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RESPONSE TO SALBUTAMOL IN CHILDREN WITH ACUTE ASTHMA EXACERBATIONS

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The aim of this study was to investigate response to salbutamol in children with acute asthma exacerbations in order to estimate the efficiency and safety of its administration in pediatric population. The study included 56 children with asthma (age range 5-12) who were diagnosed and treated over a period of two years. In all children, salbutamol was administered via nebulization, in doses of 1.25 mg in children aged 5-6 and 2.5 mg in children aged 7-12. Respiratory and blood parameters were monitored before and 30 minutes after salbutamol administration. In children with acute asthma exacerbations, respiratory frequency, potassium level, sodium level and $PaCO_2$ decreased significantly after salbutamol administration, while PEF, PEF%, glycemia, PaO_2 and $SatO_2$ significantly increased. Hypokalemia due to salbutamol effect occurred in 15 (26.8%) children. Most significant improvement in oxygenation, with increase of PEF, PEF%, PaO_2 and $SatO_2$, after salbutamol administration was achieved in patients with mild acute exacerbations. Salbutamol administered via nebulization leads to the occurrence of adverse metabolic effects, hypokalemia and hyperglycemia. However, it can be safely used in the treatment of acute asthma exacerbations and demonstrates high clinical efficacy in the management of acute bronchospasm. The most effective salbutamol treatment is achieved in patients with mild exacerbations.

Descriptors: ALBUTEROL; CHILD; ASTHMA

INTRODUCTION

The prevalence of asthma is growing in industrialized and developing countries (1). In Serbia, every seventh school age child suffers from asthma and 70% of them are hospitalized at least once a year due to acute exacerbations (2). Despite the introduction of many international treatment guidelines since 1995, asthma exacerbations are still a major problem in emergency medicine. Inhaled rapid-acting β2 agonists are the most effective and widely used bronchodilator drugs for treatment of acute exacerbations in all age groups of asthmatic patients because of their potent and rapid bronchodilatory effects (3). Ever since their introduction, β2 agonists have been associated with adverse effects and even death in asthma (4).

Salbutamol is a selective β2 adrenergic agonist administered either by inhalation or orally for treatment of patients with bronchospasm (5). When administered by inhalation, it produces significant bronchodilation within 15 minutes and may still be effective for 3-4 hours. Inhalation therapy with nebulizers is advantageous because the risk of adverse effects is lower than in systemic drug administration, such as oral route. Salbutamol acts on β adrenergic receptors (ADRB) type 1 in bronchial musculature cells, but not on ADRB type 2 in the heart. Due to its selectivity, salbutamol exerts its main effect, bronchodilation, without adverse cardiovascular effects. The most common side effects of salbutamol are fine tremor, anxiety, headache, muscle cramps, dry mouth, and palpitation (6). Other symptoms may include tachycardia, arrhythmia, flushing, myocardial ischemia, and disturbances of sleep and behavior. High doses of salbutamol may cause hypokalemia and hyperglycemia.

The aim of this study was to investigate response to salbutamol in children with acute asthma exacerbations in order to estimate the efficiency and safety of its administration in pediatric population.

MATERIAL AND METHODS

Patients

This study included 56 children with asthma (age range 5-12) who were diagnosed and treated over a period of twelve consecutive months at Department of Pulmonology and Allergology, University Children's Hospital in Belgrade. Written informed consent was obtained from all patients' parents and the investigation was approved by the hospital's ethics committee. Diagnosis and classification of asthma and assessment of acute exacerbation

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Table 1. *Baseline clinical characteristics of study patients*

Total number	56
Gender	
Male	39
Female	17
Age	
Preschool (5-6)	28
School (7-12)	28
Type of asthma	
Intermittent	10
Mild persistent	19
Moderate persistent	20
Severe persistent	7
Acute exacerbation severity	
Mild	17
Moderate	26
Severe	13

severity were based on the Global Initiative for Asthma guidelines (3). Baseline clinical characteristics of patients are given in Table 1.

Data collection

In children aged 5-6, 1.25 mg of salbutamol was administered *via* mask nebulization, while in children aged 7-12, 2.5 mg of salbutamol was administered *via* mouthpiece nebulization. In all patients, the following parameters were monitored before and 30 minutes after salbutamol administration: levels of glycemia, potassium, sodium and chlorides, arterial blood gases, hemoglobin saturation with oxygen in arterial blood ($SatO_2$) and peak expiratory flow (PEF).

