Electrolyte Disturbances in Patients With Chronic, Stable Asthma*

Effect of Therapy

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Objective: **To determine the prevalence of electrolyte disturbances in patients with chronic, stable asthma, and to assess whether the therapeutic agents used to treat chronic asthma have an effect on abnormal electrolyte levels.**
Design: **Prospective, hospital-based, cross-sectional study.**
Setting: **University teaching hospital in Jeddah, Saudi Arabia.**
Patients: **Patients with chronic, stable asthma.**
Method: **Ninety-three consecutive patients with chronic, stable asthma were involved in the study. On the day of the visit to the asthma clinic, particulars such as age, sex, duration of asthma, and details of drug therapy were obtained from each asthmatic patient. Serum potassium, magnesium, phosphorus, calcium, and sodium levels were measured. Normal values were as follows: potassium, 3.5 to 5 mmol/L; magnesium, 0.74 to 1.2 mmol/L; phosphorus, 0.8 to 1.4 mmol/L; and calcium, 2.1 to 2.6 mmol/L.**
Results: **Electrolyte disturbances were found in 43% of the patients; 85% of the patients had one electrolyte disturbance, 10% had two electrolyte disturbances, and 5% had three electrolyte disturbances. The highest proportions were for magnesium (26.9%) and phosphorus (15.1%) [serum levels were 0.69 ± 0.04 mmol/L and 0.64 ± 0.09 mmol/L, respectively], the lowest proportions were for potassium (5.4%) and sodium (4.3%) [serum levels were 3.3 ± 0.01 mmol/L and 133 ± 0.01 mmol/L, respectively], and no patient had a calcium disturbance. Logistic regression analysis showed no statistically significant association between the therapy used and electrolyte disturbances.**
Conclusion: **Hypomagnesemia and hypophosphatemia were found to be the two most common electrolyte disturbances in patients with chronic, stable asthma. Therapeutic agents used to treat patients with chronic asthma have no effect on abnormal electrolyte levels. The underlying cause still remains unclear.** ***(CHEST 2001; 120:431–436)***

Key words: chronic asthma; hypocalcemia; hypokalemia; hypomagnesemia; hyponatremia; hypophosphatemia

Interest in electrolyte disturbance in asthma patients has so far been focused on serum potassium especially linked to therapy with β_2-agonists.[1–5] For acute asthma, repeated doses of nebulized β_2-agonists and to a lesser extent IV aminophylline are the mainstay therapies used to relieve bronchospasm and airway obstruction.[6–8] Tremors, tachycardia, palpitations, and anxiety are well-known side effects of such treatments.[9] Hypokalemia was the earliest electrolyte disturbance reported in acute asthma, and it was related to the use of β_2-agonists and aminophylline therapy.[1–4] Recently, hypomagnesemia, hypophosphatemia, and hypocalcemia have also been reported after administration of β_2-agonists in normal subjects and in asthmatic patients as well.[5,10–12] The mortality rate in patients with asthma is still rising and has been partly attributed to the adverse effects of β_2-agonists administered for asthma management.[13–15] Hypokalemia, hypomagnesemia, and hypocalcemia are well-known causes of cardiac arrhythmia.[16,17] In addition, hypophosphatemia can worsen respiratory failure in severely ill asthmatic patients through impairment of respiratory muscle performance.[18] In contrast to acute asthma, the therapeutic agents used for the management of chronic asthma were mainly inhaled steroids and β_2-agonists.[19] In patients with chronic asthma, the prevalence of electrolyte disturbance and the effect of therapy on these changes (if any) is un-

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known. Therefore, in this prospective study, the measurement of serum potassium, magnesium, phosphorus, calcium, and sodium was performed to determine which electrolyte disturbances may occur in patients with chronic, stable asthma, and to assess whether the therapeutic agents used have an effect on abnormal electrolyte levels.

Materials and Methods

Ninety-three consecutive patients with chronic, stable asthma during regular follow-up in the outpatients' asthma clinic were studied. The study was approved by the human ethics committee of King Abdulaziz University Hospital and was conducted in strict compliance with their policy. Asthma was diagnosed according to American Thoracic Society criteria.[19,20] Diagnosis was based on clinical history, reversibility of FEV_1, or peak expiratory flow $> 15\%$ and diurnal variations of peak expiratory flow rate $> 20\%$.

