

BETA ADRENERGIC MODULATION OF EXTRARENAL POTASSIUM DISPOSAL IN TERMINAL URAEMIA

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Summary

In order to study the effect of epinephrine on potassium (K) metabolism, an epinephrine infusion ($0.1\mu\text{g}/\text{kg}/\text{min}$ for 30 min) was carried out in 12 essentially anuric and usually hyperkalaemic haemodialysis patients, 72 hr post-dialysis. Two groups emerged, group I (five patients) serum K decreased at least 0.75 mEq/L (from 6.6 ± 0.2 to $5.4 \pm 0.1\text{ mEq/L}$) and there were increases in heart rate, serum glucose and insulin values, group II (seven patients), serum K did not decrease and heart rate remained unchanged, but serum glucose and insulin increased slightly. Plasma renin, aldosterone and arterial pH did not change in either group. Propranolol blocked the epinephrine induced decrease in serum K in group I patients. Patients from group II had higher pre-infusion endogenous epinephrine concentrations than patients from group I.

In haemodialysis patients beta adrenergic stimulation enhances extrarenal K disposal but about 50 per cent of patients fail to respond, perhaps because of receptor occupancy due to higher endogenous epinephrine concentrations.

Introduction

Beta adrenergic stimulation has been recently shown to induce intracellular potassium uptake in normal subjects [1,2]. Other factors known to influence the balance between intracellular and extracellular fluid potassium content are pH, plasma bicarbonate, aldosterone and insulin [3].

Patients with terminal renal failure on maintenance haemodialysis offer a unique opportunity to study potassium metabolism, because of their spontaneous tendency to hyperkalaemia and because any short-term changes in their serum potassium must be extrarenal in origin. This article describes the effect of beta adrenergic stimulation on the potassium concentration of hyperkalaemic patients with terminal and irreversible uraemia.

Methods

Twelve non-diabetic essentially anuric patients with chronic renal failure on maintenance haemodialysis were selected because of their known tendency to hyperkalaemia. There were six males and six females, mean age 48 years (range 29 – 69) and mean time on dialysis 47 ± 9 months (\pm = SEM).

In these 12 patients, an i.v. epinephrine infusion ($0.1 \mu\text{g}/\text{kg}/\text{min}$ for 30 min) was performed by an infusion pump after an overnight fast, one hour recumbency and 72 hours post-dialysis. Throughout the infusion heart rate and blood pressure were automatically measured at five minute intervals (Dinamap® 845)

Immediately before and after the epinephrine infusion and at 15 min from its beginning, the following parameters were determined: serum potassium (K) by flame photometry, arterial pH, pCO_2 and total CO_2 and serum glucose by standard techniques, and plasma renin activity (PRA), serum aldosterone and insulin by radioimmunoassay. Pre-infusion endogenous epinephrine was measured in basal conditions by radioenzymatic assay.

In addition, in four of the patients and using a similar protocol, propranolol ($1.4 \mu\text{g}/\text{kg}/\text{min}$) was administered i.v. simultaneously with epinephrine by infusion pump.

The results, which are expressed as mean \pm SEM, were statistically analysed employing Student's t test, paired or unpaired, as appropriate.

Results

Immediately following the epinephrine infusion, two groups emerged. In group I (five patients), serum K decreased at least $0.75\text{mEq}/\text{L}$, from a mean basal value of 6.6 ± 0.2 to $5.4 \pm 0.1\text{mEq}/\text{L}$ ($p < 0.005$), whereas in group II (seven patients) serum K did not change from its basal value (Figure 1). Both groups were similar in age and duration of dialysis. Mean total decrement in serum K was significantly greater in group I than in group II (1.22 ± 0.18 vs $0.18 \pm 0.04\text{mEq}/\text{L}$, $p < 0.001$) (Figure 1).

In group I, epinephrine induced increases in heart rate ($68 \pm 3 - 87 \pm 3$ beats per min, $p < 0.005$), serum glucose ($76.4 \pm 2.8 - 128.4 \pm 3.2\text{mg}/100\text{ml}$, $p < 0.001$) and insulin ($16.4 \pm 1.8 - 22.8 \pm 1.8 \text{mU}/\text{ml}$, $p < 0.05$). However, in group II epinephrine did not significantly increase heart rate ($70 \pm 2 - 79 \pm 3$ beats per min, NS) or insulin ($16.5 \pm 1.8 - 19.7 \pm 1.3\text{mU}/\text{ml}$, NS) despite an elevation in serum glucose ($83.3 \pm 3.3 - 116.6 \pm 6.2\text{mg}/100\text{ml}$, $p < 0.001$) (Table I). Mean increment in heart rate at 15 min from the start of the epinephrine infusion was significantly higher in group I than in group III (18 ± 3.7 vs 8.6 ± 3.4 beats per min, $p < 0.05$).

