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Controlled trial of enalapril in patients with chronic fluid overload undergoing dialysis

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Abstract

About one third of patients receiving dialysis for end stage renal failure have chronic fluid overload despite advice to restrict their oral fluid intake. To investigate the potential of an angiotensin converting enzyme inhibitor in reducing the urge to drink and consequent gain in weight, a double blind, placebo controlled crossover trial of enalapril was conducted in 25 patients receiving dialysis who had fluid overload. The trial comprised a baseline period of four weeks; two periods of treatment, each of four weeks, during which patients received either placebo or enalapril 5 mg twice each week; and a follow up period of four weeks. Five patients withdrew from the trial, one because of an adverse drug reaction to enalapril. A range of biochemical and behavioural variables was measured during the baseline period, at the completion of periods 1 and 2, and during follow up. These variables included gain in weight between dialysis sessions; blood pressure; plasma concentrations of sodium, angiotensin II, and vasopressin; plasma renin and angiotensin converting enzyme activities; osmolality; and estimations of thirst, intake of fluid, and control of drinking. Enalapril caused a significant reduction in gain in weight between dialysis sessions, thirst, and oral intake of fluid in parallel with significantly increased renin activity, significantly decreased angiotensin converting enzyme activity, and decreased concentrations of angiotensin II. Gain in weight and angiotensin converting enzyme activity returned to baseline values once patients stopped taking enalapril.

These results suggest that enalapril may act on the renin-angiotensin system and reduce intake of fluid by inhibiting angiotensin converting enzyme.

Introduction

Restriction of water intake is an important part of the management of most patients having dialysis for end stage renal failure. Water that is ingested in excess of urine volume and insensible losses accumulates in the extracellular space, resulting in peripheral and pulmonary oedema or, in less acute cases, chronic left ventricular hypertrophy and congestive cardiomyopathy. Most patients whose output of urine is below their previous habitual daily intake of water are therefore advised to restrict their drinking to a volume that will result in a gain in weight of less than 0.6 kg daily between dialyses.

This restriction is one of the more irksome aspects of the treatment regimen for chronic renal failure, and one third of patients receiving dialysis may have chronic fluid overload by the above criteria.¹ Failure to comply is probably due to many factors, but reports suggest that, in some cases at least, high plasma concentrations of the dipsogen angiotensin II² may be an important cause.³⁻⁷ Angiotensin converting enzyme inhibitors, which block conversion of the precursor angiotensin I to angiotensin II, suppressed drinking in animals given intravenous infusions of angiotensin I.⁸ If angiotensin II is a cause of the excessive thirst felt by patients undergoing dialysis inhibition of angiotensin converting enzyme might reduce the urge to drink and hence the cardiovascular risks associated with expansion of the extracellular space. To date evaluation of such treatment in patients undergoing dialysis has been attempted in only one study, in which thirst and weight gain between dialysis sessions were reduced in four patients with the angiotensin converting enzyme inhibitor captopril⁶; as the trial was not double blind, however, placebo effects could not be ruled out.

We report a double blind, placebo controlled, crossover trial of an angiotensin converting enzyme inhibitor, enalapril, in patients with chronic fluid overload receiving dialysis.

Patients and methods

STUDY DESIGN AND TREATMENT

We used a crossover study and carried out procedures within the study according to the standards of the ethics committee of this hospital. Each patient was given either enalapril or placebo in the first period of treatment and the alternative treatment in the second period; the order in which treatment was given was randomised, 13 patients receiving enalapril first and 12 placebo first. Randomisation was carried out by the suppliers of the drug

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with random numbers. Neither the doctors nor the patients were ever aware of which treatment was being received. The code was broken only after all patients who had entered the trial had been followed up.

Once written informed consent had been obtained and patients had entered the trial they were assessed for four weeks (baseline period). This was followed by treatment for four weeks (period 1), a crossover ("wash-out") period of two weeks, further treatment for four weeks (period 2), and follow up assessment for four weeks. Thus each patient was enrolled in the trial for 18 weeks. During the baseline period all patients spent 45 minutes with a dietitian and viewed a 10 minute tape-slide show to standardise their understanding and knowledge of the essentials of fluid balance and the importance of restrictions on drinking.

