

THEOPHYLLINE-INDUCED ALTERATION IN SERUM ELECTROLYTES AND URIC ACID OF ASTHMATIC CHILDREN

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ABSTRACT

Theophylline, (1,3-dimethylxanthine) is widely used as a smooth muscle relaxant, myocardial stimulant and a diuretic agent. The most frequent use of theophylline is in treatment of acute and chronic asthma as a bronchodilator.

To determine the effect of Theophylline on serum electrolyte and uric acid, 21 asthmatic children (age range 1.5-7 years) with severe acute asthma and 25 patients with chronic asthma (5-15 years) who were being treated with slow-release theophylline were enrolled in this study. Fifty age and sex matched normal children took part as control. Blood samples (5ml) were withdrawn before, during and after completion of the course of intravenous theophylline treatment (0.05-0.70 mg/kg/ hr). Sera obtained were used for analysis of K⁺, Na⁺, phosphorus, calcium and uric acid by RA-1000 automated analyzer and the following results were obtained:

(1) After treatment, total serum calcium in acute asthmatic patients decreased significantly compared with controls ($P < 0.01$); (2) serum phosphate and K⁺ levels of acute and chronic asthmatic patients after therapy decreased as compared with controls ($P < 0.01$). (3) Post therapy increase in serum level of uric acid in acute and chronic asthmatic patients was statistically significant as compared with control ($P < 0.001$).

We conclude that the serum levels of phosphate, potassium, calcium and uric acid should be monitored in patient receiving theophylline especially during prolonged use and critical emergency cases.

Keywords: Asthma, Theophylline, Hypokalemia, Hypocalcemia.

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INTRODUCTION

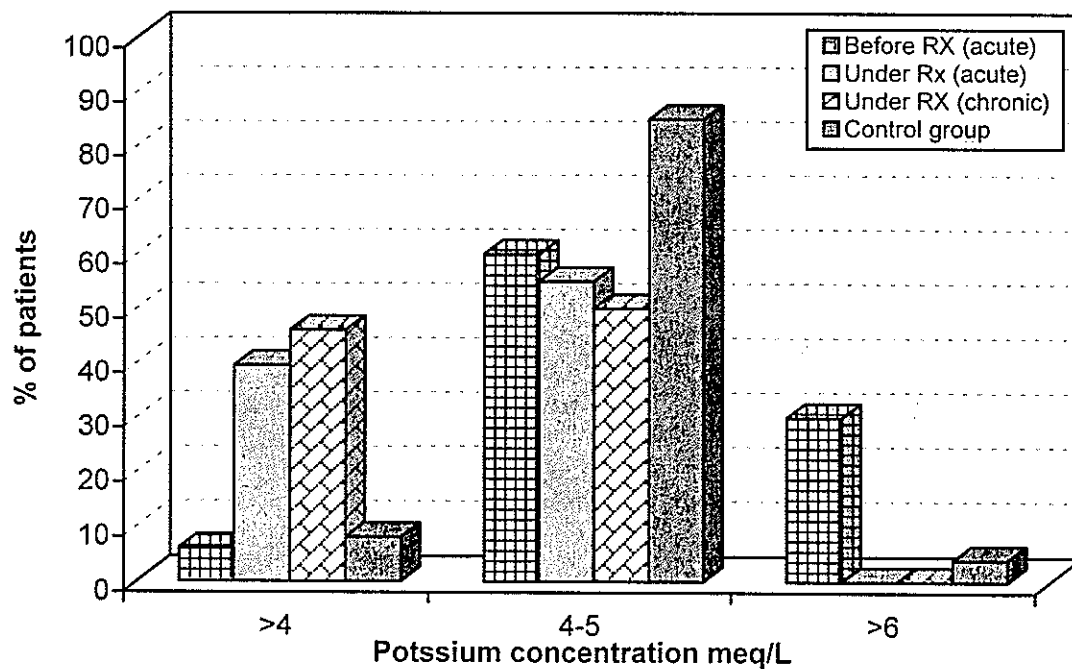
Theophylline has bronchodilatory and immunomodulatory action that may account for its clinical effectiveness for the control of acute and chronic asthma. Its immunomodulatory action includes inhibition of cytokine and leukotriene synthesis and inflammatory cell activation. (1,2)

Theophylline affects serum electrolyte balance through its action on hormonal control of electrolytes. The alteration in serum Na⁺ and K⁺ levels may be due to beta-adrenergic action of theophylline caused by stimulation of adenylate cyclase increasing cAMP level which in turn enhances Na⁺/K⁺ ATP-ase activity resulting in shift in the K⁺ from extracellular into intracellular fluid.

