

## Lactic acidosis associated with the usual theophylline dose in a patient with asthma

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*Metabolic and electrolyte abnormalities, including hypokalemia, hyperglycemia and lactic acidosis, are associated with theophylline overdose. However, we report an unusual case of sinus tachycardia, lactic acidosis, hypokalemia and hyperglycemia associated with the usual theophylline dose in a patient with asthma. The theophylline dose was 200 mg orally twice daily. Three hours after administration of the third dose, the patient experienced palpitation. An electrocardiogram showed a sinus tachycardia. Arterial blood gas analysis revealed a mixed metabolic acidosis and respiratory alkalosis. Serum lactate level was 51 mmol/L (normal 0.7~2.1 mmol/L). Biochemistry results were sodium 136 mEq/L, chloride 99 mEq/L, potassium 1.9 mEq/L and glucose 204 mg/dL. Our case suggests that a possibility of theophylline-associated metabolic abnormalities should be considered when an asthmatic patient given the usual theophylline dose presents with lactic acidosis, hypokalemia and hyperglycemia of unknown etiology.*

**Key Words :** *Asthma, Hyperglycemia, Hypokalemia, Acidosis, Lactic, Theophylline*

### INTRODUCTION

Metabolic and electrolyte abnormalities, including hypokalemia, hyperglycemia and lactic acidosis, are associated with theophylline overdose<sup>1-3</sup>. We herein report the first case, to our knowledge, of sinus tachycardia, lactic acidosis, hypokalemia and hyperglycemia associated with the usual theophylline dose in a patient with asthma.

### CASE

A 30-year-old woman presented to our emergency room with chest palpitation. Two days before, she was diagnosed with mild persistent asthma for the first time in our Allergy Clinic. At that time, biochemistry results were

sodium 138 mEq/L, potassium 4.8 mEq/L, chloride 108 mEq/L and glucose 103 mg/dL and an electrocardiogram (ECG) showed normal sinus rhythm at 80 beats/min. She was a non-smoker and weighed 50 kg. She did not have acute and chronic hepatic dysfunction, cardiac decompensation, cor pulmonale and febrile illness. She began to take asthma medications, including sustained-release theophylline (200 mg twice a day), pranlukast hydrate (112.5 mg twice a day), salmeterol xinafoate inhaler (25 mg twice a day) and fluticasone propionate (250 mg twice a day). She and her family denied taking any other medications. She took a total of three doses of the medication before her visit to the emergency room. Three hours after taking the third dose, she experienced the palpitation. Two hours later, she inhaled 5 consecutive puffs of salbutamol, a short acting  $\beta_2$ -agonist, regarding the palpitation as one of asthma symptoms and the palpitation continued for 3 hr before presentation. On physical examination, she was awake and alert, although restless. There was no cyanosis or dehydration and she appeared clinically well perfused. Blood pressure was

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120/80 mmHg, pulse was regular at 126 beats/min, respirations were 20/min and temperature was 36.7 °C. ECG showed a sinus tachycardia. Forced vital capacity and forced expiratory volume in one second were 3.59 L (108% of predicted value) and 3.23 L (111%), respectively. Arterial blood gas analysis on room air revealed a mixed metabolic acidosis and respiratory alkalosis with a pH of 7.46, Pco<sub>2</sub> of 19.3 mmHg, Po<sub>2</sub> of 96.7 mmHg and bicarbonate of 13.4 mmol/L and biochemistry results were sodium 136 mEq/L, chloride 99 mEq/L, potassium 1.9 mEq/L and glucose 204 mg/dL. Serum lactate level measured at 5 hr after admission was 51 mmol/L (normal 0.7–2.1 mmol/L). Serum theophylline concentration measured at 13 hr after admission was 8.64 mg/mL. Intravenous administration of normal saline with potassium replacement was done. The rate of potassium infusion was 1.8 mEq/hr and the potassium deficit was corrected rapidly after 5 hr. Thereafter, only normal saline was administered. Heart rates on ECG monitoring were gradually decreased and returned to normal at approximately 10 hr after admission. The glucose level returned to normal 5 hr after admission. The abnormal bicarbonate, Pco<sub>2</sub> and serum lactate levels returned to near normal 5 days after admission. Blood and urine tests for pheochromocytoma were negative.

Although the serum theophylline level was within therapeutic range, a possibility of theophylline-associated sinus tachycardia, lactic acidosis, hypokalemia and hyperglycemia was considered. Because she was afraid of the possible symptoms, she refused a challenge test with theophylline. Instead, after getting approval from the institutional review board and her informed consent, the same asthma medications as before, except theophylline, were given again at 6 days after admission. No palpitation occurred for 5 days after the medications. Measurements for arterial blood gas, serum electrolytes and serum lactate at 5 days after the medications showed no abnormal findings. At two months after discharge, her asthma has been well controlled with regular medications, including pranlukast hydrate (112.5 mg twice a day), salmeterol xinafoate inhaler (25 mg twice a day) and fluticasone propionate (250 mg twice a day), without adverse effects.

## DISCUSSION

In our case, it is most likely that theophylline was the

culprit for our patient's sinus tachycardia, lactic acidosis, hypokalemia and hyperglycemia, in view of the time course of events and absence of occurrence of these metabolic abnormalities after taking the other asthma medications, except theophylline. Our patient showed no clinical evidence of tissue hypoxia. Possible concurrent drug ingestion contributing to the acidosis was excluded by the scrupulous history taking, although not demonstrated by negative toxicology screen.

It is known that toxic ingestions of theophylline cause elevated blood levels of the catecholamines, epinephrine and norepinephrine<sup>4</sup>. This may lead to lactic acidosis, as has been described in pheochromocytoma<sup>5</sup>, hyperglycemia<sup>4</sup> and hypokalemia<sup>6</sup>. On the other hand, studies on normal volunteers given therapeutic doses of theophylline have shown concentration-related changes in plasma glucose, free fatty acids and insulin<sup>7</sup> and increases in plasma catecholamines<sup>7, 8</sup>. It is possible that our patient's sinus tachycardia and metabolic abnormalities associated with the usual theophylline dose may be mediated in part by stimulation of the sympathetic nervous system. Also, the short acting  $\beta_2$ -agonist, misused for palpitation control in our case, may aggravate the abnormalities.

Unfortunately, the serum theophylline concentration was measured at an inappropriate time because we did not expect the theophylline-associated tachycardia and metabolic disturbances. An earlier measurement of the concentration might have revealed a higher level. It is likely that the serum theophylline level was beyond the therapeutic range, although our patient took the usual dose of theophylline. On the other hand, a possibility of theophylline drug intolerance might be considered if the earlier measurement showed that the serum theophylline level was within therapeutic range.

This unusual case suggests that a possibility of theophylline-associated metabolic abnormalities be considered when an asthmatic patient, given the usual dose of theophylline, presents with lactic acidosis, hypokalemia and hyperglycemia of unknown etiology.

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