Effects of salbutamol given by metered-dose inhaler on dispersion of ventricular repolarization

Ölçülü doz inhalerle verilen salbutamolün ventrikül repolarizasyonunun dispersiyonu üzerine etkisi

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ABSTRACT

Objective: Salbutamol has previously been shown to increase the QT dispersion (QTd), which may be associated with high risk of cardiac arrhythmia in asthmatics. Cardiac effects of salbutamol occur in dose-related manner and salbutamol dose given by metered-dose inhaler (MDI) during acute asthma attack is commonly lower than the dose given by nebulizer. This prospective cohort study aimed to assess the effect of salbutamol given by MDI on QTd in the course of moderate acute asthma attack.

Methods: Thirty-two children, between 5-15 years of age, who were able to perform spirometric maneuvers and salbutamol administration by MDI through the spacer, were enrolled. Salbutamol was administered at a dose of 50 μg/kg three times at 15-20 minute intervals. Clinical features, spirometric parameters and QT measurements from the standard electrocardiograms were studied at baseline and 15 minute after the third inhalation of salbutamol. The relation between the continuous variables was evaluated by using paired Student’s t-test.

Results: Overall, treatments were well-tolerated, significant improvement of pulmonary index scores and spirometric parameters were observed after treatment. No significant difference was observed between the pre and post-treatment values in QTd (30.4±5.6 ms; 33.7±6.2 ms, p=0.086) and corrected QTd (38.8±6.4 ms; 40.7±7.7 ms, p=0.18).

Conclusion: Salbutamol administered using metered dose inhaler showed satisfying clinical improvement with notably lower doses than the dose given by nebulizer and does not affect ventricular repolarization in children with moderate acute asthmatic attack.

(Anadolu Kardiyol Derg 2011; 11: 232-6)

Key words: Salbutamol, metered-dose inhaler, QT dispersion, moderate acute asthma attack

ÖZET

Amaç: Daha önceki çalışmalarında salbutamolün astım hastalarda QT dispersiyonunu (QTd) artırduğu ve bununda kardiyak arıtımlı ile ilişkili gösterilmiştir. Salbutamolün kardiyak etkileri verilen doza bağlıdır ve akut astım atığı sırasında ölçülen doz inhalerle (ODI) verilen doz miktari nebulizatörle verilen dozların genellikle altındadır. Bu prospektif kohort çalışmada orta şiddette akut astım atığı sırasında ODI ile verilen salbutamolun QTd üzerine etkisi değerlendirilmüşdür.


Bulgular: Tedavi tüm hastalarda iyi toler edildi, tedavi sonrası pulmoner indeks puanlarında ve spirometrik parametrelerde anlamlı düzeltme izlendi. Tedavi öncesi ve sonrası QTd (30.4±5.6 ms; 33.7±6.2 ms, p=0.086) ve düzeltilmiş QTd (38.8±6.4 ms; 40.7±7.7 ms, p=0.18) değerlerinde farklıklar saptanmıştır.

Sonuç: Çocuklarda orta şiddetedeki akut astım atağında ölçülen doz inhalerle verilen salbutamol ile nebulizatörle verilen miktara göre, oldukça düşük dozlarla tamaçı edici klinik düzeltme sağlanmaktadır ve ventrikül repolarizasyonu etkilenmemektedir.

(Anadolu Kardiyol Derg 2011; 11: 232-6)

Anahtar kelimeler: Salbutamol, ölçülen doz inhaler, QT dispersiyonu, orta şiddet astım atığı

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Introduction

Beta-2 agonists were shown to increase the cardiac repolarizing current and have previously shown to increase QT dispersion (QTd) which is thought to represent regional differences in ventricular repolarization (1-4). QTd has been proposed as non-invasive electrocardiogram (ECG) parameter and may predict increased risk of malignant arrhythmias (5-8).

Standard dose of nebulized salbutamol in acute asthmatic attack is associated with high QTd values (4). Previous studies showed that treatment with beta-2 agonists, in particular salbutamol, might increase the incidence of cardiac arrhythmia at high doses in asthmatics (1, 2, 8). Such doses of salbutamol are commonly given by nebulizer during acute asthmatic attacks. It has been demonstrated that intravenous salbutamol resulted in significant discordant electrophysiological effects on ventricular conduction, which slowed, and the refractoriness of the ventricular myocardium, which shortened and QT dispersion was increased (9).

