QT AND QTc PROLONGATION AND DECREASED HEART RATE AFTER IV ADMINISTRATION OF LEVAMISOLE HYDROCHLORIDE IN CONSCIOUS RABBITS

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Abstract

Intravenous doses of 2.5 mg/kg and 5.0 mg/kg of levamisole on RR, QT, QTc (corrected QT), and heart rate in conscious rabbits were evaluated. The study was performed on 14 New Zealand rabbits, 1 year old, weighing between 2.5-3 kg. The animals were assigned to 2 equal groups. Rabbits of groups I and II received via the auricular vein 2.5 mg/kg and 5 mg/kg of levamisole HCl, respectively. Alligator clips were attached to four limbs. ECG records were taken by direct writing electrocardiograph before the study and after 2, 4, 6, 8, 10, 15, and 20 min of the experiment. The QT interval was manually calculated from the beginning of Q wave to the end of T wave. The same leads (II and aVR) were selected for all QT interval measurement. The animals were not given any sedatives or anaesthetics before and during ECG recording. In group I, two rabbits had the second degree atrial block at the 2nd and 4th min after the injection, which disappeared later. Heart rates were 216-230 beats/min at min 0 and dropped to 193-210 beats/min at the 2nd min after the injection in both groups, and remained low throughout the study. Heart rates of both groups taken at 2, 4, 6, 8, 10, 15, and 20 min after the injection were significantly lower than the values taken at 0 min except for the values of the 15th min in group II. QT and QTc prolongation was noticed in both groups when compared to 0 min values. Although we have no solid data to explain the mechanism involved in bradycardia and atrial block provoked by levamisole, its use resulted in bradycardia, second-degree atrial block, and acute prolongation of QT and QTc in conscious rabbits.

Key words: rabbit, levamisole, electrocardiography, heart rate.

Levamisole, a well-known anthelmintic and drug commonly used in veterinary and human medicine, has gained promising results in recent years in the treatment of cancer in humans. Its use in cancer therapy, especially in the treatment of colon and breast cancers, along with other antineoplastic drugs prolonged the survival of patients (2, 4, 17, 18).

Studies involving animals revealed that high doses of levamisole induced cardiotoxic effect (11, 12) but low doses had no adverse effect (7, 16). However, there is a lack of sufficient number of studies on the effect of immunstimulant doses of levamisole on the heart. Two previous studies disclosed a high blood pressure in animals given intravenously different doses of levamisole (1, 5). In other studies, the effect of levamisole used in rats and guinea pigs under anaesthesia ranged from bradycardia, sino-atrial depression, A-V block, to tachycardia or fibrillation (11, 12). However, many anaesthetic drugs also change electrophysiology of the heart thus the results of such studies may be misleading.

One of the most diagnostic parameters used in the evaluation of drug effects on heart is QT/QTc interval as the extension of QTc interval may result in torsade de pointes due to fatal ventricular tachycardia (15).

This study was designed to evaluate the acute effects of intravenous administration of levamisole on HR, QT, and QTc intervals in conscious rabbits.

Material and Methods

The study was performed on 14 New Zealand rabbits, aged 1 year, and weighing 2.5-3 kg. The animals were assigned to 2 equal groups and were fed ad libitum in their individual cages. They were brought to the laboratory around 1 h before the experiment. ECGs were taken a day before the experiment for adaptation purpose. Those who were extremely excited and not
suitable for the study were replaced by others. Area where clips would be attached was clipped of hair 3 d before the experiment. The Laboratory Animal Care and Use Committee of Veterinary Faculty approved all the experimental protocols.

Groups I and II were injected via the auricular vein with 2.5 mg/kg and 5 mg/kg of levamisole HCl (Actipar® inj, ALKE, Turkey) per rabbit, respectively. Alligator clips were attached to four limbs. ECG records were taken by direct writing electrocardiograph (Logos 8821, Logos Medical Co. Ltd., Japan) before the study and after 2, 4, 6, 8, 10, 15, and 20 min of the experiment. ECG was standardised at 1 mV=20mm, with chart speed of 50 mm/s with filter off. Leads I, II, III, aVR, aVL, and aVF were determined. QT interval was manually calculated from the beginning of Q wave to the end of T wave. The same leads (II and aVR) were selected for all QT interval measurement. The heart rate (HR) was estimated during ECG recording. The animals were not given any sedatives or anaesthetics before and during ECG recording.

