Congestive heart failure and converting enzyme inhibition: failure of current prognostic criteria for predicting subsequent renal insufficiency

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Summary: Angiotensin-1-converting enzyme inhibitors have an effective and established role in the treatment of patients with congestive heart failure. However, a small number of such patients will subsequently develop renal insufficiency. These patients may be identified prior to, or shortly after, commencement of therapy by recognized criteria. This report describes 4 patients with congestive heart failure who developed severe renal insufficiency secondary to either enalapril or captopril therapy in the absence of any currently recognized predisposing factors. One patient died.

Introduction

Angiotensin-1-converting enzyme (ACE) inhibition is a well-established therapy, in combination with diuretics, in the treatment of congestive heart failure. However, a small number of patients will develop renal functional deterioration subsequently. It has been suggested that the development of renal failure in these patients is largely predictable, and has been the subject of a recent 'state of the art' paper by Packer.¹ Indicators as to which patients will develop renal insufficiency are: (1) excessive reduction in blood pressure by ACE inhibition; (2) intravascular volume and/or sodium depletion prior to ACE inhibition; (3) pre-existing hyponatraemia; (4) bilateral renal artery stenosis; (5) diabetic patients.

We report 4 patients referred to the renal unit after development of severe renal insufficiency secondary to converting enzyme inhibition in the absence of any of the above predisposing factors. One patient died.

Case 1

A 64 year old woman was diagnosed as having severe bi-ventricular heart failure in 1985. She underwent mitral valve replacement in April of the same year. In October 1986 she was admitted to hospital with deteriorating congestive cardiac failure of uncertain cause. Her medication consisted of

frusemide 120 mg daily, amiloride 10 mg daily, digoxin and warfarin. Clinically, her jugular venous pressure (JVP) was raised, she had pitting sacral and ankle oedema, and mild pulmonary oedema. Her blood pressure was 145/85 mmHg. On admission her serum biochemistry showed urea 7 mmol/l, sodium 138 mmol/l, potassium 4.1 mmol/l and creatinine 92 µmol/l. She was commenced on enalapril 2.5 mg daily in addition to the above. She was discharged after 7 days on this medication. Serum electrolytes remained normal. In May 1987 her enalapril was increased to 10 mg daily in view of worsening symptoms, with no change in diuretic dosage. Serum urea and electrolytes were normal the same day.

On review in February 1988, symptomatically she was well and clinically there were no signs of heart failure. Her JVP was visible at 45° and blood pressure was 125/80 mmHg lying and standing. However, her renal function had markedly deteriorated with a serum urea of 36.9 mmol/l, creatinine 160 µmol/l and potassium 4.0 mmol/l. Enalapril was discontinued. Within 1 week her renal function had returned to normal. Subsequently, a diethyltri-aminepentacetic acid (DTPA) isotope renogram showed no evidence of renovascular disease. She is not diabetic and has never had proteinuria.

Case 2

A 59 year old non-diabetic woman was admitted to hospital in 1987 with congestive cardiac failure of ischaemic origin. She was commenced on fruse-

mid 80 mg daily and amiloride 10 mg daily. However, after 7 days her symptoms persisted, and she continued to exhibit a raised JVP and peripheral oedema. Blood pressure was 130/70 mmHg. Plasma urea and electrolytes at this time were normal. She was commenced on enalapril 2.5 mg daily with the frusemide and amiloride having been omitted on the first day. Hypotension was not observed after the initial dose, and therefore enalapril was given at a dose of 5 mg daily for the next 3 days in addition to the frusemide 80 mg daily. The amiloride was discontinued. Plasma biochemistry on the 4th day of enalapril therapy was markedly abnormal: urea 32.3 mmol/l, sodium 130 mmol/l, potassium 7.4 mmol/l and creatinine 300 μ mol/l. All medication was discontinued and intermittent peritoneal dialysis started. Hypotension had not been observed following the first dose of enalapril, and blood pressure on the 4th day was 120/80 mmHg. Also, her central venous pressure was +10 cm water above the mid-axilla. Renal function remained markedly abnormal over the next 2 weeks, at which time she suffered a severe left hemiparesis. She subsequently died of her stroke 2 weeks later. Post-mortem examination revealed normal renal arteries.

