Reversible Renal Failure Due to Captopril in a Patient with Transplant Artery Stenosis

Case Report


SUMMARY A patient who was subsequently shown to have stenosis of the artery to a transplanted kidney sustained three episodes of impaired renal function during treatment with low doses of captopril. On each occasion this was reversed by withdrawal of therapy. The effect was not related to reduction of blood pressure since lower pressures were recorded during treatment with minoxidil, without deterioration of renal function. A possible mechanism involving blockade of the intrarenal renin-angiotensin system is discussed. (Hypertension 5: 623-627, 1983)

KEY WORDS • hypertension • hyperkalemia • hyponatremia • renin-angiotensin system

THERE have been several reports of reversible renal failure and hyperkalemia associated with captopril treatment.1-5 This has usually been attributed to renal ischemia following reduction of blood pressure to normal or subnormal levels. We report a further case in which impairment of renal function was associated on three separate occasions with captopril administration. Reduction of blood pressure to similar levels of minoxidil did not affect renal function. We suggest that this represents a specific effect of captopril and consider a possible mechanism.

Case Report

The patient, a 32-year old Filipino nurse, presented in April, 1980, with headache, blurred vision, and nausea. She was found to be hypertensive (170/110 mm Hg), with Grade 3 retinopathy and impaired renal function (serum creatinine = 8.0 mg/dl). Intravenous urography (IVU) revealed small nonobstructed kidneys, and renal biopsy showed segmental mesangial proliferative glomerulonephritis progressing to glomerulosclerosis. Satisfactory blood pressure control was achieved with hydralazine (150 mg/day) and furosemide, but renal function declined and maintenance hemodialysis became necessary in September, 1980.

On June 22, 1981, the patient received a renal transplant (single end-to-end arterial and end-to-side venous anastomoses) from her sister, of identical HLA type. Immediate function was good, and serum creatinine fell to less than 1.0 mg/dl. Two minor episodes of rejection at 10 days and 5 weeks after transplant responded well to intravenous (i.v.) methylprednisolone, 0.5 and 1.0 g respectively. Hypertension was an early problem, and treatment was reintroduced at 3 days postoperatively, initially with propranolol (160 mg/day) and hydralazine (150 mg/day), and with the subsequent addition of methyldopa (1 g/day). A further problem was a tendency to maintain an elevated jugular venous pressure (JVP), gallop rhythm, and constricted peripheral circulation in the absence of peripheral edema. On two occasions acute dyspnea responded to intravenous furosemide. Chest x-ray revealed a grossly enlarged heart and pulmonary edema.

The patient was eventually discharged 6 weeks postoperatively but required readmission 10 days later (August 12, 1981, fig. 1) because of deteriorating blood pressure control and a rising serum creatinine (1.7 mg/dl). Treatment then included propranolol (320 mg/day), prazosin (10 mg/day), hydrochlorothiazide (100 mg/day), furosemide (250 mg/day), spironolactone (200 mg/day), prednisolone (15 mg/day), and azathioprine (87.5 mg/day). A renogram showed good perfusion and uptake, and IVU and ultrasound examination provided no evidence of obstruction. A further episode of rejection was thought likely, and methylprednisolone was given i.v. in 0.5 g doses. Serum creatinine decreased slightly (1.4 mg/dl) but blood pressure control
remained inadequate despite frequent parenteral hydralazine (fig. 1). Renal artery stenosis had already been suspected on the basis of a soft bruit over the transplant and high peripheral venous renin (recumbent 4.5, ambulant 7.3 nmol/hr/ml, normal < 2.7 and < 4.5 respectively) and aldosterone (1070 pmol/liter, normal = 100–500) levels, although repeated radioisotope renogram did not provide confirmation.

On August 15, 1981, a trial of captopril was therefore started at low dosage (fig. 1). Within 24 hours, renal function had declined seriously, with oliguria, rapidly rising serum creatinine, and hyperkalemia, requiring treatment with i.v. glucose and insulin, oral calcium resonium, and one period of hemodialysis. No blood pressure below 150/90 mm Hg had been recorded, and there were no postural symptoms. Although not then directly incriminated, captopril therapy was stopped, a total of 28 mg in divided doses having been given. Continuing rejection could not be excluded and further i.v. methylprednisolone was administered. Within 36 hours, urine output increased, and within 5 days, serum creatinine had returned to normal. During this period, acceptable blood pressure control was achieved with minoxidil (5 mg/day) and pressures at this time were not higher than during the previous period of oliguria.