The QT interval was corrected for heart rate with Carlsson (QTcC) formula: QTcC=QT-0.175 (RR-10.0, 2000). The data are presented as mean ± SEM (Duncan test) using SPSS statistical package (Version 10.0, 2000). The study unveiled that of 2.5-5.0 mg/kg of levamisole resulting in a decrease heart rate starting at the 2nd min after injection. On the other hand, Onuaguluchi and Igbo (11, 12) found no changes in heart rates after the administration of different doses of levamisole in guinea pigs. This discrepancy between the studies might be explained by different species used, where rabbits may be more prone to levamisole side effect than guinea pigs.

Levamisole decreased HR in both groups. To the best of our knowledge, there is no single study yet indicating that levamisole may cause changes in heart action potential and influence ion channels but previous studies shown that levamisole decreased heart rate (6). In this study, 2.5 mg/kg dose of levamisole resulted in a more remarkable decrease in the heart rate when compared to 5 mg/kg dose. The heart rate in rabbits of group II returned to normal 15 min after the injection. On the other hand, Onuaguluchi and Igbo (12) found no changes in heart rates after the administration of different doses of levamisole in guinea pigs. This discrepancy between the studies might be explained by different species used, where rabbits may be more prone to levamisole side effect than guinea pigs.

Levamisole induced QT and QTc prolongation in both groups. These values increased from 145 msec to 172 msec in group I, and from 143 msec to 167 msec in group II, respectively. Prolongation of the QTc interval on surface ECG reflects the summation of delay in repolarisation in all ventricular myocytes and when drug induced, it is almost always due to inhibition of the rapid component of the delayed rectifier potassium current (IKr) (15). Levamisole has been shown to posses the antiarrhythmic effect (10). However, drug induced QTc prolongation can also be pro-arrhythmic and can induce torsade de pointes (TdP), a potentially fatal and unique form of polymorphic ventricular tachycardia. However, polymorphic ventricular tachycardia was not observed in any rabbits in this study. For TdP to occur, QTc prolongation must exceed beyond certain values. The doses we used were within the safe range reported for levamisole but our findings require more attention as the second-degree heart block occurred in two rabbits of group I when the drug was used.

In conclusion, although we have no solid data to explain the mechanism involved in bradycardia and atrial block provoked by levamisole, its use resulted in bradycardia, second-degree atrial block, and acute prolongation of QT and QTc. Levamisole, beside other side effects, has potential cardiotoxic effects and thus caution should be exercised when using the drug. Further detailed studies are required to understand the mechanism(s) involved in this effect.
Table 1
Mean time course change of RR, QT, QTcC, and HR intervals in non anaesthetised rabbits injected with 2.5 mg/kg or 5 mg/kg of levamisole HCl

<table>
<thead>
<tr>
<th>Values</th>
<th>Dose</th>
<th>Time (min) after levamisole HCl injection (n=7 for each dose)</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>Baseline</td>
</tr>
<tr>
<td>RR</td>
<td>2.5 mg/kg</td>
<td>279±3.65&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>5 mg/kg</td>
<td>262±3.11&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>QT</td>
<td>2.5 mg/kg</td>
<td>145±0.92&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>5 mg/kg</td>
<td>142±1.13&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>QTcC</td>
<td>2.5 mg/kg</td>
<td>146±0.92&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>5 mg/kg</td>
<td>143±1.13&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>HR</td>
<td>2.5 mg/kg</td>
<td>216±2.74&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>5 mg/kg</td>
<td>230±2.86&lt;sup&gt;a&lt;/sup&gt;</td>
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</tbody>
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<sup>a, b</sup> values are different from the baseline levels with different superscript in the same line.
References