INCREASE IN SERUM POTASSIUM CAUSED BY BETA-2 ADRENERGIC BLOCKADE IN TERMINAL RENAL FAILURE: ABSENCE OF MEDIATION BY INSULIN OR ALDOSTERONE

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Summary

To test the hypothesis that beta-blockade might impair potassium (K) tolerance in terminal renal failure we gave propranolol, and then atenolol, to a group of 12 clinically stable non-diabetic patients on chronic haemodialysis and on a constant diet containing approximately 50mEq of K/day.

Propranolol, 60 to 80mg/day for 10 days induced a significant increase in predialysis serum K from 5.1 ± 0.1 to 5.8 ± 0.2mEq/L (p<0.005). Atenolol (50mg/day for 10 days) in the same group of patients did not produce a significant change in predialysis serum K (5.5 ± 0.2 vs 5.2 ± 0.2mEq/L). Both propranolol and atenolol decreased heart rate but neither drug induced significant changes in plasma aldosterone, arterial pH, serum insulin or blood glucose. Thus in haemodialysis patients, beta-2 adrenergic blockade by propranolol is associated with a significant increase in serum K not mediated by pH, aldosterone or insulin, and probably due to inhibition of intracellular K uptake. Selective beta-1 adrenergic blockade by atenolol at low doses does not change serum K, and therefore, if indicated, cardioselective beta-blockers might be preferable to non-selective drugs in haemodialysis patients.

Introduction

The balance between intracellular and extracellular potassium (K) content is influenced by pH, plasma bicarbonate, aldosterone and insulin [1]. In addition, beta-adrenergic stimulation has been recently shown to induce intracellular K uptake in normal subjects [2, 3] through a mechanism involving stimulation of the beta-2 adrenoreceptor [4] and independent from insulin or aldosterone changes [3].

In approximately half of uraemic patients, we have noted that an epinephrine infusion lowers serum K. This effect is not mediated by changes in arterial pH, serum insulin or aldosterone and the simultaneous administration of propranolol blocks the effect of epinephrine on serum K [5]. Accordingly, beta-blockade
might be expected to impair K tolerance in renal failure. To test this hypothesis we gave propranolol and then atenolol to a group of haemodialysis patients to determine if these drugs could modify the equilibrium between intracellular and extracellular K.

Methods

After informed consent, 12 essentially anuric, non-diabetic and clinically stable haemodialysis patients were selected to participate in the study. There were six males and six females, aged 35 to 71 years (mean 54 years). Time on dialysis ranged from 6 to 108 months (mean 66 months). All patients were normotensive or had occasional and slight volume-dependent hypertension. Throughout the study the patients were maintained on their usual diet, containing approximately 50mEq of K/day. No clinical incidences that could result in hypercatabolism occurred during the study period. No patient was taking medication other than aluminium hydroxide and/or iron. Atrioventricular block or clinically evident liver disease was absent in every case.

Propranolol was administered for 10 days; 60mg/day in three divided doses to patients with dry weights up to 60kg, patients over 60kg received 80mg of propranolol/day in two divided doses.

Immediately before and after the period of drug administration, the following pre-haemodialysis values were measured: blood pressure, heart rate, arterial pH, blood glucose, and serum K by standard techniques, and serum insulin and aldosterone by radioimmunoassay.

After completion of the propranolol trial there was a two week period without beta-blocking medication followed by a second phase using the cardioselective beta-1 blocker atenolol in a single daily dose of 50mg for 10 days. The dose was kept intentionally low to avoid losing cardioselectivity. The same procedures and laboratory determinations carried out during the propranolol trial were employed during atenolol administration.

Patient compliance was ensured by tablet counts and by monitoring heart rate.

Results

Two patients were withdrawn from the study, one for non-compliance and one for intolerance to medication (hypotension during dialysis) in the other patient.

In the remaining 10 patients, propranolol induced a significant increase in serum K, from $5.1 \pm 0.1\text{mEq/L} (\pm = \text{SEM})$ to $5.8 \pm 0.2\text{mEq/L}$ ($p<0.005$). In this group of patients, a control serum K measured three months prior to the initiation of the study, was essentially equal to that obtained immediately before the initiation of propranolol (Figure 1).

