Effects of ranitidine and cimetidine on ventricular fibrillation threshold and old dispersion of refractory period in early myocardial ischemia

Luo Xiao-Xing, Tan Yue-Hua

Abstract The effects of two H2-receptor antagonists, ranitidine (Ran) and cimetidine (Cim), on the ventricular fibrillation threshold (VFT) and dispersion of the refractory period in animals with early acute myocardial ischemia induced by coronary artery ligation (CAL) were studied. The measurement of VFT was obtained in anesthetized rats. The control group showed a decrease in VFT from 8.7 ± 0.4 to 3.1 ± 0.7 V 5 min after CAL, whereas Ran (15 mg/kg iv) and Cim (40 mg/kg iv) increased VFT from 2.8 ± 0.7 to 5.4 ± 1.7 V and from 3.1 ± 0.8 to 8.1 ± 2.7 V, respectively. By means of suction electrodes, FRP in different ischemic zones were recorded in anesthetized rabbits, and differences between FRP in different zones were taken as the dispersion of FRP. After CAL, the control group exhibited a prolongation of FRP in central ischemic zone and a shortening of FRP in boundary zone, i.e., a dispersion of FRP was increased. Both Ran (5 mg/kg iv) and Cim (25 mg/kg iv) markedly decreased the extent of dispersion of FRP. It is concluded that the anti-arrhythmic effects of Ran and Cim may be attributable to increases in VFT and decreases in dispersion of FRP.

Key words ranitidine, cimetidine, histamine, myocardial infarction, ventricular fibrillation, myocardial refractory period

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Materials
Ren for the intramuscular preparation, 100 mg/kg; Cin for the intravenous preparation, 15 mg/kg; and ECG for the monitoring of blood pressure.

Methods and results
Ran and Cin对大鼠缺血性心肌损伤的保护作用

Sprague-Dawley rats (100 ± 10 g) were randomly divided into four groups: control group (C), model group (M), Ran group (R), and Cin group (C). The model group was induced by occlusion of the left anterior descending coronary artery for 1 h followed by reperfusion for 1 h. The Ran and Cin groups were given Ran (5 mg/kg) and Cin (15 mg/kg) intravenously, respectively, for 1 h before reperfusion.

The heart was removed after reperfusion and the left ventricular weight was measured. The heart was then fixed in formalin and cut into 5 mm thick slices in the transverse plane. The slices were then stained with hematoxylin and eosin (H&E) and the myocardial infarction area was measured.

The results showed that the Ran and Cin groups had a significantly lower myocardial infarction area compared to the model group. The Ran group had a lower myocardial infarction area than the Cin group. These results indicate that Ran and Cin have a protective effect on the myocardium after ischemia.

Discussion
Ran and Cin have been shown to have anti-inflammatory and anti-oxidative effects, which may contribute to their protective effect on the myocardium. Further studies are needed to elucidate the mechanism of action of these drugs.

Tab 1. Effects of ranitidine (Ran) and cimetidine (Cim) on ventricular fibrillation (VF) threshold of myocardial ischemia induced by coronary artery ligation (CAL) in anesthetized rats, n = 6, *p < 0.05, ***p < 0.001 vs Pre-CAL, †p < 0.05, ‡p < 0.01 vs Post-CAL.

<table>
<thead>
<tr>
<th>Drug</th>
<th>VF threshold (V)</th>
<th>Pre-CAL</th>
<th>Post-CAL</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ren 2 (mg/kg)</td>
<td>4.7 ± 0.4</td>
<td>3.1 ± 0.4</td>
<td><strong>p &lt; 0.01</strong></td>
<td></td>
</tr>
<tr>
<td>Cim 20</td>
<td>7.4 ± 0.4</td>
<td>5.4 ± 0.4</td>
<td><strong>p &lt; 0.01</strong></td>
<td></td>
</tr>
</tbody>
</table>

Tab 2. Functional refractory period (ms) in different myocardial zones influenced by intravenous administration of Ran 5 mg/kg or Cin 25 mg/kg in anesthetized rabbits with coronary artery ligation (CAL), n = 7, *p < 0.05, **p < 0.01 vs NS.

<table>
<thead>
<tr>
<th>Zone</th>
<th>Drug</th>
<th>Before CAL</th>
<th>After CAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central NS</td>
<td>127 ± 13</td>
<td>137 ± 11**</td>
<td></td>
</tr>
<tr>
<td>Ran 5</td>
<td>129 ± 15</td>
<td>137 ± 11**</td>
<td></td>
</tr>
<tr>
<td>Cin 25</td>
<td>128 ± 12*</td>
<td>137 ± 11**</td>
<td></td>
</tr>
<tr>
<td>Boundary NS</td>
<td>117 ± 14</td>
<td>136 ± 10**</td>
<td></td>
</tr>
<tr>
<td>Ran 5</td>
<td>130 ± 10*</td>
<td>137 ± 11**</td>
<td></td>
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Discussion
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动员电位时程呈平行缩短，中枢区的FRP延长，可超过动员电位时程出现复极最后不应期（PRR），致不规则离散，不应期离散在延迟性心律失常形成中起重要作用，**心率减慢**2-6 min 后，不应期离散最明显，这与心律失常的发生时间一致**[**4**]**。本实验通过循环血池CPA及6 min 后的FRP，结果表明，NS能FRP变化与实验**[**4**]**一致，Ran 与Clm 则可明显防止延迟性心律失常**[**4**]**造成及中央区FRP的延迟，降低不应期的离散度，进而有助于消除迟后，提高最低起搏心率的敏感度和提高不应期的敏感度。可能是Ran与Clm 抑制心律失常的作用的生理基础，心率减慢心肌耗氧增量增加，NS可通过β2受体增加心苷Clm 内的血流量**[**4**]**。Ran 与Clm 则可选择性地阻断H2受体，因此可能通过抑制Clm 内的血流量，防止H2所导致心律失常。

Ran 拟似阻断H2 受体的作用约为Clm 的10倍**[**4**]**。若两药的上述作用的阻断H2 受体所致，则其效果相类似，Clm 的作用应为Ran 剂量的10 倍，而本实验中 Clm 的作用仅为Ran 剂量的2.6-5 倍，由此可以看出Clm 提高VTF 的作用优于Ran，降低FRP敏感度的作用与Ran 相同。表明Clm 对VTF 和FRP的抑制作用优于H2 受体外，可能尚有其它机制参与。

References
11. Fleischmann A. Calcium antagonism in heart.