In addition theophylline increases production of urine and enhances excretion of water and electrolytes. Theophylline has been found to

increase the glomerular filtration rate (GFR) and enhances excretion of Na⁺, Cl⁻ and K⁺ in patients with congestive heart failure. However infusion of aminophylline (3.5 mg/kg) in normal human subjects appears to inhibit solute reabsorption without changing GFR or renal blood flow. (3)

Hypophosphatemia has been highlighted as a reversible cause of respiratory muscle hypocontractility and reduced O₂ extraction in asthmatic patients. (5,6) Hypokalemia plays a part in the sudden deaths seen in some asthmatic patients (7,8), so it is suggested that alteration in serum phosphate, Ca⁺⁺, K⁺ and uric acid in asthmatics are known to effect the outcome of management of asthma. This study, prospectively, evaluates whether the changes are due to complications of the disease itself or due to the side effects of drug therapy.



Statistical X=4.8 X=4.1 X=4 X=4.4
Indices SD=0.57 SD=0.5 SD=0.27 SD=0.3

Fig. 1. Potassium concentration in control group and a group of acute and chronic asthmatic under treatment with theophylline

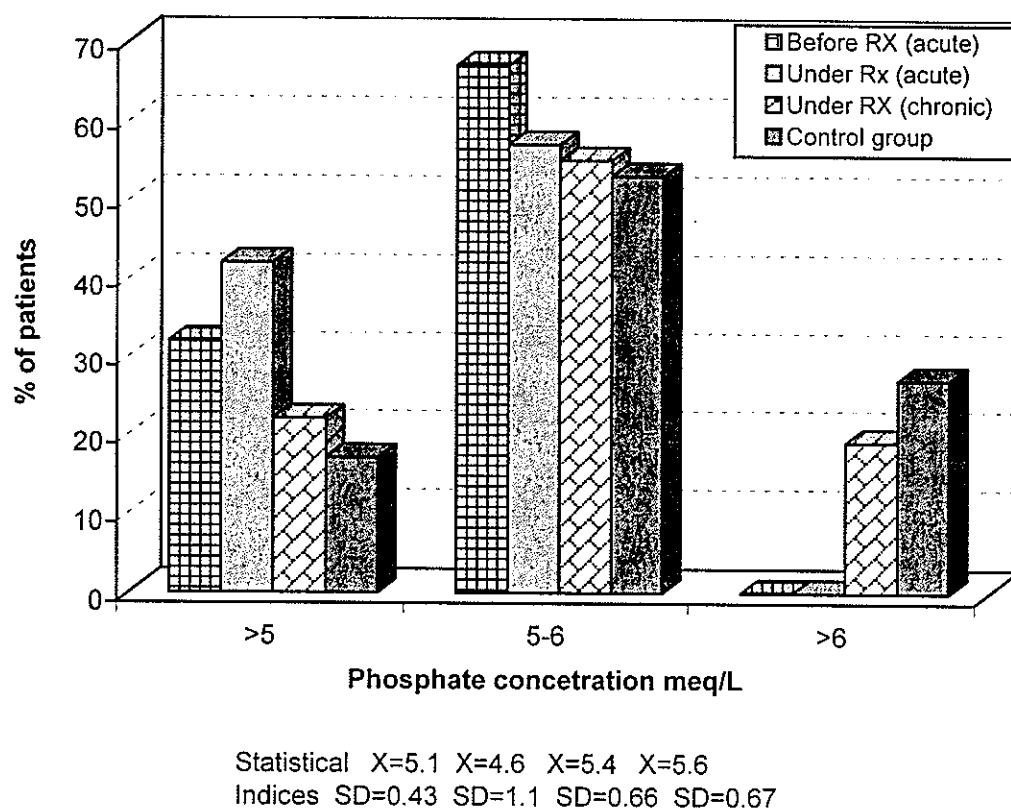


Fig. 2. Phosphate concentration in control group, acute and chronic asthmatic patients under treatment with theophylline

PATIENTS AND METHODS

Twenty-one known asthmatic children: (n=14 male and n=7 female, age range 1.5-7 years), who had been referred to Nemazee Hospital Emergency ward and were diagnosed as cases of asthma by history of repeated reversible attacks of wheezing were studied. Because of exacerbation of asthma, bronchodilator therapy was standardized.

