PAPERS AND SHORT REPORTS

Severe hypotension after first dose of enalapril in heart failure

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Abstract

The new, long acting converting enzyme inhibitor enalapril was given to 26 patients with moderate to severe heart failure. In 23 cases the mean systolic blood pressure fell from 120 (SD 22) to 108 (25) mm Hg without adverse effects. Profound hypotension with severe bradycardia and sweating, however, occurred in three patients, most pronounced two to four hours after the first dose. The haemodynamic and biochemical changes in these patients were similar to those seen in patients with severe symptomatic hypotension after the first dose of the converting enzyme inhibitor captopril, except that with enalapril the changes occurred later and were longer lasting. Evidence of myocardial damage and reversible renal failure was seen in one patient, and acute reversible deterioration in renal function occurred in one other.

In patients with heart failure converting enzyme inhibitors should be administered initially under strict medical supervision with appropriate facilities available for dealing with occasional profound hypotension.

Introduction

Enalapril is the second orally active converting enzyme inhibitor to become available for use in hypertension^{1,2} and heart failure.^{3,4} Occasional severe hypotension has been described after the first dose of captopril in patients with heart failure^{5,7} and hypertension.⁸ Syncope with captopril administration coincides with a rapid fall in angiotensin II concentration, which occurs usually within 30 to 45

minutes after oral dosage.⁵ Unlike captopril, enalapril requires conversion by the liver to the active metabolite enalaprilat,^{9,10} thus delaying the onset of action. We report the effects of enalapril in a consecutive series of 26 patients with cardiac failure, with particular reference to the time of onset of the hypotensive effect and its magnitude.

Patients and methods

We studied 26 patients (mean age 59 (SD 4) years) with moderate to severe heart failure (New York Heart Association grades II-IV; median III) of more than six months' duration and for which treatment with diuretics and digoxin had remained unchanged for at least one month. All patients received frusemide in a mean dose of 123 (SD 60) mg/day and, in addition, four were taking bendroflumazide 5-10 mg/day and seven amiloride 5-10 mg/day. All were also receiving digoxin (0.22 (SD 0.05) mg/day). All patients had a dilated, poorly functioning left ventricle on echocardiography. The aetiology of heart failure was ischaemic heart disease in 14, idiopathic dilated cardiomyopathy in 10, and severe residual impairment of left ventricular function after valve replacement in two. No patient was noticeably hypertensive before treatment and all had systolic pressures above 90 mm Hg.

Before being given enalapril the serum urea, creatinine, and electrolyte and plasma active renin (normal range 10-50 mU/l¹¹) and angiotensin II (normal range 5-35 pmol/l; 53-368 pg/100 ml¹²) concentrations were measured. Plasma catecholamine¹³ and vasopressin¹⁴ values were also assayed in one patient. Diuretics were administered with the enalapril in the first 20 patients but withheld for 24 hours in a further five, including cases 1 and 2. Blood pressure was recorded routinely before and for four hours after the first dose of enalapril. Further readings were taken if the patient noted any symptoms. Mean blood pressure was calculated as (systolic - diastolic)/3 (+ diastolic). Patients were kept in bed for a minimum of four hours after the first dose of enalapril. Angiotensin II (Hypertensin; Ciba) was given by intravenous infusion when required.

Statistics—Correlations were performed using the least squares technique for normally distributed data and Spearman's rank correlations for non-parametric data. The response to treatment was tested by Student's *t* test with prior log transformation of the data where indicated. A *p* value of <0.05 was considered significant.

Results

Before enalapril plasma sodium and plasma active renin concentrations were closely and inversely correlated ($r = -0.75$; $p < 0.001$). The change in blood pressure with the first dose of enalapril was modestly correlated with

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the pretreatment plasma active renin ($r = -0.42$; $p < 0.05$) and angiotensin II ($r = -0.59$; $p < 0.01$) concentrations (fig 1) but the correlation with serum sodium was not significant ($r = 0.34$; NS).

In the first 20 patients enalapril caused no adverse effects. Subsequently after the first dose three of six patients developed profound hypotension, bradycardia (fig 2), and sweating. The falls in heart rate and mean blood pressure were significantly correlated ($r = 0.66$; $p < 0.002$). Table I shows the treatment and baseline recordings of the three patients who developed severe hypotension (cases 1-3) compared with the mean (and median where appropriate) values of the 23 patients who did not.

