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Original article

Lactatemia during treatment of status asthmaticus in children

Background: *Transient increase of lactate levels with or without metabolic acidosis has been seldom reported as a complication of β_2-adrenergic therapy administered during asthma attacks in children.*
Objective: *The study is aimed to investigate the frequency of lactatemia in children with acute asthma treated with nebulized β_2-agonists, and to delineate its causes and effects on prognosis.*
Methods: *We studied 32 asthmatic children; 68.8% had intermittent asthma, and 31.2% had mild persistent asthma. Their ages ranged from 6 to 8 years with a mean of 6.48±0.68 years. Patients were enrolled during acute asthma exacerbation (62.5% had severe and 37.5% had moderate attacks)from the Cairo University Children's Hospital. Patients underwent clinical evaluation, and routine investigations (CBC, PEFR, and total serum IgE) then received nebulized salbutamol at 0.1 mg/kg/dose (minimum 2.5 mg) every 20 min for three doses together with O_2. Plasma lactate was determined before, 1 h after, and 24 h following the inhalation therapy. Blood gases were also evaluated before and after the β_2-agonist treatment.*
Results: *At 1 h post-treatment, all patients had appreciable lactatemia (4.44±0.78 mmol/L, $p<0.001$) compared to the pre-treatment level with a rise of 257±121.5%. Patients with severe attacks demonstrated a higher mean value compared to those with moderate attacks (4.69±0.8 mmol/L versus 4.02±0.6 mmol/L, $p<0.05$). At 24 h post-treatment, lactate levels returned to the normal values in most patients (1.91±0.59 mmol/L, $p<0.001$) as compared to the 1 h post-treatment level. None of our patients developed metabolic acidosis and all of them showed significant clinical improvement. Our results strongly accuse nebulized salbutamol as the possible pathogenetic factor for lactatemia during therapy of acute asthma attacks, while overworked respiratory muscles and hypoxemia have been excluded as contributing factors.*
Conclusion: *Transient lactatemia is not uncommon during β_2-agonist therapy in asthmatic children with acute exacerbation, and is harmless in most cases. Prediction of lactic acidosis prevents inappropriate intensification of therapy especially in patients with more severe attacks or impending respiratory failure.*

Key words: Asthma, exacerbation, lactate, lactatemia, β_2-agonist, salbutamol.

Zeinab M. Radwan, Tarek F. Ali, Hisham W. Bader*, Sally M. Gouda

From the Departments of Pediatrics, Faculty of Medicine, Cairo University, and Child Health, National Research Center, Giza, Egypt.*

Correspondence:
Dr. Tarek F. Ali
Assist. Prof. of Pediatrics, Faculty of Medicine, Cairo University, Giza, Egypt.
E-mail: tali @islamway.net

INTRODUCTION

Asthma is a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role, in particular mast cells, eosinophils, T-lymphocytes, neutrophils, and epithelial cells. In susceptible individuals, this inflammation causes recurrent episodes of wheezing, breathlessness, chest tightness, and cough particularly at night and/or in the early morning. These episodes are usually associated with widespread but variable airflow obstruction that is often reversible either spontaneously or with treatment. The inflammation also causes an associated increase in the existing bronchial hyperresponsiveness to a variety of stimuli[1].

In the New Children's Hospital of Cairo University, respiratory illnesses were the most frequent cause of admission (20.6%) and bronchial asthma constituted 8.6% of them[2]. β_2-agonists remain the mainstay of therapy for acute asthma and, for most patients, standard doses are acceptable[3]. Lactic acidosis is infrequently reported in children with status asthmaticus, although it has been documented[4,5]. Transient increase of lactate

levels (lactatemia) has been seldom observed as a complication of β-adrenergic agents administered during an asthma attack[6]. Our aim through this work is to detect the incidence of lactatemia in children with acute asthma treated with nebulized β_2-agonists, and to delineate its causes and effects on the patient's prognosis.