The efficacy of salbutamol administered by metered-dose inhaler (MDI) is equivalent at lower doses to that of the nebulized salbutamol in children with acute asthma attack (10-12), however, the data regarding the effect of inhaled salbutamol administered through the spacer device on QTd is limited.

This study was designed to test a hypothesis that salbutamol given by MDI, commonly lower than the dose given by nebulizer, may not affect ventricular repolarization during acute asthma attack. We therefore examined the changes on the QTd during salbutamol therapy given by MDI in children with moderate acute asthma attack.

Methods

Study population

Thirty-eight consecutive patients with moderate acute attack of asthma who presented to the pediatric allergy and asthma unit formed the study population. Patients were included if they were between 5-15 years of age, were able to perform spirometric maneuvers and salbutamol administration by MDI through the spacer. All patients met the American Thoracic Society criteria for asthma (13) in which asthma was defined as a clinical syndrome characterized by paroxysmal coughing, wheezing and dyspnea and caused by the hyperresponsiveness of the tracheobronchial system to different stimuli, resulting in airway obstruction. Children with established cardiac or renal disease, or who had received treatment by a bronchodilator within the last 15 days or who had been given systemic corticosteroids in the last 30 days were excluded from the study. The baseline demographic characteristics of the cases are shown in Table 1.

Study design and protocol

This prospective cohort study was carried out at the pediatric emergency department. The protocol was approved by the institutional ethical committee and informed consent was obtained from parents.

Moderate acute asthma attacks were defined as the presence of audible wheezing, use of accessory muscles retraction, increased respiratory rate and an inability either to walk or to speak more than three to five words per breath (14, 15) and modified pulmonary index scoring ≥7 and ≤9 (16).

All study medications were packed individually for each child including AeroChamber-Plus® (Forest Pharmaceuticals, St Louis, MO) and one MDI (Ventolin®, GlaxoSmithKline, Evreux, France). One puff per 2 kg body weight of salbutamol (50 μg/kg, maximum 10 puffs) was administered by MDI through the spacer (17-19). Each puff was followed by eight breaths. Each treatment administration lasted 5 minutes and was followed by a 10-15 minute rest period. Treatments were given 3 times for total study duration of 45-60 minutes.

Heart rate, arterial blood pressure, standard 12-lead ECG, O2 saturation, pulmonary index scores and spirometric parameters including peak expiratory flow rate (PEFR), forced expiratory volume in 1 sec (FEV₃), forced expiratory vital capacity (FVC) were studied in all cases at baseline and also 15 minute after the third inhalation of salbutamol.

12-Lead surface ECG

All the QT interval measurements were performed from the 12-lead standard ECG recorded at a paper speed of 50 mm/s. ECG tracings were blindly analyzed in all patients by two independent investigators initially and at 15 min later after the third inhalation of salbutamol. Heart rate, QTd and corrected QTd (QTc) were calculated in four successive complexes for each lead. The QT interval was measured starting from the onset of the QRS complex until the end of the T wave, which is the return of the T wave to the baseline. When T waves were inverted, the end was taken at the point where the trace returned to the T-P baseline, and when U waves were present, the end of the T wave was taken as the nadir between the T and U waves (20). The QT interval was corrected for heart rate using Bazett’s formula (21). QTd, defined as the difference between

Table 1. Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>M/F</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>7.9±2.3 (5-15)</td>
<td></td>
</tr>
<tr>
<td>Weight, kg</td>
<td>21.6±6.3 (15-40)</td>
<td></td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>20.9±3.9 (11-27)</td>
<td></td>
</tr>
<tr>
<td>High serum IgEA</td>
<td>All</td>
<td></td>
</tr>
<tr>
<td>Positive skin prick test, n (%)#</td>
<td>24 (75)</td>
<td></td>
</tr>
<tr>
<td>Positive family history, n (%)#</td>
<td>26 (78)</td>
<td></td>
</tr>
<tr>
<td>Salbutamol dose*, μg/kg</td>
<td>45.4±7.6 (41-50)</td>
<td></td>
</tr>
</tbody>
</table>

Values are expressed as mean ± standard deviation (range) and number (percentage)

BMI - body mass index, IgE - immunoglobulin E
*a for each repeated dose
# Total serum IgE ≥100 IU/L
# Family history of asthma and/or atopy (allergic rhinitis or eczema)
maximum and minimum QT, was calculated based on the QT intervals obtained in the 12 leads. The same was done for the QTc dispersion, which was corrected using the RR interval.

