnosed; three had previously been investigated. Of these three, one was not on any hypotensive treatment and the other two stopped treatment for at least two weeks before the study. Eighteen were studied as part of a period of inpatient investigation and five attended as day patients. All children were receiving their usual diets before the study and none had received diuretics within the preceding two weeks.

Children with malignant hypertension requiring urgent treatment and those with severe renal failure (creatinine >200 $\mu\text{mol/l}$) were excluded from the study. Six children had slightly increased plasma creatinine or a moderately reduced glomerular filtration rate, indicating a small degree of renal impairment.

All patients were investigated to find a possible cause for their hypertension, thus all had blood samples taken for full blood count, and measurement of urea, electrolyte, and creatinine concentrations, as well as plasma renin activity and aldosterone concentration. Urinary vanillylmandelic acid concentration was also measured. In addition further samples were taken for serum complement C3 and autoantibody estimations if these were clinically indicated. All patients had chest radiographs and electrocardiograms, as well as urine analysis. All had some form of renal imaging, usually an ultrasound scan and ^{99m}Tc dimercaptosuccinic acid (DMSA) scan, with other more invasive investigations if appropriate.

TEST PROCEDURE

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At the start of the procedure a small vein in the hand or forearm was cannulated to permit blood sampling

and to provide venous access for volume replacement if needed. This was kept patent with a slow infusion of heparinised saline (<2 ml/hour).

All blood pressure readings were carried out with the patient supine. Three readings were made in each arm using a Dinamap vital signs recorder with appropriate size cuff on the left arm, and a Hawkesley random zero sphygmomanometer on the right arm. The mean of three readings for each instrument was recorded.

Blood pressure was recorded every 20 minutes during an initial two hour 'run in' period (fig 1). This period was used to get baseline blood pressure recordings and to allow the children to become accustomed to the test procedure. It was also a prerequisite for the baseline measurement of plasma renin activity.

After the two hour 'run in' period, blood was taken for investigations (including measurement of plasma renin activity) and a single oral dose of captopril 0.7 mg/kg—which was obtained by dissolving a 25 mg tablet of captopril in water—was given by administering the appropriate aliquots of the resulting solution with a drink of juice. The children then remained supine, and blood pressure was measured every 10 minutes for a further two hours. A second sample of blood was collected for measurement of plasma renin activity two hours after the captopril had been given. Hourly blood pressure recordings were made for a further four hours, with a final specimen for measurement of plasma renin activity collected six hours after the dose of captopril. Children were permitted to be active in the ward for two hours after the second blood sample had been taken, but remained supine for the final two hours.

With the exception of one patient, all tests were undertaken by the same person (CEDW) and the same Dinamap recorder and sphygmomanometer were used.

Blood for measurement of plasma renin activity

Fig 1 *Captopril test protocol.*

was collected into prechilled plastic tubes and analysed by radioimmunoassay of generated angiotensin I (AI).¹⁶ Results were compared with our normal range for age.⁷

Results

GENERAL

The test procedure was well tolerated by the children. Because they were asked to lie down for quite long periods suitable distractions (for example, video recordings of popular films) were useful. Three subjects were momentarily dizzy on standing up after four hours, but none of them had a significant postural drop in blood pressure and all recovered within 2–3 minutes. One complained of feeling a little sleepy during the afternoon. None of the children experienced profound falls in blood pressure requiring volume expansion.

Patients all preferred the Dinamap recorder, as use of the Hawkesley Random zero sphygmomanometer requires inflation of the cuff to pressures of at least 180 mm Hg (usually >200) to permit filling of the reservoir. In general there was good agreement between both sets of readings. The Dinamap recorder was acutely sensitive to cuff size, which must therefore be chosen carefully. In one child the cuff slipped down the arm and gave falsely high readings. Some children found the Hawkesley cuff uncomfortable, and in these circumstances arm movements made readings more difficult.

AETIOLOGY OF HYPERTENSION

Investigations showed a possible underlying renal cause in 15 of the children (65%). Patients were considered to have renal parenchymal disease if scarring was identified on renal imaging, and this was found in 12 of these 15 children (52% of the total). Of the 12, 11 had scarring secondary to reflux nephropathy, and one boy had a small scarred kidney with hypertrophy of the contralateral kidney. He had no history of urinary tract infection, no reflux on micturating cystourethrogram, and normal arteriography. The other three had renovascular disease detected by arteriography, and in all three the disease was affecting the small to medium sized arteries. Of the 15 children with underlying renal disease, 10 had plasma renin activity above the normal range for age, three had normal plasma renin activity, and two had plasma renin activity below the normal range for age. In the remaining eight children no renal abnormalities or other reason for their hypertension could be identified, and they were therefore considered to have essential hypertension. Seven of eight had plasma renin activity within the normal range for age, and one

child had a slightly raised plasma renin activity. The data on renin activity were not available to the investigators at the time of the captopril study.

