Further evidence that chronic perindopril treatment maintains neurohormonal suppression but does not lower blood pressure in chronic cardiac failure

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Aims Previous studies in heart failure (CHF) after temporary diuretic withdrawal have suggested that perindopril is associated with no first dose hypotension in comparison with other ACE inhibitors (ACEI) or placebo. The aim of this study was to explore further the profile of perindopril during chronic dosing.

Methods We report the effects of acute and chronic (8 weeks) treatment with the ACE inhibitor perindopril (Per, 2→4 mg daily) or placebo (P) in a double-blind parallel group study of 24 diuretic treated patients (17M; 67 ± 8 years, 80 ± 17 kg) with ischaemic cardiomyopathy (fractional shortening, 19 ± 5%; radionuclide ejection fraction, 31 ± 3%). Baseline biochemical, hormonal (ACE, Ang I, Ang II), isotopic renal function (GFR, ERPF, ECFV), pretreatment diuretic dose and heart failure scores were similar between groups. Concomitant cardiac treatments remained unchanged and diuretic withdrawal was not used to introduce treatment.

Results There were no significant effects on electrolytes, liver function tests, serum or erythrocyte magnesium. There was no significant first dose fall in SBP over 6 h) (P, baseline 137 ± 18; min 115 ± 16 mmHg; Per, baseline 137 ± 15; min 118 ± 17 mmHg). Neither supine nor erect BP was significantly affected by chronic treatment (P, erect baseline 134 ± 23/76 ± 10 to 124 ± 41/74 ± 10 mmHg; Per, baseline 135 ± 21/76 ± 14 to 128 ± 22/70 ± 12 mmHg, P = NS). Active treatment was associated with significant ACE inhibition (P, baseline 47 ± 17 to 43 ± 17; Per baseline 49 ± 15 to 14 ± 7); aldosterone (P, baseline 337 ± 179 to 375 ± 306; Per, baseline 335 ± 357 to 293 ± 155 pg ml^{-1}) and Ang II suppression (P, baseline 9 ± 9 to 20 ± 39; Per baseline 10 ± 9 to 3 ± 3 pM). Isotopic renal function was unaffected by either treatment.

Conclusions At this dose (2–4 mg orally) chronic perindopril therapy has no significant effect on blood pressure or renal function. Sustained neurohormonal suppression of ACE and AII occurred without evidence of AII reactivation. A lack of effect on BP at these doses may make perindopril suitable for study in unstable patients with acute HF or useful in those patients where there are concerns over ACEI induced hypotension.

Keywords: chronic cardiac failure, ACE inhibition, perindopril, neurohormones, isotopic renal function studies, electrolyte handling, blood pressure response, differential profile of effect

Introduction

Angiotensin converting enzyme (ACE) inhibition is an increasingly important therapy in cardiovascular medicine. In addition to diuretic therapy these drugs now dominate the management of symptomatic chronic cardiac failure of whatever origin and are becoming increasingly used in asymptomatic left ventricular dysfunction. Their role has recently been extended into the management of myocardial infarction complicated by symptomatic or asymptomatic left ventricular dysfunction [1–4]. There is now a wide range of agents available within this drug class [5]. Although each ACE inhibitor has differing properties, most have similar pharmacodynamics, efficacy and side effect profiles. However, the magnitude and duration of first dose blood pressure response may differ between ACE inhibitors. Regardless of the relatively low incidence of *symptomatic* first dose hypotension (1–10% by variable trial evidence; [2, 3]), it remains a concern for general practitioners when they prescribe ACE inhibitors to this patient group [6] and may explain why ACE inhibitors are underutilised in heart failure [7–10]. It is clear that combination treatment with diuretics and ACE inhibition is important in this regard and hypoperfusion can be damaging in some circumstances. Regardless of this the key concern is whether or not an individual clinician takes a decision to avoid ACE inhibitor therapy because of a rational or irrational concern over the consequences of treatment.

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What little data are available in general practice suggests that this is unfortunately common [6, 10].

