Effect of different β-Adrenoceptor blocking Agents on Plasma Concentration and myocardial Content of K and Mg in Rats

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Zusammenfassung

Es wurden die Wirkungen von d-Propranolol, Propranolol und Atenolol auf Elektrolyte im Plasma und Myokard bei Ratten untersucht. In allen Gruppen wurden nach Behandlung signifikante Erhöhungen des Magnesiumgehaltes im Myokard und in der Propranolol- und Atenololgruppe des Kaliumgehaltes im Myokard beobachtet. Durch diese Studie kann der Mechanismus dieser Veränderungen nicht bestimmt werden, aber eine Kombination β-blockierender Wirkungen auf den Magnesiumtransport durch die Zellmembran, Änderungen der Aldosteronsekretion und membranstabilisierende Eigenschaften werden vermutet.

Summary

The effects of d-propranolol, propranolol and atenolol on plasma and myocardial electrolytes were studied in rats. Significant elevations of myocardial magnesium were observed in all groups following treatment, and of myocardial potassium in the groups on propranolol and atenolol. The mechanism for these changes cannot be determined by this study, but a combination of β-blocking effects on Mg transport over the cell membrane, changes of aldosterone secretion, and membrane stabilizing properties is suggested.

Résumé

Les effets de de-propranolol, propranolol et aténolol sur les électrolytes plasmatiques et myocardiales chez des rats étaient étudiés. On observait des élevations significatives de magnésium myocardial dans tous les groupes aprés le traitement, et une élevation dans les groupes avec propranolol et aténolol. Cet étude ne peut pas déterminé le méchanisme de ces changements, mais on suppose une combinaison des effets béta-bloquants du transport de magnésium á travers le membrane cellulaire, des changements de la sécrétion de l'áldostérone et des propriétés qui stabilisent les membranes.

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Introduction

Since the introduction of diuretic therapy it has been demonstrated that this treatment may give rise to sizable potassium (K) losses from the body and that these losses may achieve clinical significance in certain settings. Magnesium (Mg) losses have also been observed, the main importance of these losses being to prevent the correction of a simultaneous K deficiency by K supplementation alone [7, 20].

Recently, it has been suggested that the combination of diuretic therapy with β-blocking agents may abolish the unwanted effects of the diuretic drug on K metabolism [19]. The infusion of β-agonists has been demonstrated to lower serum K levels [5], and therapy with β-adrenoceptor blocking agents to raise serum K concentration [2, 15]. The supposedly beneficial effects of β-blockers on K metabolism has been challenged, though, and in two studies *Steiness* claims an additive, negative effect of β-blockers and diuretic therapy on intracellular K levels [17, 18]. The mechanism behind the effect of β-blockers on K metabolism has not been definitely settled. Therapy with β-blockers result in a decrease of plasma renin activity and of aldosterone secretion [1] and that would favour a positive effect on both K and Mg metabolism. On the other hand, membrane transport of sodium (Na) and K appears to be dependent on the activation of β-receptors [9], and the effect of β-blockers in this situation would be a negative influence on the intracellular K concentration.

The aim of the present investigation was to study the effects of a non-selective β-blocker, propranolol, a β_1-selective blocker, atenolol, and d-propranolol that has virtually no β-blocking activity (Tab. 1), on plasma concentration and myocardial content of K and Mg in rats.

Material and Methods

67 rats of the R-strain were used for this investigation. These rats had been inbred for 50 generations and were genetically very

Tab. 1: Some properties of the β-adrenoceptor blocking agents used in the study

	Affected receptors	Intrinsic sympathomimetic activity	Membrane stabilizing effect
d-propranolol	0	0	++
propranolol	β_1, β_2	0	++
atenolol	β_1	0	0

similar. There were 39 females and 28 males with weights ranging from 167 to 455 g. At the start of the study the rats were 18 months old. They were fed a regular diet and water ad libitum. The rats were divided into four groups. One group, (I, n = 17) continued without therapy, but were injected intraperitoneally with 0.9 % NaCl, 0.2 mg/kg body weight per day for 14 days. Group II (n = 17 received 0.2 mg propranolol/kg weight, group III (n = 16) 0.2 mg atenolol/kg body weight and group IV (n = 17) 0.2 mg d-propranolol/kg body weight daily for 14 days as an intraperitoneal injection. After the study period the animals were sacrificed by decapitation. Blood was collected and analyzed for Na, K, Cl (conventional Auto Analyzer technique) and Mg (atomic absorption spectrophotometry). The heart and soleus muscles were rapidly excised, and the left ventricle and the skeletal muscle were then treated and analyzed (Na, K, Mg, Cl) as earlier described for skeletal muscle biopsies [6].

Statistics

The formula for arithmetic means was used to calculate the mean values. The Student's t-test was used to determine whether any significant differences existed between the mean values obtained in the different groups.

Results

A. Plasma

The plasma values for the different groups are shown in Tab. 2. There were no significant differences between any of the groups regarding plasma K or plasma Mg. The groups on d-propranolol and propranolol had significantly higher values for both plasma Na ($p < 0.05$ and $p < 0.02$ respectively) and plasma Cl ($p < 0.005$ for both groups) compared to the control group.

B. Myocardium

The values from the myocardium are shown in Tab. 3. There were no significant differences between any of the groups regarding myocardial Na content. The d-propanolol group had a significantly higher myocardial Cl content compared to the controls ($p < 0.05$).