Statistical analysis

The following descriptive statistics methods were applied on data processing: central tendency measures (arithmetical mean values), variability measures (variation interval and standard deviation) and relative numbers. Statistical significance was calculated based on the following inferential statistics methods: Student's t-test, McNemar's test and Pearson's linear correlation coefficient. Values of $p \leq 0.05$ were considered statistically significant.

RESULTS

In this study, 56 children with asthma (69.6% male) were treated with salbutamol during acute exacerbations. In all children, the type of asthma and severity of acute exacerbation were determined.

Table 2. *Respiratory and blood parameters before and after salbutamol administration*

Parameter	Before salbutamol, mean ± SD	After salbutamol, mean ± SD	Difference, mean ± SD	T	p-value
Respiratory frequency (/min)	34.0±7.1	31.6±6.8	2.3±4.9	3.562	0.001
Heart rate (/min)	106.1±8.9	105.1±9.3	1.0±6.0	1.266	>0.05
PEF (L/min)	175.9±73.5	206.6±84.9	-30.7±28.4	-8.098	<0.0001
PEF (%)	71.7±13.0	83.2±9.6	-11.5±9.7	-8.861	<0.0001
Potassium (mmol/L)	4.3±0.6	3.8±0.7	0.5±0.5	7.279	<0.0001
Glycemia (mmol/L)	5.1±0.8	5.3±0.7	-0.2±0.5	-2.690	0.009
Sodium (mmol/L)	138.9±3.6	137.7±3.8	1.2±2.7	3.308	0.002
Chloride (mmol/L)	99.9±2.9	100.1±2.8	-0.2±2.8	-0.472	>0.05
PaO_2 (mm Hg)	6.6±1.5	7.0±1.5	-0.4±1.6	-2.089	0.041
$PaCO_2$ (mm Hg)	5.4±0.9	5.0±0.8	0.4±0.7	3.817	<0.0001
$SatO_2$ (%)	81.9±13.2	87.2±9.8	-5.3±9.8	-4.104	<0.0001

Table 3. *Correlation of response to salbutamol and asthma severity*

	Total number	Responsive patients		Nonresponsive patients	
		Number	%	Number	%
Type of asthma					
Intermittent	10	8	80.0	2	20.0
Mild persistent	19	14	73.7	5	26.3
Moderate persistent	20	13	65.0	7	35.0
Severe persistent	7	2	28.6	5	71.4
Severity of acute exacerbation					
Mild	17	12	70.6	5	29.4
Moderate	26	20	76.9	6	23.1
Acute	13	5	38.5	8	61.5
Total	56	37	66.1	19	33.9

On initial evaluation, prior to salbutamol treatment, basal values of several respiratory and blood parameters were measured. In 28 (50%) preschool children aged 5-6, 1.25 mg of salbutamol was administered *via* mask nebulization, while in 28 (50%) school children aged 7-12, 2.5 mg of salbutamol was administered *via* mouthpiece nebulization. In order to assess acute effects of salbutamol treatment, respiratory and blood parameters were measured 30 minutes after salbutamol administration in all patients. Differences in measured parameters before and after salbutamol administration are given in Table 2. Statistical analysis revealed that respiratory frequency, potassium level, sodium level and $PaCO_2$ decreased significantly after salbutamol administration, while PEF, PEF%, glycemia, PaO_2 and $SatO_2$ significantly increased. Patients with intermittent asthma were not subjected to any treatment prior to salbutamol administration, while patients with persistent asthma (mild, moderate or severe) were treated with low doses of inhaled corticosteroids.

Hypokalemia due to salbutamol effect occurred in 15 (26.8%) children. In one (1.8%) child, potassium level was below the reference values and remained so after salbutamol treatment, while in another 40 (71.4%) children potassium level remained within the reference values and no hypokalemia was observed.

Measured parameters before and after salbutamol administration were compared among the groups of children with mild, moderate and severe acute exacerbations. Statistically significant differences were observed for the following parameters: PEF ($p=0.027$), PEF% ($p=0.029$), PaO_2 ($p=0.049$) and $SatO_2$ ($p=0.023$). The values of PEF, PEF% and $SatO_2$ were statistically significantly different in patients with mild in comparison to patients with moderate and severe acute exacerbations, while PaO_2 values were statistically significantly different in patients with mild in comparison to patients with severe acute exacerbations.

Response to salbutamol differed between the groups of children with different types of asthma and also depended on the severity of acute exacerbations. Children with intermittent type of asthma responded best to salbutamol treatment (80%). Children with mild and moderate

exacerbations responded to salbutamol significantly better than children with severe exacerbations. Correlation of response to salbutamol and asthma severity is given in Table 3.

