The effects of cardioselective and non-selective
\(\beta\)-adrenoceptor blockade on the hypokalaemic and
cardiovascular responses to adrenomedullary hormones
in man

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Summary

1. Adrenaline was infused intravenously in nine
normal volunteers to plasma concentrations similar
to those found after myocardial infarction. This
study was undertaken on three occasions after
5 days' treatment with placebo or the \(\beta\)-adreno-
ceptor antagonists, atenolol or timolol.

2. Adrenaline increased the systolic pressure by
11 mmHg, decreased the diastolic pressure by
14 mmHg, and increased the heart rate by 7 beats/
min. These changes were prevented by atenolol.
However, after timolol the diastolic pressure rose
(+19 mmHg) and heart rate fell (−8 beats/min).

3. Adrenaline caused the corrected QT interval
\(QT_c\) to lengthen (0.36 ± 0.02 s to 0.41 ± 0.06 s).
No significant changes were found in the \(QT_c\)
when subjects were pretreated with atenolol or
timolol.

4. The serum potassium fell from 4.06 to 3.22
mmol/l after adrenaline. Serum potassium fell to a
lesser extent to 3.67 mmol/l after atenolol and
actually increased to 4.25 mmol/l after timolol.
Adrenaline-mediated hypokalaemia appears to
result from the stimulation of a \(\beta_2\)-adrenoceptor
linked to membrane \(Na^+/K^+/ATPase\) causing
potassium influx.

Key words: \(\beta\)-adrenoceptors, atenolol, catechol-
amines, hypokalaemia, potassium, timolol.

Introduction

There is increasing evidence of the link between
\(\beta_2\)-adrenoceptors and a membrane-bound \(Na^+/K^+
-ATPase in skeletal muscle. In animals this has been
demonstrated principally in studies of rat soleus
muscle [1]. In man, \(\beta\)-receptor agonists increase
the intracellular concentration of potassium in
erthrocytes and decrease intracellular sodium [2].
The subtype of adrenoceptor involved in this
potassium influx has been shown to be \(\beta_2\) from
studies of both human volunteers and patients
undergoing open heart surgery [3-5].

This mechanism may have important impli-
cations for patients with acute myocardial in-
farction. These patients have increased circulating
catecholamine levels [6, 7], especially of adrena-
line, which may act both directly on pacemaker
cells and indirectly by the above mechanism to
provoke arrhythmias. In the indirect mechanism,
increased adrenaline may stimulate potassium
influx into cells causing systemic hypokalaemia.
Hypokalaemia after myocardial infarction is
associated with an increased incidence of ventricu-
lar arrhythmias [8-10].

Adrenaline has already been shown in much
higher doses to lower the serum potassium in man
[11]. We have investigated whether the circulating
adrenaline levels observed after myocardial in-
farction can stimulate potassium influx and cause
significant hypokalaemia in normal volunteers. We
have also investigated the effect of cardioselective
and non-selective \(\beta\)-blockers on these potassium
changes.
A preliminary report of this study was presented at the Medical Research Society in London in December 1981 [12].

Methods

Nine normal male volunteers aged 24-32 years were studied. They had normal electrocardiograms, chest radiographs, serum biochemistry and haematology. They were infused with adrenaline to produce plasma adrenaline levels similar to those found after myocardial infarction [6]. Informed written consent was obtained from each subject. In addition, the study was approved by the Research and Ethical Committee of the Northern District of the Greater Glasgow Health Board. Each subject was studied on three occasions on the fifth day of treatment with either timolol 10 mg twice daily (Blocadren: Merck, Sharp and Dohme Ltd), atenolol 50 mg twice daily (Tenormin: Stuart Pharmaceuticals Ltd) or placebo in a randomized single blind fashion.

Exercise-induced tachycardia was measured on days 2 and 4 preceding each study. The doses of atenolol and timolol were then adjusted in each individual to produce the same degree of β₁-blockade (i.e. 20% reduction in exercise-induced tachycardia) with each treatment. On each study day, intravenous cannulae were inserted into the antecubital veins of both arms. They then received three 90 min infusions of 5% glucose solution containing ascorbic acid (1 mg/ml) and 0.01 and 0.06 μg min⁻¹ kg⁻¹ respectively of L-adrenaline (Antigen Ltd, Roscrea, Ireland), infused at 55 ml/h by a Braun Perfusor VI pump. Blood pressure, heart rate, serum electrolytes and plasma catecholamines were followed for 1.5 h before, during and for 2 h after the infusions.

