Original articles

Evaluation of renal function in elderly heart failure patients on ACE inhibitors

O M P Jolobe

Summary

A total of 187 heart failure patients aged 65-92 years, with pretreatment serum creatinine levels below 200 µmol/l, were monitored for more than 12 months on angiotensin-converting enzyme (ACE) inhibitor therapy. Optimal ACE inhibitor dosage was found in 27% of patients, while a significant deterioration in renal function, characterised by >20% increase in serum creatinine to >200 µmol/l, occurred in 25 patients. This was most closely attributable to ACE inhibitor treatment *per se* (implying co-existence of bilateral renal artery stenosis) in only four cases, including one in whom renal deterioration was reproducible on inadvertent rechallenge. In the other 21, renal deterioration was attributable to diuretic-related blood volume depletion (two cases), nonsteroidal anti-inflammatory drugs (two cases), obstructive uropathy (two cases), preterminal renal shutdown (two cases), and the interaction between diuretic and ACE inhibitor dosage (including long-acting *vs* short-acting drugs) (13 cases). This study could serve as the basis for future comparisons of ACE-inhibitor-related renal deterioration when the entry requirement is optimal ACE inhibitor dosage.

Keywords: heart failure; elderly patients; angiotensin-converting enzyme inhibitors; renal deterioration

The advent of angiotensin-converting enzyme (ACE) inhibitors has been accompanied by an increasing recognition of the dilemma arising from the fact that the increase in heart failure prevalence which is associated with advancing age,¹ is paralleled by an age-related increase in the prevalence of renovascular disease (including bilateral renal artery stenosis).² In consequence, population subgroups such as the elderly, who are at highest risk of heart failure and renovascular disease, are also those most susceptible to drug-related renal failure, when the two disorders co-exist. Renal autoregulatory defences, such as angiotensin II-mediated renal efferent arteriolar vasoconstriction, ranged against the threat of heart failure-related glomerular hypoperfusion, are most readily breached when ACE blockade is utilised in the presence of bilateral renal artery stenosis (RAS).³ Even in the absence of bilateral RAS, the autoregulatory defence against heart-failure-related glomerular hypop-

erfusion is stretched to the limit by prolonged blockade of angiotensin II-mediated renal vasoconstriction.⁴ The threat of ACE-inhibitor-mediated breakdown of renovascular autoregulation is compounded by overdiuresis,⁵ and also by depletion of vasodilator prostaglandins (through the use of nonsteroidal anti-inflammatory drugs (NSAIDs)), since the compensatory increase in bradykinin levels, and hence prostaglandin E₂ synthesis, which accompanies ACE blockade,⁶ may well compensate for the attenuation of renovascular tone which results from the use of ACE inhibitors. Finally, even in the absence of iatrogenic disease, mechanisms such as obstructive uropathy may be operative in the older heart failure patient, irrespective of ACE inhibitor therapy.

The purpose of this study was to document the prevalence, and to outline the spectrum of renal deterioration in elderly heart failure patients receiving ACE inhibitor therapy with a pretreatment serum creatinine <200 µmol/l, the cut-off level acknowledged to signify relative contraindication to ACE inhibitor therapy.⁷ The criterion for renal deterioration was a >20% increase in creatinine to >200 µmol/l.

Patients and methods

Over a period of 13 years, I have prospectively enrolled into a databank, all heart failure patients under my care who were commencing, or had recently commenced ACE inhibitor therapy. These were predominantly in-patients with pretreatment serum creatinine levels <200 µmol/l, since the policy was to initiate this treatment on an in-patient basis, a serum creatinine level >200 µmol/l being a relative contraindication. Serum creatinine levels were monitored weekly during the in-patient phase and, subsequently, on every 3-6 monthly out-patient visit.

Results

A total of 483 patients were enrolled, but only 194 (125 women) of mean age 78 years (range 65-92) have been monitored for >12 months. Peak doses of ACE inhibitor treatment consisted of enalapril ≥20 mg daily in 40 cases, 10-15 mg daily in 49 cases, and ≤7.5 mg daily in 41 cases; lisinopril ≥20 mg daily in 11 cases, 10-15 mg daily in 21 cases, and ≤7.5 mg daily in eight cases. Two received peak doses of captopril 50 mg tid, the rest other ACE inhibitors.