CASE HISTORIES OF PATIENTS WITH SYNCOPE

Case 1—A 64 year old man with a history of two myocardial infarctions was admitted with orthopnoea. His jugular venous pressure was raised and he had an enlarged liver and peripheral oedema. Diuretics were withheld for 24 hours and 10 mg enalapril administered. Four hours later he abruptly developed syncope (table I). Head down tilt and infusion of angiotensin II (6 ng/kg/min) restored his blood pressure to 92/64 mm Hg but bradycardia persisted. Attempts to withdraw angiotensin resulted in further syncopal episodes until 24 hours afterwards, when it was stopped, the blood pressure remaining at 90/66 mm Hg and the heart rate at 62 beats/min. Four hours after the onset of syncope a 12 lead electrocardiogram showed new anterior T wave inversion. The myocardial specific creatinine kinase MB fraction was mildly raised 18 hours later (239 IU, 8% of total creatine kinase; normal range <160 IU, $<6\%$). In the 24 hours after stopping the infusion of angiotensin II he passed 2.7 l of urine (sodium 72 mmol/mEq/l, creatinine 2.4 mmol/l (27.1 mg/100 ml)). Serum sodium fell to a nadir of 124 mmol/mEq/l and creatinine rose to 297 μ mol/l (1.4 mg/100 ml; see table I for initial values). Forty eight hours later the patient received 2.5 mg enalapril without ill effect, his systolic pressure remaining above 80 mm Hg. In the following months he had a good symptomatic response to the drug with a reduction in diuretic requirements and improved exercise performance.

Case 2—A 61 year old man with a history of three myocardial infarctions was admitted with orthopnoea and dyspnoea. The jugular venous pressure was raised.

FIG 1—Relation between log plasma angiotensin II value and fall in mean blood pressure (Spearman's rank correlation: $r = -0.59$; $p < 0.01$).

Conversion: SI to traditional units—Angiotensin II: 1 pmol/l ≈ 10.5 pg/100 ml.

TABLE II—Plasma hormone concentrations in case 2 before and after enalapril

	Active renin (mU/l)	Angiotensin II (pmol/l)	Noradrenaline (nmol/l)	Adrenaline (nmol/l)	Vasopressin (ng/l)
Basal	191	64	4.1	0.1	0.3
2.5 hours	2096	16	3.8	0.4	1.6

Conversion: SI to traditional units—Angiotensin II: 1 pmol/l ≈ 10.5 pg/100 ml. Noradrenaline: 1 nmol/l ≈ 169 pg/ml. Adrenaline: 1 nmol/l ≈ 183 pg/ml.

FIG 2—Relation between fall in mean blood pressure and fall in heart rate (Spearman's rank correlation: $r = -0.66$; $p < 0.002$).

Diuretics were withheld for 24 hours and he was given 5 mg enalapril. Two and a half hours later, however, he felt faint; blood pressure fell from 94/74 to 56/30 mm Hg and heart rate from 82 to 52 beats/min over 15 minutes. Blood samples showed that the previously high plasma angiotensin II concentration had fallen into the normal range, while the plasma active renin concentration showed a brisk rise (table II). Plasma noradrenaline concentration failed to rise in response to the fall in blood pressure but adrenaline and antidiuretic hormone increased. Head down tilt increased his pressure to 78/42 mm Hg; heart rate remained at 56 beats/min. After 1.2 mg atropine given 15 minutes later his blood pressure increased to 90/64 mm Hg and heart rate to 70/min. After a further 24 hours of bed rest he was given 2.5 mg enalapril without ill effect. Subsequently he had a good symptomatic response with an increase in exercise performance.

Case 3—A 66 year old man with a dilated cardiomyopathy was admitted with increasing dyspnoea. Jugular venous pressure was raised. Diuretics were not withheld. Two and a half hours after a 5 mg dose of enalapril he became abruptly hypotensive with bradycardia (fig 3). Plasma angiotensin II concentration had fallen from 58 to 18 pmol/l (609 to 189 pg/100 ml). After 1.2 mg atropine given 10 minutes later his blood pressure increased from 38/20 to 58/40 mm Hg and pulse rate from 38 to 50 beats/min. An angiotensin II infusion (6 ng/kg/min) partially restored his blood pressure to 90/74 mm Hg, although bradycardia persisted at 54 beats/min. Attempts to stop the angiotensin II infusion resulted in further episodes of syncope. Diuretics were withheld for the next four days. Angiotensin II concentration measured 24 hours after the initial syncopal episode and during an infusion of 2 ng/kg/h was 189 pmol/l (1985 pg/100 ml), though his

TABLE I—Comparison of patients with and without hypotension on first administration of enalapril

