Hypermagnesemia*
A Potential Complication During Treatment of Theophylline Intoxication with Oral Activated Charcoal and Magnesium-Containing Cathartics
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Toxic reaction to theophylline compounds is common. Oral activated charcoal (OAC) is a widely accepted mode of therapy for management of moderate to severe cases of theophylline toxicity. Magnesium-containing cathartics are generally recommended in conjunction with OAC in the treatment of drug or toxin ingestions. We report two cases of hypermagnesemia complicating the treatment of theophylline toxicity with OAC and magnesium citrate. In both patients, the hypermagnesemia contributed significantly to morbidity or mortality. In light of these cases and after review of the literature, we suggest that sorbitol be considered the cathartic agent of choice in the treatment of theophylline toxicity with OAC. (Chest 1989; 95:56-59)

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heophylline toxicity remains a common clinical occurrence. Oral activated charcoal (OAC) has recently been shown to enhance significantly the clearance rate of several drugs and has been successfully utilized in the management of theophylline-intoxicated patients.1,2 Activated charcoal appears to work by adsorbing the remaining drug within the gastrointestinal (GI) tract, preventing further systemic absorption,3 and by promoting the movement of theophylline down a concentration gradient from the intestinal mucosal circulation into the lumen of the gut.4 Since the binding of theophylline to charcoal within the gut is potentially reversible,5 the use of a cathartic agent along with the activated charcoal is generally recommended. These agents theoretically decrease the transit time of the activated charcoal through the gut, prevent reabsorption of charcoal-adsorbed drug, and help maintain a concentration gradient across the gut wall that favors further drug excretion. Among cathartic agents, magnesium citrate and magnesium sulfate are commonly used in the management of a variety of drug toxicities. Despite their common use, we are unaware of any data on their efficacy as it specifically applies to the treatment of theophylline toxicity or of their potential for producing hypermagnesemia.

We present two cases recently admitted to Wilford Hall USAF Medical Center in which treatment of theophylline toxicity with OAC and magnesium citrate resulted in iatrogenic hypermagnesemia, which contributed significantly to the morbidity or mortality of the patients involved.

**CASE REPORTS**

**CASE 1**
A 61-year old white woman had a history of hypertension and severe chronic obstructive pulmonary disease. Her outpatient treatment consisted of continuous home oxygen therapy, inhaled B2-agonists, TheoDur 300 mg orally twice daily, and captopril. On arrival to the Emergency Room at Wilford Hall Medical Center on 10 April 1987, she experienced a respiratory arrest following a questionable period of generalized seizure activity. She was intubated and received mechanical ventilation. The patient was hypertensive with a rapid, irregular pulse and ECG findings of multifocal atrial tachycardia (MAT) at a rate of 150 beats/min. Shortly after arrival in the medical ICU, the laboratory reported an admission serum theophylline level of 42.4 µg/ml. The initial serum magnesium level was 1.5 mg/dl (normal, 1.8 to 2.4 mg/dl). Treatment for theophylline toxicity was begun with activated charcoal, 30 g via a nasogastric tube, and 150 ml (8.7 g) of magnesium citrate, each repeated every 2 h. Two 1-g boluses of IV magnesium sulfate were also given because of hypomagnesemia and MAT. Soon after admission, status epilepticus developed, which required IV diazepam, diphenhydantoin, and phenobarbital for control. Serum theophylline levels quickly fell to 24.1 µg/ml, and hemoperfusion was deferred. During therapy with anticonvulsants and the charcoal/magnesium mixture, hypotension ensued, requiring dopamine support at 30 µg/kg/min. A pulmonary artery (PA) catheter was placed revealing a PA pressure of 31/25 mm Hg, mean pulmonary artery occlusion pressure of 20 mm Hg, cardiac index of 1.8 L/min/sq m, and a systemic vascular resistance index of 2,431 dynes·sec·cm-5. Systemic blood pressure was 90/60 mm Hg, associated with a sinus rate of 80 beats/min. Several hours after admission, a serum magnesium level was found to be 6.9 mg/dl. Initial BUN was 6 mg/dl, and serum creatinine was 0.6 mg/dl; however, oliguria occurred soon after admission. The patient had received 2 g of magnesium sulfate IV as well as six doses of magnesium citrate enterally, for a total of 55 g of magnesium over an 8-h period. Blood pressure remained low with relative bradycardia while receiving various vasopressor agents. An echocardiogram revealed a dilated left ventricle with diffuse hypokinesis. A head CT scan was...
unremarkable. Intravenous calcium chloride boluses were without apparent hemodynamic benefit. Urine output remained low, with a creatinine clearance of <10 ml/min. Hemodialysis was performed on day 4 of hospitalization in an attempt to lower the serum magnesium level. Following hemodialysis, the serum magnesium level decreased, and over the next 24 to 36 h the patient was successfully weaned from all vasopressor agents. During the first four days of hospitalization, the cardiac index ranged from 1.8 to 2.2 L/min/m². Following dialysis and lowering of the serum magnesium level to normal, cardiac index improved to values of 2.9 to 3.6 L/min/m² without significant changes of other hemodynamic variables. The patient remains hospitalized six months later with mild to moderate cognitive deficits.