DISCUSSION

This study was conducted in order to assess clinical efficiency and safety of salbutamol administration *via* nebulization in acute asthma exacerbations in pediatric population. In general, β2 agonist administered *via* nebulizer is the standard treatment for acute exacerbation, especially in young children, and it is recommended as the most cost effective treatment for mild to moderate exacerbations (3). There are some limitations for the use of nebulization, e.g., its inconvenience, slow implementation, high cost and uncontrolled particle sizes (7). However, understanding of salbutamol nebulization has matured with recent advances in clinical therapy, delivery systems and understanding of dosing, having led to substantial improvements in delivery as well as refinements of research protocols for asthma exacerbations.

Salbutamol administration *via* nebulization in the treatment of acute asthma exacerbations in children enables its main pharmacological effect, bronchodilation. In this study, it was shown that salbutamol treatment led to significant decrease in respiratory frequency and $PaCO_2$ and significant increase in PaO_2, $SatO_2$ and PEF. The finding that salbutamol leads to acute improvement in oxygenation is in correlation with previous findings (8, 9). Studies conducted in patients with chronic obstructive pulmonary disease have shown that the use of salbutamol improves the resistive and reactive properties of the respiratory system (10, 11). Salbutamol appears to be most efficacious in children with mild or moderate acute asthma exacerbations (12). Also, it was demonstrated to be a safe and effective therapy for patients with mild and moderate bronchiolitis (13).

Hypokalemia is one of the main side effects of β2 agonists and may lead to sudden death in asthmatic patients (5, 6). Plasma potassium level in this study was significantly reduced by salbutamol administration, leading to hypokalemia, especially in patients with moderate asthma exacerbations. Other β2 agonists, fenoterol and terbutaline, have greater hypokalemic effect than salbutamol when administered in equal doses (14). Also, the risk of death due to asthma exacerbation is much higher for fenoterol and terbutaline than for salbutamol (15).

Ethnic-specific differences in the response to drug treatment may contribute to differences in asthma morbidity and drug responsiveness. Ethnic-specific pharmacogenetic differences exist between ADRB2 genotypes, asthma severity and bronchodilator response in asthmatic patients (16, 17). When it comes to salbutamol adverse effects, the presence of ADRB2 gene polymorphisms should also be taken into consideration, since ADRB2 genetic variants may influence PEF or lung function parameters in patients treated with salbutamol (18).

Based on this and previous studies, it can be concluded that short-acting β2 agonists, although displaying many adverse effects when administered regularly in long-term management of bronchial asthma, can be safely administered and demonstrate high clinical efficacy in the treatment and prevention of acute bronchospasm. Salbutamol administration *via* nebulization in the treatment of acute asthma exacerbations in children enables bronchodilation as its main pharmacological effect and the most effective treatment is achieved in patients with mild exacerbations.

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S a ž e t a k

ODGOVOR NA SALBUTAMOL U DJECE S AKUTNIM EGZACERBACIJAMA ASTME

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Cilj istraživanja bio je utvrditi odgovor na salbutamol u djece s akutnim egzacerbacijama astme kako bi se procijenila učinkovitost i sigurnost njegove primjene u dječjoj populaciji. Studija je obuhvatila 56 djece s astmom (dobni raspon 5-12 godina) dijagnosticirane i liječene kroz razdoblje od dvije godine. Kod sve djece salbutamol se davao putem nebulizatora u dozi od 1,25 mg kod djece stare 5-6 godina i od 2,5 mg kod djece stare 7-12 godina. Respiracijski i krvni parametri pratili su se prije i 30 minuta nakon davanja salbutamola. Nakon davanja salbutamola kod djece s akutnim egzacerbacijama astme značajno su se snizile razine kalija i natrija te $PaCO_2$, dok su se PEF, PEF%, glikemija, PaO_2 i $SatO_2$ značajno povisili. Hipokalemija izazvana učinkom salbutamola pojavila se u 15 (26,8%) djece. Najznačajnije poboljšanje oksigenacije, uz porast PEF, PEF%, PaO_2 i $SatO_2$ nakon davanja salbutamola postiglo se u bolesnika s blažim akutnim egzacerbacijama. Salbutamol primijenjen pomoću nebulizatora dovodi do pojave štetnih metaboličnih učinaka, hipokalemije i hiperglikemije. Međutim, može ga se sigurno primjenjivati u liječenju akutnih egzacerbacija astme, a klinički je učinkovit i u liječenju akutnog bronhospazma. Liječenje salbutamolom najučinkovitije je u bolesnika s blažim egzacerbacijama.

Deskriptori: ALBUTEROL; DIJETE; ASTMA

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