A series of pharmacokinetic and bioavailability studies in patients receiving dialysis showed that plasma concentrations of the active moiety of enalapril, enalaprilat, remained within the therapeutic range over two periods of dialysis after a 5 mg dose of enalapril taken orally immediately after dialysis. With a twice weekly dose of 5 mg enalapril taken after the first and second dialysis sessions of the week, plasma angiotensin converting enzyme activity was reduced throughout the whole week in six patients. During the trial, therefore, we instructed patients to take one 5 mg tablet after the first and after the second dialysis sessions in each week of treatment.

PATIENTS

We obtained informed consent from 25 patients (15 men and 10 women) having dialysis who had a history of either fluid overload or complaints of chronic thirst according to clinical data. The mean age was 40, and they had been receiving dialysis for a mean of 16 months. Ten patients were having haemodialysis at home, 13 were having haemodialysis in hospital, and the remainder (two) were having intermittent peritoneal dialysis.

Of the 25 patients formally entered into the trial, five (four of whom were allocated to take placebo first) withdrew during period 1 and were not included in subsequent analyses. The reasons for withdrawing were: receipt of a cadaveric transplant (two patients), technical difficulties with dialysis at home (one), admission to hospital after an episode of peritonitis (one), and an adverse reaction (a burning sensation in the throat) to enalapril (one).

MEASUREMENTS

Blood pressure, weight gain, and thirst—We measured systolic and diastolic blood pressures with the patients recumbent before dialysis, and weight before and after dialysis, for all dialysis sessions conducted during the trial. Before each session the patients' weight after the previous session was subtracted from the current weight and the difference divided by the number of days (either two or three) between the two sessions, yielding a mean daily weight gain for that period between the two sessions. For each week of the trial the average weekly mean systolic blood pressure, weekly mean diastolic blood pressure, and mean daily weight gain between dialysis sessions were calculated. In addition, 100 mm visual analogue rating scales of thirst (not thirsty at all to very thirsty) and dry mouth (not dry at all to very dry) were completed once a week by all patients before their first dialysis of that week.

Biochemical variables—We performed a comprehensive biochemical assessment of patients on three occasions: at the start of the baseline period

Mean daily gain in weight between dialysis sessions during trial in 13 patients given enalapril (period 1) followed by placebo (period 2) and in 12 given placebo (period 1) followed by enalapril (period 2). Duration of each period of trial was four weeks.

(before the educational briefing); within 24-48 hours after the administration of the final tablet in period 1; and at the corresponding time at the end of period 2 (that is, during weeks 8 and 14, respectively). Blood collected at each of these trials was analysed for plasma concentrations of renin,⁹ vasopressin,¹⁰ angiotensin II,¹¹ and sodium; osmolality; and activity of angiotensin converting enzyme. At the assessments at the end of periods 1 and 2 blood samples for determining the concentrations of enalapril were also taken but not assayed until each patient had completed both parts of the study.

Behavioural and psychological variables—During each of the three assessment periods (the baseline period and after the administration of the final tablet in periods 1 and 2) we asked patients to record their oral intake of fluid for five consecutive days, two of which always included a Saturday and Sunday, when social pressures to drink are greatest. In addition patients were asked to complete the 30 item general health questionnaire, a self reported inventory of psychological symptoms¹²; the locus of control of behaviour scale, a self reported test designed to measure the extent to which subjects perceive responsibility for their problems and difficulties¹³; and a thirst and drinking scale developed by us to measure the psychological, behavioural, and physical results of chronic thirst and fluid overload.¹

STATISTICS

Systolic and diastolic blood pressures, mean daily weight gain between dialysis sessions, and the visual analogue rating scales of thirst and dry mouth were measured on 16 occasions (the intervening two weeks of washout between periods 1 and 2 being omitted from the analysis). Subsequently these measurements were reduced to four monthly values by averaging the values for each of the four weeks of the baseline period, period 1, period 2, and the follow up period.

