Skeletal Muscle Digoxin Concentration and its Relation to Serum Digoxin Concentration and Cardiac Effect in Healthy Man

T. Jogestrand and K. Sundqvist
Department of Clinical Physiology, Karolinska Hospital, Stockholm, Sweden

Summary. Blood samples and skeletal muscle biopsies (m. quadriceps femoris, vastus lateralis) were taken from seven healthy subjects for analysis of serum and skeletal muscle digoxin concentrations by radioimmunoassay using a percutaneous needle biopsy technique for muscle sampling. The subjects were investigated on two digoxin dose levels and on the third day after withdrawal of digoxin. It was found that the skeletal muscle/serum digoxin ratio was significantly higher than the corresponding ratio obtained in a previous study with muscle sampling (m. rectus abdominis) from patients during open heart surgery. The present study indicates a significant correlation between the digoxin concentrations in serum and skeletal muscle as well as between cardiac effect, measured by changes in QS1, and skeletal muscle digoxin concentration. A doubling of the digoxin dose gave a proportional increase in skeletal muscle digoxin concentration. The magnitude of the estimated half-life of skeletal muscle digoxin was the same as previously reported for serum or plasma digoxin.

Key words: digoxin, muscle biopsy; skeletal muscle levels, serum levels, systolic time intervals

Increased knowledge of the clinical pharmacology of digoxin in man has been gained by estimation of digoxin concentration in blood and various tissues using 3H-digoxin and digoxin radioimmunoassay (see Doherty et al. 1978), and serum or plasma digoxin analysis is now used in clinical practice (Smith et al. 1969). In addition to digoxin concentration in blood, interest has been focussed on digoxin concentration in the effector organ, the heart (see Malcolm and Coltart 1977). Comparatively few studies have been published (e.g. Doherty et al. 1967) in which the digoxin concentration in skeletal muscle has been analyzed. Skeletal muscle is, however, an interesting and important tissue in this respect, for three main reasons: 1) The major depot for digoxin in man is skeletal muscle; about 50% of the total body content of digoxin is bound to this tissue (Steiness 1978). 2) The effect of cardiac glycosides on skeletal muscle is similar to that on the heart, with an increased contractile force being produced by a high concentration of glycoside in the tissue (Smulyan and Eich 1976). 3) The percutaneous needle biopsy technique proposed by Bergström (1962) makes skeletal muscle accessible for digoxin assay without surgical intervention.

As has recently been shown, a highly significant correlation exists between the digoxin concentration in skeletal muscle and right atrial myocardium in patients with sinus rhythm, using biopsies taken during open heart surgery (Jogestrand 1980). The purposes of the present investigation were 1) to investigate the intra-individual relation between the dose of digoxin and the skeletal muscle digoxin concentration, 2) to find out if there were any relation between digoxin concentration in skeletal muscle and the effect of the drug on the heart, 3) to estimate the elimination rate of digoxin from skeletal muscle, and 4) to compare the digoxin level in the thigh muscle with that previously found in biopsies taken from the rectus abdominis muscle during open heart surgery (Jogestrand 1980). For this purpose a method of analysis of the digoxin concentration in skeletal muscle (m. quadriceps femoris – vastus lateralis) using the percutaneous needle biopsy technique was developed.
Subjects and Procedures

Seven healthy volunteers (6 men and 1 woman, aged 25-41 years), with normal resting and exercise ECG and heart volume, took part in the study, which was approved by the Ethical Committee at the Karolinska Hospital. The nature and purpose of the investigation were explained to the subjects and their consent was obtained.