The risk of hypertrichosis was considered unacceptable, however, and a further trial of captopril was started on September 29, 1981 (fig. 1). A starting dose of 5 mg, increasing to 10 mg, was given every 8 hours. This produced a more definite reduction of pressure initially, the lowest recorded value being 120/70 mm Hg. There were no associated symptoms. Within 24 hours, however, oliguria again ensued, with severe hyperkalemia and a rapidly rising serum creatinine. At 48 hours, there was evidence of returning urine output and three further doses of captopril (10 mg) were given before a further reduction in urine flow terminated the trial. A probable explanation for the intermediate increase in urine flow was the patient's subsequent confession that she had deliberately not taken two of the captopril doses on that day. Recovery of renal function was rapid with restoration of normal serum creatinine values within 4 days.

**Figure 1.** Simultaneous record of serum Na (○), serum K (●), serum creatinine, body weight, blood pressure, and 24-hour urine volume during treatment with captopril and minoxidil.
Blood pressure control remained difficult despite trials of atenolol (300 mg/day), sotalol (480 mg/day), and debrisoquine (40 mg/day) while continuing maximum doses of hydralazine and prazosin. Bilateral nephrectomy of native kidneys was performed on October 14, 1981, without improvement. Because of the extreme difficulty in controlling the blood pressure, a further trial of captopril at a very low dosage was considered indicated. Before this, it was necessary to examine whether adequate blood pressure control would inevitably result in transplant ischemia and impaired function. Good control (approximately 145/85 mm Hg) was achieved with minoxidil 5 to 10 mg/day, with no impairment of renal function nor hyperkalemia (fig. 2). Low-dose captopril was then given on an outpatient basis starting at a dose of 1 mg/day and increasing to a dose of 16 mg/day over 14 days. During this time, blood pressure control was inadequate (table 1) and renal function became progressively impaired. After 16 days, serum creatinine had doubled (1.7 mg/dl) and further captopril therapy was considered unjustified. Five days later serum creatinine had returned to normal.

Shortly after, a renal transplant arteriogram demonstrated >50% stenosis at the anastomosis to the iliac artery. This was confirmed at surgery on December 15, 1981, but unfortunately an attempt at reconstruction resulted in infarction of the kidney. Histology showed widespread areas of cortical necrosis but little evidence of rejection. The artery was considerably narrowed with intimal proliferation and damage to the elastica. The patient returned to maintenance hemodialysis. She is no longer hypertensive, her blood pressure showing the usual relationship to body weight.

Discussion

The potential risk of induction of precipitous blood pressure reduction by inhibitors of the renin-angiotensin system in patients with high circulating renin levels is well recognized. Typically, this may arise in patients with a combination of severe renal artery stenosis and sodium depletion when blood pressure maintenance becomes almost exclusively dependent on the renin-angiotensin system. However, there are a number of other reports in which captopril administration has been associated with renal failure, reversible on cessation of therapy, in which the blood pressure reduction has been more moderate. The renal failure has been ascribed to normotensive renal ischemia or drug nephrotoxicity; in both these cases renal biopsies were performed but were nondiagnostic. The report of Collste et al. is persuasive in that a second episode of reversible renal impairment was induced by

<table>
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<tr>
<th>Date</th>
<th>Blood pressure (mm Hg)</th>
<th>Serum K+ (mEq/liter)</th>
<th>Blood urea (mg/dl)</th>
<th>Serum creatinine (mg/dl)</th>
<th>Captopril dose</th>
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</thead>
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<tr>
<td>2 November 1981</td>
<td>160/100</td>
<td>2.8</td>
<td>33.6</td>
<td>0.84</td>
<td>1 mg O.D.</td>
</tr>
<tr>
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<td>39.0</td>
<td>0.95</td>
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</tr>
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<td>7 November 1981</td>
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<td>3.0</td>
<td>45.6</td>
<td>0.97</td>
<td>2 mg B.D.</td>
</tr>
<tr>
<td>10 November 1981</td>
<td>160/115</td>
<td>4.5</td>
<td>63.6</td>
<td>1.21</td>
<td>2 mg T.D.S.</td>
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<tr>
<td>14 November 1981</td>
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<td>66.6</td>
<td>1.27</td>
<td>3 mg Q.D.S.</td>
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<tr>
<td>18 November 1981</td>
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<td>82.2</td>
<td>1.71</td>
<td>4 mg Q.D.S. (stopped)</td>
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<tr>
<td>23 November 1981</td>
<td>170/110</td>
<td>3.3</td>
<td>55.8</td>
<td>1.13</td>
<td></td>
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a comparable reduction of blood pressure following therapy with minoxidil.