Patients with chronic asthma were treated according to the recommendations of international protocols for management of asthma.[18] Generally, β_2-agonists were administered on an as-needed basis, while inhaled steroids were administered regularly.[18] In this study, 82.8% of patients with chronic asthma were receiving regular inhaled steroids and 45.2% were receiving inhaled β_2-agonists, while only 7.5% were receiving oral theophylline therapy. The inhaled steroids administered were either budesonide or beclomethasone, administered regularly in divided doses ranging from 800 to 2,000 μg/d. The inhaled β_2-agonist administered was either salbutamol or terbutaline, administered on an as-needed basis in doses ranging from 200 to 500 μg per puff. The dosage of oral theophylline was 150 mg bid. All asthmatic patients who participated in the study were not recently hospitalized or discharged from the hospital, and none were receiving IV aminophylline. No patients were receiving IV, nebulized, or oral β_2-agonists, or oral prednisone therapy.

In addition, none of the patients were smokers or had a history of renal disease, diabetes, hypertension, cardiac disease, diarrhea, alcohol abuse, diuretic use, or were currently pregnant. None of them showed evidence of hyperthyroidism or hypothyroidism, or had malignant disease.

While attending the asthma clinic, information concerning age, sex, duration and severity of asthma, and details of current drug therapy used for management of asthma was obtained from each asthmatic patient. A score for drug therapy according to Rolla et al[21] with modifications was assigned to each asthmatic patient according to inhaled β_2-agonist use (0 = no use, 1 = less than once per day, 2 = every day, 3 = more than recommended dose), inhaled steroid (1 = use, 2 = no use irrespective of duration of therapy), theophylline (1 = use, 2 = no use), and oral steroid (1 = use, 2 = no use).[21] Serum potassium, magnesium, phosphorus, calcium, sodium, urea, creatinine, and albumin levels were measured using atomic absorption spectrophotometry (Hitachi 917; Hitachi; Tokyo, Japan).

Normal values for electrolytes in our laboratory are as follows: potassium, 3.5 to 5 mmol/L; magnesium, 0.74 to 1.2 mmol/L; phosphorus, 0.8 to 1.4 mmol/L; calcium, 2.1 to 2.6 mmol/L; and sodium, 135 to 145 mmol/L. In this study, hypokalemia, hypomagnesemia, hypophosphatemia, hypocalcemia, and hyponatremia were considered to be present if the serum levels were < 3.5 mmol/L, < 0.74 mmol/L, < 0.8 mmol/L, < 2.1 mmol/L, and < 135 mmol/L, respectively. Laboratory tests were performed at the Biochemistry Department at King Abdulaziz University Hospital.

Data Management and Statistical Analysis

Data were entered into a database file and were scrutinized for outliers and influential points. The statistical analysis was done using statistical software (SPSS; Chicago, IL). Descriptive statistics and frequency distributions were performed to describe the studied variables. χ^2 test, t test, and analysis of variance were used as appropriate. Level of significance was set to be < 0.05 throughout the analysis.

Results

A total of 93 consecutive patients with chronic asthma were studied; 83.9% of the patients studied were female. Overall mean age was recorded as 39.7 ± 13.1 years (minimum, 14 years; maximum, 70 years). Table 1 summarizes their characteristics. Electrolyte disturbance was found in 40 patients (43%). In 85% of patients, there was one electrolyte disturbance; 10% had two electrolyte disturbances; and 5% had three electrolyte disturbances. Table 2 shows the ranking of the most commonly disturbed electrolytes. The highest proportion was for magnesium, followed by phosphorus; no patient had a calcium disturbance. Tables 3, 4 show the distribution of asthmatic patients with normal and disturbed electrolytes for any type and specific type of electrolytes according to mean age, sex, duration, severity, and type of therapy. The proportion of patients with severe asthma was higher among those with electrolyte disturbances as compared to those with normal electrolyte levels, with the exception of phosphorus.