The subjects were investigated on four different occasions: before digoxin, after 2-3 weeks' intake of digoxin at lower (0.13-0.25 mg/day) and higher (0.25-0.50 mg/day) doses (last dose of digoxin taken about 24 h before the investigation), and on the 3rd day after withdrawal of digoxin (about 72 h after the last dose). The subjects were investigated on each occasion according to the following schedule: after about 15 min at rest in the supine position, blood samples were taken for analysis of electrolyte, creatinine and digoxin concentrations. ECG, phonocardiogram and external carotid arterial pulse were recorded at rest in the supine position. A percutaneous muscle biopsy was taken from the quadriceps femoris muscle (vastus lateralis) using the needle biopsy technique. The needle was inserted into the muscle through a small incision made in anesthetized skin. The results of the exercise tests (ECG-reaction during exercise before, during and after digoxin intake) will be reported elsewhere (Sundqvist and Jogestrand, in preparation).

Methods

Skeletal Muscle and Serum Digoxin Concentrations

The skeletal muscle samples were freeze-dried and carefully freed from connective tissue and fat. Appropriate amounts of the freeze-dried muscle tissue were weighed and homogenized in phosphate buffer, and digoxin was extracted from tissue with dichloromethane. After evaporation of the dichloromethane phase, the residue was re-dissolved in human serum and digoxin concentration was measured by radioimmunoassay (Smith et al. 1969) using a commercial 125I-RIA-kit (New England Nuclear, MA, USA). Serum samples (50 or 100 μl depending upon the expected digoxin concentration) were added to phosphate buffer, and serum digoxin was then extracted and assayed in the same way as tissue digoxin, the method has previously been described in detail (Jogestrand 1980). The lowest measurable digoxin concentration by this method was 0.03 nmol/l.

Table 1. Age, sex, dose of digoxin, digoxin concentration in serum and skeletal muscle and skeletal muscle digoxin/serum digoxin ratio in seven healthy subjects

<table>
<thead>
<tr>
<th>Subject No.</th>
<th>Age [years]</th>
<th>Sex</th>
<th>Dose of digoxin [μg/kg b.w.]</th>
<th>Dose I</th>
<th>Dose II</th>
<th>Dose I</th>
<th>Dose II</th>
<th>Dose I</th>
<th>Dose II</th>
<th>Dose I</th>
<th>Dose II</th>
</tr>
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<tbody>
<tr>
<td>1.</td>
<td>36</td>
<td>M</td>
<td>3.7</td>
<td>0.4</td>
<td>0.8</td>
<td>23</td>
<td>36</td>
<td>58</td>
<td>45</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.</td>
<td>28</td>
<td>M</td>
<td>1.9</td>
<td>0.3</td>
<td>0.5</td>
<td>14</td>
<td>31</td>
<td>46</td>
<td>62</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.</td>
<td>35</td>
<td>M</td>
<td>3.4</td>
<td>0.6</td>
<td>1.4</td>
<td>40</td>
<td>58</td>
<td>66</td>
<td>41</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4.</td>
<td>41</td>
<td>M</td>
<td>3.8</td>
<td>0.4</td>
<td>0.9</td>
<td>16</td>
<td>37</td>
<td>40</td>
<td>41</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5.</td>
<td>26</td>
<td>M</td>
<td>3.6</td>
<td>0.8</td>
<td>1.4</td>
<td>&lt;22</td>
<td>(inadequate material)</td>
<td>48</td>
<td>&lt;28</td>
<td>34</td>
<td></td>
</tr>
<tr>
<td>6.</td>
<td>25</td>
<td>M</td>
<td>3.2</td>
<td>0.5</td>
<td>1.0</td>
<td>-</td>
<td>41</td>
<td>-</td>
<td>41</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7.</td>
<td>25</td>
<td>F</td>
<td>1.9</td>
<td>0.4</td>
<td>0.8</td>
<td>&lt;13</td>
<td>(inadequate material)</td>
<td>25</td>
<td>&lt;32</td>
<td>31</td>
<td></td>
</tr>
</tbody>
</table>

Mean ± SD

N

30.8 ± 6.4

3.07 ± 0.82

6.10 ± 1.72

0.48 ± 0.16

0.97 ± 0.33

23.2 ± 11.8

39.4 ± 10.9

52.5 ± 11.7

42.1 ± 10.0

4

7

7

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