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EFFECTS OF URAEMIA AND DIALYSIS TREATMENT ON ADRENOCEPTOR RESPONSIVENESS

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Summary

The effects of uraemia and of a dialysis session on beta adrenoceptor responsiveness were evaluated from the changes in plasma cyclic AMP caused by subcutaneous epinephrine administration. Four groups of subjects were studied: normal, uraemic (GFR: 11ml/min; SEM 3) (pre-dialysis patients), uraemic on regular dialysis treatment with acetate dialysis (acetate-dialysis patients) and uraemic on regular dialysis treatment by bicarbonate-dialysis (bicarbonate-dialysis patients).

The changes in response to epinephrine administration were similar in normal, pre-dialysis and acetate-dialysis patients. In contrast, in the bicarbonate-dialysis patients the per cent increment in plasma cyclic AMP was lower than in the other groups. A single-acetate dialysis caused a depression in cAMP response after epinephrine, while a single bicarbonate-dialysis did not. These results indicate that adrenoceptor responsiveness is unaffected by uraemia, but is impaired by dialysis treatment, probably due to an acetate-associated effect. Bicarbonate-dialysis prevents such reduction.

Introduction

The pathogenesis of autonomic nervous dysfunction in uraemic patients is not fully understood. Abnormal responsiveness of target organs to catecholamines is a possible mechanism resulting in autonomic insufficiency. This possibility has been investigated by studying the changes in arterial blood pressure and heart rate after catecholamine administration. The results, however, have been conflicting and, therefore, inconclusive [1–4].

In this study, beta-adrenergic responsiveness has been investigated in uraemic patients measuring plasma cyclic AMP (cAMP) after subcutaneous epinephrine.

Methods

The study was carried out in twenty-one patients, including five subjects with normal renal function (normal subjects). Seven uraemic patients (pre-dialysis

patients), five uraemic patients on regular dialysis treatment with acetate dialysis (acetate-dialysis patients) and four uraemic patients on bicarbonate dialysis (bicarbonate-dialysis patients). Patients with clinical or laboratory evidence of systemic, metabolic or hypertensive disease were excluded from the study. In pre-dialysis patients the mean age was 40±6 years; GFR, measured by creatinine clearance, was 11±3ml/min. In acetate-dialysis patients the mean age was 41±6 years and the duration of dialysis averaged 36±14 months (range 6–96). Bicarbonate-dialysis patients were treated by this procedure to prevent the symptomatic vascular instability associated with acetate-dialysis. The mean age in this group was 38±6 years; mean duration of dialysis averaged 12.7±7.8 months (range 6–36). Both acetate- and bicarbonate-dialysis patients received four hours of haemodialysis three times weekly: none presented clinical symptoms, nor laboratory findings of under-dialysis syndrome: plasma calcium and phosphate were kept normal by administration of Al $(OH)_3$ and vitamin D analogues in all the patients; anaemia, present in all patients, was not particularly severe (Htc: 24–35%); clinical signs of pericarditis or peripheral neuropathy were absent.

In all patients, beta-adrenergic responsiveness was tested by administering epinephrine. Patients on dialysis were studied both immediately before and after a dialysis session. All patients were kept resting in the supine position for at least 20 minutes and an indwelling IV catheter was inserted to a forearm vein at least 15 minutes before obtaining the basal blood sample. Then, epinephrine (7μg/kg) was administered subcutaneously (time 0). Subcutaneous administration was chosen for patient's safety. Pulse rate and blood pressure were registered and blood specimens were obtained through the indwelling catheter every 10 minutes for 70 minutes. Plasma cAMP concentration was measured by radioimmunoassay [5].

Statistical analysis

Paired and unpaired Student's 't' test was used for statistical analysis.

Results

No side effects due to sympathetic stimulation occurred in any patient, nor any significant change in pulse rate or blood pressure was observed confirming the clinical safety of our test.

Basal average plasma cyclic AMP concentration was similar in all groups, ranging between 16.2±0.9pmol/ml (the lowest numerical mean in acetate-dialysis patients) and 19.5±1.5pmol/ml (the greatest numerical mean in pre-dialysis patients; not significantly different).