Table 1—*Distribution of the Main Characteristics of the Asthmatic Patients

Characteristics	Data
Age, yr	39.7 ± 13.1
Sex	
Male	15 (16.1)
Female	78 (83.9)
Duration of BA, yr	9.8 ± 9.8
Severity	
Mild	52 (55.9)
Moderate	26 (28)
Severe	15 (16.1)
Electrolyte levels	
Magnesium	0.78 ± 0.09
Calcium	2.35 ± 0.11
Potassium	3.96 ± 0.35
Sodium	139.9 ± 3.43
Phosphorus	1.03 ± 0.23
PEFR, L/min	317.7 ± 104.8
Therapy	
Steroids	77 (82.8)
β-Agonists	42 (45.2)
Theophylline	7 (7.5)

*Data are presented as mean ± SD or No. (%). BA = bronchial asthma; PEFR = peak expiratory flow rate.

Table 2—*Serum Level, Frequency, and Percentage of Patients With Disturbed Electrolytes

Electrolytes	Serum Level	Frequency
Magnesium	0.69 ± 0.04	25 (26.9)
Phosphorus	0.64 ± 0.09	14 (15.1)
Potassium	3.3 ± 0.08	5 (5.4)
Sodium	133 ± 0.05	4 (4.3)
Calcium	—	0 (0.0)

*Data are presented as mean ± SD or No. (%).

In addition, the use of therapy showed no effect on electrolyte disturbance. The use of β_2-agonists was not significantly different between those with normal or disturbed electrolytes.

Logistic regression analysis was performed to study the association between therapy and electrolyte disturbance while controlling for the effect of other factors, such as severity, duration of asthma, sex, and age. No statistically significant association was found, and none of the additional factors contributed significantly to the model.

Discussion

In this study, the prevalence of electrolyte disturbance in patients with chronic asthma was common and reached up to 43%. Contrary to our expectation, hypomagnesemia and hypophosphatemia rather than hypokalemia were found to be the two most common electrolyte disturbances in patients with chronic, stable asthma, with prevalences of 26.9% and 15.1%, respectively. There was no effect of therapy (inhaled β_2-agonists, inhaled steroids, and oral theophylline) on serum electrolyte levels in patients with chronic asthma.

Recently, hypomagnesemia (serum level < 0.74 mmol/L) was found to be a common disorder in patients with chronic asthma.[22] Although the cause of hypomagnesemia in patients with chronic asthma was unknown, asthmatic patients with low serum magnesium levels were found to have more severe asthma and a higher incidence of asthma exacerbation and hospitalization than asthmatic patients with normal serum magnesium levels.[22] Some earlier reports showed an association between magnesium deficiency and increased airway hyperreactivity, pulmonary vascular resistance, and ventricular arrhythmia.[23–25]

Low dietary magnesium was also found to be associated with wheezes and impairment of lung function in normal subjects,[26] while magnesium supplementation can reduce asthma symptoms.[27] In previous studies, the cause of hypomagnesemia in patients with acute asthma has been related to the use of β_2-agonists either orally[5] or IV,[11] or by nebulization,[28] rather than by inhalation. Treatment with β_2-agonists can reduce serum magnesium levels through urinary loss or intracellular shift.[29] Moreover, in another study,[21] the concomitant use of diuretics and oral steroids rather than inhaled β_2-agonists was also found to be responsible for the higher prevalence of hypomagnesemia in patients with chronic obstructive airway disease.

In this study, patients with chronic asthma were receiving only the inhaled form of β_2-agonists when their serum electrolyte levels were measured. In addition, the use of inhaled β_2-agonists was not significantly different in asthmatic patients with normal and with low electrolytes. IV aminophylline therapy has been reported[8] to cause hypomagnesemia in susceptible individuals by increasing the urinary secretion of magnesium. Interestingly, this in turn may cause increased pulmonary irritability and consequently increase the risk of acute asthma.[30]

In this study, aminophylline therapy was found to have no significant effect on electrolyte disturbance; however, it was administered orally and only in a small number of asthmatic patients ($n = 7$). Therefore, the underlying cause of hypomagnesemia in patients with chronic asthma remains unclear and further studies may be needed.