	Case 1	Case 2	Case 3	Group mean (SD) [range]	p Value*
Age (years)	64	61	66	58 (4) [48-65]	
New York Heart Association functional class	IV	III	III	III [II-IV]	
Systolic blood pressure (mm Hg):					
Basal	106	120	128	120 (22) [92-166]	
Nadir	40	56	38	108 (25) [72-154]	$p < 0.001$
Mean blood pressure (mm Hg):					
Basal	78	93	97	89 (12) [72-121]	
Nadir	27	39	26	79 (15) [60-109]	$p < 0.001$
Heart rate (beats/min):					
Basal	78	86	82	81 (11) [64-102]	
Nadir	44	52	34	77 (10) [58-94]	$p < 0.05$
Basal plasma active renin concentration (mU/l)	695	191	202	132 [3-828]; median = 61	
Plasma angiotensin II (pmol/l):					
Basal	196	64	58	57 [0.5-229]; median = 30	
Four hours	ND	16	18	26 [0.5-72]; median = 23	$p < 0.01$
Serum sodium (mmol/l)	136	139	132	138 (4) [129-143]	
Serum urea (mmol/l)	8.5	8.0	15.6	6.7 (2.4) [3.8-12.6]	
Serum creatinine (μ mol/l)	134	119	228	102 (25) [68-162]	
Dose of enalapril (mg)	10	5	5	5	
Dose of frusemide (mg/day)	160	120	200	118 (61) [60-240]	
Dose of bendroflumazide (mg/day)	5	—	10	See text	

ND = Not done.

* Significance of response to enalapril.

Conversion: SI to traditional units—Angiotensin II: 1 pmol/l ≈ 10.5 pg/100 ml. Sodium: 1 mmol/l = 1 mEq/l. Urea: 1 mmol/l ≈ 6 mg/100 ml. Creatinine: 1 μ mol/l ≈ 11.3 μ g/100 ml.

blood pressure and heart rate were incompletely restored (108/68 mm Hg; 64 beats/min). Forty eight hours after the initial syncope 1 litre physiological saline was infused over two hours and angiotensin discontinued without further syncope. Over 48 hours of oliguria his serum sodium concentration fell to 120 mmol(mEq)/l and serum creatinine value rose to 430 μ mol/l (4.9 mg/100 ml). A diuresis ensued after stopping angiotensin II (24 hour urine volume 3.7 l; sodium concentration 105 mmol(mEq)/l, creatinine 1.8 mmol/l (20.4 mg/100 ml)). Three days later 2.5 mg enalapril was administered without untoward effect. Subsequently he had a fair clinical response in terms of symptoms and exercise performance.

FIG 3—Case 3. Changes in systolic (●) and diastolic (○) blood pressure and heart rate (Δ) after 5 mg enalapril by mouth.

Discussion

We have observed severe hypotension after the first dose of enalapril in three patients with heart failure. Severe hypotension associated with bradycardia and sweating is characteristic of vasomotor syncope and does not appear to be simply the extreme of the continuous distribution of drug induced falls in blood pressure. Similar findings have been described with captopril,^{6,7} even in small doses,⁵ when large reductions in left ventricular filling pressure were noted resulting in a fall in cardiac output. With both captopril and enalapril there appears to be a dilatation of venous capacitance vessels, leading to a diminution of venous return to the heart. There is also an absence of appropriate compensatory vasoconstriction in response to hypotension, and particularly of increased sympathetic activity,⁵ as suggested by the lack of tachycardia and failure of the plasma noradrenaline concentration to increase. Adrenal and pituitary responses seem preserved, however, as evidenced by the rise in plasma adrenaline and vasopressin values. The severe hypotension coincides with a fall in angiotensin II concentration,⁵ and failure of the sympathetic response might be explained by the loss of the putative presynaptic facilitatory effect of angiotensin II on sympathetic nerve terminals,^{15,17} though it may also be a common feature of vasomotor syncope. Zusman *et al* have described a similar phenomenon with a renin inhibitor, which lowers angiotensin II in a more specific fashion.¹⁸

The significant, apparently linear relation between the fall in heart rate and fall in mean blood pressure was striking (fig 2). It is unlikely that the fall in heart rate observed in our patients can be explained entirely by a fall in sympathetic tone. An increase in parasympathetic nerve activity, as when normal people faint, seems very likely in these patients. Angiotensin II has been shown to have vagolytic effects both in experimental preparations and in man,^{20,21} and simultaneous sympathetic activation and vagal inhibition have been noted in dogs,^{22,23} though not in normal man.²⁴ Withdrawal of angiotensin II might therefore lead to both decreased sympathetic nerve activity and enhanced vagal tone. Support for an increase in vagal activity comes from the heart rate response to intravenous atropine observed in cases 2 and 3. Digoxin may also have enhanced parasympathetic tone by central or peripheral mechanisms.^{25,26} Infusion of angiotensin II to greater than basal values did not restore blood pressure completely. This may indicate continuing depletion of vascular wall angiotensin II. Other possibilities include incomplete reversal of autonomic effects, as suggested by the continuing bradycardia. It is interesting to speculate that angiotensin II may be responsible for the parasympathetic dysfunction seen in heart failure.²⁷

First dose hypotension has also been noted with prazosin, a

vasodilator with effects on both capacitance vessels and the arterial circulation. Hypotension induced by prazosin differs in several respects from that seen in our patients: firstly, it rarely if ever occurs in patients with heart failure²⁸; secondly, it occurs in the upright position²⁹; thirdly, the plasma renin^{29,30} and angiotensin II³⁰ concentrations increase; and, fourthly, the plasma noradrenaline concentration rises during syncope,²⁹ although the rise is less than in those who do not faint on standing after prazosin administration.