Blood pressure was measured by a semi-automatic sphygmomanometer (Bosomat) and heart rate by a polygraph (Grass model 7D). The electrocardiogram was continuously displayed on an oscilloscope and also recorded at intervals on the polygraph. Serum electrolyte samples were centrifuged within 30 min to prevent haemolysis and subsequently analysed on a Technicon SMA 6/60 (Technical Instrument Corporation, Tarrytown, New York, U.S.A.) by using standard methods. Plasma adrenaline samples were collected into heparinized tubes kept on ice, centrifuged at 4°C and stored at −70°C until assayed. The adrenaline levels were measured by the sensitive radioenzymatic method of Da Prada & Zurcher [13]. The QT interval was measured from the onset of the Q wave to the point where a tangent to the descending limb of the T wave crossed the baseline. The QT interval was corrected for heart rate (QTc) by the Bazett Formula [14]. Statistical analysis was performed by repeated measures of analysis of variance and paired t-tests where appropriate.

Results

The results are given as the mean values ± SD. During placebo treatment, the baseline blood pressure was 103 ± 9/61 ± 7 mmHg and the heart rate was 60 ± 6 beats/min. After atenolol pretreatment the blood pressure was 95 ± 7/58 ± 6 mmHg and the heart rate 51 ± 6 beats/min. The dose of atenolol was 50 mg twice daily in seven volunteers but in two further volunteers this was required to be increased to 100 mg twice daily to produce the same degree of β₁-blockade as timolol. After timolol pretreatment, the blood pressure was 98 ± 7/55 ± 6 mmHg and the heart rate 52 ± 7 beats/min. The dose of timolol was 10 mg twice daily in all subjects.

<table>
<thead>
<tr>
<th>Infusion</th>
<th>Placebo</th>
<th>Atenolol</th>
<th>Timolol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before</td>
<td>0.45 ± 0.33</td>
<td>0.71 ± 0.54</td>
<td>0.45 ± 0.48</td>
</tr>
<tr>
<td>Glucose</td>
<td>0.53 ± 0.48</td>
<td>0.76 ± 0.61</td>
<td>0.40 ± 0.44</td>
</tr>
<tr>
<td>Adrenaline (0.01 μg min⁻¹ kg⁻¹)</td>
<td>1.36 ± 1.25</td>
<td>1.49 ± 0.74</td>
<td>1.10 ± 0.56</td>
</tr>
<tr>
<td>Adrenaline (0.06 μg min⁻¹ kg⁻¹)</td>
<td>4.67 ± 2.40</td>
<td>4.24 ± 2.31</td>
<td>3.90 ± 2.07</td>
</tr>
</tbody>
</table>

The plasma adrenaline levels (mean ± SD) during each infusion did not differ significantly between the placebo, atenolol or timolol study day (repeated measures analysis of variance).
Adrenaline, hypokalaemia and β-blockade

Fig. 1. Haemodynamic changes during infusion of adrenaline at 0.06 μg min⁻¹ kg⁻¹ after pretreatment with placebo, atenolol or timolol. Results are shown as the means ± SD. *P<0.05; **P<0.005.

Fig. 2. Serum potassium during the infusion of glucose solution containing adrenaline at 0, 0.01 and 0.06 μg min⁻¹ kg⁻¹ after pretreatment with placebo, atenolol or timolol. Results are shown as the means ± SD.

more, the plasma levels found during the adrenaline infusions at 0.06 μg min⁻¹ kg⁻¹ were similar to those previously found in patients with acute myocardial infarction [6].

The changes in blood pressure and heart rate during infusion of adrenaline at 0.06 μg min⁻¹ kg⁻¹ were compared with the effects of the control glucose infusion (Fig. 1). Adrenaline increased systolic blood pressure (+11 ± 6 mmHg), decreased diastolic pressure (−14 ± 9 mmHg) and increased heart rate (+7 ± 9 beats/min), although the actual changes produced are small. Atenolol partially prevented all of these haemodynamic effects. After timolol, however, there was a different haemodynamic response to infused adrenaline; the systolic blood pressure rose as before (+12 ± 5 mmHg) but the diastolic pressure also rose (+19 ± 4 mmHg) and there was a compensatory bradycardia (−8 ± 5 beats/min). In the presence of non-selective β-blockade infused adrenaline stimulated α-adrenoceptors, causing vasoconstriction and a rise in the diastolic blood pressure with a reflex bradycardia. Similar haemodynamic effects have been reported with another non-selective β-blocker, propranolol [15].

The serum potassium changes after the infusion of adrenaline are shown in Fig. 2. During low dose adrenaline infusion, there was a small fall in the serum potassium and at the higher level (0.06 μg min⁻¹ kg⁻¹) adrenaline caused a highly significant (P<0.0001) fall in the serum potassium to 3.22 ± 0.25 mmol/l. The serum potassium returned to baseline values 90 min after the end of the infusions. Atenolol partially blocks the potassium influx caused by adrenaline whereas after timolol the adrenaline-mediated potassium influx is completely blocked.