Hypophosphatemia (serum level < 0.8 mmol/L) has also been reported in patients with acute asthma treated with nebulized β_2-agonists, IV aminophylline, and hydrocortisone.[4,8,28] IV infusion of β_2-agonists can cause dose-related hypophosphatemia probably through intracellular shifts of phosphorus ions.[4] Aminophylline can also cause hypophosphatemia either through increased urinary excretion or through increased intracellular shifts.[8,10] In addition, corticosteroids increase urinary phosphorus excretion.[31,32] In acute asthma, the adrenaline and insulin levels were increased, secondary to β_2-agonist stimulation. This may cause influx of phosphorus from the extracellular to the intracellular compartments.[31,32]

In this study, the prevalence of hypophosphatemia in patients with chronic asthma was found, unexpectedly, to be high (15%); however, there was no previous study to compare our results with others. Hypophosphatemia can cause myocardial depression, respiratory muscle fatigue, and reduction of tissue oxygen extraction in patients with acute asthma and with COPD.[18,28,33,34] Therefore, patients with chronic asthma and hypophosphatemia may be at high risk if they have an exacerbation.

Logistic regression analysis showed that the therapeutic agents used for management of chronic asthma have no effect on the serum phosphorus level. Therefore, the underlying cause remains ob-

Table 3—*Distribution of Asthmatic Patients With Normal and Disturbed Electrolytes by Age and Duration**

Characteristics	Any Type (Hypo = 40)	Magnesium (Hypo = 25)	Potassium (Hypo = 5)	Phosphorus (Hypo = 14)	Sodium (Hypo = 4)
Age, yr					
Hypo	38.3 ± 11.8	36.8 ± 10.3	35.6 ± 15.8	38.6 ± 10.4	53.0 ± 10.1
Normal	40.8 ± 14.0	40.8 ± 13.9	40.0 ± 13.0	39.9 ± 13.5	39.1 ± 12.9
Duration					
Hypo	10.1 ± 10.1	8.4 ± 7.3	11.4 ± 9.7	10.4 ± 13.4	12.3 ± 12.1
Normal	9.6 ± 9.6	10.3 ± 10.6	9.7 ± 9.9	9.7 ± 9.1	9.7 ± 9.7

*Data are presented as mean ± SD. Hypo = serum electrolyte level below normal value.

scure. Further studies are needed to confirm our findings, to investigate for the underlying cause(s), and to evaluate the clinical effect of hypophosphatemia on patients with chronic asthma with and without exacerbation.

Hypokalemia (serum level < 3.5 mmol/L) has been reported[1,2] earlier than hypomagnesemia and hypophosphatemia in patients with acute asthma. It was also related to the use of β_2-agonist and aminophylline infusion during the management of asthma exacerbations.[1–4] Administration of β_2-agonists can cause hypokalemia through increased cellular influx of potassium, mediated by β_2 stimulation of membrane sodium potassium-dependent adenosine triphosphatase.[16,35]

A study on healthy subjects receiving terbutaline infusion showed reduction of serum level and urinary excretion of potassium.[11] Hypokalemia may also occur due to active inhibition of potassium secretion in the cortical collecting tubule, possibly caused by stimulation of membrane sodium potassium-dependent adenosine triphosphatase that results in hyperpolarization of the cellular membrane potential.[36] For chronic asthma, there was no previous study to evaluate the prevalence of hypokalemia in patients with chronic asthma receiving inhaled steroids and β_2-agonists. Although hypokalemia was only found in small number of our asthmatic patients (5.4%), the therapeutic drugs administered for the management of chronic asthma were found to have no effect on the serum potassium level.

In asthmatic patients with acute exacerbation, hypokalemia may reach up to 57% in subjects treated with repeated doses of nebulized β_2-agonists.[4] This indicates that the use of inhaled β_2-agonists in patients with chronic asthma may have no effect on serum potassium level when it is compared with the use of nebulized or IV β_2-agonist in acute asthma. However, in a previous study[1] of healthy individuals, hypokalemia was reported following administration of inhaled fenoterol rather than salbutamol or terbutaline. This may not contradict our findings, as our asthmatic patients received only inhaled salbutamol or terbutaline rather than inhaled fenoterol.