Case 3

A 59 year old man was first noted to have congestive cardiac failure secondary to coronary ischaemia in January 1986. He was commenced on frusemide 80 mg daily, amiloride 10 mg daily and digoxin. In October of the same year he was admitted to hospital following a deterioration of his heart failure. He was eventually discharged taking frusemide 120 mg twice daily, enalapril 10 mg daily and digoxin. His plasma urea and electrolytes on discharge were normal. Twelve months later, in September 1987, when reviewed, he was again in mild congestive heart failure with a raised JVP and peripheral oedema. Blood pressure was normal at 120/70 mmHg lying and standing. Plasma electrolytes were: urea 7.7 mmol/l, sodium 141 mmol/l, potassium 3.2 mmol/l and creatinine 136 μ mol/l. Enalapril was increased to 15 mg daily.

Two months later he was admitted as an emergency in acute renal failure with a plasma urea 97.2 mmol/l, potassium 6.3 mmol/l and creatinine 1210 μ mol/l. Blood pressure was 110/75 mmHg lying and 105/60 mmHg standing. Central venous pressure was +8 cm water from the mid axilla. All medication was discontinued and peritoneal dialysis instituted. His initial 24-hour urine output was 200 ml, but this rapidly rose to over 2 litres. Similarly, his renal function improved dramatically, and within 5 days his urea had fallen to 4.8 mmol/l, potassium to 4.1 mmol/l and creatin-

ine to 113 μ mol/l. His blood pressure following discontinuation of enalapril rose to 125/80 mmHg lying and standing.

He has never exhibited proteinuria, is not diabetic, and a DTPA renogram has subsequently shown no evidence of renovascular disease.

Case 4

A 65 year old woman was first seen in 1985 with congestive heart failure secondary to mitral valve disease. She was treated with frusemide 120 mg twice daily, amiloride 10 mg once daily and digoxin. Her symptoms were controlled until April 1988 when she was admitted to hospital with severe heart failure. She made a good response to treatment and was discharged taking the above medication plus metolazone 2.5 mg daily and captopril 6.25 mg 3 times daily. On discharge, plasma urea was 8 mmol/l, potassium 3.6 mmol/l and creatinine 130 μ mol/l.

On review in clinic 1 month later, her heart failure had deteriorated symptomatically, clinically and radiographically. Her JVP was raised, and she had both pulmonary and peripheral oedema. Her captopril dosage only was increased to 12.5 mg 3 times daily. Plasma urea and electrolytes performed on the same day were unchanged from 1 month previously. Blood pressure was 125/90 mmHg.

One month later there had been a marked improvement in her heart failure, but a significant deterioration in her renal function. Plasma electrolytes on this occasion revealed a urea of 28.8 mmol/l, potassium 4.0 mmol/l, sodium 134 mmol/l and creatinine 259 μ mol/l. Significantly, her JVP was 4 cm above the sternal angle and her blood pressure was slightly lower at 115/60 mmHg. All her medication was left unchanged and she was reviewed 1 week later. There had been a further reduction in renal function in the absence of volume depletion or hypotension. On this occasion her urea was 34.0 mmol/l, and creatinine 357 μ mol/l. On discontinuation of her captopril, renal function returned to normal within 1 month.

Subsequently, a DTPA renogram showed no evidence of renovascular disease. She is not diabetic and does not have proteinuria.

Discussion

Inhibition of the renin angiotensin system (RAS), with ACE inhibitors, is a well-established approach in the treatment of patients with congestive heart failure.²⁻⁷ Patients report an increase in well-being, and indeed may improve sufficiently to alter grading on the New York Health Association (NYHA) scale.

The haemodynamic changes that are apparent in patients with congestive heart failure may be dramatically ameliorated by the introduction of an ACE inhibitor. Of note, ACE inhibition causes a reduction in mean arterial blood pressure, left ventricular filling pressure, mean right atrial pressure and systemic vascular resistance.^{8,9}

Activation of the RAS in congestive heart failure may be to preserve renal function in the face of renal hypoperfusion,^{10,11} rather than to maintain sodium and water homeostasis or blood pressure. The preferential action of angiotensin II on the glomerular efferent arteriole maintains filtration in the presence of renal hypoperfusion. By removing this stimulus (as with an ACE inhibitor) to the efferent arteriole, one may observe a reduction in the glomerular filtration rate, despite an increase in renal plasma flow.