Perindopril is an effective non thiol, ester prodrug ACE inhibitor with a prolonged duration of effect dependent on the generation of an active diacid metabolite [11]. It increases exercise capacity in heart failure patients at doses substantially less than those used to achieve blood pressure lowering in patients with hypertension [12, 13]. One property of perindopril is the absence of a first dose fall in systemic blood pressure in diuretic treated heart failure patients given a standard initial dose of 2 mg perindopril after temporary diuretic withdrawal [14, 15]. The reason for this lack of first dose hypotension is unclear. It could be due to perindopril having balanced regional haemodynamic effects, an interaction between the parent ester prodrug, perindopril and the active diacid metabolite ACE inhibitor perindoprilat [16] or it may simply be a dose dependent effect not evident on chronic dosing.

In this study we have further explored the profile of perindopril during chronic dosing in heart failure patients. Firstly, we examined the first dose effects of perindopril. Secondly, we investigated whether hypotension was avoided during chronic therapy with perindopril. Thirdly we examined the renal effects of perindopril to assess whether blood pressure changes influenced renal function, since renal dysfunction is the other main concern when ACE inhibitors are combined with chronic diuretic therapy.

Methods

Patients

Twenty-four patients (17 male; 23 Caucasian) were recruited from our outpatient clinic. These subjects were aged 67 ± 8 years; height 1.67 ± 0.9 m; weight 80 ± 17 kg with an average duration of cardiac failure of 1.8 ± 1.9 years (range 0.2–6 years). The origin of cardiac failure in all instances was underlying previous myocardial infarction; seven patients had concomitant hypertension (29%) and one patient had concomitant valvular heart disease. Most patients were on loop diuretics which were held constant throughout the study (Table 1). Concomitant drug therapy was as described in Table 2 and remained constant for each individual for the duration of study. Patients on another ACE inhibitor (42%) had this agent withdrawn for a minimum of 2 weeks prior to inclusion in the study. Treatment allocation was not allocated on the basis of prior ACE inhibitor usage. All patients gave their written and informed consent to investigation prior to inclusion in the study. The protocol and procedures of the study were reviewed and passed by the local research and ethics committee prior to investigation.

Procedure

Following a screening visit during which demographic characteristics, biochemistry, haematology and ECG in addition to clinical history and physical examination were documented, patients were assigned to randomized double-blind treatment in a parallel group design. Left ventricular dysfunction was documented and confirmed by transthoracic echocardiography (16 patients; calculated fractional shortening $19 \pm 5\%$; left ventricular end diastolic diameter (6.4 ± 0.7 cm) or by multiple uptake gated acquisition radionuclide scan (15 patients; $31 \pm 3\%$). Prestudy symptomatic assessment assigned 12 patients to NYHA Grade II symptoms and 12 patients to NYHA Grade III. Prestudy

Table 1 Diuretic therapy in patients completing the study (total daily dose, mg).

	Patient	*Bendrofluazide*	*Bumetanide*	*Frusemide*	*Triamterene*
Placebo	1	0	4	0	0
$n=11$	5	0	0	40	0
	7	0	0	40	50
	10	0	0.5	0	0
	11	0	0	20	0
	15	5	0	0	0
	16	0	0	40	0
	17	0	0	40	50
	19	2.5	0	0	0
	23	0	0	40	50
	24	0	0	160	0
Perindopril	3	0	0	40	50
$n=12$	4	0	2	0	0
	6	0	0	80	100
	8	0	0	80	100
	9	0	0	40	50
	12	0	1.5	0	0
	13	0	0	20	0
	14	0	0	20	0
	18	0	0	120	100
	20	0	0	120	100
	21	0	0	0	0
	22	0	0	40	0

Patient 002 from the placebo group is omitted from this table as related data were not taken into account in comparisons of renal function parameters.

Table 2 Numbers of patients with concomitant treatment.