There were no changes in either group in arterial pH, PRA or serum aldosterone (Table I).

When propranolol was infused simultaneously with epinephrine to four patients from group I, it totally blocked the decrease in serum K ($6.6 \pm 0.3 - 6.6 \pm 0.2\text{mEq}/\text{L}$).

Patients from group II had higher pre-infusion endogenous epinephrine values than those from group I (286.1 ± 79.6 vs $151.3 \pm 52.6\text{pg}/\text{ml}$ respectively).

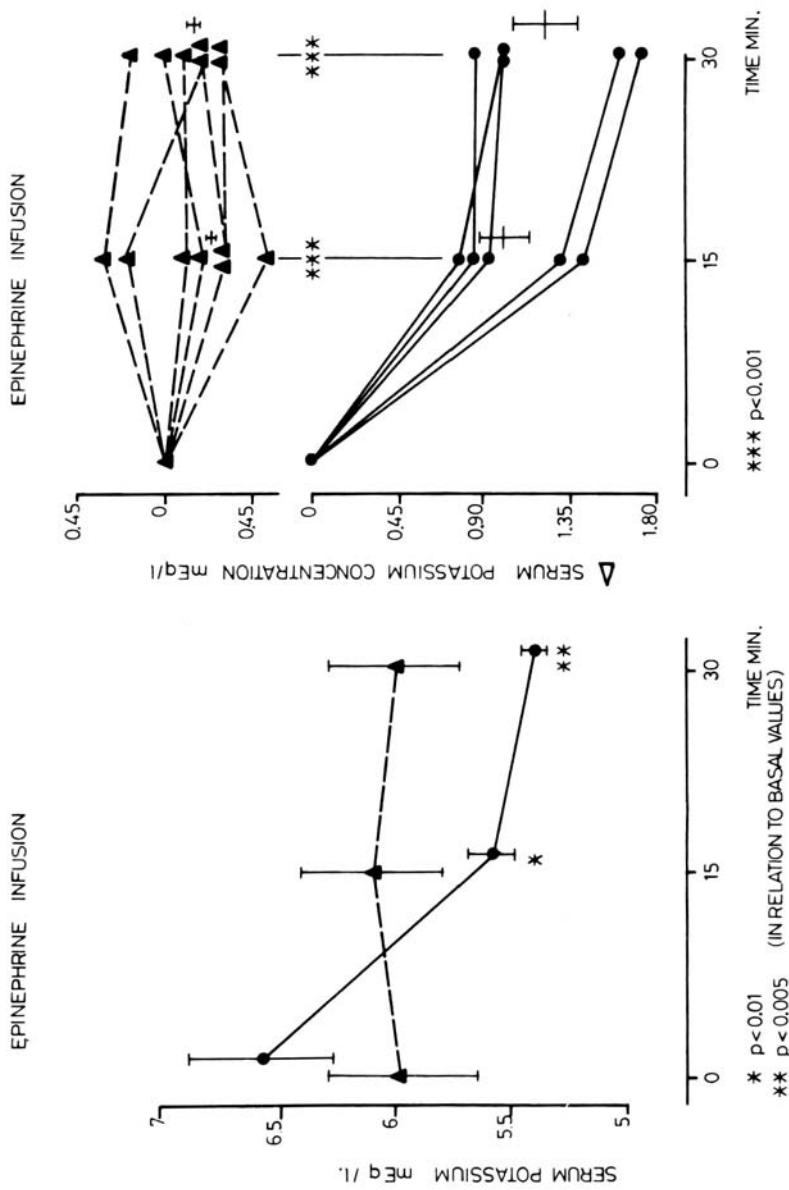


Figure 1. Changes in serum K induced by epinephrine in patients from group I (circles) and group II (triangles). Left, in absolute values. Right : in change from basal value

TABLE I. Effect of epinephrine on serum glucose, aldosterone, insulin, arterial pH, mean arterial pressure (MAP) and heart rate