METHODS

The study included 32 asthmatic children (22 males and 10 females), their ages ranged from 6 to 8 years with a mean of 6.48±0.68 years. Intermittent asthma was diagnosed in 68.8% of patients while 31.2% of them had mild persistent asthma. The duration of their disease ranged from 2-6 years with a mean of 3.8±1 years. They were referred over the period from October to December 2003 to the emergency department of Cairo University Children's Hospital because of acute asthma exacerbation.

All patients were subjected to the following:

1. Complete history taking especially for the duration of disease, frequency of acute attacks, nocturnal symptoms, precipitating factors, and drug therapy.
2. Clinical examination with special reference to the mental status, vital signs, criteria of respiratory distress, and chest signs.
3. Peak Expiratory Flow Rate (PEFR) was done after initial bronchodilator therapy using a portable Mini-Wright Peak Flow Meter.
4. Laboratory investigations:

- Complete blood and differential count (CBC) using the ADVIA 120 cell counter (Bayer Diagnostics, Ireland).
- Total serum IgE was determined by the ELISA (International Immuno-Diagnostics, USA).
- Blood gases were done before, and 1 h after nebulized salbutamol therapy using IL International (Japan).
- Plasma lactate level was determined[7] using the Randox kit. Samples for lactate levels were taken before treatment [H0], 1 h [H+1], and 24 h [H+24] after treatment with nebulized salbutamol.

After assessment, patients were divided into 2 groups according to the severity of their asthma attacks: those with severe attacks (20 patients, 62.5%), and those with moderate attacks (12 patients, 37.5%). All patients received nebulized salbutamol up to 3 doses at 20 minutes intervals (0.1 mg/kg/dose, minimum 2.5 mg, mixed with normal saline to final volume 3-4 ml) together with O_2 at 6-7 L/min. IV hydrocortisone was used after the first 40 minutes for patients showing incomplete response to salbutamol, while ipratropium bromide was added after the 1st hour if needed. Theophylline was not used in the management of our patients during their acute attacks.

Statistical methods:

Results were analyzed and statistically compared using the 9th version of the statistical package SPSS. Qualitative data were presented as numbers and percentages, and chi-squared test [χ^2] was used for comparison between each two variables. The quantitative data were described as mean±SD, and range. The student's [*t*-test] was used to compare between each two groups. Pearson's correlation coefficient [r] was used to evaluate the relations between the studied numerical variables. The p-values ≤ 0.05 were considered significant in all tests.

RESULTS

From history taking in our series, spring was the highest season for the occurrence of asthma exacerbations (65.6%). The precipitating factors for asthma symptoms include irritants (96.9%), viral upper respiratory infections (84.4%), chemicals (59.4%), food (12.5%), and exercise (6.3%). Concerning the associated atopic disorders, 75% of patients had at least one atopic disease [allergic rhinitis was the most prevalent, it was present alone or with other atopic disorders in 93.7% of patients], while 25% of patients had two atopic diseases. Other atopic diseases encountered in our patients were allergic conjunctivitis and atopic dermatitis. Considering current medications; inhaled steroids were not prescribed to any of our mild persistent asthmatic children, but only a combination of oral drugs e.g. β_2-agonists, theophylline. Six of our patients were using oral steroids during their current acute attack [data not shown].

Table [1] and Figures [1, 2] showed marked and statistically highly significant improvement in the degree of wheezing, vital signs, and blood gas parameters of our patients at H+1 after nebulized salbutamol therapy. This improvement was equally highly significant in patients with either moderate or severe asthma attacks ($p < 0.001$ compared to that at H0 for all parameters).

Table [2] and Figure [3] demonstrated that plasma lactate levels on admission and before treatment were within the normal values in all patients [1.35±0.38 mmol/L]. One hour after starting nebulized salbutamol, a highly significant rise in plasma lactate occurred [4.44±0.78 mmol/L, $p < 0.001$ vs H0]. Twenty-four hours after starting treatment plasma lactate levels had returned to normal values in all patients' groups [although slightly higher than the H0 levels] (1.91±0.59

mmol/L, $p < 0.001$ for the comparison between each of the H0 vs H+1, H+1 vs H+24, and H0 vs H+24).

