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

ÖZET

Amaç: Daha önceki çalışmalarda salbutamolün astımlı hastalarda QT dispersiyonunu (QTd) arttırdığı ve bununda kardiyak aritmi ile ilişkisi gösterilmiştir. Salbutamolün kardiyak etkileri verilen dozla ilişkilidir ve akut astım atağı sırasında ölçülü doz inhalerle (ÖDİ) verilen doz miktarı nebulizatörle verilen dozların genellikle altındadır. Bu prospektif kohort çalışmada orta şiddette akut astım atağı sırasında ÖDİ ile verilen salbutamolün QTd üzerine etkisi değerlendirilmiştir.
Yöntemler: Spirometrik manevraları yapabilecek ve ÖDİ ile salbutamol alabilecek 5-15 yaş arası 32 hasta çalışmaya dahil edildi. Salbutamol doz başına 50 µg/kg olacak şekilde 15-20 dakika arayla üç dozda verildi. Hastaların klinik durumu, spirometrik parametreler ve standart elektrokardiyogramdan QT ölçümleri, salbutamol verilmeden önce ve üçüncü dozdan 15 dakika sonra değerlendirildi. Sürekli değişkenlere bağlı olarak, tedavi öncesi ve sonrası ilişki eşleştirilmiş Student's t-testi ile değerlendirildi.
Bulgular: Tedavi tüm hastalarda iyi tolere edildi, tedavi sonrası pulmoner indeks puanlarında ve spirometrik parametrelerde anlamlı düzelme izlendi. Tedavi öncesi ve sonrası QTd (30.4±5.6 msn; 33.7±6.2 msn, p=0.086) ve düzeltilmiş QTd (38.8±6.4 msn; 40.7±7.7 msn, p=0.18) değerlerinde farklılık saptanmadı.
Sonuç: Çocuklarda orta şiddette akut astım atağında ölçülü doz inhalerle verilen salbutamol ile nebulizatörle verilen miktara göre, oldukça düşük dozlarda tatmin edici klinik düzelme sağlanmaktadır ve ventrikül repolarizasyonu etkilenmemektedir.
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Anahtar kelimeler: Salbutamol, ölçülü doz inhaler, QT dispersiyonu, orta şiddette astım atağı

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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 noninvasive 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.

Table 1. Baseline characteristics

M/F, n	18/14
Age, years	7.9±2.3 (5-15)
Weight, kg	21.6±6.3 (15-40)
BMI, kg/m^2	20.9±3.9 (11-27)
High serum IgE[&]	All
Positive skin prick test, n (%)	24 (75)
Positive family history, n (%)[#]	25 (78)
Salbutamol dose*, µg/kg	45.4±7.6 (41-50)

Values are expressed as mean ± standard deviation (range) and number (percentage)
BMI - body mass index, IgE - immunoglobulin E
*for each repeated dose
[&]Total serum IgE ≥100IU/L
[#]Family history of asthma and/or atopy (allergic rhinitis or eczema)

Study design and protocol

This prospective cohort study was carried out at the pediatric emergency department. The protocol was approved by the Institutional Ethic 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 (FEV_1), 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 (QTcd) 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

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 2. Clinical features and spirometric variables of subjects at baseline and 15 minute after the third inhalation of salbutamol

Variables	Pre-treatment	Post-treatment	95% CI for mean difference	t*	p*
SBP, mmHg	109.4±9.2	106.2±8.8	(-7.9, 1.48)	-1.4	0.173
Heart rate, beat/min	109.1±10.	113.1±8.1	(-0.3, 8.3)	1.9	0.067
Potassium, mg/dL	4.1±0. -	3.9±0.4	(-0.34, 0.03)	-1.7	0.093
Urea nitrogen, mg/dL	11.6±2.3	12.3±2.2	(0.11, 1.49)	1.75	0.090
O2 saturation, %	96.5±1.8	97.1±1.2	(-0.12, 1.43)	1.7	0.094
Pulmonary index score	8.03±0.78	1.93±0.71	(-6.4, -5.7)	-32.5	<0.001
FEV_1, % predicted	72.6±2.7	94.5±2.7	(20.3, 23.4)	28.1	<0.001
FVC, % predicted	74.2±3.1	93.8±2.3	(18.2, 20.9)	29.4	<0.001
FEV1/ FVC ratio, %	70.5±3.5	88.6±3.6	(16.1, 20.1)	19.1	<0.001