**Statistical analysis**

The SPSS statistical software package program (version 9.0, SPSS, Inc, Chicago, IL, USA) was used to perform all statistical calculations. Data are expressed as mean±SD. The comparison of continuous variables before and after treatment was evaluated using paired Student’s t-test. A p-value <0.05 was considered significant.

**Results**

Table 1 displays the baseline demographic characteristics, family history and immunoglobulin E (IgE) data of the 32 subjects. The diagnosis of asthma was confirmed by baseline IgE data, positive skin prick test and family history.

None of them were followed by hospitalization and all were treated at outpatient unit with regular salbutamol.

Clinical characteristics and spirometric variables of subjects at baseline and 15 minute after the third inhalation of salbutamol are displayed in Table 2. Significant improvement of pulmonary index scores and spirometric parameters was observed after treatment (p<0.001 for all). In addition, O2 saturation values and heart rate of patients were increased after treatment, but the difference was not statistically significant (p=0.094). However, systolic blood pressure values were similar before and after treatment (p=0.173).

None of the patients displayed evidence of conduction abnormalities on the pre and post-treatment ECG. QT measurements of subjects at baseline and 15 minute after the third inhalation of salbutamol are shown in Table 3. No significant difference between the pre and post-treatment values was observed in QTd (30.4 ms versus 33.7 ms, p=0.086) and QTcd (38.8 ms versus 40.7 ms, p=0.18).

**Discussion**

In the present study, salbutamol therapy given by MDI did not affect ventricular repolarization during acute asthma attack, thus no changes in QT measurements were observed. We considered that this might also approve the cardiac safety of regular salbutamol use in asthmatic children for whom the drug is recommended substantially lower doses.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Pre-treatment</th>
<th>Post-treatment</th>
<th>95% CI for mean difference</th>
<th>t*</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP, mmHg</td>
<td>109.4±9.2</td>
<td>106.2±8.8</td>
<td>(-7.9, 1.48)</td>
<td>-1.4</td>
<td>0.173</td>
</tr>
<tr>
<td>Heart rate, beat/min</td>
<td>109.1±10.0</td>
<td>113.1±8.1</td>
<td>(-0.3, 8.3)</td>
<td>1.9</td>
<td>0.067</td>
</tr>
<tr>
<td>Potassium, mg/dL</td>
<td>4.1±0.9</td>
<td>3.9±0.4</td>
<td>(-0.34, 0.03)</td>
<td>-1.7</td>
<td>0.093</td>
</tr>
<tr>
<td>Urea nitrogen, mg/dL</td>
<td>11.6±2.3</td>
<td>12.3±2.2</td>
<td>(0.11, 1.49)</td>
<td>1.75</td>
<td>0.090</td>
</tr>
<tr>
<td>O2 saturation, %</td>
<td>96.5±1.8</td>
<td>97.1±1.2</td>
<td>(-0.12, 1.43)</td>
<td>1.7</td>
<td>0.094</td>
</tr>
<tr>
<td>Pulmonary index score</td>
<td>8.03±0.78</td>
<td>1.93±0.71</td>
<td>(-6.4, -5.7)</td>
<td>-32.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FEV1, % predicted</td>
<td>72.6±2.7</td>
<td>94.5±2.7</td>
<td>(20.3, 23.4)</td>
<td>28.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FVC, % predicted</td>
<td>74.2±3.1</td>
<td>93.8±2.3</td>
<td>(18.2, 20.9)</td>
<td>29.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FEV1/FVC ratio, %</td>
<td>70.5±3.5</td>
<td>88.6±3.6</td>
<td>(16.1, 20.1)</td>
<td>19.1</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Values are expressed as mean±standard deviation