The patients received aminophylline 0.5-0.7 mg/kg/hr intravenously by continuous infusion and hydrocortisone 5 mg/kg/dose Q6h with nasal O₂. They had no other diseases. Before and after 48 hours following aminophylline administration, 5ml blood sample was drawn from each patient and sera were collected. To study the effect of sustained - release theophylline in children with chronic asthma, 25 children (age range 5-15 years, mean 9 years) were selected. The patients received S-R theophylline round the clock for at least one month (200-400 mg / 24 hours). After treatment, blood sample was drawn and was stored at -20°C. All the

information was recorded in special form provided for the study. Also from a group of age and sex-matched healthy children, blood samples were drawn.

Measurement of total serum calcium, phosphate, Na⁺, K⁺ and uric acid was performed by RA-1000 method Ion selective electrode (ISE).

RESULT and DISCUSSION

A fall in serum phosphate, potassium and total calcium and a rise in uric acid concentration has been demonstrated in asthmatic patients receiving theophylline in our study.

Serum K⁺ level in acute and chronic asthmatics under theophylline therapy decreased as compared with control group (P<0.01) (Fig 1). Hypokalemia is a well established complication of bronchodilator therapy. (12,13,14,15) Epelbaum, reported an asthmatic case under beta-2 agonist and theophylline with sudden death due to hypokalemia (16). Theophylline increases production of urine

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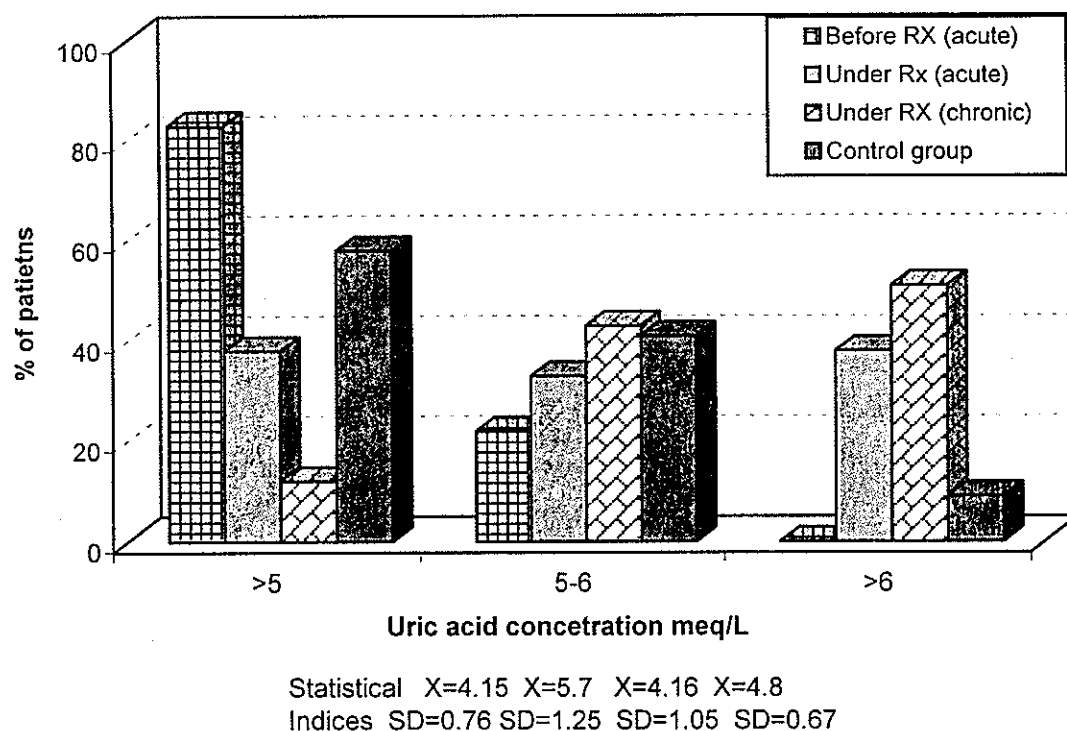


Fig. 3. Uric acid concentration in a control group and acute and chronic asthmatic patients under treatment with theophylline