**CASE 2**

A 77-year-old woman with chronic obstructive pulmonary disease was admitted to the Medical Intensive Care Unit at Wilford Hall Medical Center on 29 May 1987 with acute respiratory failure. A prolonged hospital course ensued complicated by right pneumothorax, congestive heart failure, cellulitis, and ventilator dependence. Eventually she was extubated and moved to a ward. Maintenance medications included TheoDur, 300 mg orally twice a day. On hospital day 52, the patient developed anorexia and nausea. A serum theophylline level of 44 µg/ml was noted and the patient was given activated charcoal 30 g via an enteral tube followed by a single 300-mL dose of magnesium citrate (17.5 g). Several hours later the patient was found unresponsive and tachycardic with a systolic blood pressure of 65 mm Hg. The patient was transferred to the Medical ICU and initially responded to fluid administration and dopamine infusion. Supraventricular tachyarrhythmias ensued requiring cardioversion. She subsequently developed bilateral infiltrates on chest x-ray film, was intubated and mechanically ventilated. Laboratory data included the following values: a WBC count of 7,900/cu mm, with a marked left shift; BUN, 44 mg/dl; creatinine, 3.1 mg/dl; glucose, 304 mg/dl; serum potassium, 3.3 mEq/L; serum magnesium, 7.8 mg/dl (later increasing to 10.3 mg/dl); serum calcium, 7.6 mg/dl; serum phosphate, 5.3 mg/dl; and serum albumin, 1.6 g/dl. One week before the patient had had a serum magnesium level of 2.0 mg/dl, serum creatinine, 1.5 mg/dl, and BUN, 24 mg/dl. Pulmonary artery catheter measurement revealed a mean pulmonary artery occlusion pressure of 10 mm Hg, cardiac output of 3.5 L/min, and a systemic vascular resistance of 900 (dynes·sec·cm⁻²) (measurement taken during infusions with dopamine and levartenol). Hypotension persisted, and the patient was treated with broad-spectrum antibiotics. There was no hemodynamic response to IV calcium gluconate. Blood cultures were positive for *Staphylococcus aureus* and a Gram-negative rod.

Although the possible contribution by hypermagnesemia to this patient's hemodynamic status was recognized, hemodialysis was not pursued. The patient died within 48 h of the recognition of theophylline toxicity. An autopsy study revealed evidence of charcoal aspiration, diffuse alveolar damage, and acute tubular necrosis. Lung cultures grew *Staphylococcus aureus*.

**DISCUSSION**

Hypermagnesemia is frequently an iatrogenic disorder resulting from the use of magnesium-containing medications in the setting of renal impairment. The effects can be profound and may include refractory hypotension, bradycardia, CNS depression, muscle weakness and paralysis with secondary respiratory failure, bowel hypomotility, and hypocalcemia. The kidneys are responsible for maintaining magnesium homeostasis. Seventy-five percent of magnesium in plasma is unbound and freely filtered at the level of the glomerulus, the majority of which is then reabsorbed. The fractional excretion of magnesium varies greatly with changes in serum magnesium levels and, to a minimal extent, with the effects of parathyroid hormone and diuretics. Serum magnesium levels are normally maintained in a physiologic range, but the ability of the kidneys to excrete a magnesium load falls proportionally to decreases in creatinine clearance, and hypermagnesemia (in the setting of a normal dietary magnesium intake) occurs when the creatinine clearance falls below 30 ml/min. Moreover, large magnesium loads may overcome the renal excretory capacity (about 6 g/day), and symptomatic hypermagnesemia may even occur in the setting of normal or near-normal renal function.