PLASMA RENIN ACTIVITY

Eleven patients had raised plasma renin activity for age (>900 ng AI/hour), 10 had normal plasma renin activity, and two had plasma renin activity less than the normal range for age (<150 ng AI/hour).

HYPOTENSIVE RESPONSE TO CAPTOPRIL

Because the initial blood pressure among subjects varied, results were analysed as the percentage change from the mean of the two hour 'run in' period. When the patients were considered in three groups depending on initial plasma renin activity—that is, high (>900 ng AI/hour), normal (150–900 ng AI/hour), or low (<150 ng AI/hour)—patterns of hypotensive response were seen. Patients with high plasma renin activity had greater and more sustained falls in blood pressure than those with normal plasma renin activity, while the two patients with low plasma renin activity had almost no response to the test dose (fig 2). Although these patterns tended to hold for the groups as a whole, individual children had less consistent responses. When the hypotensive response to the test dose at a given time was analysed, however, significant results were found. Thus two hours after the test dose of 0.7 mg/kg of captopril, the percentage changes, in both systolic and diastolic blood pressure were significantly correlated with initial plasma renin activity (figs 3 and 4) ($r = -0.68$, $p < 0.001$ and $r = -0.76$, $p < 0.001$, for systolic and diastolic pressure, respectively).

A fall to 90% of the mean systolic blood pressure before captopril had been given (that is a 10% fall) or to 85% of the mean diastolic blood pressure before captopril had been given (that is, a 15% fall) suggested a plasma renin activity of >900 ng AI/hour. Using these criteria, there were three false negative results and one false positive. The test thus had a sensitivity of 73%, a specificity of 92%, and a positive predictive value of 89%.

RENIN RESPONSE TO CAPTOPRIL

Although not the principal aim of the study, renin response to a test dose of captopril was analysed in 22 of the 23 children to see whether any further information about the aetiology of the hypertension could be gained. In general patients with renovascular disease had pronounced increases in renin after taking captopril and patients with essential hypertension had more modest responses. The patients with renal parenchymal disease had only a small, or in some cases no, increase in plasma renin

Fig 2 Percentage mean initial diastolic blood pressure for group with low plasma renin activity ($n=2$), group with normal plasma renin activity ($n=10$), and group with high plasma renin activity ($n=11$).

Fig 3 Percentage mean initial systolic blood pressure two hours after captopril given correlated with initial plasma renin activity.

Fig 4 Percentage mean initial diastolic blood pressure two hours after captopril given correlated with initial plasma renin activity.

activity after taking captopril. Although these results were interesting, the small numbers precluded statistical analysis and there was overlap between the three groups.

Discussion

Knowledge of the degree of activation of the renin-angiotensin system helps to differentiate between primary and secondary hypertension in childhood.

Though secondary hypertension is often associated with high plasma renin activity, there are patients in whom it is either normal or even low for age. The mechanism for the low plasma renin activity in these children is uncertain, but it may be explained by the second pressor effect of angiotensin as described by Dickinson and Laurence.¹⁷ They showed experimentally that doses of angiotensin II that were too small to produce an increase in blood pressure when given as a single dose may cause sustained hyper-

tension when given as a prolonged infusion. Thus in these children the plasma renin activity may be higher than it was before their kidneys were damaged even though the absolute renin activity is not above the normal range for age.

Our data suggest that the hypotensive response to a single dose of 0.7 mg/kg captopril forms a safe and effective screening test for identifying children with hyper-reninaemic hypertension. Where ready access to renin measurement is not available, or where normal ranges for childhood are not established, the captopril test can be used instead of measurement of plasma renin activity although, as in the case of plasma renin activity, measurements should be interpreted in conjunction with other investigations. In our centre, where measurement of plasma renin activity is routine, the captopril test seems to discriminate rapidly between high, normal, and low reninaemic hypertension. This enables us to plan investigation of hypertensive children more rationally and to discuss the possible cause of hypertension with the parents at an earlier stage in the child's admission.