	Glucose mg/dl	Insulin mU/ml	Aldosterone ng/dl	Arterial pH	MAP mmHg	Heart rate beats/min
GROUP I						
Basal	76.4±2.8	16.4±1.8	44.2±15.4	7.33±0.01	109.8±3.9	68 ±3.0
30 min	128.4±3.2	22.8±1.8*	38.5±13.2	7.32±0.03	103.4±3.3	87.2±3.4**
GROUP II						
Basal	83.3±3.3	16.5±1.8	37.1±11.6	7.37±0.02	111.5± 7	70.2±2.7
30 min	116.6±6.2***	19.7±1.3	32.9± 9.3	7.38±0.01	102.7±12	79.1±3

* p < 0.05

** p < 0.005

*** p < 0.001

Discussion

Experimental studies in animals and humans have demonstrated that the infusion of epinephrine, after an initial and transient increase in serum K due to alpha adrenergic stimulation in the liver induces a persistent decrease in serum K, which is mediated by beta-2 adrenoreceptor facilitation of intracellular K uptake primarily in the liver and muscle cells [1,2,4–8]. This effect is independent of epinephrine-induced insulin secretion and of changes in aldosterone [2].

Our study demonstrates that beta adrenergic stimulation directly facilitates extrarenal K disposal in some uraemic patients. This is supported by the fact that propranolol blocks the epinephrine induced reduction in serum K in the absence of pH or aldosterone changes. Other observations indicate that glucose and insulin do not effect the potassium lowering effect of beta adrenergic agonists [2]. In our study, patients from group I had an average increase in insulin levels of only 6.30mU/ml, whereas in other studies, exogenous insulin administration to obtain peripheral values of 45mU/ml did not produce a decline in basal K concentration [9] nor did the simultaneous infusion of glucose and K enhance intracellular K uptake [10].

A striking finding in the present study was the lack of response to the K lowering action of epinephrine in slightly more than half of our hyperkalaemic patients on chronic haemodialysis. In addition to the lack of K changes, the non-responders had other signs of unresponsiveness to beta adrenergic stimulation, such as the absence of a significant increase in heart rate or insulin concentrations. Since these patients had higher pre-infusion epinephrine values than those from group I, it is tempting to speculate that the lack of response to exogenous beta adrenergic agonists is due to receptor occupancy by endogenous epinephrine, but firm conclusions cannot be drawn due to the relatively small number of patients involved. Indirect data supporting the notion of adrenergic receptor occupancy in uraemia were recently presented, showing that hypotensive haemodialysis patients have higher norepinephrine values and a diminished response to the pressor effect of alpha adrenergic agonists than their

normotensive counterparts [11]. An alternative hypothesis explaining why some uraemic patients do not respond to the K-redistributing effect of beta adrenergic agents would be the existence of an unidentified toxic uraemic substance capable of blunting the action of exogenously administered epinephrine. This hypothesis remains speculative at the moment.

Although the demonstration of the facilitation of intracellular K uptake in uraemia by beta adrenergic agonists is mainly of pathophysiological interest, it could have practical implications: for instance, beta blocking agents, widely used in the haemodialysis patients, could potentiate the spontaneous tendency of these patients to become hyperkalaemic by limiting the possible contributory effect of beta adrenergic agonists to the maintenance of an adequate equilibrium between intracellular and extracellular potassium.

References

- 1 Rosa RM, Silva PS, Young JB et al. *N Engl J Med* 1980; 302: 431
- 2 De Fronzo RA, Bia M, Birkhead G. *Kidney Int* 1981; 20: 83
- 3 Sterns RH, Cox M, Feig PU, Singer I. *Medicine (Baltimore)* 1981; 60: 330
- 4 Vick RL, Todd EP, Luedke DW. *J Pharmacol Exp Ther* 1972; 181: 139
- 5 Lockwood RH, Lum BKB. *J Pharmacol Exp Ther* 1974; 189: 119
- 6 Silva P, Spokes K, Epstein FH. *Kidney Int* 1977; 12: 544
- 7 Hiatt N, Chapman LLW, Davidson MB. *J Pharmacol Exp Ther* 1979; 209: 282
- 8 Tyler K, De Fronzo R, Bia M. *Kidney Int* 1982; 21: 159 (abstract)
- 9 Guerra SMO, Kitabchi AE. *J Clin Endocrinol Metab* 1976; 42: 869
- 10 Sterns RH, Feig PU. *Clin Res* 1979; 27: 431A
- 11 Botey A, Gaya J, Montoliu J et al. *Proc EDTA* 1981; 18: 586

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