Considering various degrees of asthma severity, no significant difference in the H0 plasma lactate was observed between patients with severe or moderate attacks (a mean of 1.37±0.38 and 1.32±0.4 mmol/L respectively, $p = 0.7$). On the other hand, plasma lactate was elevated to a greater degree at H+1 in patients with severe attacks compared to those with moderate attacks (a mean of 4.69±0.8 and 4.02±1.6 mmol/L respectively, $p < 0.05$).

Our work demonstrated that the rise in plasma lactate levels at H+1 was significantly more obvious in patients currently using oral steroids before enrollment compared to non-users (a mean of 5.11±0.89 and 4.28±0.68 mmol/L respectively, $p < 0.05$) [data not shown].

Table [3] showed the different correlations done between plasma lactate and various patients' data. There were statistically significant positive correlations between the respiratory rate [both at H0 and H+1] and plasma lactate level at H+1 ($r = 0.44$, 0.47 respectively, $p < 0.05$). Also, total serum IgE showed a statistically significant positive correlation with the plasma lactate level at H+1 ($r = 0.44$, $p < 0.05$).

Table 1. Clinical and blood gas parameters before and after treating exacerbations of asthma.

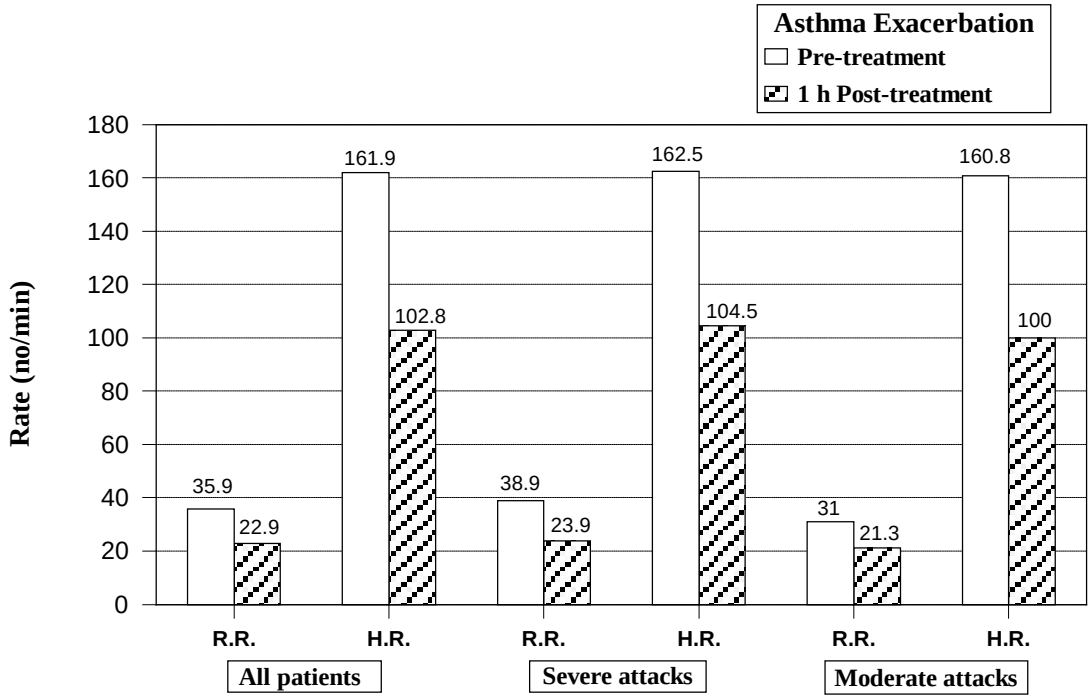
Parameters	**Asthma Exacerbation**		**[a] p-value**
	Pre-Treatment	Post-Treatment	
Wheeze (% of patients)			
(+++)	100.0	0.0	< 0.001
(+)	0.0	100.0	
Respiratory rate (breaths/min)			
Mean±SD	35.9±4.7	22.9±3.3	< 0.001
Range	28-40	18-32	
Heart rate (beats/min)			
Mean±SD	161.9±11	102.8±8.1	< 0.001
Range	140-180	90-120	
PaO_2 (mmHg)			
Mean±SD	68.8±8.3	99.7±0.6	< 0.001
Range	50-80	98-100	
$PaCO_2$ (mmHg)			
Mean±SD	56.3±9.2	39.9±1.9	< 0.001
Range	44-69	37-45	
SaO_2 (%)			
Mean±SD	90.6±1.7	98.7±0.5	< 0.001
Range	87-95	98-99	