Adrenaline caused the corrected QT interval (QTc) to lengthen from 0.36 ± 0.02 s to 0.41 ± 0.06 s (P<0.025). After atenolol, no significant

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**Adrenaline, hypokalaemia and β-blockade**

**Systolic B.P.**  **Diastolic B.P.**  **Heart rate**

Δ Blood pressure (mmHg)

Δ Heart rate (beats/min)

Placebo  Atenolol  Timolol

**Fig. 1.** Haemodynamic changes during infusion of adrenaline at 0.06 μg min⁻¹ kg⁻¹ after pretreatment with placebo, atenolol or timolol. Results are shown as the means ± SD. *P<0.05; **P<0.005.

**Fig. 2.** Serum potassium during the infusion of glucose solution containing adrenaline at 0, 0.01 and 0.06 μg min⁻¹ kg⁻¹ after pretreatment with placebo, atenolol or timolol. Results are shown as the means ± SD.
QTc changes were seen (0.35 ± 0.02 s to 0.36 ± 0.03 s). Similarly, no significant QTc changes were seen after timolol (0.35 ± 0.02 s to 0.34 ± 0.02 s). T wave amplitude was reduced by adrenaline (-2.4 ± 1.9 mm; P < 0.002). No significant changes were seen after atenolol (-0.01 ± 0.8 mm) whereas timolol pretreatment was associated with an increase in T wave amplitude (+1.3 ± 0.8 mm; P < 0.001).

Discussion

Intravenous infusions of adrenaline have haemodynamic, metabolic and electrocardiographic effects. Our study confirms that the levels of plasma adrenaline found after myocardial infarction could cause significant hypokalaemia. The pulse rate and pulse pressure also increase and in the electrocardiogram, there is T wave flattening and prolongation of the QT interval. The latter electrocardiographic changes in particular have been associated with a predisposition to ventricular arrhythmias [16]. In our study, both atenolol and timolol prevented this potentially arrhythmogenic change in ventricular repolarization.

The metabolic effects of adrenaline on potassium homeostasis were first noted in 1934 by D'Silva, who found that an intravenous bolus of adrenaline in cats caused an immediate short-lived increase followed by a prolonged decrease in the serum potassium [17]. In 1960, Lepeschkin et al. infused adrenaline into normal human subjects and recorded the electrocardiogram changes of a reduction in T wave height and an increase in U wave amplitude [18]. Subsequently, infused adrenaline, at very high dose, was found to cause hypokalaemia in man [11]. Our study has shown that the levels of plasma adrenaline found after myocardial infarction can cause significant hypokalaemia. In coronary care units, approximately 15-20% of all patients have hypokalaemia on admission and this is commoner in those taking thiazide diuretics [8, 10, 19]. Furthermore, these hypokalaemic patients have an increased incidence of ventricular tachycardia and fibrillation [8, 19]. Of the patients with potassium levels less than 3.1 mmol/l, 67% experienced ventricular arrhythmias [8]. This study shows that adrenaline-induced hypokalaemia develops rapidly and also reverses relatively quickly in normal volunteers. We have also previously demonstrated that hypokalaemia during the acute phase of myocardial infarction is often transient [20]. Thus the often quoted figure of 20% having hypokalaemia in coronary care units may be an underestimate, especially if one considers those who die before reaching hospital.

The present study helps to characterize the type of β-adrenoceptor responsible for adrenaline-mediated potassium influx. Our results are similar to those obtained in salbutamol-induced hypokalaemia, where practolol partially blocked but propranolol completely blocked potassium influx [21]. In man, there is circumstantial evidence linking β2-adrenoceptors to Na+/K+-ATPase in studies of β-blockade during open heart surgery [4, 5]. Our study suggests that either Na+/K+-ATPase is linked to both β1- and β2-receptors or that β2-adrenoceptors alone are responsible and atenolol at the dose used is only relatively cardio-selective, exerting some action on β2-receptors.

Evidence is accumulating that β-blockade is beneficial in the secondary prevention of myocardial infarction [22-27]. There are many potentially beneficial properties of β-blockade after myocardial infarction in addition to the direct anti-arrhythmic or membrane stabilizing effect [28]. The reduction in oxygen demand with its resulting decreased infarct size would also seem to be of prime importance [29]. Seemingly of lesser importance are the antagonistic effects of β-blockade on the transmembrane flux of sodium, potassium or calcium [11, 30]. Overall the beneficial effects of β-blockade after myocardial infarction are likely to be multifactorial. The present study, however, demonstrates the importance of metabolic factors and in particular the inhibition of adrenaline-mediated potassium influx and hypokalaemia.

In our study, there was a difference between cardio-selective and non-selective β-blockade. Atenolol reduced the fall in serum potassium but did not, as timolol did, block it completely. In contrast, timolol but not atenolol caused an increase in diastolic blood pressure due to unopposed α-adrenoceptor-mediated vasoconstriction. This increase in diastolic pressure may be undesirable, at least in the acute phase of myocardial infarction. It would seem that cardio-selective β-blockers have a haemodynamic advantage whereas non-selective β-blockers have a metabolic advantage. It remains unclear, however, whether haemodynamic or metabolic factors are of more importance during increased sympathoadrenal activity.

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References