The K content of the left ventricle was significantly higher in the groups on propranolol and atenolol compared to the controls ($p < 0.05$ for both comparisons), while the group on d-propranolol had virtually the same mean value as the control group.

Regarding Mg content, all the treatment groups had elevated mean values compared to the controls, even the d-propranolol group ($p < 0.05$). The greatest difference was observed in the propranolol group ($p < 0.01$) with the atenolol group to follow ($p < 0.05$).

The same pattern was observed in the analyses from the soleus muscles.

Discussion

In this study the groups on active β-adrenoceptor blocking therapy demonstrated a significant elevation of myocardial K content compared to the control group and the group on d-propranolol. From these results and from the fact that both the non-selective and the β_1-specific β-blocker came out with the same result, it is quite obvious that the mechanism of action cannot have been through inhibition of the β_2-mediated Na-K-ATPase dependent transport of K into the cell. Nor can receptor stimulation be the explanation since both propranolol and atenolol lack intrinsic sympathomimetic activity. Membrane stabilizing effects differ

Tab. 2: Plasma values (mmol/l) for Na, K and Cl in the different groups. Mean ± SD. * significant compared to the control group, $p < 0.05$; ** $p < 0.02$; *** $p < 0.005$

	Na	K	Mg	Cl
Controls n = 17	140 ± 6.0	4.81 ± 1.07	1.07 ± 0.31	97.5 ± 4.0
d-propranolol n = 17	144 ± 3.3*	4.79 ± 0.75	1.11 ± 0.09	101 ± 2.2***
propranolol n = 17	144 ± 2.7***	4.63 ± 0.75	1.08 ± 0.07	101 ± 1.3***
atenolol n = 16	140 ± 7.6	4.66 ± 0.70	1.10 ± 0.08	99.6 ± 14.1

Tab. 3: Myocardial content (mmol/100 g fat free dry solids) of Na, K, Mg and Cl in the different groups. Mean ± SD. * significant compared to the control group, $p < 0.05$; ** $p < 0.01$

	Na	K	Mg	Cl
Controls n = 17	14.77 ± 4.22	31.09 ± 1.40	3.90 ± 0.33	11.13 ± 1.35
d-propranolol n = 17	16.46 ± 1.88	31.07 ± 2.26	4.18 ± 0.37*	12.69 ± 2.21*
propranolol n = 17	14.99 ± 1.50	33.03 ± 3.00*	4.54 ± 0.89**	11.14 ± 1.68
atenolol n = 16	15.13 ± 1.36	32.88 ± 2.66*	4.24 ± 0.58*	11.93 ± 1.28

between the two drugs, atenolol being devoid of this property, and cannot be inferred as the mechanism for increasing the cellular K content.

Both propranolol and atenolol decrease plasma renin activity and aldosterone secretion, though, and this is in contrast to d-propranolol. Thus, the effects on aldosterone could explain the cellular increase of K in the propranolol and the atenolol group.

Mg-transport across the cell-membrane seems to be regulated by a β-adrenergic response, not mediated by cyclic AMP [8]. Thus, isoproterenol has been demonstrated to inhibit the cellular uptake of Mg in wild-type S49 cells. Through kinetic experiments there are indications that the effects of isoproterenol are solely on Mg influx. The effects of terbutalin on Mg transport is similar to isoproterenol. These effects may be inhibited by propranolol [11]. The myocardial Mg content was raised in all treatment groups and cannot be explained by β-adrenoceptor blocking effects alone, since d-propranolol has no such effect. However, a combination of β-blocking and membrane stabilizing effects is a possibility. The highest mean value for Mg was observed in the propranolol group, propranolol having both β-blocking and membrane stabilizing properties. The second highest value was recorded in the atenolol group, atenolol having only β_1-blocking effects, and the third highest value was seen in the d-propranolol group, this drug having only membrane stabilizing effects. The combination of a β-blocker effect on membrane transport, an effect through a decrease of aldosterone and a stabilizing effect on the cell membrane could thus explain the recorded changes in Mg metabolism.

Recently, an effect of β-adrenoceptor blockade on parathyroid hormone (PTH) concentration has been suggested by some investigators [3, 4]. A decrease of PTH induced by β-blocking therapy could theoretically mean an increased cellular Mg content, but this mechanism would certainly not explain the results in the d-propranolol group. Besides, small changes of PTH levels do not seem to have any appreciable effects on Mg metabolism [14]. Challenging views on the effect of β-blockers on PTH have also been expressed in a recent study [12].

The release of insulin may be affected by β-blocking therapy [10], and this could lead to changes of the intra-/extracellular distribution of electrolytes. However, these changes would be expexted to occur in the opposite direction to those found, and besides, this mechanism does not apply to the d-propranolol group.

Our results are contradictory to the balance studies presented by *Steiness* [17, 18], where a negative K balance of about 150 mmol was found after six days on timolol treatment. However, *McCarron* et al. did not record any changes of K excretion in 39 hypertensive subjects following 2–4 weeks on propranolol therapy. Regarding Mg, these authors even observed a decrease, although insignificant, of the urinary excretion following therapy [12].

The present study was performed on rats, and caution must be exercised when extrapolating the results to man. E.g., the content of β_1- and β_2-receptors in the myocardium is different in different species. There is a majority of β_1-receptors in rat myocardium, 83 % [13], while the ratio between β_1- and β_2-receptors in the human myocardium has been found to be 50/50 [16].

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