Communications

Reversal of Theophylline Toxicity Using Oral Activated Charcoal

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Theophylline is commonly used in the treatment of bronchospasm. Serum concentrations are routinely measured for this drug because of its narrow therapeutic index and reports of nonlinear pharmacokinetic reactions in some patients (ie, a change in dose may result in a disproportionate change in serum concentration). In addition, elimination of theophylline is influenced by a variety of disease states and concomitant drug therapy. Concentration-dependent adverse effects range from nausea, vomiting, and tachycardia at lower serum concentrations to cardiac arrhythmias and seizures at higher levels.[1,2]

Acute ingestion of excessive amounts of theophylline have traditionally been treated by inducing emesis with syrup of ipecac followed by activated charcoal to decrease absorption.[3] Charcoal hemoperfusion has been used for rapid reduction of toxic serum concentrations.[4,5] Orally administered activated charcoal has been shown to enhance the clearance of phenobarbital, methotrexate, and carbamazepine.[6-9] Recent literature has indicated that activated charcoal is also effective in increasing theophylline elimination.[10-12] This report presents a patient with toxic theophylline concentrations that were rapidly reduced to nontoxic levels with oral administration of activated charcoal several hours following the last theophylline dosage.

Case Report

A 27-year-old pregnant Indonesian woman was hospitalized with a one-week history of dyspnea, wheezing, and cough. Her prenatal course had been complicated by poor weight gain and the development of a chronic cough and bronchospasm, only mildly responsive to standard medications. Outpatient evaluation revealed eosinophilia (2,840/mm^3), nasal polyps, normal serum immunoglobulin E levels, unremarkable antigen skin testing, positive tuberculin test (PPD), and negative chest roentgenogram. Cultures were positive only for an atypical mycobacteria obtained from the sputum.

Pertinent findings on physical examination included a 3 kg weight loss (48 kg), a respiratory rate of 32/min, generalized wheezing and intermittent cough. Arterial blood gases showed a pH of 7.52, an oxygen partial pressure (tension) of 73 mmHg and a carbon dioxide partial pressure of 26 mmHg. Medications on admission included theophylline (Theodur), 1,200 mg daily, and albuterol and beclomethasone inhalers. The admitting serum theophylline concentration measured by fluorescence-polarization immunoassay (Abbott TDX) was 12.0 μg/mL. Treatment with oxygen, systemic corticosteroids, and nebulized metaproterenol was initiated. Theodur was continued at the same dosage.

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Because hypoxia and bronchospasm continued, Theodur was increased to 1,400 mg daily. Omission of theophylline doses by hospital staff resulted in misinterpretation of serum theophylline concentrations and continuation of inappropriately high medication doses. The patient subsequently complained of gastrointestinal upset, prompting evaluation of her serum-theophylline level, which was found to be 42.5 μg/mL. Results of serial electrocardiograms and neurologic examinations were stable.

Twelve hours following ingestion of her last dose of Theodur, 15 g of activated charcoal were administered orally, approximately every two hours for four doses. Three hundred milliliters of magnesium citrate were given as a cathartic. One hour after the last dose of activated charcoal, she complained of increased wheezing and shortness of breath. Serum theophylline concentration measured 6.9 μg/mL.

Comment

Theophylline has concentration-dependent therapeutic and toxic effects. Serious adverse reactions are uncommon with serum concentrations below 20 μg/mL. Most patients become tolerant to the caffeine-like and mild gastrointestinal side effects that are common in the therapeutic range of 10 to 20 μg/mL. Between 20 and 40 μg/mL sinus tachycardia and ventricular arrhythmias may occur.[1,2] Seizures that are unresponsive to anticonvulsant treatment are possible when serum concentrations exceed 40 μg/mL. The onset of seizures may not be preceded by minor adverse effects such as nausea, vomiting, and tachycardia; therefore, serum concentrations must be measured to prevent serious neurotoxicity from occurring.[13]

In this patient, treatment with activated charcoal resulted in a rapid reduction in toxic theophylline serum concentrations, significant reduction in half-life (from 7.5 hours to 2.2 hours) and an increase in theophylline clearance (from 1.2 L/h to 4.7 L/h. These findings are consistent with results of studies in normal volunteers in which theophylline half-life was reduced 38 to 72 percent after activated charcoal administration.[10-12]

Theophylline is eliminated by biotransformation in the liver with urinary excretion of metabolites. Less than 10 percent is eliminated in the urine as unmetabolized drug.[2] The mechanism by which activated charcoal enhances theophylline clearance has not been elucidated, but probably results from adsorption of the drug onto the charcoal after diffusion into the gastrointestinal lumen from the circulation. Charcoal has been shown to rapidly adsorb theophylline in vitro.[14] Although biliary excretion of theophylline has not been demonstrated in humans,[3] activated charcoal appears to enhance the rate of diffusion into the intestines by adsorbing theophylline in gastrointestinal fluids, thereby maintaining a constant diffusion gradient into the intestine.[15]

The administration of small, repeated doses of activated charcoal is a safe and effective way to manage mild-to-moderate theophylline toxicity.

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