Even with detailed knowledge of past treatment and serum electrolyte and plasma renin or angiotensin II concentrations it may be difficult to predict first dose syncope after converting enzyme inhibition.⁸ Though all three patients in our study had raised renin values, we have described the same phenomenon with captopril in a patient with plasma renin and angiotensin II concentrations in the normal range.⁵ Moreover, several patients without syncope had more depressed serum sodium concentrations and higher plasma active renin concentrations than those who fainted. Interestingly, syncope has also been described in a subject with normal plasma renin values given a renin inhibitor.¹⁸ Invasive measurements of cardiac output, pulmonary wedge pressure, and systemic vascular resistance are also of little use in predicting this event.⁵ In two out of three patients who developed syncope and in three out of 23 who did not diuretics were withheld for 24 hours before giving enalapril. Short term withdrawal of diuretics does not therefore prevent severe hypotension; longer term withdrawal of diuretics may not be practicable for many patients with heart failure.

In this study with enalapril hypotension did not occur until at least 150 minutes after dosing, in contrast with the much earlier occurrence (within one hour) in patients given captopril.^{5,31} The time to syncope is similar to that of the expected maximal hypotensive effect observed in other studies.^{32,33} The delay in enalapril's effect is consistent with its requirement for metabolism to an active compound. Nevertheless, when it occurs the onset of syncope seems equally abrupt with captopril, enalapril, and apparently renin inhibitors alike.

Severe symptomatic hypotension may occur after beginning converting enzyme treatment. Enalapril does not, then, seem to confer any advantage in this respect over captopril, though until more patients have received these drugs the exact incidence of syncope with either agent remains to be established. When patients with severe heart failure are given converting enzyme inhibitors they should be observed carefully for at least four hours after the initial dose, with full facilities for resuscitation available. Furthermore, although reduction of dosage may not eliminate syncope, it seems wise to use a much lower initial dose than currently recommended—perhaps 2.5 mg rather than 10 mg—in an attempt to reduce the period of ensuing hypotension.

JGFC is supported by a Medical Research Council training fellowship and SGB by a grant from the British Heart Foundation. We are grateful to Merck Sharp and Dohme Ltd for supplies of enalapril and Ciba Ltd (Horsham) for supplies of angiotensin II.

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(Accepted 19 July 1985)

Fibrinogen: a possible link between social class and coronary heart disease

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Abstract

Mortality from coronary heart disease in civil servants in the lowest grade of employment has been found to be about three times that of men in the highest grade of employment. As part of an investigation of this finding several haemostatic variables were measured in a sample of 29 men in lower grades of employment and 45 men in higher grades. There was a significant difference in plasma fibrinogen concentrations between men in lower grades of employment and those in higher grades (mean 3.39 g/l v 2.95 g/l, respectively; $p < 0.01$) but not in other haemostatic variables. Multiple regression analyses showed significant independent associations of fibrinogen concentration with smoking ($p < 0.05$) and grade of employment ($p < 0.05$). The size of the observed difference between the grades of employment was similar to that between those dying of coronary heart disease or surviving during longitudinal study; it may therefore be an important part

of the mechanism underlying social class differences in coronary heart disease.

The statistical relation between fibrinogen concentrations and other characteristics that may be concerned in the aetiology of coronary heart disease was examined. A summary measure of job stress was significantly related to fibrinogen concentration ($p < 0.01$) and made a substantial contribution to explaining the differences between grades of employment. Behaviour type and a score of physical activity were not significantly related to fibrinogen concentration.

Introduction

In England and Wales mortality from coronary heart disease in 1971 was 26% higher in social class V than social class I.¹ The Whitehall study of London civil servants showed larger differences in mortality from coronary heart disease between different grades of employment: the relative risk was more than three times greater in the lowest grade of employment (predominantly messengers) compared with the highest grade of employment (administrators).² Much of this difference remained unexplained after the effect of other measured risk factors (plasma total cholesterol concentration, smoking, blood pressure, glucose tolerance, and obesity) had been taken into account.³

The new Whitehall (Department of Environment) study was set up in 1978 to seek other explanations for the difference in mortality from coronary heart disease between the different grades of employment, including possible differences in haemostatic variables.

Clinical studies have implicated poor fibrinolytic activity⁴ and higher plasma fibrinogen concentration⁵ in the onset of thromboembolic disease, but epidemiological studies of the role of haemostatic variables are few. The Northwick Park heart study showed an association between high concentrations of plasma fibrinogen and clotting factors VII and VIII and subsequent risk of death.

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