[a] p-value ≤ 0.05 is considered significant.
$PaCO_2$: Arterial CO_2 tension. PaO_2: Arterial O_2 tension. SaO_2: Arterial O_2 saturation. SD: Standard deviation.

Table 2. Plasma lactate levels before and after treating exacerbations of asthma.

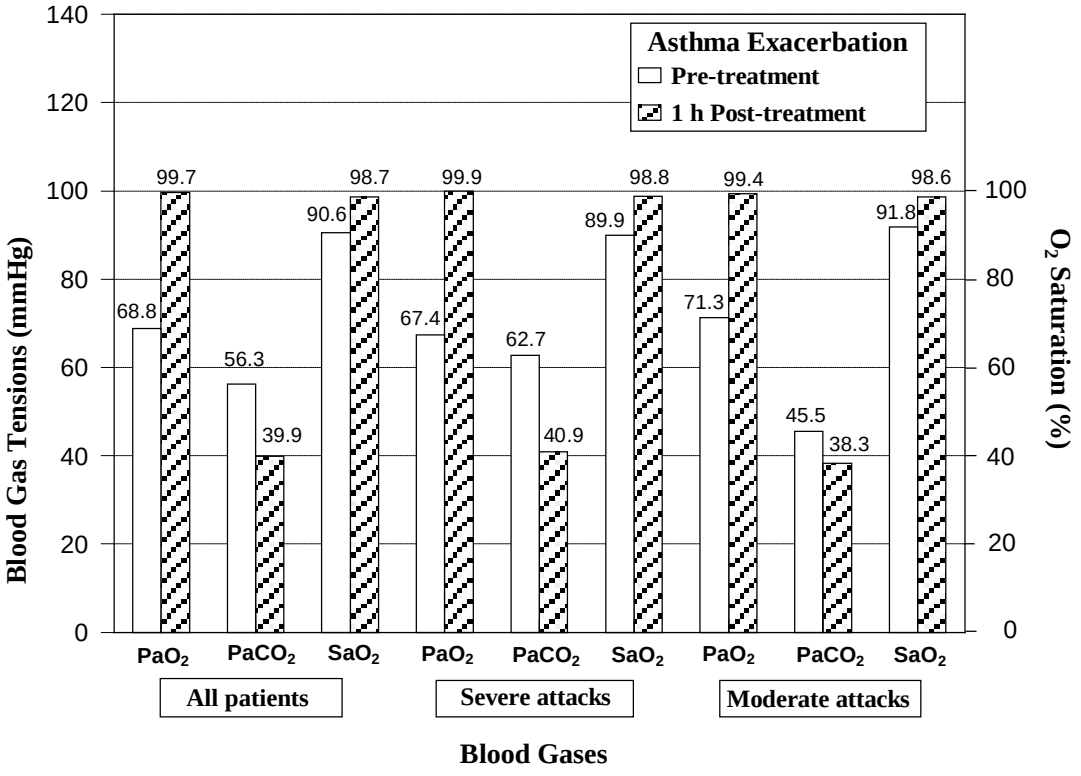
Plasma Lactate (mmol/L)	**Asthma Exacerbation**			**[a] p-value**
	Pre-Treatment	1 h Post-Treatment	24 h Post-Treatment	
Mean±SD	1.35±0.38	4.44±0.78	1.91±0.59	< 0.001*
Range	0.8-2.1	3-6.2	0.9-3.2	

[a] p-value ≤ 0.05 is considered significant. SD: Standard deviation.
*Pre-treatment vs 1 h post-treatment, 1 h post-treatment vs 24 h post-treatment, and pre-treatment vs 24 h post-treatment.