In control subjects plasma cyclic AMP started to increase 10 minutes after epinephrine injection, attained a peak at 30 minutes and by 70 minutes had almost returned to baseline value. Both pre-dialysis patients (Figure 1) and acetate dialysis patients exhibited a similar response to epinephrine injection. In contrast, in the bicarbonate dialysis group the per cent increment in plasma cyclic AMP compared to the basal value after epinephrine injection was

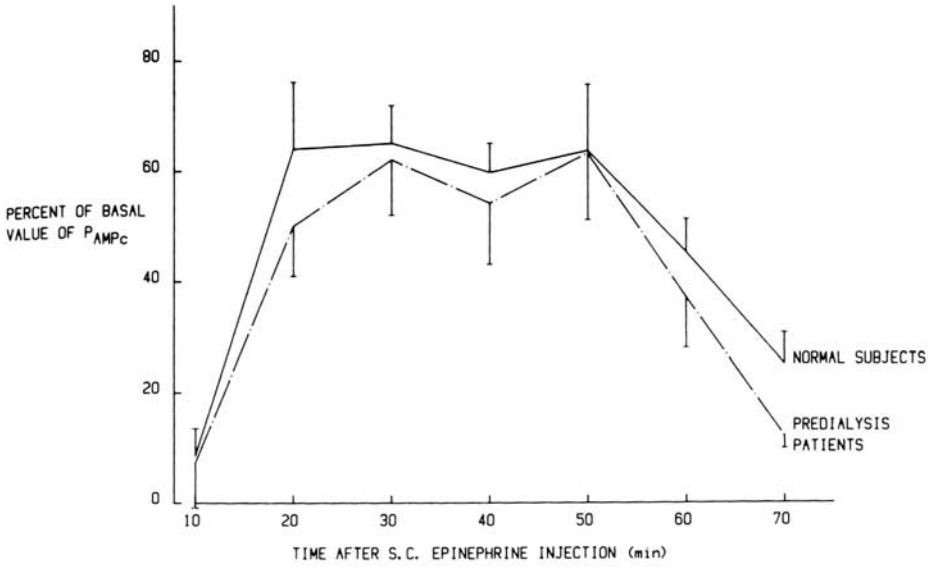

Figure 1. Relative changes in plasma cyclic AMP (P_{cAMP}) after subcutaneous epinephrine injection in pre-dialysis patients and controls. Bars are SEM

lower than in normal subjects (at 30 min, 43.5% vs 63.7%, $p<0.05$), pre-dialysis (at 50 min 42% vs 63%, $p<0.05$) and acetate-dialysis patients (at 50 min, 42% vs 64%, $p<0.05$).

The effects of a single dialysis session on plasma cAMP are shown in Figures 2 and 3. In acetate-dialysis patients the rate of increase of cyclic AMP after epinephrine injection was reduced soon after a dialysis session in comparison with before. No change was observed between the tests performed before and after the dialysis session in bicarbonate-dialysis patients.

Discussion

The reactivity of target organs to catecholamines has been studied both in patients with chronic renal failure and in an experimental model of chronic uraemia [1–3]. Campese et al [1] found a reduced increase in blood pressure and heart rate during norepinephrine infusion only in uraemic patients not yet undergoing dialysis, but not in patients on dialysis. Similarly, Rascher et al [2], in an experimental model of chronic uraemia in the rat, showed a decreased vascular responsiveness to norepinephrine. Ulman et al [3] found a reduced beta-adrenergic responsiveness in uraemia, associated with high plasma levels of PTH. Kersh et al [4] found a normal responsiveness of target organs to norepinephrine in patients on dialysis with haemodialysis-induced hypertension.

In our study beta-sympathetic reactivity was investigated by measuring the changes in plasma cAMP in response to epinephrine. The changes in plasma cAMP are a reliable index of the cAMP release rate from beta-adrenoceptors [6].