Department of
Medicine for the
Elderly, Tameside
General Hospital,
Fountain Street,
Ashton-under-Lyne
OL6 9RW, Lancashire,
UK
O M P Jolobe

Accepted 30 November 1998

Thus, 53 out of 194 received the ACE inhibitor doses recognised as being of optimum efficacy.⁸

Most of the patients monitored for >12 months (187/194) had pretreatment serum creatinine levels of <200 µmol/l; 25 of these experienced significant increases in serum creatinine. Only five of the 25 were on optimal daily doses of ACE inhibitors, namely, enalapril ≥20 mg, in three, and lisinopril ≥20 mg in two. Twelve others were on 10–15 mg enalapril (seven cases) or lisinopril 10–15 mg (five cases), while the rest were on lower doses. Concomitant daily diuretic doses were frusemide 40 mg in five cases, 60 mg in one, 80 mg in 11, 120 mg in two, and 160 mg in three. Two patients were on bumetanide 5 mg daily (co-prescribed with metolazone 5 mg in one instance), and one was on bumetanide 8 mg daily.

Deterioration in renal function was unequivocally attributable to lisinopril in one patient who experienced a relapse in renal dysfunction after inadvertent rechallenge, serum creatinine having increased from 123 to 280 µmol/l after the first challenge using lisinopril 5 mg/day, and from 130 to 450 µmol/l after rechallenge with enalapril 5 mg/day. In three others, the fall in serum creatinine, from peak levels of 220, 277, and 266 µmol/l, respectively, to trough levels of 187, 180, and 171 µmol/l, respectively, after stopping ACE inhibitors, constituted circumstantial evidence of involvement of these agents in the aetiopathogenesis of renal deterioration. The evidence was strongest for the first of the three, in whom the fall in serum creatinine following ACE inhibitor withdrawal occurred without any concomitant change in diuretic dosage. In the second and third cases, proof of ACE inhibitor culpability was weakened by concomitant reduction in diuretic dosage, by 33% and 50%, respectively, after stopping ACE inhibitors. The aetiopathogenetic role of ACE inhibitors seemed even weaker in the remaining 21 cases, due to co-existence of other mechanisms for renal deterioration. These comprised blood volume depletion, correctable by intravenous fluids (one case), and a reversible uraemic reaction to metolazone, almost certainly due to blood volume depletion as well, although unequivocal proof of excessive urine output was unobtainable (one case). NSAIDs were implicated in two cases, and obstructive uropathy in two other cases. In 13 instances renal deterioration was reversed by therapeutic manoeuvres which included changing from long-acting to short-acting ACE inhibitors, reduction in ACE inhibitor dosage in patients with hypotension, and adjustments in diuretic dosage. Preterminal renal shutdown seemed to be the operative mechanism in two cases experiencing, respectively, 48% and 240% increases in serum creatinine relative to blood levels obtained, respectively, 10 days and 9 months previously, following several months of uneventful ACE inhibitor use. In both instances, peak serum creatinine levels were documented within 24 hours of demise.

The time scale of renal deterioration was as follows: in the four cases most closely attribut-

Learning points

- the prevalence of renal deterioration attributable to ACE inhibitors in heart failure patients aged 65–92 years with pretreatment serum creatinine levels of <200 µmol/l, is approximately 2%
- onset or detection of a significant increase in serum creatinine may be delayed by >12 months
- approximately 10% of instances of renal deterioration in ACE inhibitor-treated patients may be due to other mechanisms which undermine autoregulation of renal perfusion, such as diuretic-related blood volume depletion, NSAID-related depletion of vasodilator prostaglandins, and subtle derangements in renovascular haemodynamics amenable to adjustments in duration and dose of ACE inhibitor and/or diuretic medication
- co-existing obstructive uropathy also needs to be recognised as a potentially reversible non-iatrogenic mechanism of renal deterioration in ACE inhibitor-treated patients