Treatment	*Placebo*	*Perindopril*
Atenolol	2	4
Digoxin	1	2
Calcium channel Blocker	3	4
Nitrate	11	12
Antiplatelet	9	7
Warfarin	—	1
Inhaled bronchodilators	3	2
Oral antidiabetic drugs	3	4

clinical examination included a documented heart failure score [17] which was elevated (mean 4.7 ± 2.1).

In addition to clinical examination, symptomatic assessment and graded heart failure scoring patients had supine blood pressure and heart rate determined (Critikon Vital Signs Monitor, Tampa Bay, Florida) after the insertion of a heparinised venous cannula and 30 min supine rest. Following triplicate blood pressure and heart rate determinations, blood samples were taken for the determination of angiotensin converting enzyme [18], aldosterone [19], angiotensin peptides I and II [19], atrial natriuretic factor [19], serum chemistry and haematology and measurement of serum and erythrocyte magnesium.

Patients were randomized to receive in addition to their concomitant therapy either perindopril 2 mg progressing to 4 mg daily from the second dose or matched placebo for the duration of study (8 weeks). Following first dose administration patients remained under observation for a period of 6–8 h. Clinical review was conducted at 4 weeks and 8 weeks during chronic dosing. In addition at baseline and following approximately 7 weeks treatment subjects had renal function studies using isotope scintigraphic techniques to determine both glomerular filtration rate (GFR), effective renal plasma flow (ERPF) and extracellular fluid volume (ECFV) [20].

Statistical analysis

Data are illustrated as mean ± 1 s.d. Parameters were compared using repeated measures analysis of variance for a treatment effect although a time effect was not specifically included in the analysis. Bonferoni correction was applied throughout.

Results

General safety and tolerability, baseline comparisons

Patients were well matched in terms of demographic variables, pretreatment diuretic dose, heart failure classification and prestudy renal function and neurohormones (Tables 1, 2 and 3). There were no significant adverse effects and no treatment withdrawals.

Biochemical effects of treatment (Table 3)

There was no significant effect of active treatment on sodium, chloride, bicarbonate, protein, calcium, urea, creatinine, uric acid nor liver function tests (Table 3). There was a small, statistically significant rise in serum potassium associated with perindopril treatment. Neither serum nor erythrocyte magnesium was affected by active treatment. There was sustained suppression of ACE activity in serum in those patients receiving perindopril compared to placebo.

Neurohormones

There was a statistically significant difference in the baseline levels of supine plasma aldosterone; (placebo, 337.3 ± 179 pg ml^{-1}, perindopril 635.8 ± 357 pg ml^{-1}, $P = 0.021$). During the treatment phase plasma aldosterone was unaffected by placebo (375 ± 306 pg ml^{-1}) in contrast to the perindopril treated group where there was suppression from the elevated baseline (293.7 ± 155 pg ml^{-1}, $P = 0.002$). Baseline levels of angiotensin I (placebo, 33.7 ± 13 pM; perindopril 45.4 ± 18 pM) and plasma angiotensin II (placebo,

Table 3 Biochemical effects of treatment.

	Placebo		*Perindopril*	
Parameter	*Baseline*	*8 weeks*	*Baseline*	*8 weeks*
Sodium (mM)	138 ± 3	139 ± 3	138 ± 3	138 ± 3
Potassium (mM)	4.1 ± 0.2	4.1 ± 0.4	3.8 ± 0.4	4.2 ± 0.4*
Urea (mM)	7.9 ± 2	7.7 ± 2	7.4 ± 2	7.8 ± 2
Creatinine (μM)	99 ± 22	103 ± 16	106 ± 10	107 ± 10
Chloride (mM)	104 ± 3	104 ± 3	104 ± 4	104 ± 3
Bicarbonate (mM)	28 ± 2	28 ± 2	28 ± 3	28 ± 3
Calcium (mM)	2.27 ± 0.1	2.23 ± 0.1	2.28 ± 0.1	2.26 ± 0.18
Uric acid (μM)	427 ± 58	441 ± 83	453 ± 78	447 ± 83
Total protein (gl^{-1})	67 ± 6	66 ± 3	65 ± 7	67 ± 4
SG0PT (ul^{-1})	22.2 ± 10	47 ± 84	20 ± 10	18 ± 9
ACE activity (eul^{-1})	46.9 ± 17	43.3 ± 14	48.6 ± 15	14.3 ± 7*
Magnesium (mM)	0.86 ± 0.14	0.85 ± 0.13	0.82 ± 0.14	0.84 ± 0.16
Erythrocyte magnesium (M/10^6 cells)	0.033 ± 0.008	0.027 ± 0.005	0.038 ± 0.007	0.029 ± 0.009

*Treatment effect $P < 0.001$.

