CAPTOPRIL AND SALT SUBTRACTION TO TREAT ‘UNCONTROLLABLE’ HYPERTENSION IN HAEMODIALYSIS PATIENTS

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Summary

Eight patients on chronic haemodialysis for six months to 7 years with hypertension resistant to ultrafiltration and antihypertensive therapy, received Captopril (SQ 14, 225) an orally active inhibitor of converting enzyme. With this therapy, blood pressure was controlled in the 4 patients with the highest plasma renin activity. In the other 4, this treatment had to be supplemented with ‘isovolumetric salt subtraction’, i.e. following conventional dialysis, 1–2 litres of ultrafiltrate were replaced by an equal volume of 5% glucose. The slight hyponatraemia induced by this procedure (plasma sodium 128mmol/L) was well tolerated. This procedure allows the removal of an excess of body sodium and seems to be effective even when conventional ultrafiltration during dialysis has failed. Administration of Captopril either alone or combined with ‘isovolumetric salt subtraction’ induced good control of blood pressure in all 8 patients.

Introduction

Almost 80% of patients with end-stage renal failure are hypertensive when haemodialysis treatment is initiated [1]. With adequate ultrafiltration, blood pressure can be controlled in the majority of them [1,2]. However, hypertension persists in some cases and has therefore been defined as ‘dialysis-resistant’.

The active participation of the renin system in this type of hypertension has often been suggested, and bilateral nephrectomy proposed as treatment [2–4]. Captopril (SQ 14, 225), an orally active inhibitor of the angiotensin converting enzyme, has made long-term blockade of the renin system possible [5]. This new drug was used in chronic haemodialysis patients with ‘uncontrollable’ hypertension, i.e. hypertension resistant to ultrafiltration and conventional medical therapy. In some patients, to control blood pressure, additional removal of excess body sodium was necessary which was accomplished using a new procedure which we call ‘isovolumetric salt subtraction’.

610
Methods

Patients

Eight patients, 4 male and 4 female, aged 10 to 61, were included in the study. They had been on chronic haemodialysis for six months to 7 years. All had hypertension refractory to ultrafiltration and were on hypertensive therapy consisting of beta-blockers, clonidine and/or dihydralazine. Six had chronic glomerulonephritis and 2 chronic interstitial nephritis; residual diuresis in all except one was less than 100ml/day.

Procedures

Patients were dialysed three times a week for 3 to 5 hours on Gambro Major, Travenol CF 1500 or Cordis 2.5. Dialysate composition was: sodium 138mmol/L, potassium 2mmol/L, calcium 1.5 or 1.75mmol/L, magnesium 0.75mmol/L, acetate 38mmol/L, chloride 107mmol/L. Two days after interruption of the previous antihypertensive therapy, and at least 18hr after the last dialysis session, Captopril was started at a dose of 25mg p.o. and then progressively increased to a dose of 100mg twice daily. Analytical methods have been described previously [5].

‘Isovolumetric salt subtraction’ was carried out as follows: after a conventional dialysis session with appropriate ultrafiltration, dialysate delivery was interrupted and, by placing a screwclamp on the venous line, the pressure in the blood compartment of the dialyser was progressively increased to above 250mmHg. Ultrafiltrate was collected in a graduated cylinder. Simultaneously, the volume of ultrafiltrate removed was replaced by equal amounts of glucose 5% which was infused into the arterial blood line. By ultrafiltering 1 to 2 litres with this technique, up to 260mEq of sodium could be subtracted during each procedure.

Results

On previous therapy, blood pressure averaged 179/105 ± 6/3mmHg before and 182/103 ± 7/3mmHg after dialysis. This blood pressure further increased after interruption of treatment to 194/113 ± 8/4 before and 209/114 ± 7/6mmHg following dialysis. After 4 to 6 days of Captopril therapy, when the full dose was reached, blood pressure averaged 164/90 ± 10/4 and 172/97 ± 9/4mmHg pre- and post-dialysis. Although this decrease as a whole is significant, blood pressure was not normalised in all patients: 4 responded well and blood pressure remained under control for up to 9 months of treatment with Captopril alone. These 4 patients had the highest renin values (8.9–97ng/ml/hr).

In the 4 patients with the lowest renin values (0.71–6.9ng/ml/hr), ‘isovolumetric salt subtraction’ had to be added in order to bring blood pressure under control.