Values are expressed as mean±standard deviation
*paired Student's t-test
FEV_1 - forced expiratory volume in 1 second, FVC - forced vital capacity, SBP - systolic blood pressure

Table 3. QT measurements of subjects at baseline and 15 minute after the third inhalation of salbutamol

Variables	Pre-treatment	Post-treatment	95% CI for mean difference	t*	p*
Heart rate, beat/min	109.1±10.4	113.1±8.1	(-0.3, 8.3)	1.9	0.067
QT max, ms	319.0±7.4	321.0±7.2	(-1.37, 2.93)	0.74	0.46
QT min, ms	289.0±8.9	287.0±9.1	(-2.76, 0.19)	1.76	0.087
QT dispersion, ms	30.4±5.6	33.7±6.2	(-0.3, 4.4)	1.77	0.086
QTc max, ms	396.0±21.1	390.0±13.9	(-14.1, 0.5)	-1.9	0.065
QTc min, ms	358.0±22.9	349.0±14.1	(1.6, 15.9)	-2.4	0.052
QTc dispersion, ms	38.8±6.4	40.7±7.7	(-0.9, 4.7)	1.3	0.18

Values are expressed as mean±standard deviation
* 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

1. Sarubbi B, Esposito V, Duccesschi V, Meoli I, Grella E, Santangelo L, et al. Effect of blood gas derangement on QTc dispersion in severe chronic obstructive pulmonary disease: evidence of an electropathy? Int J Cardiol 1997; 58: 287-92.
2. Conradson TB, Eklundh G, Olofsson B, Pahlm O, Persson G. Cardiac arrhythmias in patients with mild-to-moderate obstructive lung disease. Comparison of beta-agonist therapy alone and in combination with a xanthine derivative, enprofylline or theophylline. Chest 1985; 88: 537-42.
3. Kiely DG, Cargill RI, Grove A, Struthers AD, Lipworth BJ. Abnormal myocardial repolarisation in response to hypoxemia and fenoterol. Thorax 1995; 50: 1062-6.
4. Coşkun S, Yüksel H, Tıkız H, Danahaliloğlu S. Standard dose of inhaled albuterol significantly increases QT dispersion compared to low dose of albuterol plus ipratropium bromide therapy in moderate to severe acute asthma attacks in children. Pediatr Int 2001; 43: 631-6.
5. Barr CS, Naas A, Freeman M, Lang CC, Struthers AD. QT dispersion and sudden unexpected death in chronic heart failure. Lancet 1994; 343: 327-9.
6. Higham PD, Campbell RW. QT dispersion. Br Heart J 1994; 71: 508-10.
7. Steinberg JS, Berbari EJ. The signal-averaged electrocardiogram: update on clinical applications. J Cardiovasc Electrophysiol 1996; 7: 972-88.
8. Finn AF Jr, Thompson CM Jr, Banov CH, O'Connor BK, Case CL. Beta-2 agonist induced ventricular dysrhythmias secondary to hyperexcitable conduction system in the absence of a long QT syndrome. Ann Allergy Asthma Immunol 1997; 78: 230-2.
9. Insulander P, Juhlin-Dannfelt A, Freyschuss U, Vallin H. Electrophysiologic effects of salbutamol, a beta2-selective agonist. J Cardiovasc Electrophysiol 2004; 15: 316-22.
10. Newman KB, Milne S, Hamilton C, Hall K. A comparison of albuterol administered by metered-dose inhaler and spacer with albuterol by nebulizer in adults presenting to an urban emergency department with acute asthma. Chest 2002; 121: 1036-41.
11. Kerem E, Levison H, Schuh S, O'Brodovich H, Reisman J, Bentur L, et al. Efficacy of albuterol administered by nebulizer versus spacer device in children with acute asthma. J Pediatr 1993; 123: 313-7.