9.2 ± 9.9; perindopril, 10.2 ± 9 pM) were not significantly different. Two months of treatment with placebo had no significant effect on a plasma angiotensin I (58.7 ± 67 pM) but active treatment with perindopril caused substantial elevation of angiotensin I approximately 3 fold (171 ± 156 pM, $P = 0.009$ c.f. baseline and placebo). Angiotensin II was unaffected by placebo therapy (20.7 ± 39 pM) whereas chronic treatment with perindopril showed effective suppression of angiotensin II without evidence of neurohormonal reactivation (3.6 ± 2.7 pM). Atrial natriuretic factor was similar in both groups prior to the study (placebo, 17.7 ± 7.3 pM; perindopril 15.4 ± 5.5 pM). Chronic treatment with placebo or perindopril had no impact on this hormone (placebo, 17.5 ± 4.7 pM; perindopril, 14.1 ± 5.2 pM, $P = 0.51$).

Blood pressure responses

After their screening visit and treatment allocation all patients underwent monitoring of their blood pressure following first dose administration with a continuous observation period of 6 h in the supine position. Patients took their normal diuretic dose on the day of attendance. Baseline systolic blood pressure was very similar in both treatment groups (placebo, 137.5 ± 18 mmHg; perindopril 137.5 ± 15-mmHg). There was a similar diurnal fall in blood pressure in both treatment groups which showed no significant difference between placebo (minimum value 115.3 ± 16 mmHg) or perindopril (117.8 ± 17 mmHg). In no patients were there any symptoms during the test dose phase of the protocol and all patients went on to chronic dosing uneventfully. Blood pressures and heart rate were taken at regular intervals in triplicate during the study after 30 min supine rest. Erect blood pressure was taken at 1, 3 and 5 min thereafter. Only baseline and 8 week pressures are presented in Table 4. During chronic therapy with placebo or perindopril there was no significant difference in the blood pressure profile between the two treatment arms for either supine or erect blood pressure or heart rate (Table 4). No patient in either treatment group reported postural symptoms at any time.

Clinical and physical examination

There was a reduction in total heart failure score with perindopril treatment (4.9 ± 5.3 baseline *vs* 3.4 ± 1.9 at conclusion) compared with placebo (3.7 ± 2.3 at baseline *vs* 3.6 ± 2.3 at conclusion). NYHA classification was not significantly altered but all patients in the placebo group remained in the same NYHA class (7 Class II, 5 Class 3) whereas in the perindopril treated group three patients shifted from Class III to Class II (five Class II, seven Class III at baseline assessment became, eight Class II, four Class III at conclusion of treatment phase; $P = 0.106$).

Renal function studies

There were no changes in electrolytes associated with active treatment with the exception of the small rise in potassium (Table 3). The results of isotopic renal function studies conducted at baseline and at the end of the treatment phase are illustrated in Table 5. Overall there were no significant effects on calculated glomerular filtration rate, effective renal plasma flow or extracellular fluid volume.

Discussion

In the current study we have examined perindopril, a long acting ACE inhibitor used in the management of hypertension and cardiac failure. The dose of perindopril advised for heart failure management is effectively half that employed in its role as an antihypertensive drug [13]. Perindopril improves exercise tolerance in heart failure patients at this lower dose [12]. Mortality data in stable chronic heart failure have not been published for this drug. As yet there are no data to suggest that effects on exercise tolerance will occur

Table 4 Blood pressure and heart rate responses to acute and chronic treatment with perindopril or placebo.