able to ACE inhibitor therapy, the latent period before significant renal deterioration was 3, 11, 28, and 33 months. In the other 21, the latent period ranged from 2 to 114 months. The seven with pretreatment serum creatinine >200 µmol/l, were characterised by levels of 201, 207, 212, 216, 236, 246, and 277 µmol/l. In spite of 14–36 months of ACE inhibitor therapy, serum creatinine levels subsequently fell to 129 and 164 µmol/l, respectively, in two cases, whilst, in two other cases more modest falls resulted in serum creatinine levels which remained above 200 µmol/l. The reverse occurred in three other cases, with consequent increases in serum creatinine by 3%, 5%, and 35%, respectively. The most striking ACE inhibitor-related increase in creatinine in this type of patient, occurred in a 67-year-old diabetic with peripheral vascular disease who was monitored for <12 months. Over a 68-day period, her serum creatinine increased from a pretreatment level of 213 µmol/l, to a peak level of 460 µmol/l whilst taking captopril 25 mg tid and frusemide 40 mg daily. Nine days after stopping captopril (whilst continuing frusemide in unchanged dose), serum creatinine fell to 181 µmol/l.

Discussion

Among 187 elderly heart failure patients with pretreatment serum creatinine levels below 200 µmol/l, the prevalence of renal deterioration authentically attributable to ACE inhibitors was, at most, 2%. In the absence of angiographic or magnetic resonance validation of bilateral renal artery stenosis, this adverse response to therapeutic challenge, analogous to validation by captopril renography, appeared to be the closest approach to this diagnosis, when other causes of reversible renal failure had been ruled out. Apart from renovascular disease, other risk factors for renal deterioration in ACE-inhibitor-treated patients include volume depletion, NSAID co-prescription, and non-iatrogenic factors such as obstructive uropathy.

The reassuringly low prevalence of renal deterioration attributable to ACE inhibitors reported here might have been the outcome of the policy of qualified contraindication of these drugs in patients with serum creatinine >200 $\mu\text{mol/l}$. Fortuitously, patients with serum creatinine levels of the order of $210 \pm 56 \mu\text{mol/l}$ (mean and standard deviation) are significantly ($p < 0.001$) more likely to have renovascular

disease than counterparts with serum creatinine levels of the order of $136 \pm 40 \mu\text{mol/l}$.⁹

This study also highlighted the prevalence of suboptimal dosing in elderly heart failure patients. This could be a starting point for audit, while providing the opportunity to document the prevalence of renal deterioration in the context of optimal ACE inhibitor dosage.

- 1 McKee PA, Castelli WP, McNamara PM, *et al.* The natural history of congestive heart failure: the Framingham study. *N Engl J Med* 1971;**285**:1441–6.
- 2 Nicholls A. Renovascular disease: the fifth frontier. *J R Soc Med* 1997;**90**:315–8.
- 3 Hricik DE, Brownin PJ, Kopelman R, *et al.* Captopril-induced functional renal insufficiency in patients with bilateral renal artery stenoses or renal artery stenosis in a solitary kidney. *N Engl J Med* 1983;**308**:373–6.
- 4 Packer M, Lee WH, Yushak M, *et al.* Comparison of captopril and enalapril in patients with severe chronic heart failure. *N Engl J Med* 1986;**315**:847–53.
- 5 Packer M, Lee WH, Medina N, *et al.* Functional renal insufficiency during long-term therapy with captopril and enalapril in severe chronic heart failure. *Ann Intern Med* 1987;**106**:346–54.
- 6 Townend JN, Doran J, Lote CJ, *et al.* Peripheral haemodynamic effects of inhibition of prostaglandin synthesis in congestive heart failure and interaction with captopril. *Br Heart J* 1995;**73**:434–41.
- 7 Dargie HJ, McMurray JJV. Diagnosis and management of heart failure. *BMJ* 1994;**308**:321–8.
- 8 Gattis WA, Larsen RL, Hasselbad BA, *et al.* Is optimal angiotensin-converting enzyme inhibitor dosing neglected in elderly patients with heart failure? *Am Heart J* 1998;**136**:43–8.
- 9 McDowall P, Kalra PA, O'Donoghue DJO, *et al.* Risk of morbidity from renovascular disease in elderly patients with congestive cardiac failure. *Lancet* 1998;**352**:13–6.