12. Amirav I, Newhouse MT. Metered-dose inhalers accessory devices in acute asthma. Efficacy and comparison with nebulizers: a literature review. Arch Pediatr Adolesc Med 1997; 151: 876-82.
13. American Thoracic Society. Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease (COPD) and asthma. Am Rev Respir Dis 1987; 136: 225-44.
14. Warner JO, Naspitz CK. Third International Pediatric Consensus Statement on the Management of Childhood Asthma. Pediatr Pulmonol 1998; 25: 1-17.
15. Nuhoğlu Y, Ataş E, Nuhoğlu C, Iscan M, Özcay S. Acute effect of nebulized budesonide in asthmatic children. J Investig Allergol Clin Immunol 2005; 15: 197-200.
16. Scarfone RJ, Fuchs SM, Nager AL, Shane SA. Controlled trial of oral prednisone in the emergency department treatment of children with acute asthma. Pediatrics 1993; 92: 513-8.
17. De Blic J, Mahraoui C, Che´ron G, Scheinmann P. Acute asthma in children: are jet nebulizers obsolete? Am J Respir Crit Care Med 1995; 151: 364
18. British Thoracic Society; National Asthma Campaign; Royal College of Physicians of London in association with the General Practitioners in Asthma Group; British Association of Accident and Emergency Medicine; British Pediatric Society; Royal College of Paediatrics and Child Health. The British guidelines on asthma management 1995 review and position statement. Thorax 1997; 52: 1-21.
19. National Heart, Lung, and Blood Institute/World Health Organization. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention. Bethesda, MD/Geneva, Switzerland: National Institutes of Health; 1995. Publication No. 95.3659.
20. Barr CS, Naas A, Freeman M, Lang CC, Struthers AD. QT Dispersion and sudden unexpected death in chronic heart failure. Lancet 1994; 343: 327-9.
21. Bazett HC. An analysis of the time-relations of electrocardiograms. Ann Noninv Electrocardiol 1997; 2: 177-94.
22. Rees J, Price J. ABC of asthma. Asthma in children: treatment. BMJ 1995; 310: 1522-7.
23. Lipworth BJ. Treatment of acute asthma. Lancet 1997; 350: 18-23.
24. Henry RL, Robertson CF, Asher I, Cooper DM, Cooper P, Dawson KP, et al. Management of acute asthma. Respiratory pediatricians of Australia and New Zealand. J Pediatr Child Health 1993; 29: 101-3.
25. The Nebulizer Project Group of the British Thoracic Society Standards of Care Committee. Current best practice for nebulizer treatment. Thorax 1997; 52: 1-3.
26. American Academy of Pediatrics, Provisional Committee on Quality Improvement. Practice parameter: the office management of acute exacerbations of asthma in children. Pediatrics 1994; 93:119-26.
27. Katz RW, Kelly HW, Crowley MR, Grad R, McWilliams BC, Murphy SJ. Safety of continuous nebulized albuterol for bronchospasm in infants and children. Pediatrics 1993; 92: 666-9.
28. Jenne JW. Physiological actions of beta-adrenergic agonists. In: Leff AR (ed). Pulmonary and Critical Care Pharmacology and Therapeutics. New York: McGraw-Hill; 1996.p.451-62.
29. Viegas CA, Ferrer A, Montserrat JM, Barbera JA, Roca J, Rodriguez-Roisin R. Ventilation-perfusion response after fenoterol in hypoxaemic patients with stable COPD. Chest 1996; 110: 71-7.
30. Gorecka D. Cardiac arrhythmias in chronic obstructive pulmonary disease. Monaldi Arch Chest Dis 1997; 52: 278-81.
31. Steward AG, Waterhouse JC, Howard P. The QTc interval, autonomic neuropathy and mortality in hypoxaemic COPD. Respir Med 1995; 89: 79-84.
32. Yüksel H, Coşkun S, Polat M, Onag A. Lower arrhythmogenic risk of low dose albuterol plus ipratropium. Indian J Pediatr 2001; 68: 945-9.
33. Ploin D, Chapuis FR, Stamm D, Robert J, David L, Chatelain PG, et al. High-dose albuterol by metered-dose inhaler plus a spacer device versus nebulization in preschool children with recurrent wheezing: A double-blind, randomized equivalence trial. Pediatrics 2000; 106: 311-7.