The data from periods 1 and 2 were analysed by the methods proposed by Hills and Armitage for the analysis of two period crossover trials.¹⁴ For each variable we determined, firstly, whether there was a significant difference between treatment with enalapril and placebo irrespective of the sequence of administration (that is, the treatment effect was estimated from the combined results of periods 1 and 2) and, secondly, whether there was a significant interaction between treatment and period. When such an interaction was present (that is, the effect of treatment varied with the order of administration) results from period 1 only were compared, as recommended.¹⁴

Results

There were no significant differences during the baseline period between the patients who received enalapril first and those who received placebo first in any of the variables measured except for renin activity, which was at the upper end of the distribution in two of the patients given placebo first.

Blood pressure, weight gain, and thirst—Table I shows systolic and diastolic blood pressures, weight gain between dialysis sessions, and scores on the visual analogue rating scales in the patients. No significant interactions

TABLE I—Mean (SD) blood pressure, gain in weight, thirst, and dryness of mouth at each phase of trial in patients receiving enalapril and placebo

Variable and sequence of treatment	Baseline	Period 1	Period 2	Follow up
Systolic blood pressure (mm Hg):				
E-P	145 (18)	137 (16)	144 (16)	146 (16)
P-E	143 (15)	149 (13)	134 (8)	139 (8)
Diastolic blood pressure (mm Hg):				
E-P	86 (11)	79 (8)	85 (8)	83 (8)
P-E	82 (13)	88 (9)	79 (8)	81 (10)
Gain in weight between dialysis sessions (kg/day):				
E-P	0.9 (0.2)	0.6 (0.2)	0.8 (0.2)	0.8 (0.2)
P-E	0.9 (0.2)	1.0 (0.3)	0.7 (0.3)	0.8 (0.3)
Degree of:				
Thirst (mm)*:				
E-P	62 (20)	36 (19)	47 (21)	51 (20)
P-E	67 (19)	53 (14)	47 (17)	50 (11)
Dryness of mouth (mm)*:				
E-P	56 (24)	39 (20)	48 (25)	54 (24)
P-E	63 (23)	57 (19)	48 (12)	55 (12)

*From visual analogue scale.

E-P=Enalapril, placebo (n=13).

P-E=Placebo, enalapril (n=12).

between treatment and period were detected. Both systolic and diastolic blood pressures were significantly reduced by the treatment with enalapril ($F=11.54$, $p<0.01$; $F=12.30$, $p<0.01$, respectively). Mean daily weight gain between dialysis sessions was also significantly reduced when enalapril was being taken ($F=25.01$, $p<0.01$) (figure). When data from both groups of patients were combined the mean daily weight gain between dialysis sessions was reduced by 0.25 kg with enalapril; during follow up, however, the gain in weight of patients in both groups approached those measured during the baseline period. Thirst, as measured on the visual analogue scale, was significantly reduced by enalapril ($F=5.27$, $p<0.05$).

Biochemical variables—Table II shows that enalapril had no significant effect on the plasma concentrations of sodium and antidiuretic hormone and osmolality. There was, however, a significant increase in renin activity during treatment with enalapril ($F=9.51$, $p<0.01$). The serum concentrations of angiotensin II were significantly reduced with enalapril ($F=7.12$, $p<0.05$), but there was also a significant interaction between treatment and period ($F=6.53$, $p<0.05$). Accordingly, further analysis with data from period 1 alone was performed; this showed that the effect of enalapril was significant ($F=7.96$, $p<0.05$). The activity of angiotensin converting enzyme was greatly reduced by enalapril ($F=68.13$, $p<0.01$), but, unlike the concentrations of angiotensin II, it returned quickly to baseline values once enalapril was withdrawn.