H.R.: heart rate; R.R.: respiratory rate.

Figure 1. Vital signs before and after treating asthmatic exacerbations of the children.



$PaCO_2$: Arterial CO_2 tension; PaO_2: Arterial O_2 tension; SaO_2: Arterial O_2 saturation.

Figure 2. Blood gases before and after treating asthmatic exacerbations of the children.

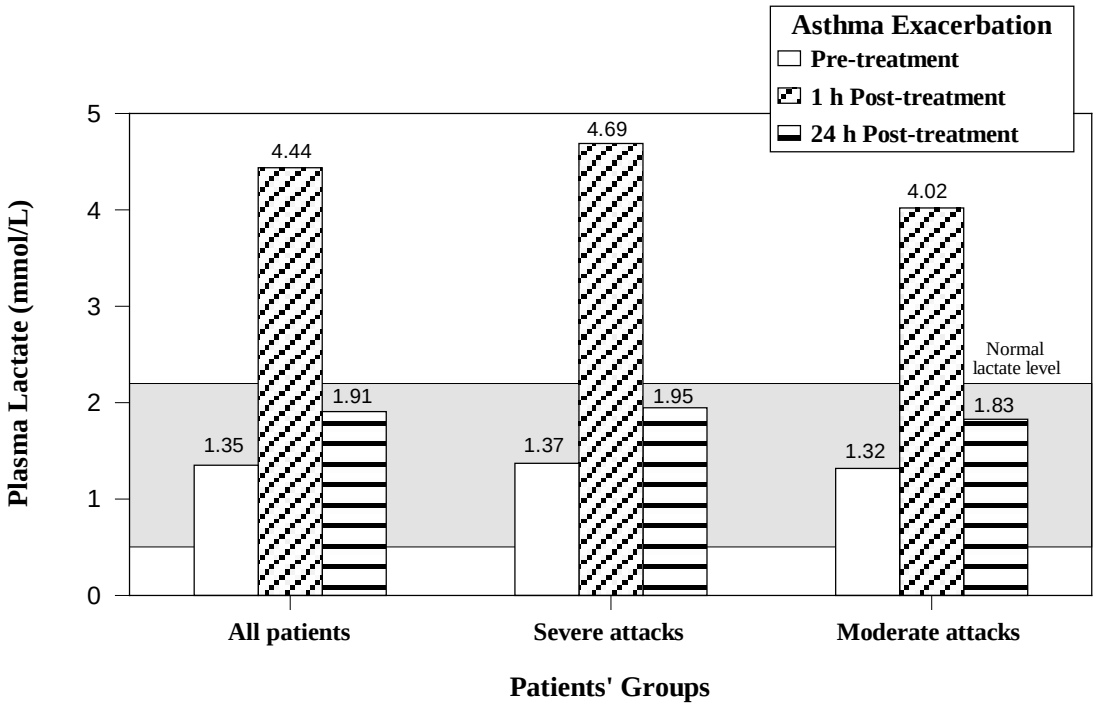


Figure 3. Plasma lactate before and after treating exacerbations of asthma in the studied sample.

Table 3. Correlations of plasma lactate with patients' demographic, baseline and laboratory parameters.