With Captopril therapy alone, mean blood pressure in these patients remained at 185/85 ± 10/6mmHg pre- and 191/93 ± 10/4mmHg post-dialysis. When 1 to 4 ‘isovolumetric salt subtractions’ were administered, blood pressure was further reduced. Depending on salt intake during inter-dialytic periods, subsequent ses-
sions of isovolumetric salt subtraction became necessary. At the last check after 13 to 32 weeks, blood pressure was at 143/68 ± 13/6mmHg pre- and 156/78 ± 15/9mmHg post-dialysis. The procedure was well tolerated; no signs of dialysis disequilibrium other than fatigue and minor muscle cramps were observed.

The biochemical changes induced by 'isovolumetric salt subtraction' are depicted in Figure 1. These preliminary results represent the mean of the values

Figure 1. Metabolic effects of isovolumetric salt subtraction
observed in 3 patients. During haemodialysis, urea and osmolality decreased as expected from 27.4 ± 1.6 to 10.6 ± 0.9mmol/L and from 302 ± 7 to 283 ± 4mmol/kg H₂O respectively. During ‘isovolumetric salt subtraction’, plasma sodium decreased from 135 ± 1 to 128 ± 1mmol/L; plasma osmolality however remained unchanged at 282 ± 3mOsm/kg due to a transient increase in plasma glucose levels to 19.9 ± 2.4mmol/L. In the ultrafiltrate (1 litre) sodium concentration was 125mmol/L. During the hours following the procedure, plasma glucose decreased rapidly while plasma sodium increased progressively until the next dialysis.

Discussion

Although the specific effect of Captopril on the angiotensin converting enzyme is still a matter of debate [5,6], this drug was effective in lowering the blood pressure of chronic haemodialysis patients with previously ‘uncontrollable’ hypertension. In those patients with high renin values, Captopril was effective alone, while in those with renin values that were not clearly elevated, ‘isovolumetric salt subtraction’ had to be superimposed in order to bring blood pressure under control. The inappropriateness of renin secretion for a given state of sodium balance in patients with chronic renal failure has been recently pointed out [7]. In the early days of haemodialysis, dialysate with low sodium concentrations (130 to 135mmol/L) was used on the assumption that with higher concentrations sodium accumulation with consequent hypertension and cardiac failure tends to develop. To a certain extent low sodium dialysate allowed the removal at each dialysis of the sodium that had accumulated during the interdialytic period. Subsequently, Stewart et al have shown that increasing sodium dialysate concentration reduced the occurrence of weakness, nausea, vomiting, hypotensive episodes and muscle cramps observed frequently following haemodialysis with low sodium dialysate [8].

Shorter dialysis schedules, higher sodium concentration in the dialysate and less severe dietary sodium restriction have made it more difficult to maintain a normal sodium balance in haemodialysis patients. Probably, over a prolonged period of time, subtle sodium accumulation often develops and this may be reflected by the slowly increasing prevalence of ‘dialysis-resistant’ hypertension in patients on haemodialysis. Thus, according to the recent survey of Fillastre et al [9] 31% of 1868 haemodialysis patients have ‘dialysis-resistant’ hypertension, a prevalence confirmed by our own dialysis population. These figures are in sharp contrast to the 10% reported some years ago [1].

Different techniques have recently been used in an attempt to reduce the symptoms associated with sodium or volume removal: sequential ultrafiltration [10], addition of glycerol [11] or urea [12] to the dialysate or even a sodium concentration of 165mmol/L in the dialysate [13]!

‘Isovolumetric salt subtraction’ seems to represent an efficient tool to achieve a reduction of total body sodium. The prolonged slight hyponatraemia observed following the procedure may induce a shift of sodium from the intra-cellular to the extra-cellular space and allows the removal of sodium which cannot be
mobilised with conventional ultrafiltration. This induced hyponatraemia, however, is well tolerated probably because the transient hyperglycaemia prevents major changes in plasma osmolality.

References
4 Onesti, G, Swartz, C, Ramirez, O and Brest, AN (1968) Trans. ASAIO, 14, 361
8 Stewart, WK, Fleming, LW and Manuel, MA (1972) Lancet, i, 1049

Open Discussion

KOKOT (Chairman) We will take the discussion of these last two papers together.

DONKER (Groningen) Did you observe in any of your dialysed patients during Captopril treatment alone, an improvement in residual renal function? We observed in one of our patients on dialysis with intractable hypertension, due to a previous haemolytic uraemic syndrome, an increase in GFR from 2 to 26ml/min. After 1½ years haemodialysis treatment was no longer necessary.

WAUTERS We published a few months ago 4 cases of patients who had been on dialysis from 2 months to 20 months, and we could stop haemodialysis after control of their blood pressures. But those patients were treated with other methods than Captopril, and those patients who were treated with Captopril had been on haemodialysis mostly for more than 3 years and their residual diuresis was less than 100ml and we did not see any improvement in renal function.