All three patients with false negative responses to captopril had only modest increases in plasma renin activity. In one the plasma renin activity could well have been normal if the measurement had been repeated (943 ng AI/hour). In a second (plasma renin activity 1031 ng AI/hour) the blood pressure settled on admission to hospital (130/90 to 110–120/60–70 mm Hg), and has subsequently remained normal on out patient review. The third patient (plasma renin activity 1009 ng AI/hour) was incidentally discovered to have a large intake of sodium chloride that was associated with his increased appetite since taking steroids. Though we did not restrict the diets of any of the patients it would seem prudent in future to identify patients with abnormally high or low sodium intakes before performing the test.

The false positive result was found in a boy whose plasma renin activity was 833 ng AI/hour and who had had a coarctation repaired in infancy. There was no gradient across the repair site and no difference in renal function shown on DMSA scan.

We chose 0.7 mg/kg as our test dose of captopril after a pilot study had suggested that a dose of 0.3 mg/kg was insufficient to show a clear cut response. Increasing the dose of captopril from 0.7 to 1.0 mg/kg might have increased the sensitivity of the test but could have run the risk of decreasing the specificity and, more worryingly, increasing the risk of profound falls in blood pressure in patients with high initial plasma renin activity. In the children with the highest initial plasma renin activity there was greater fall in blood pressure (up to 30% of the

initial) even with the dose of 0.7 mg/kg. Other studies, primarily in adults, have used either a standard dose of captopril for all subjects, or have given varied doses without defining the rationale for the differing amounts.^{12 13 18} In children it is most appropriate to relate dosage to size. Long term use of captopril in patients with critical renal perfusion interferes with renal function, but we felt justified in using a single dose of captopril in the patients studied. All of them had moderately increased blood pressure, and other studies in our centre had shown that—even in patients with critical perfusion—the decline in function with captopril identified on DMSA scanning recovered completely.

The hypotensive response to angiotensin converting enzyme inhibition relates to renin and not necessarily to the aetiology of the hypertension. Studies have examined the use of the hypotensive response to captopril as a diagnostic agent in differentiating between renovascular and essential hypertension.¹² The patients in these studies were therefore grouped according to the aetiology of their hypertension rather than initial plasma renin activity. There was overlap among the groups and the test was not sufficiently discriminatory. We would agree that the hypotensive response to captopril is a poor guide to the underlying cause of the hypertension except in so far as it identifies renin level.

Because renin assay is readily available in our centre we examined the use of the renin response to captopril as a further aid in understanding the aetiology of hypertension in these patients. Others have suggested that large increases in renin after taking captopril are associated with a greater likelihood of surgical cure of hypertension.¹² Two of our patients with renal parenchymal disease and only small increases in renin after captopril have been 'cured' by nephrectomy. In addition, pronounced reactive hyper-reninaemia occurred in two of our patients with renovascular disease who were not thought to be amenable to surgical repair as the vessels affected were small intrarenal vessels in both kidneys. We would therefore not consider the renin response a useful indicator of surgical curability.

The renin response as opposed to the hypotensive response to captopril may, however, relate to the underlying cause of the raised blood pressure. Unlike other published work, our study examines the effect of captopril on renin in three groups of hypertensive patients: those with renovascular disease, those with renal parenchymal disease, and those with essential hypertension. Like other workers¹⁸ we found an exaggerated renin response in patients with renovascular hypertension, with more modest increases in plasma renin activity in the patients with essential hypertension. Interestingly,

most (10 of 12) of our patients with renal parenchymal disease had only a small or in some cases no renin response to angiotensin converting enzyme inhibition, yet those with high plasma renin activity had a positive hypotensive response. This group of patients has not been previously studied and the mechanism of this lack of renin rise following angiotensin converting enzyme inhibition is not clear; it may, however, imply that there is no reserve availability of renin responsiveness in patients with renal parenchymal disease. The groups in this study were unfortunately too small for statistical analysis, but the above results were interesting. Further investigation will be required to understand the mechanism of the renin response in different types of hypertension and we would not at present recommend the application of this aspect of the test protocol.

In conclusion, therefore, we suggest that the hypotensive response two hours after a test dose of captopril may be used as a diagnostic aid in identifying hypertensive children with raised plasma renin activity especially if renin assay is not available. It is possible that information about the aetiology of hypertension may be deduced by examining the renin response to angiotensin converting enzyme inhibition, although this is not clear cut.

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Accepted 24 August 1988