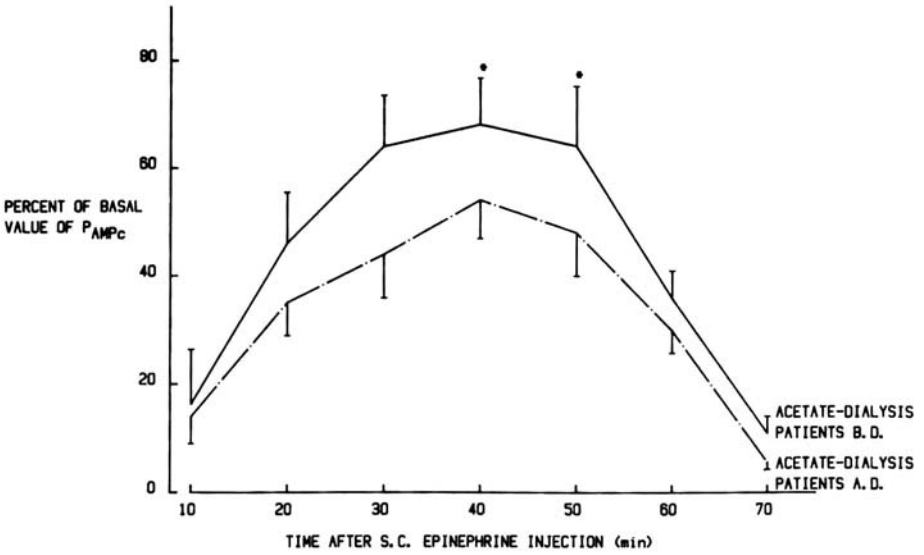

Figure 2. Relative changes in plasma cyclic AMP (P_{cAMP}) after subcutaneous epinephrine injection in acetate-dialysis before (B.D.) and after (A.D.) a single dialysis session. Bars are SEM. *$p<0.025$

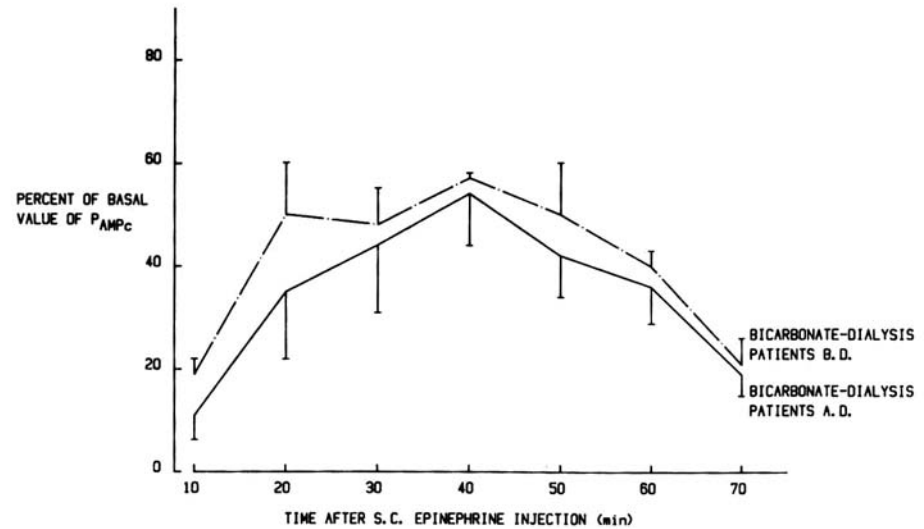

Figure 3. Relative changes in plasma cyclic AMP (P_{cAMP}) after subcutaneous epinephrine injection in bicarbonate-dialysis patients before (B.D.) and after (A.D.) a single dialysis session. Bars are SEM

This test has the advantages of both allowing a precise quantitative evaluation of receptor responsiveness and being absolutely safe. Receptor responsiveness was normal in uraemic patients and acetate-dialysis patients (before the single dialysis session). This clearly indicates that neither uraemia nor chronic dialysis treatment per se are associated with abnormal reactivity of target organs to epinephrine. Beta-receptors responsiveness, however, was significantly depressed in bicarbonate-dialysis patients. Since these patients represented a clinically pre-selected group, and the selection was based on intra-dialytic vascular instability, these results suggest that a beta-receptor dysfunction contributed to the circulatory disturbances bothering these patients during acetate-dialysis. It is of interest that acetate-dialysis lowered beta-receptor responsiveness, while bicarbonate-dialysis did not. This different effect of bicarbonate-dialysis fits well with clinical benefits observed in our group of bicarbonate-dialysis patients and indicates that absent depression of adrenergic responsiveness with this kind of dialysis accounts for successful treatment of intra-dialytic circulatory malaise.

In conclusion, our study shows that some uraemic patients (the ones who probably suffer from intra-dialytic instability) have defective adrenergic responsiveness at the target organ receptor level. This defect may become evident during acetate-dialysis since beta-adrenoceptor reactivity is decreased after this treatment. The benefits of bicarbonate-dialysis are, at least in part, due to not worsening the beta-adrenoceptor responsiveness.

References

1 Campese VM, Romoff MS, Levitan D et al. *Kidney Int 1981; 20:* 246
2 Rascher W, Schomig A, Kreye AV, Ritz E. *Kidney Int 1982; 21:* 20
3 Ulmann A, Drueke T, Zingraff J, Crosnier J. *Clin Nephrol 1977; 7:* 58
4 Kersh ES, Kronfield SJ, Unger A et al. *N Engl J Med 1974; 290:* 650
5 Steiner AL, Pagliara AS, Chase LR, Kipnis DM. *J Biol Chem 1972; 247:* 1114
6 Ball HJ, Kaminsky IN, Hardman GJ et al. *J Clin Invest 1972; 51:* 2124