CASE REPORT
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Acute Theophylline Toxicity and the Use of Esmolol to Reverse Cardiovascular Instability

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Theophylline overdoses are frequent conditions that may require emergency treatment. Clinical features common to severe theophylline toxicity include nausea and vomiting, tachydysrhythmias, metabolic disturbances, seizures, and cardiovascular collapse. Several reports have described these manifestations and their treatments. We report the case of a patient suffering from an acute, intentional theophylline overdose who exhibited the classic features of a toxic ingestion and describe the first reported use of IV esmolol in the treatment of accompanying cardiovascular manifestations. [Seneff M, Scott J, Friedman B, Smith M: Acute theophylline toxicity and the use of esmolol to reverse cardiovascular instability. Ann Emerg Med June 1990;19:671-673.]

INTRODUCTION

Acute intentional and chronic accidental overdoses of theophylline have been well described.[1-3] Reviews highlight several issues unique to the management of theophylline toxicity, including differences in treatment strategies between acute and chronic ingestion, indications for charcoal hemoperfusion or other aggressive modalities of theophylline removal, and use of β-blocker therapy.

We report the case of a patient with an acute, intentional overdose of sustained-release theophylline that illustrates many of the classic and unique features of theophylline overdose. In addition, we describe the use of esmolol, an ultrashort-acting IV β-blocker, for the treatment of accompanying cardiovascular side effects of theophylline overdose.

CASE REPORT

A 28-year-old man was brought to the George Washington University Hospital emergency department by friends after a multiple-drug ingestion as a suicide attempt. On the morning of the day preceding admission, the patient ingested approximately 30 25-mg desipramine, ten 75-mg doxepin, 60 1-mg lorazepam, and 50 0.25-mg flurazepam tablets. He slept for 24 hours and awoke the morning of admission somewhat lethargic and depressed. Approximately eight hours before admission, he ingested 18 tablets, each containing 300 mg anhydrous theophylline. Four hours later, he vomited spontaneously, and pill fragments were identified by friends. During the subsequent four hours, he became increasingly agitated and confused and was brought to the ED. His medical history was significant for depression for which he had been prescribed desipramine 25 mg one week before admission. The remainder of the medications that he ingested were his roommate's or mother's.

Examination in the ED revealed a delirious and agitated man requiring four-point leather restraints. Systolic blood pressure was 70 mm Hg; pulse, 180 to 200 with no alteration with carotid sinus massage; respirations, 24; and temperature, 36.9 C. The general physical examination was unremarkable. Neurologic examination was notable for extreme agitation and confusion but was nonfocal.

The initial management consisted of maintaining the patient in leather restraints, administering oxygen at 2 L/min by nasal cannula, establishing an IV line, and placing the patient on a cardiac monitor. The patient, albeit agitated, had a stable and protected airway and was not intubated. A his-

tory of probable overdose was obtained from the paramedics. A 36F Ewald tube was placed through the mouth and the stomach lavaged with water; no pill fragments were returned. Sixty grams of activated charcoal with magnesium citrate was administered through the orogastric tube before its removal. Added to each liter of IV fluid was 44 mEq sodium bicarbonate.

More extensive questioning of the patient's friends and a thorough search for empty pill bottles revealed empty bottles of desipramine, doxepin, lorazepam, and sustained-release theophylline. Because of the evidence of a toxic theophylline ingestion, the nephrology department was contacted immediately to prepare for charcoal hemoperfusion.

Laboratory studies revealed sodium, 137 mmol/L; potassium, 2.3 mmol/L; chloride, 101 mmol/L; HCO_3, 15 mmol/L; BUN, 10 mg/dL; creatinine, 2.8 mg/dL; glucose, 437 mg/dL; PO_4, 1.4 mg/dL; hemoglobin, 14.6 g/dL; hematocrit, 41%; WBC, 15,300; and platelets, 155,000. Arterial blood gas analysis on 2 L oxygen (nasal cannula) was pH of 7.47; P_{CO_2}, 23 mm Hg; and P_{O_2}, 165 mm Hg. Chest radiograph was normal. A 12-lead ECG showed a supraventricular rhythm at a rate of 180 with a QRS duration of 0.11 seconds.

The patient was admitted to the ICU, where he became more agitated and required IV diazepam 10 mg and haloperidol 25 mg in titrated doses for sedation. Vital signs at that time were blood pressure, 90/30 mm Hg; pulse, 180; respirations, 20; and temperature, 36.6 C. The remainder of the examination was unchanged. The serum theophylline level from the sample drawn in the ED was 198 μg/mL.

The tachycardia and relative hypotension were presumed to be secondary to theophylline toxicity, and the patient was started on IV esmolol. This was administered as a 500-μg/kg bolus over one minute, followed by a 50-μg/kg/min continuous infusion. The pulse immediately decreased to 110 to 120, and blood pressure increased to 100 to 110/60 to 70 mm Hg.

Because of the presence of central nervous system symptoms and an extremely high serum level of theophylline, charcoal hemoperfusion was initiated. A Quintan catheter was inserted into the left femoral artery, and the patient was hemoperfused with a Hemo-Kart-140® cartridge (National Medical Care, Rockleigh, New Jersey) for 150 minutes (blood flow, 300 mL/min).

