Digitalis enhances exercise-induced hyperkalaemia

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Received: January 31, 1991/Accepted in revised form: April 13, 1991

Summary. In 9 patients with atrial fibrillation the effect of zero, low and high levels of serum digoxin on exercise-induced hyperkalaemia was assessed by bicycle exercise tests.

Exercise at each level of serum digoxin was associated with a significant (up to 20%) rise in plasma potassium. At a work load of 75 W the highest level of serum digoxin was associated with a significantly higher maximum plasma potassium concentration as compared to the maximum value at zero serum digoxin.

The enhancement of exercise-induced hyperkalaemia may add to the arrhythmogenic effect of digitalis.

Key words: Digitalis, Exercise; hyperkalaemia

Digitalis is widely used in the management of congestive heart failure and supraventricular tachyarrhythmias. Intoxication by digitalis is associated with a number of serious arrhythmias caused by changes in membrane polarization, and ensuing changes in the conduction, automaticity and excitability of the myocardium. Its mechanisms of action and clinical use have recently been reviewed [5]. Digitalis glycosides cause reversible inhibition of the Na,K-pump, which is generally accepted to be the cellular receptor for the therapeutic and toxic actions of digitalis. In the present study the effect of serum digoxin on exercise-induced hyperkalaemia has been assessed by measuring plasma potassium during bicycle exercise tests at 3 different levels of serum digoxin in each patient.

Materials and methods

The study was approved by the local Ethics Committee according to Helsinki Declaration II. Nine male patients ranging in age from 27 to 67 y (mean 53.5 y) with atrial fibrillation were studied. Patients with clinical or echocardiographic features of valvular heart disease were excluded. The patients had experienced atrial fibrillation for a period of 8 to 94 months (mean 32.6 months). The aetiology of atrial fibrillation was ischaemic heart disease in 6 patients, previous cardiac constriction in 1 patient, and lone atrial fibrillation in 2 patients. For comparison, 8 male subjects ranging in age from 39 to 62 y (mean 53.3 y) with ischaemic heart disease, in sinus rhythm, were studied. None of the patients nor the control subjects had clinical or radiological evidence of congestive heart failure, and none had angina pectoris at the time of examination. All patients and control subjects were normotensive and euthyroid, and all had normal plasma electrolyte and creatinine concentrations. None of the patients was receiving any other medication than digoxin. The control subjects received no medication for one week prior to the study.

The patients performed 3 series of exercise tests at intervals of 2 weeks, at 3 different levels of serum digoxin, i.e. zero, low and high within the therapeutic range (1.3 to 2.6 nmol.l⁻¹), respectively. The required dose of digoxin at each level was based upon the patient’s maintenance dose and serum concentration before the study. To avoid development of possible digoxin tolerance during the study, the order of the 3 doses was randomized. The dose schedules were kept constant for at least 10 days before each exercise test. At each serum digoxin level the patient performed three consecutive bicycle exercise tests at increasing work loads of 25, 50 and 75 Watt (W). Each exercise test lasted 20 min and was followed by a 1 h period of supine rest. The heart rate was recorded and blood samples were obtained from the cubital vein every 5 min during the exercise period and every 15 min during the rest period. To accommodate the considerable variation of heart rate in atrial fibrillation, the rate was recorded over 1 min at the end of each period. The control subjects performed one series of exercise tests and only the heart rate was recorded.

Serum digoxin concentrations were determined in triplicate using a commercial radioimmunoassay (Diagnostic Products Corp.). Serum potassium was determined by flame photometry. The data are expressed throughout as mean (SEM). The statistical significance of any difference was ascertained using the two-tailed t-test.
for non-paired groups of observations, unless otherwise stated. Linear regression analysis was performed using the least squares method. $P < 0.05$ was considered significant.

**Results**

The initial serum digoxin concentrations were 0.0 (0.0), 1.1 (0.1) and 2.5 (0.3) nmol·L$^{-1}$ ($P < 0.001$), respectively, at zero, low and high doses of digoxin (Table 1). As reported previously, there was a significant decrease in serum digoxin during each exercise test, followed by near normalization during the rest period [6, 7]. The maximum heart rate during the three consecutive exercise tests at 25, 50 and 75 W in patients with atrial fibrillation, at various levels of serum digoxin, is also listed in Table 1. When compared to control subjects in sinus rhythm, the heart rate was not adequately controlled during exercise at any serum digoxin level, despite the reduction in heart rate with increasing serum digoxin.

The plasma potassium concentrations during the consecutive bicycle exercise tests at 25, 50 and 75 W, each followed by 1 h of rest, at zero, low and high levels of serum digoxin, are shown in Fig. 1. As can be seen, exercise at each work load was associated with a significant rise in plasma potassium ($P < 0.05$, paired $t$-test), and at each level of serum digoxin there was a highly significant correlation between work load and maximum plasma potassium concentration ($r=0.99$, $P < 0.001 \times 3$, respectively). Although there was a tendency to a larger rise, the maximum plasma potassium concentrations were not significantly different ($P < 0.30$) at low and zero levels of serum digoxin. At work loads of 25 and 50 W there was no significant difference ($P < 0.20$) between the maximum plasma potassium concentration at the various levels of serum digoxin. However, at the highest work load of 75 W, the maximum plasma potassium concentration was significantly higher ($P < 0.05$) at the highest level of serum digoxin as compared to the maximum value at a zero serum digoxin.

The initial plasma potassium concentrations were not significantly different at the various levels of serum digoxin ($P > 0.20$). During the rest periods there was a rapid fall in plasma potassium which reached the initial values within the first 15 min ($P > 0.10$, paired $t$-test) at all levels of serum digoxin.

**Table 1.** Heart rate in response to exercise at zero, low and high levels of serum digoxin in patients with atrial fibrillation and in control subjects in sinus rhythm

<table>
<thead>
<tr>
<th>Serum digoxin (nmol·L$^{-1}$)</th>
<th>Heart rate (beats·min$^{-1}$)</th>
<th>Rest</th>
<th>25 W</th>
<th>50 W</th>
<th>75 W</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.0 (0.0)</td>
<td>92 (10)</td>
<td>125 (14)</td>
<td>136 (14)</td>
<td>158 (12)</td>
<td></td>
</tr>
<tr>
<td>1.1 (0.1)</td>
<td>75 (6)</td>
<td>114 (12)</td>
<td>126 (12)</td>
<td>147 (11)</td>
<td></td>
</tr>
<tr>
<td>2.5 (0.3)</td>
<td>71 (6)</td>
<td>101 (8)</td>
<td>119 (11)</td>
<td>141 (11)</td>
<td></td>
</tr>
<tr>
<td>Controls</td>
<td>0.0 (0.0)</td>
<td>75 (2)</td>
<td>91 (3)</td>
<td>102 (3)</td>
<td>117 (2)</td>
</tr>
</tbody>
</table>

**Discussion**

The present study has confirmed the finding that even moderate exercise is associated with a significant increase in plasma potassium [1, 2]. During the action potential and