	Placebo		*Perindopril*		P *value* (*Placebo* vs *Perindopril*)
a) *First dose effect*	*Baseline*	*Minimum*	*Baseline*	*Minimum*	
Supine SBP (mmHg)	137	115	137	118	0.63
(95% C.I.)	(102,172)	(83,146)	(108,166)	(85,151)	
b) *Chronic dosing*	*Baseline*	*8 weeks*	*Baseline*	*8 weeks*	
Supine SBP (mmHg)	145	129	140	130	0.38
	(102,188)	(94,164)	(105,175)	(103,157)	
Supine DBP (mmHg)	70	71	75	67	0.21
	(33,107)	(38,104)	(46,104)	(47,87)	
Supine HR (beats min^{-1})	71	72	73	69	0.21
	(42,100)	(45,99)	(37,108)	(34,104)	
Erect SBP (mmHg)	134	124	135	128	0.78
	(89,179)	(80,169)	(94,176)	(85,171)	
Erect DBP (mmHg)	76	74	76	70	0.32
	(57,95)	(55,94)	(49,103)	(47,94)	
Erect HR (beats min^{-1})	77	76	74	76	0.66
	(54,100)	(31,121)	(35,123)	(45,107)	

Table 5 Renal responses to treatment with placebo or perindopril in chronic cardiac failure.

			Baseline		*8 weeks*		*Treatment effect*		*Group effect*
Parameter	*Treatment*	n	*Mean*	*95% C.I.*	*Mean*	*95% C.I.*	*Mean*	*95% C.I.*	(P)
GFR	Placebo	11	85.82	47.9,123.7	79.20	51.3,107.1	−6.62	−27.7,14.5	0.766
(ml min^{-1} 1.73 m^{-2})	Perindopril	12	78.47	37.6,88.7	70.77	36.9,104.7	−7.70	−19.3,3.9	
ERPF	Placebo	11	288.09	118.4,457.7	292.73	110.1,475.3	4.64	−48.3,57.6	0.397
(ml min^{-1} 1.73 m^{-2})	Perindopril	12	281.83	92.3,471.3	301.75	160.2,443.3	19.92	−85.6,125.5	
ECFV (1)	Placebo	11	17.73	11.9,23.6	17.82	13.5,22.1	0.09	−3.4,3.6	0.464
	Perindopril	12	18.00	9.3,26.6	17.58	10.1,25.1	−0.42	−3.2,2.4	

GFR = glomerular filtration rate. ERPF = effective renal plasma flow. ECFV = extracellular fluid volume.

at different doses from effects on mortality but the dose of any ACE inhibitor used in CHF continues to be surrounded by controversy.

In this small controlled double-blind parallel group study, symptoms were not a primary endpoint but there was an appreciable effect on heart failure score which would support symptomatic efficacy at this dose. We also found non significant changes in NYHA class to support this notion. In addition, there were no biochemical adverse events in either treatment group.

ACE inhibitors are proven to be of major benefit in heart failure but recently it has been noted that some patients exhibit 'neurohormonal escape' during chronic ACEI therapy. Reactive hyperreninaemia is thought to cause elevation of angiotensin I with subsequent reappearance of near normal if not elevated levels of circulating angiotensin II despite chronic ACEI therapy [21, 22]. Another explanation for the reappearance of normal angiotensin II levels is that patients may simply fail to comply with ACE inhibitor therapy. Regardless of the mechanism it is clear from population studies that those CHF patients who fail to maintain angiotensin II suppression despite ACE inhibitor therapy have a higher level of morbidity and mortality [22]. In the present study not only was there the expected suppression of serum ACE on chronic dosing with perindopril, but effective suppression of angiotensin II was also maintained in all patients during the 2 month treatment period. This suggests that neurohormonal escape does not occur with low dose perindopril. Alternatively poor compliance rather than hyperreninaemia may be the real reason for angiotensin II 'reactivation' when it occurs and AII reactivation did not occur in this trial because patient compliance is typically better during clinical trials. Another possible, but unlikely explanation is that the 2 month treatment period was too short for angiotensin II reactivation to be seen.