In this study, only four asthmatic patients were found to have low serum sodium (serum level < 135 mmol/L). Increased urinary sodium secretion with normal serum level has been reported in asthmatic patients with repeated asthma attacks treated with IV aminophylline.[8] Although the total number of

Table 4—*Distribution of Asthmatic Patients With Normal and Disturbed Electrolytes by Sex, Severity, and Therapy**

	Any Type (Hypo = 40)		Magnesium (Hypo = 25)		Potassium (Hypo = 5)		Phosphorus (Hypo = 14)		Sodium (Hypo = 4)	
Characteristics	Low	N	Low	N	Low	N	Low	N	Low	N
Sex										
Male	17.5	15.1	8.0	19.1	0.0	17.0	35.7	12.7	0.0	16.9
Female	82.5	84.9	92.0	80.9	100	83.0	64.3	87.3	100	83.1
Severity										
Mild	60.0	52.8	52.0	57.4	80.0	54.5	78.6	51.9	75.0	55.1
Moderate	20.0	34.0	20.0	30.9	0.0	29.5	21.4	29.1	0.0	29.2
Severe	20.0	13.2	28.0	11.8	20.0	15.9	0.0	19.0	25.0	15.7
Therapy										
Steroids	87.5	79.2	84.0	82.4	100	81.8	85.7	82.3	75.0	83.1
Theophylline	5.0	9.4	4.0	8.8	0.0	8.0	7.1	7.6	0.0	7.9
β-Agonists	45.0	45.3	48.0	44.1	40.0	45.5	50.0	44.3	50.0	44.9

*Data are presented as %. N = normal; see Table 3 legend for expansion of abbreviation.

patients with chronic asthma and low serum sodium levels was too small to draw a clear conclusion about its prevalence and clinical significance, further studies with larger number of subjects are needed to evaluate the significance of this finding, if any.

Hypocalcemia (serum level < 2.1 mmol/L) has been reported in healthy subjects following administration of IV β_2-agonists that cause an increase in the urinary excretion of calcium.[11] In acute asthma, an increase in urinary excretion of calcium has also been reported in asthmatic patients treated with IV aminophylline.[8,10] In patients with chronic asthma, the prevalence of hypocalcemia has not been evaluated. In this study, all asthmatic patients had a normal serum calcium level. This finding may not contradict previous studies, as none of our asthmatic patients were receiving IV β_2-agonists or IV aminophylline during the measurement of their serum electrolytes.

In this study, the prevalence of an electrolyte abnormality was found to be high, and about 15% of the subjects had two or more abnormal electrolyte levels. Therefore, in patients with chronic asthma and exacerbation, care should be taken during acute management to avoid the adverse effects of bronchodilator therapy. Nebulized β_2-agonists and IV aminophylline are usually the mainstay therapies for asthma exacerbation. So, in the presence of one or more abnormal electrolyte levels (hypomagnesemia, and or hypophosphatemia, and or hypokalemia), the use of such therapies will increase the derangement of the existing abnormal electrolyte levels. Consequently, this may pose potential cardiac and respiratory hazards in the form of myocardial depression, ventricular arrhythmia,[16,25] and respiratory muscle fatigue, which consequently may increase the incidence of fatal asthma.[13,32,33] It is likely that these complications may occur especially in the presence of hypoxia or acidosis, or in asthmatic patients with preexisting cardiovascular disease.[17] Therefore, the measurement of the serum electrolyte levels before and during the management of asthma exacerbation with bronchodilators may reduce such risks if corrected.

Although this study has important clinical findings, it has several possible limitations. The first limitation is the absence of a control group. Secondly, the sample size was not large enough to permit extensive analysis on the effect of therapy on asthmatic patients with low sodium and potassium levels. Thirdly, the effect of the electrolyte abnormality on patients with chronic asthma was also overlooked; however, this was not among the objectives of the study.

In conclusion, hypomagnesemia and hypophosphatemia were found to be the most common electrolyte abnormalities in patients with chronic, stable asthma. The underlying cause still remains unknown. The possibility of dietary[37] or genetically determined factors[38] may explain some of the other underlying causes. However, further studies are needed to confirm our findings and to clarify these speculations. In addition, to avoid any potential cardiac and respiratory hazards in patients with chronic asthma and exacerbation, we recommend the measurement of serum electrolyte levels before bronchodilator therapy is administered.

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