TABLE II—Mean (SD) values of biochemical variables in patients during baseline and treatment periods in patients receiving enalapril and placebo

Variable and sequence of treatment	Baseline	Period 1	Period 2
Sodium (mmol/l):			
E-P	140 (1)	140 (1)	140 (2)
P-E	139 (3)	138 (2)	139 (2)
Osmolality (mmol/kg):			
E-P	308 (9)	309 (10)	309 (7)
P-E	310 (8)	310 (16)	310 (7)
Renin activity (nmol angiotensin I/l/h):			
E-P	1 (1)	6 (8)	1 (2)
P-E	7 (7)	8 (11)	16 (18)
Angiotensin II (pmol/l):			
E-P	17 (19)	6 (5)	5 (4)
P-E	26 (15)	20 (14)	5 (3)
Antidiuretic hormone (pmol/l):			
E-P	3 (1)	3 (2)	3 (2)
P-E	4 (2)	3 (2)	5 (8)
Angiotensin converting enzyme (μmol/ml/min):			
E-P	36 (8)	19 (13)	39 (11)
P-E	36 (8)	35 (9)	16 (8)

E-P=Enalapril, placebo (n=13).
P-E=Placebo, enalapril (n=12).

Behavioural and psychological variables—Table III shows that treatment with enalapril resulted in only a trend for reduced thirst as measured on the thirst and drinking scale. The significant reduction in the gain in weight between dialysis sessions was reflected in a significant reduction in oral fluid intake recorded by the patients when they were taking enalapril (average reduction 159 ml) ($F=9.97$, $p<0.05$). During treatment with enalapril there was only a trend towards improvement in general psychological functioning as assessed by scores on the general health questionnaire and locus of control of behaviour scale (that is, patients were able to exert more self control over the desire to drink in response to thirst).

TABLE III—Means (SD) and scores for behavioural variables during baseline and treatment periods in patients receiving enalapril and placebo

Variable and sequence of treatment	Baseline	Period 1	Period 2
Thirst and drinking scale:			
E-P	30 (7)	25 (6)	27 (7)
P-E	33 (9)	29 (7)	28 (7)
General health questionnaire:			
E-P	7 (8)	4 (6)	4 (5)
P-E	8 (8)	6 (8)	6 (5)
Locus of control of behaviour:			
E-P	34 (9)	30 (8)	32 (13)
P-E	32 (13)	35 (14)	31 (12)
Mean daily intake of fluid (ml):			
E-P	853 (295)	698 (232)	833 (353)
P-E	1009 (302)	963 (248)	798 (253)

E-P=Enalapril, placebo (n=13).
P-E=Placebo, enalapril (n=12).

Discussion

We found that mean daily gain in weight between dialysis sessions was significantly reduced by enalapril but not by placebo or as a result of an educational briefing during the baseline period of the study. By the end of the follow up period, which for the patients who received enalapril before placebo was two months after they had received enalapril, the mean daily increase in weight between dialysis sessions had returned to baseline values. The oral intake of fluid recorded by patients varied in parallel with mean weight gain between dialysis sessions; this supports the contention that the reduced gain in weight resulted mainly from less drinking rather than from reduced intake of dietary fluid or some other confounding variable affected by treatment, such as a change in dialysis routines.

The subjective effects of the treatment on perceived thirst were more difficult to define; the method of measurement was less precise than that for body weight and more susceptible to placebo effects. Patients felt much less thirsty (as measured in particular on the thirst and drinking scale rating) when they were taking enalapril compared with placebo. Mean body weight and recorded intake of fluid decreased similarly in the two groups of patients (0.24 kg and 154 ml in the patients who received enalapril first; and 0.26 kg and 164 ml in the patients who received placebo first). Though a reduction in perceived thirst is the logical connection between these two sets of values, these data are more consistent with the hypothesis that reduced intake of water, and hence gain in weight between dialysis sessions, resulted from a subversion of the "unconscious" drive to drink.

According to the behavioural measurements, enalapril reduced thirst and drinking and, to a less extent, blood pressure. The values obtained for the biochemical variables showed that these effects were probably mediated by a blockade of the renin-angiotensin system, with other biochemical functions remaining substantially unaffected.

Further research is required to ascertain whether inhibition of angiotensin converting enzyme as outlined in this study together with psychological treatment, such as behaviour modification, leads to a long term reduction in the chronic thirst and excessive gain in weight between dialysis sessions experienced by many patients undergoing dialysis.

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