Two additional patients denied permission for continuation of the study with atenolol. In the remaining eight patients from the original group, atenolol did not produce a significant change in predialysis serum K, which in fact decreased slightly, from $5.5 \pm 0.2$ to $5.2 \pm 0.2\text{mEq/L}$, $p = \text{NS}$ (Figure 1).
Figure 1. Changes in serum K induced by propranolol and atenolol in haemodialysis patients

Figure 2. Percent change in serum K in relation to basal values after administration of propranolol or atenolol. Bars for each drug indicate mean magnitude of percentual change
In relative terms, propranolol induced a 14 ± 3 per cent increase in serum K in relation to basal values, whereas atenolol actually favoured a small decrement (-4 ± 4%) (Figure 2). The comparison in the difference in the percentual changes in serum K observed with the two drugs was statistically significant (p<0.005).

Both propranolol and atenolol decreased heart rate (72 ± 2 to 66 ± 2 and 76 ± 3 to 62 ± 3 beats per minute respectively, p<0.02 for both). As shown in Table I, neither propranolol nor atenolol induced significant changes in predialysis plasma aldosterone, arterial pH, serum insulin or blood glucose.

| TABLE I. Values of various measurements before and 10 days after propranolol or atenolol |
|---------------------------------|-----------------|-----------------|--------------|--------------|-----------------|-----------------|
| Heart rate beats/min           | Mean arterial   | Renin activity  | Plasma aldosterone | Serum glucose | Serum insulin   | Arterial pH     |
|                                | blood pressure  | ng ml⁻¹ h⁻¹     | ng/dl             | mg/dl        | mU/ml           |                 |
|                                | mmHg            |                 |                 |              |                 |                 |
| Pre                             | 72±2            | 108±8           | 1.19±0.7         | 57±11        | 90.4±5          | 31.6±6          | 7.34±0.01       |
| At 10 days                      | 66±2            | 108±8           | 0.26±0.1         | 51±10.7      | 93.3±3.5        | 29.6±3.5        | 7.34±0.01       |
| p                               | <0.02*          | NS              | NS               | NS           | NS              | NS              |

**PROPRANOLOL**

**ATENOLOL**

| Pre                             | 76±3            | 107±8           | 1.13±0.5         | 63.7±14       | 94.5±3.7        | 23.6±2.7        | 7.34±0.01       |
| At 10 days                      | 62±3            | 107±13          | 0.68±0.4         | 44.6±18       | 88±3.3          | 18±1.7          | 7.35±0.01       |
| p                               | <0.02*          | NS              | NS               | NS           | NS              | NS              |

* In relation to initial values

**Discussion**

The results obtained in this study indicate that the use of propranolol in haemodialysis patients is associated with a significant rise in serum K. Since there were no simultaneous changes in arterial pH, blood glucose, serum insulin or plasma aldosterone, it must be deduced that the increase in serum K seen with propranolol was not mediated by any of these factors and was probably due to inhibition of beta adrenergic facilitation of intracellular K uptake. Furthermore, this effect seems to be due to specific blockade of a beta-2 adrenergic receptor, because the administration in the same group of patients of the cardioselective beta-1 blocker atenolol at low doses failed to produce any significant change in serum K or in the other parameters measured, with the exception of heart rate. In addition the existence in our patients of end-stage renal failure with negligible residual urine output makes it highly unlikely that variations in the urinary excretion of K could have accounted for the decrease in serum K. It could be argued that whereas propranolol and atenolol are supposed to have similar beta-blocking
potency, as measured by their inhibition of isoproterenol-induced tachycardia [6], some of our patients received atenolol doses that were slightly lower than those used for propranolol. However, whereas propranolol is metabolised mainly by the liver, atenolol has a predominant renal route of excretion and small doses can accumulate in patients with renal failure [7]. We have observed severe hypotension caused by a single 100mg dose of atenolol [8], and indeed in this study, the reduction in heart rate was more pronounced with atenolol than with propranolol. Therefore we believe that the disparity between atenolol and propranolol with respect to their action on serum K in this group of patients cannot be explained by dose differences, which were minimal.

An increase in serum K has been observed in normal subjects during propranolol treatment [9]. Recently, this increase has been shown to be unrelated to the renin-angiotensin-aldosterone system [10], thus lending further support to our hypothesis of a mechanism based on blockade of the normal beta-2 adrenergic facilitation of intracellular K uptake. Nevertheless it should be noted that while the increase in serum K with the use of propranolol in normal subjects is small and clinically insignificant [9, 10], patients with renal failure are obviously at an increased risk of hyperkalaemia from beta-blockade.

Beta-blockers are commonly employed in patients with chronic renal failure, for the treatment of hypertension or ischaemic heart disease. The results of this study favour the view that propranolol should be used with caution in this group of patients because it can accentuate their spontaneous tendency to hyperkalaemia. When indicated, and since they do not seem to adversely influence serum K, cardioselective beta-blockers at low doses are therefore preferable to non-selective drugs.

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