Variable	Plasma Lactate					
	Pre-Treatment		1 h Post-Treatment		24 h Post-Treatment	
	r	[a] p	r	[a] p	r	[a] p
Age	- 0.16	NS	0.06	NS	- 0.22	NS
Duration of asthma	- 0.09	NS	0.16	NS	- 0.23	NS
PEFR (after initial bronchodilator)	- 0.21	NS	- 0.06	NS	- 0.23	NS
Respiratory rate						
Pre-treatment	- 0.13	NS	0.44	< 0.05	0.20	NS
1 h Post-treatment	0.05	NS	0.47	< 0.05	0.27	NS
Heart rate						
Pre-treatment	0.13	NS	- 0.03	NS	0.08	NS
1 h Post-treatment	0.03	NS	0.20	NS	0.04	NS
Total s IgE (pre-treatment)	0.20	NS	0.44	< 0.05	0.08	NS
PaO_2						
Pre-treatment	0.08	NS	- 0.22	NS	0.24	NS
1 h Post-treatment	0.06	NS	- 0.05	NS	0.02	NS
$PaCO_2$						
Pre-treatment	0.15	NS	- 0.15	NS	- 0.003	NS
1 h Post-treatment	0.07	NS	0.01	NS	0.20	NS
SaO_2						
Pre-treatment	0.11	NS	0.08	NS	- 0.08	NS
1 h Post-treatment	- 0.05	NS	0.003	NS	- 0.05	NS

[a] p-value ≤ 0.05 is considered significant, NS = not significant.
$PaCO_2$: Arterial CO_2 tension. PaO_2: Arterial O_2 tension. PEFR: Peak expiratory flow rate. SaO_2: Arterial O_2 saturation. Total s IgE: Total serum immunoglobulin E.

DISCUSSION

Lactic acidosis is a well described phenomenon in adults with severe exacerbations of asthma[8,9]. However this entity is infrequently reported in children with status asthmaticus, although it has been documented[4,5].

On admission to the emergency department [H0], all our patients had normal lactate levels. These levels were slightly higher in patients with severe exacerbations compared to those with moderate attacks; this difference was statistically not significant. Also, the baseline lactate levels were slightly higher in patients with mild persistent asthma compared to those with intermittent asthma; the difference was again statistically not significant.

One hour post-treatment, all patients developed appreciable lactatemia representing a 257±121.5% increase above the H0 levels. In patients with severe attacks the increase in plasma lactate was significantly higher than in those with moderate attacks. Also, patients with mild persistent asthma showed a higher mean lactate level at H+1 compared to those with intermittent asthma.

Our results are in agreement with data provided by Rabbat et al.[10] who reported hyperlactatemia in all patients during the course of treatment. On the other hand, our results contradict those of Yousef and McGeady[5] who demonstrated lactic acidosis in only 1% of pediatric patients admitted to the ICU with status asthmaticus. The timing of determination of lactate levels could explain this discrepancy in the frequency of hyperlactatemia in various published studies.

The pathogenesis of lactic acidosis in asthma is not well understood. Yousef and McGeady[5] stated that this phenomenon may be caused by lactate accumulation (through excessive production, and inadequate clearance) together with the loss of bicarbonate. Excess lactate production in acute asthma exacerbation may be multifactorial and attributable to overuse of respiratory muscles under hypoxic conditions, reduced tissue perfusion, and administration of β-agonists and glucocorticoids. However, in the case-report studies by Maury et al.[8] and Manthous[9], increased work of breathing has been excluded as a factor in producing lactic acidosis.

In our work, while lactate levels were rising; bronchial obstruction was improving as evidenced by the statistically highly significant ($p < 0.001$) improvement of clinical as well as blood gas parameters at H+1. These findings preclude overworked respiratory muscles as a cause of lactatemia, and they go hand-in-hand with previous reports[5,8,9]. However, they are not in accordance to observations made by Appel and colleagues[11] who noticed that the development of lactic acidosis was associated with persistent severe obstruction of expiratory airflow.

Hypoxemia and tissue hypoxia have been hypothesized as pathogenetic factors precipitating lactic acidosis in asthma[12]. In our series, all patients were hypoxemic at presentation and the SaO_2 was below 90% in a quarter of them. At that time [H0], plasma lactate levels were normal. At H+1 hyperlactatemia appeared despite a significant improvement in SaO_2, and this excludes hypoxemia as a contributing factor in lactatemia during treatment of acute asthma exacerbations.