At the doses of perindopril empirically selected for cardiac failure patients there is no first dose blood pressure response when this drug is administered following temporary diuretic withdrawal [14, 15]. In the present study there was *no* diuretic withdrawal employed but again the 2 mg first dose of perindopril had no significant effect on blood pressure compared with placebo. Regardless of the mechanisms involved, this is a positive safety feature for the initiation of therapy in ambulant patients. This property differentiates perindopril from other ACE inhibitors where in a few cases marked falls in blood pressure [23–25] have been demonstrated irrespective of dose and in most instances demonstrable blood pressure fall is routine [26]. A hypothesis to explain this failure of first dose hypotension with perindopril has been put forward based on ester diacid interaction with the different components of perindopril [11, 27]. In the present study chronic dosing with perindopril has revealed no additional effect on supine or erect blood pressure over and above placebo. As a proportion of the patients in our controlled study (42%) had already received an ACE inhibitor as part of their ongoing clinical care, without symptoms, then we may have unwittingly selected out those prone to symptomatic hypotension. This may be relevant to the occurrence of postural dizziness in individual patients which is accepted as a troublesome albeit infrequent complication of chronic ACE inhibitor therapy in heart failure [3]. However this does not influence the measured blood pressure response to treatment nor the fact that the relationship between measured blood pressure and symptoms is frequently obscure on an individual patient basis. Nevertheless, the lack of hypotension in a small study ($n = 12$) does not rule out a population frequency of almost 3% (rule of threes $100/3n \times 100\%$).

Whatever the real frequency of hypotension in diuretic treated heart failure patients given an ACEI, and this appears low yet variable in controlled trials, it remains a matter of concern that fear of first dose hypotension is used as a common reason for physicians to withold ACEI treatment especially in elderly heart failure patients [6–8]. Current evidence for the UK suggests that only 17% of heart failure patients actually receive an ACE inhibitor [8].

The patients studied in this report started with normal renal electrolytes although their age, concomitant loop diuretic use and baseline renal perfusion assessment (see Table 5) are accepted to predispose to adverse effects on renal perfusion following the addition of an ACE inhibitor to a loop diuretic [29]. We found no significant changes in renal function following perindopril. In individual patients ACE inhibitors may cause a fall in renal function [29]. For the most part this relates specifically to the combination of a loop diuretic and an ACE inhibitor where the angiotensin II mediated efferent arteriolar tone, which was maintaining glomerular filtration, is withdrawn. It has been suggested that these renal responses to ACE inhibition support the use of short acting agents where haemodynamic and neurohormonal effects last only a matter of hours [30]. By contrast, long acting drugs whose impact is sustained from one dose interval into the next might be more likely to produce renal

dysfunction [30, 31]. In the present study, perindopril, which has a protracted duration of effect, had no significant effect on renal function. This is a limited observation given the absence of abnormal renal electrolytes at baseline but a reassuring response in keeping with longer term open label safety studies of this agent [32].

In summary, our study has demonstrated that the profile of perindopril at the dose selected may be useful for some patients with cardiac failure. Despite the dose, sustained neurohormonal suppression was seen without any detrimental renal changes in the presence of loop acting diuretic therapy. Perindopril did not lower BP compared with placebo after the first dose *or* during chronic therapy. In this report initiation of therapy did not require diuretic withdrawal.

Another possible consequence of this profile is that perindopril may prove useful in *acute* heart failure or even in cardiogenic shock where ACE inhibitor induced reductions in BP and organ perfusion could prove disastrous. This view is supported by the poor results for intravenous enalaprilat in the CONSENSUS II study. Yet more recently re-examination of ACEI therapy in this setting does suggest that important benefits may ensue from controlled introduction of this class of therapy [33]. There is a reasonable case therefore for studying perindopril for its efficacy and safety in these settings in a controlled trial.

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