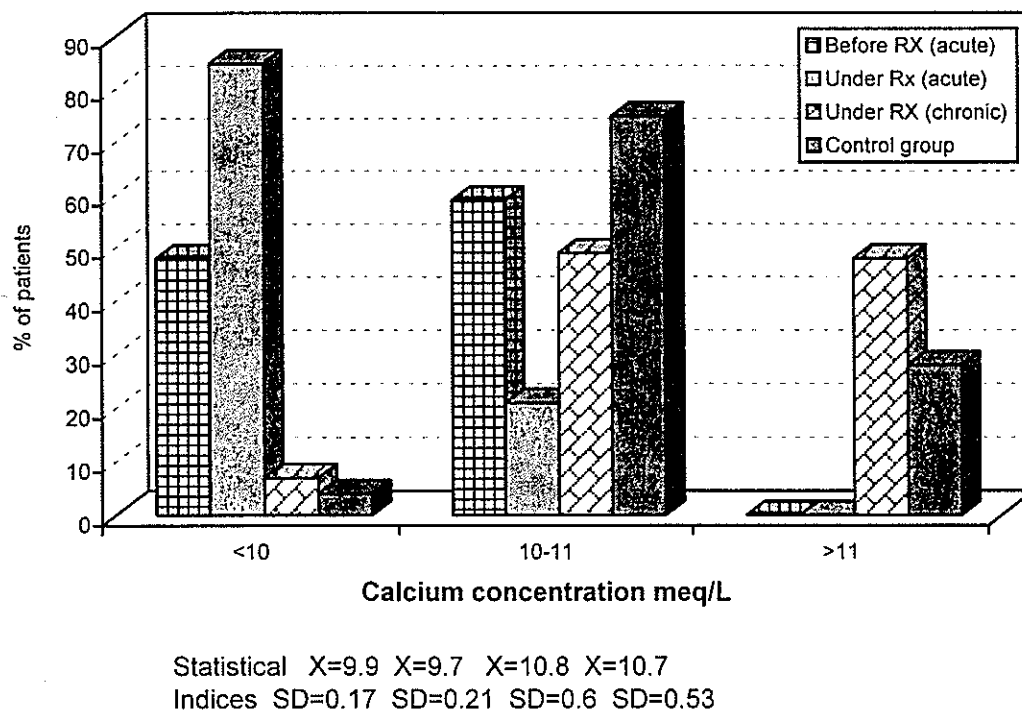


Fig. 4. Total calcium concentration in control, acute and chronic groups of asthmatic patients under treatment with theophylline