The idea that renal ischemia results simply from a combination of tight arterial stenosis and moderate blood pressure reduction does not explain the present case. On two occasions a comparable or lower blood pressure was achieved by minoxidil with no change in renal function, yet doses of captopril, small in comparison with those previously reported, were associated with immediate renal impairment. Furthermore, during the final period of captopril administration, progressive deterioration of renal function occurred despite inadequate control of the blood pressure (table 1). Drug nephrotoxicity also seems unlikely, but is not excluded. There were no additional systemic features, such as pyrexia, skin rash, or bronchospasm, to suggest hypersensitivity, as in some cases and the rapidity of onset and recovery argue against the occurrence of structural damage. Of particular interest in this context was the prompt recovery of urine flow during the second period of exposure, synchronous with the brief period of withdrawal from treatment concealed by the patient (fig. 1).

In attempting to explain this sensitivity to captopril, suggestive features in the reported cases are a high circulating renin, the presence of renal artery stenosis, and an association with renal transplantation. In this combination of circumstances the maintenance of renal function seems especially dependent on the integrity of the renin-angiotensin system. Hall et al. have demonstrated, using a competitive inhibitor of angiotensin II in dogs, the importance of the renin-angiotensin system in the autoregulation of glomerular filtration rate during reduction of renal arterial pressure. They suggest a complex set of changes involving both afferent and efferent glomerular arteriolar resistances, but in which the vasoconstrictor effect of angiotensin II, acting through an intrarenal mechanism on the efferent arteriole, is of prime importance. The effect was most marked in sodium-depleted dogs with high circulating renin levels. The setting of efferent arteriolar resistance by angiotensin II may be particularly significant in the presence of renal artery stenosis. Anderson et al. have shown the importance of renal vascular tone in determining the severity of experimental renal artery stenosis in dogs. The induction of stenosis caused an immediate fall in renovascular resistance, but this was followed by a subsequent resistance increase associated with recovery of renal artery pressure distal to the stenosis, and reduction of effective stenosis resistance. This compensatory process could be inhibited by antagonists of the renin-angiotensin system, and induced by intrarenal infusions of angiotensin II. A primary action on the efferent glomerular arteriole was deduced, which would also act to preserve the glomerular filtration rate. The renal vascular bed is unique in its potential for vasoconstriction, through renin secretion in response to a fall in renal arterial pressure, although it is perhaps unwise to extrapolate too far from these experiments which are particularly concerned with the acute events following creation of a stenosis. Infusions of inhibitors of the renin-angiotensin system at later times did not reverse the compensatory changes. It is of interest to speculate whether denervation inherent in the transplant kidney increases its dependence on the integrity of the renin-angiotensin system for regulation of the glomerular filtration rate in the face of arterial stenosis.

Hyperkalemia and hyponatremia during captopril therapy were further important features of this case, the former so rapid in onset that hemodialysis was required within 48 hours of the first dose of the drug. Severe hyperkalemia at a time of increasing renal failure associated with captopril therapy has previously been reported. In one case with preexisting renal impairment, hyperkalemia following captopril therapy was not associated with further deterioration of renal function, and in these circumstances drug-induced hypoaldosteronism may be implicated.

Spironolactone therapy could have been a contributory factor in our case on the first occasion, but, having been stopped at that time, cannot explain the similar elevation of serum potassium on the second exposure to captopril. It is difficult to account for this rapid increase in serum potassium solely in terms of reduced renal excretion of the ion. Hyponatremia has been noted once previously, but we lack a satisfactory explanation for its presence during both periods of renal failure (fig. 1). The potential for preexisting sodium depletion was provided by intensive diuretic therapy but this was not apparent clinically. The jugular venous pressure was always evident, there was no postural hypotension and an episode of pulmonary edema had occurred a little earlier at a body weight of 33.5 kg (fig. 1). Unfortunately, we lack information on sodium balance for the relevant periods, but the record of body weight (fig. 1) shows no evidence of weight gain to suggest that the hyponatremia was dilutional, due to continuing water intake during the periods of renal failure. It is also unlikely that the quantity of sodium lost in the (relatively low) urine volumes of those 2 days could, in the face of a continuing sodium intake, provide more than a partial explanation for the phenomenon. The rapid rise of serum potassium may well have been accompanied by an equivalent migration of sodium into the intracellular compartment, but this again cannot fully account for the degree of hyponatremia. The possibility that greater quantities of sodium (without equivalent amounts of extracellular water) entered the cells must be considered speculative.

This case demonstrates the ability of low doses of captopril to cause a sudden, rapidly reversible loss of renal function with disproportionate hyperkalemia in a patient with stenosis of the arterial supply to a renal transplant. The phenomenon cannot be attributed to the fall in blood pressure achieved by the drug since equivalent arterial pressures induced by minoxidil were not associated with any reduction in renal function. In addition to hyperkalemia, a reproducible hyponatremia developed during two separate episodes of acute renal failure induced by captopril.
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