GONZALEZ (New Orleans) Dr Wauters, did you see any side effects such as cramps on patients where salt subtraction was done? In our experience such patients develop serious cramp problems.

WAUTERS These patients noticed fatigue after the salt subtraction but less muscle cramps than before when we tried to ultrafilter them during dialysis.

WHITWORTH (Melbourne) We have observed loss of taste in 3 patients treated
with Captopril necessitating withdrawal of treatment. Captopril plus diuretic therapy has not been uniformly successful in patients with high renin severe or accelerated hypertension, and in 2 of 5 such patients did not control blood pressure. However, Captopril alone was effective in a number of patients with mild to moderate low-renin hypertension and at the doses used in Professor Johnston's laboratory was not associated with a rise in bradykinin concentration. This raises the question of whether Captopril may lower blood pressure by another mechanism, for example an effect on local renin-angiotensin systems.

WAUTERS I don't want to say that all this was obtained just by inhibition of converting enzyme of the renin system. Loss of taste has been observed in a few patients with chronic renal failure, but not in those patients who were on haemodialysis. These were patients with renal failure with serum creatinine less than 8mg/100ml and this symptom subsided within a few days spontaneously.

PRINS I would like to add to your statement about loss of taste. I heard about it last month from Dr Brunner. He had not heard of it from anywhere else than from Switzerland and his argument that it was only found in Switzerland was that Swiss people have better taste than other Europeans or Americans. This is the second time that I have heard about loss of taste. We have asked our patients about loss of taste, but none has mentioned it.

MERY (Paris) I would like to ask Dr Wauters if he has observed hyperkalaemia in his patients treated with Captopril? As one might expect to see it due to the decrease of aldosterone secretion.

WAUTERS No, we did not observe hyperkalaemia.

AHMAD (Liverpool) Thank you Dr Wauters for introducing yet another terminology 'Isovolumetric salt subtraction' in the already complicated field of dialysis. I wonder what would have happened if you had used dextrose in priming your patients before they went on dialysis, and then ultrafiltered? You did not tell us about the salt intake of these patients. I find it completely unphysiological to let a patient take salt in the diet and then remove it later during the course of dialysis. You could perhaps have achieved similar results with sequential dialysis and ultrafiltration.

WAUTERS In those patients we used dextrose priming each time. We do not pretend to say this was the only method to treat them. We did not change anything from the previous diet of our patients. They just remained on the same diet. And in some patients there was really a very high salt intake, but they remained on that diet during treatment.

WILL (Nottingham) Did either group notice a change in appetite or thirst in treated patients? Was their normal thirst mechanism disturbed in any way when their blood pressure was better controlled?

WAUTERS I completely agree with your mention of salt intake. In fact the first patient, who came from Germany, to be put on Captopril treatment, only two salt subtractions were successful and afterwards she remained normotensive. The only thing that changes in this patient was now that she observed a more
Slide B. For explanation see text
restricted sodium diet. And so blood pressure remained under control for more than 6 months.

KOKOT As far as I saw from the data given by Dr Prins, a decrease in plasma aldosterone concentration was not so impressive as it was in your paper. Could you comment about this fact?

WAUTERS No comment.

PRINS Well, there are two answers to your question. The first one is that in two of the patients there was a low initial PRA so the renin-angiotensin II-aldosterone chain was functioning apparently on a lower level, and may be therefore more tractable for other influences directly on the plasma aldosterone secretion. The other thing is that the levels of plasma aldosterone in these patients were low and may therefore be more liable to fluctuations in the determination. At this level we could measure only low, but not very low.

KOPP (München) I wonder why you concentrate so much on body sodium, in view of the fact that chloride is probably the macula densa signal which inhibits GFR, rather than sodium, in particular with those patients regaining renal function. They must have had a rise in GFR.

PRINS I have no slide of our patient who was on chronic haemodialysis after the haemolytic uraemic syndrome. But I will show you slide B if you please, of one of our patients, with a renal graft, who had been bilaterally nephrectomised because of untreatable hypertension. The slide shows in the left upper part the previous medication and in the right part the Captopril in increasing dosages and subsequently the addition of diuretics because of no response in blood pressure, which is shown on the third line. Now, in this patient you can see that the initial PRA (on the lowest line) and the plasma aldosterone concentration (hatched bars) are low, on Captopril alone. What you see also, is that in this patient the GFR remains almost constant while there is an increase in ERPF from 326 to 350 ml/min. Thus the filtration fraction decreased from 0.28 to 0.26. What we found in this patient, we also found in our other patients. So, I would not say that it is only the macula densa signal that mediates changes in GFR but that increase in renal function also can be a result of a slight increase in RBF. For one patient in our series it made it possible to stop haemodialysis.