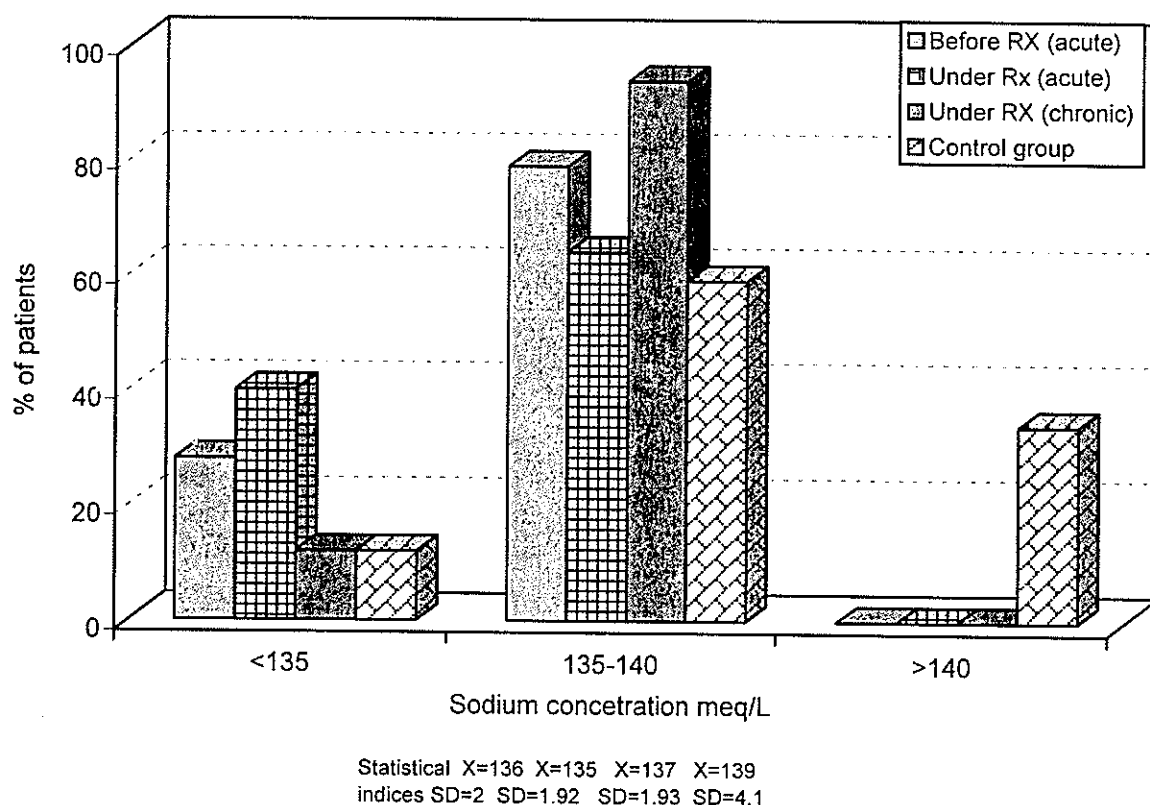


Fig. 5. Sodium concentration in a control group and acute/chronic asthmatic patients under treatment with theophylline

and enhances excretion of water and electrolytes and also increases GFR, however the infusion of aminophylline, into normal human subjects appears to inhibit solute reabsorption without changing GFR.(3) Hypokalemia and hypophosphatemia are associated commonly with acute but much less frequently with chronic aminophylline overdoses. Some of these effects may be, in part, attributable to elevated levels of norepinephrine and epinephrine transiently released by very high level of theophylline.(7) Potentiation of hypokalemia has been described from combined systemic administration of a (2 agonist and theophylline.(16,19) Because the hypokalemia occurs early in the course of theophylline before sufficient vomiting to account for gastrointestinal loss, intracellular sequestration is the most likely mechanism. (20)

In addition, hypophosphatemia was seen in all asthmatic patients (acute and chronic) who were on theophylline ($P < 0.01$) (Fig 2). Phosphate deficiency has been reported recently as a cause of respiratory

muscle fatigue and reduced oxygen extraction in patients with asthma. There is growing evidence to suggest that hypophosphatemia may be harmful in patients with obstructive disease. Alamoudi, has demonstrated that hypomagnesemia and hypophosphatemia were found to be the two most common electrolyte disturbances in patients with chronic, stable asthma.(5)

Brady showed that hypophosphatemia is a common metabolic abnormality during the emergency treatment of asthma and suggested that the serum phosphate level should be monitored in patients undergoing emergency treatment of bronchospasm, particularly if a prolonged period of bronchodilator therapy is required or if respiratory muscle fatigue supervenes. The underlying mechanism of hypophosphatemia appears to be drug induced phosphate flux from the extracellular to intracellular space. (6)

Total serum calcium following theophylline administration decreased in all asthmatic patients as compared to control group ($P < 0.01$) (Fig 4). The

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exact mechanism of its action is not known, although Knutsen et al demonstrated that theophylline may exert adverse effect on the urinary excretion of calcium, magnesium and sodium. However Almoudi showed that patients with chronic, stable asthma receiving treatment had not calcium disturbance (5) and Oner et al demonstrated that theophylline therapy at optimal doses might not exert adverse side effects on bone homeostasis. (22) In contrast Mc Pherson et al showed that theophylline causes elevation of serum calcium by a system subject to beta-adrenergic regulation.(23)

Serum sodium alteration in chronic theophylline user was not significant, but decreased among patients who were treated with intravenous aminophylline ($P = 0.02$) (Fig 5). Theophylline increases excretion of water and electrolytes like thiazides.(1,2,3) Other studies demonstrated hyponatremia induced by theophylline. (26,27)

Hyperuricemia in both acute and chronic asthmatic patients was observed ($P < 0.01$) (Fig 3). Recently, it was reported that xanthine derivatives induced hyperurecemia (11,24,25). Shimizu, et al demonstrated a significant positive correlation between the serum levels of uric acid and theophylline. All the patients in whom theophylline administration was stopped showed a significant decrease in serum uric acid.(9) Toda et al has described gout due to xanthine derivatives.(10) This has been observed in other studies (9,10,11).

We suggest that the serum phosphate, potassium and calcium levels should be monitored in patients receiving treatment of theophylline for bronchospasm, particularly if a prolonged period of bronchodilator therapy is required or if respiratory muscle fatigue supervenes. When a patient with bronchial asthma and positive family history of hyperuricemia is treated with xanthine derivatives, he or she should be carefully monitored for serum level of uric acid.

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