*paired Student’s t-test

<table>
<thead>
<tr>
<th>Variables</th>
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<td>113.1±8.1</td>
<td>(-0.3, 8.3)</td>
<td>1.9</td>
<td>0.067</td>
</tr>
<tr>
<td>QT max, ms</td>
<td>319.0±7.4</td>
<td>321.0±7.2</td>
<td>(-1.37, 2.93)</td>
<td>0.74</td>
<td>0.46</td>
</tr>
<tr>
<td>QT min, ms</td>
<td>289.0±8.9</td>
<td>287.0±9.1</td>
<td>(-2.76, 0.19)</td>
<td>1.76</td>
<td>0.087</td>
</tr>
<tr>
<td>QT dispersion, ms</td>
<td>30.4±5.6</td>
<td>33.7±6.2</td>
<td>(-0.3, 4.4)</td>
<td>1.77</td>
<td>0.086</td>
</tr>
<tr>
<td>QTc max, ms</td>
<td>396.0±21.1</td>
<td>390.0±13.9</td>
<td>(-14.1, 0.5)</td>
<td>-1.9</td>
<td>0.065</td>
</tr>
<tr>
<td>QTc min, ms</td>
<td>358.0±22.9</td>
<td>349.0±14.1</td>
<td>(1.6, 15.9)</td>
<td>-2.4</td>
<td>0.052</td>
</tr>
<tr>
<td>QTc dispersion, ms</td>
<td>38.8±6.4</td>
<td>40.7±7.7</td>
<td>(-0.9, 4.7)</td>
<td>1.3</td>
<td>0.18</td>
</tr>
</tbody>
</table>

Values are expressed as mean±standard deviation

*p paired Student’s t-test
Salbutamol provides effective bronchodilatation and it is warranted in the treatment of acute attacks characterized by expiratory obstruction in infants and young children. Nebulized salbutamol treatment is standard for asthma exacerbation in hospital emergency wards, and a dosage regimen of 150 μg/kg is widely used and recommended (14, 22-26).

For treatment with the MDI during asthma exacerbations, proposed dosage regimens of salbutamol administered vary widely. In previous comparative studies, the salbutamol dose ratio of MDI dose to nebulized dose ranged from 1:1 to 1:6 (12, 14). Repeated 50 μg/kg doses of salbutamol was administered in our study, our dose to standard nebulized dose ratio was 1:3, as previously used by de Blic et al. (17). We restricted the maximum dose to 10 puffs in accordance with British and US guidelines (18, 19). Overall, treatments were well-tolerated, and significant improvements in pulmonary index scores and spirometric parameters were observed after treatment. None of the children were hospitalized and all were treated as outpatient unit with regular salbutamol.

It is well documented that due to their excitation effect on the cardiac conduction system, beta-2 agonists used in the treatment of acute asthmatic attacks frequently increase the incidence of cardiac arrhythmias (8, 27). Beta-2 agonists were also shown to cause hypoxemia by decreasing PaO2 by increasing blood through poorly ventilated areas of the lung and thereby increasing ventilation/perfusion mismatch (28, 29). The presence of hypoxemia can also enhance the risk of rhythm disturbances (30). In particular, hypoxemic patients may have a subclinical autonomic neuropathy that has been associated with a prolonged QTc interval and risk of ventricular arrhythmias and death (31).

Adverse effects of inhaled salbutamol associated with cardiovascular system occur with high doses and such doses of salbutamol are commonly given by nebulizer during acute asthmatic attacks (10, 11). Several published reports suggest that full-dose nebulized salbutamol places pediatric patients at undue risk of adverse effects. After equivalent efficacy is determined between full and pediatric doses of nebulized salbutamol, it is sensible to compare the relative safety of the two doses and low dose of salbutamol is recommended to avoid rhythm disturbances in asthmatic children (4, 32).

The MDI, with or without the concomitant use of the spacer, may represent a safer alternative, as doses are easy to determine and administer, compared with the risks of handling a highly concentrated solution (17, 27, 33). In our study, mean salbutamol dose was 45 μg/kg for each repeated dose and significant improvement of pulmonary index scores and spirometric parameters was observed after treatment. This is the first study, to our knowledge, to demonstrate the effect of salbutamol therapy given by MDI on ventricular repolarization in children with moderate acute asthmatic attack.

**Study limitations**

The major limitations of this study were the small sample size, and lack of a randomized control design. Despite this, the aim of this study was primarily to assess safety, thus the sample size was not expected to provide enough statistical power to detect significant differences in the efficacy parameters before and after treatment.

**Conclusion**

The present study suggests that salbutamol administered using metered dose inhaler and spacer showed satisfying clinical improvement and does not affect ventricular repolarization in children with moderate acute asthmatic attack. This may be related to notably lower doses than the dose given by nebulizer and may elucidate cardiac safety of lower dose regular regimes which are widespread use of salbutamol associated with deterioration of asthma control in patients with stable asthma.

**Conflict of interests:** None declared.

**References**