In the cases we described, preexisting renal disease was absent, but the effective glomerular filtration rate likely approached zero after the magnesium had been administered and hypotension with associated decreased renal perfusion and oliguria had ensued. Both patients developed diminished bowel activity (as judged by hypoactive to absent bowel sounds and absence of stools) shortly into their courses. While likely multifactorial in etiology, hypermagnesemia was probably a contributing factor. Further, the absence of catherisation may have led to further magnesium absorption from the gut, thereby compounding the problem.

In case 1 it appears that hypermagnesemia significantly contributed to refractory hypotension and sinus bradycardia. Other causes for hypotension, in particular sepsis, myocardial infarction, elevated intracranial pressure and hypovolemia, were effectively excluded. The resolution of hypotension following hemodialysis and normalization of serum magnesium level further supports the role of magnesium toxicity in our patient's course. The hemodynamic pattern and clinical course in the second case is not as clear, but suggests that sepsis was the dominant cause for hypotension. It is difficult to determine to what extent hypermagnesemia contributed to the refractory hypotension observed in this case. However, with serum magnesium levels greater than 10 mg/dl, it is reasonable to assume that hypermagnesia played a significant role in the patient's course. As with the first patient, underlying myocardial dysfunction was present and may have made the patient more susceptible to the effects of hypermagnesemia.

To our knowledge only two previously reported cases describe symptomatic hypermagnesemia as a result of treatment with OAC and magnesium-containing cathartics. Both of those cases occurred in patients without renal disease and resulted in either respiratory failure or prolongation of ventilatory support. In one case, diminished bowel function due to tricyclic overdose may have contributed to magnesium toxicity.
There is little evidence in the literature demonstrating the efficacy of adding a cathartic to a regimen of OAC. Nonetheless, their use appears logical, particularly in the setting of sustained-release tablet ingestions, and it will likely continue to be a common practice. While firm guidelines delineating the dosages of these cathartics have not been established, the amount of magnesium citrate received by the patient in case 1 exceeded the generally recommended 30-g magnesium limit. The second patient, however, developed magnesium intoxication after a single dose of 17.5 g of magnesium citrate, which is within the dosage recommendations.

A therapeutic alternative to magnesium-containing cathartics is the use of sorbitol, a poorly absorbed sugar which acts as an effective osmotic agent following ingestion. It can be mixed with activated charcoal to produce a more palatable slurry.

In a study of normal volunteers receiving activated charcoal, sorbitol was superior to either magnesium sulfate or magnesium citrate in reducing mean GI transit time and inducing catharsis. Furthermore, Goldberg and colleagues demonstrated that the combination of sorbitol and OAC is more effective than OAC alone in enhancing elimination of ingested sustained-release theophylline. We are aware of only two reports of adverse effects following administration of sorbitol. Both occurred in pediatric patients when excessive doses of charcoal-sorbitol suspension were administered for treatment of drug toxicity, resulting in severe dehydration and marked hypernatremia.

Studies on adults show activated charcoal-sorbitol to be effective and safe, although appropriate attention to fluid balance is still a prerequisite. The recommended dosage in adults is 1 g/kg of activated charcoal in 4.3 ml/kg body weight of 70 percent sorbitol every four hours. The recommendation in children consists of the same charcoal dosage (1 g/kg) mixed in 4.3 ml/kg body weight of 35 percent sorbitol.

We described two cases in which the treatment of theophylline intoxication with OAC and magnesium-containing cathartics resulted in or contributed to refractory hypotension. We suspect that hypermagnesemia in this setting may occur with some degree of regularity, but may go unrecognized because of the nonspecific nature of symptoms and signs associated with elevated magnesium levels. Furthermore, many of the clinical findings may be incorrectly attributed to the toxicity of the ingested drug or toxin because serum magnesium levels are not routinely obtained.

Review of the clinical and experimental literature regarding the use of cathartic agents in conjunction with OAC leads us to conclude, as have others, that sorbitol should be considered the cathartic agent of choice in the treatment of a variety of drug toxicities including those caused by theophylline compounds. If magnesium cathartics are employed, their use in the hemodynamically unstable, intoxicated patient should be judicious, with close monitoring of serum magnesium levels and observation for clinical evidence of magnesium toxicity. Magnesium toxicity should also be anticipated when magnesium-containing agents are administered but catharsis does not occur due to decreased bowel function.

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