In addition, the sodium status of an individual is crucial to the activity of the RAS. Sodium-deplete patients (either through salt restriction or diuretic therapy) show a much greater response to inhibition of angiotensin II than do sodium-replete patients.^{12,13}

It has been suggested that glomerular filtration will fall only when 3 criteria are met: (1) renal perfusion is decreased; (2) the RAS is activated by sodium depletion; and (3) the action of angiotensin II within the kidney is blocked.^{14,15}

In Packer's study⁹ of 104 patients with severe heart failure treated with either enalapril or captopril, 70 patients showed an improvement in renal function and 34 a deterioration. This deterioration was associated with (1) a significantly lower right mean atrial pressure to begin with; (2) a significantly greater reduction in mean arterial blood pressure by ACE inhibition; (3) a significant number of patients being diabetic; and (4) patients taking significantly larger doses of diuretics.

Only 9 of the 34 patients experienced a marked increase in blood urea and creatinine, and these patients showed the greatest reduction in mean right atrial pressure, mean arterial blood pressure and left ventricular filling pressure. One patient died of progressive renal insufficiency despite discontinuation of therapy.

These findings confirmed those of Pierpont *et al.*¹⁶ in 1981. They treated 9 patients with severe congestive heart failure with captopril, and noted a reduction in creatinine clearance of 25% or more in 3 patients who showed the greatest reduction in blood pressure.

Packer and colleagues¹⁷ have subsequently identified pre-existing hyponatraemia (an indication of reduced renal perfusion) as the most important predictor of which patients with heart failure will develop renal functional insufficiency on the introduction of an ACE inhibitor.

The effects of long- and short-acting ACE

inhibitors on renal function in heart failure have also been addressed. One study¹⁸ compared captopril 50 mg 3 times daily with enalapril 40 mg daily. Renal function deteriorated in the enalapril-treated but not the captopril-treated group. A second study¹⁹ comparing lisinopril (an intermediate acting ACE inhibitor) with captopril in patients with severe heart failure found that increases in blood urea and creatinine were more common in the lisinopril-treated group. In both studies, these changes were mild, did not require withdrawal of the drug, and were ascribed to the longer duration of action of the drugs.

A recent symposium²⁰ on ACE inhibitors reviewed the safety of quinipril (an ACE inhibitor with a half-life slightly greater than that of captopril) in the treatment of hypertension and heart failure. It was noted that when quinipril was given twice daily increases in serum creatinine were as common as with enalapril therapy, whereas with a once daily regimen the incidence was much reduced and comparable to that which occurred with captopril treatment. It was proposed that longer-acting ACE inhibitors cause prolonged dilatation of the glomerular efferent arteriole and thus a persistent reduction in filtration, whereas shorter-acting ACE inhibitors allow an 'end of dose' efferent arteriolar constriction which maintains glomerular filtration.

All 4 of our patients were commenced on small doses of either enalapril or captopril following failure of diuretics to control their heart failure. In addition, all our patients exhibited signs of right heart failure (raised jugular venous pressure and peripheral oedema) as well as left, at the time of either the initial treatment with, or on increased dosage of, ACE inhibitor. None of the patients were hypovolaemic either clinically or as judged by central venous pressure readings when assessed with renal failure.

Similarly, none of our patients experienced anything other than the small expected fall in blood pressure associated with ACE inhibition. All patients had normal serum sodium levels and, although these patients may have been advised to reduce their salt intake at the onset of congestive heart failure, none of the patients had been specifically instructed to adopt a low sodium diet either prior to commencement of ACE inhibition or at any time thereafter. No patient was diabetic. Three patients had DTPA renograms performed and these showed no evidence of renovascular disease. The fourth had normal renal arteries at post-mortem. No patient had evidence of underlying renal disease as manifest by proteinuria and no patient had evidence of intercurrent illness preceding the development of renal impairment. There was no evidence of recent myocardial infarction in any of the 4 patients. The rapidity of the improvement in renal function following discontinuation of

either enalapril or captopril in cases 1, 3 and 4 would favour a haemodynamic disturbance as the cause.

All of our patients developed renal insufficiency on relatively small doses of either enalapril or captopril, and none of them would appear to have been predisposed to the development of renal failure as judged by the accepted criteria (see above reference). It remains likely that the predominant reason for the renal failure in these patients was a critical fall in renal perfusion despite seemingly

adequate systemic pressure, central venous expansion and lack of hyponatraemia. Whilst we fully agree with the accepted criteria for detecting susceptible patients, all patients on diuretics and converting enzyme inhibitors, with severe congestive heart failure, should be closely monitored and have ACE inhibitors withdrawn, or the dosage reduced, at the earliest signs of renal insufficiency, as a potentially fatal situation can be readily avoided.

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