Glucocorticoids are known to enhance the sensitivity of β-receptors to β-adrenergic agents, and could sometimes contribute to lactic acidosis when used during treatment of acute asthma attacks[13]. However, as the onset of action of systemic glucocorticoids is reported to be 4-6 hours[14]; the significant difference noted in lactate levels at H+1 between the groups of our patients using or not using oral glucocorticoids was thus mostly attributed to current oral glucocorticoids use before enrollment in the study and not due to the IV hydrocortisone given to these patients. This finding is in agreement with the observation reported by Stratakos and colleagues[6]. They stated that transient increase of lactate levels with or without metabolic acidosis has been seldom reported as a complication of β-adrenergic agents administered during an asthmatic attack. On the other hand, many other workers have linked the use of β-adrenergic agonists with the occurrence of lactatemia[4,5,10,15].

In our work, all patients received the same treatment regimen during the first 40 minutes and all of them developed lactatemia, thus a potential effect of treatment must be questioned[16]. None of our patients had received IV bronchodilators including theophylline, so nebulized salbutamol used for all patients can be strongly accused as the pathogenetic factor that might account for lactatemia.

The mechanisms by which β_2-agonists may cause lactic academia are proposed to be through β_2-receptor activation with consequent enhanced glycogenolysis and lipolysis[4,16]. Increased glycogenolysis eventually leads to increased concentrations of pyruvate. Pyruvate is converted to acetyl-CoA, which enters the citric acid cycle. If pyruvate does not enter this aerobic pathway, it is converted to lactate instead, thereby potentially causing lactic acidosis. In addition, an increased lipolysis also increases acetyl-CoA through a different pathway. An increased acetyl-CoA

concentration potentially inhibits pyruvate oxidation to acetyl-CoA and leads to excess pyruvate. Finally, β_2-receptor stimulation will also inhibit the pyruvate dehydrogenase complex, and this might further limit the rate of pyruvate oxidation to acetyl-CoA[16].

Concerning the effects of lactatemia on clinical indices of severity of asthma exacerbation, our results demonstrated that at H+1; while lactate levels were rising, there was a statistically highly significant improvement in the respiratory rate and heart rate (Table 1). Much improvement occurred in patients with moderate attacks compared to those with severe attacks. Our data are different from those reported by Maury et al.[8], and from the case-report by Yousef and McGeady[5] who noticed persistent hyperpnea with Kussmaul breathing despite the continuous nebulized albuterol therapy. This could be due to the metabolic acidosis present in the latter case. Also, lactate levels of our patients were related to the degree of dyspnea. A statistically significant positive correlation was observed between lactate levels at H+1 and the respiratory rate (Table 3).

Our findings demonstrate that lactate levels at H+24 returned to normal values in most of the patients and this was in parallel with the reduction in the frequency of nebulized salbutamol. No significant difference was observed in lactate levels at H+24 between patients with severe attacks compared to those with moderate attacks.

None of our patients developed metabolic acidosis, and all of them showed significant clinical improvement during the first 24 hours of treatment. This is in agreement with the work of Rabbat et al.[10] who stated that hyperlactatemia seems to have no prognostic value in acute severe asthma, and metabolic acidosis with an increased anion gap was present in only 14% of their patients. Also, Yousef and McGeady[5] did not find lactic acidosis in pediatric patients with status asthmaticus who developed respiratory failure.

From this study we conclude that delayed lactatemia is a common finding during treatment of acute severe asthma in children, however it is not predictive of bad prognosis or respiratory failure. Those who care for children and adolescents with status asthmaticus should be aware of lactatemia as a side effect of β_2-agonist treatment, observe carefully for unexplained acidosis, rising anion gap, or evidence of resistance to bronchodilator therapy. Identification of lactic acidosis prevents the inappropriate intensification of treatment regimen especially in patients with severe attacks or imminent respiratory arrest. Other factors that might be sharing in the occurrence of lactatemia remain to be explored. These include the hemodynamic disturbances occurring during acute severe asthma, and the effects of plasma catecholamine and phosphate levels.

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