The patient's mental status cleared progressively throughout charcoal hemoperfusion; by the end of the procedure, he was calm, oriented, and answering questions appropriately. No further sedation was required. The esmolol was decreased to 25 μg/kg and then discontinued two hours after charcoal hemoperfusion without change in vital signs. The theophylline level at the conclusion of charcoal hemoperfusion was 63.6 μg/mL. Other laboratory studies at that time were sodium, 142 mmol/L; potassium, 4.0 mmol/L; HCO_3, 25 mmol/L; creatinine, 1.3 mg/dL; and platelet count, 81,000.

The next morning, the patient was acting appropriately, with a normal examination and a theophylline level of 29 μg/mL. He was transferred to the psychiatry service, where he continued to improve without complications.

DISCUSSION

Theophylline overdose is a relatively frequent cause of drug overdose requiring admission to the hospital. There are many aspects to the presentation and treatment of these patients that have been reviewed extensively in recent medical literature, including the difference between acute and chronic overdose,[4] sustained-release preparations, the use of repeated oral charcoal,[5] the occurrence of seizures,[1,4,6] metabolic disturbances,[7,8] and the use and timing of charcoal hemoperfusion.[9,10] Acute delirium is an unusual manifestation of theophylline toxicity.[11] Our patient was a classic example of an acute, intentional overdose of a sustained-release preparation of theophylline in a patient who required all the therapeutic interventions listed above. In addition, we describe the use of esmolol, an IV, ultrashort-acting β-blocker, for the treatment of the cardiovascular disturbances associated with theophylline overdose.

Theophylline in toxic doses stimulates both β_1- and β_2-receptors. The β_1-receptors are present on myocardial cells and produce inotropic and chronotropic stimulation. β_2-Receptors are present on vascular and bronchial smooth muscle and produce vasodilation and bronchodilation. Some of the typical laboratory features of theophylline toxicity, including metabolic acidosis, hyperkalemia, and hyperglycemia, are also probably secondary to β-adrenergic stimulation.[7,8,12] Theophylline-induced hypotension can be severe and may be unresponsive to conventional vasopressors.[13] The hypotension may result from β-adrenergic stimulation, which results in β_2-stimulated peripheral vasodilation and decreased diastolic filling secondary to tachycardia.

The use of β-blockers to treat the metabolic effects, tachycardia, and hypotension of severe theophylline intoxication appears logical. Propranolol has been described as being effective in partially reversing the hypotension and metabolic effects.[14] Interestingly, propranolol reverses hypotension even if the heart rate is not reduced, probably by increasing peripheral vascular resistance as it antagonized the effects of theophylline on the β_2-receptors. In addition, β-blockade ameliorates the tachydysrhythmias, tremor, and agitation due to sympathetic overstimulation.

The usefulness of propranolol in theophylline toxicity is limited because most patients for whom theophylline is prescribed have chronic obstructive pulmonary disease or reactive airway disease, which may be exacerbated by a β-blocker. Furthermore, propranolol has a relatively long half-life and once given, its effects may persist for several hours.

Esmolol is a β-blocker that lacks the side effects of propranolol and may be useful for treating theophylline toxicity. Esmolol is an IV, ultrashort-acting, relatively cardioselective (β_1) β-blocker with an elimination half-life of nine minutes.[15,16] It has been particularly useful in the treatment of supraventricular tachycardias and ischemic heart disease in the perioperative setting.[17-19] It has been used safely in patients with reactive airway disease as well as those with decreased left ventricular function.[20,21] A theoretical drawback to its use in theophylline toxicity is its relative cardiac selectivity. If the mechanism by which β-blockers improve hypotension is by increasing peripheral vascular resistance and not by slowing the heart rate, then

esmolol should be less effective than propranolol.

The use of esmolol for the treatment of theophylline toxicity in human beings has not been reported previously, although data from experiments in animals for its use in both theophylline and tricyclic overdose exist.[22,23] In our patient, esmolol resulted in an immediate reduction in heart rate and a normalization of blood pressure. Its role in improving the metabolic derangements would be speculative.

Because many patients with theophylline overdose will have reactive airway disease, esmolol, with its relative cardioselectivity, may be particularly useful. The availability of this safe, short-acting, and titratable agent may elevate β-blockade to routine therapy for even mild-to-moderate theophylline toxicity. Areas that warrant further study are delineation of the mechanism of β-blocker benefit, clarification of the role of esmolol in theophylline toxicity, and a comparison of propranolol with esmolol for therapeutic efficacy.

SUMMARY

We report the case of a patient suffering from an acute, intentional overdose of theophylline who exhibited many of the classic signs and symptoms of theophylline toxicity. The initial serum theophylline level was 198 μg/dL. In addition to supportive care, sedation, aggressive gastrointestinal decontamination, and charcoal hemoperfusion, we used IV esmolol to treat the cardiovascular complications of this overdose. Esmolol resulted in the prompt resolution of the patient's tachycardia and hypotension. Esmolol may prove to be a safe and effective means of accomplishing β-blockade in these unstable patients.

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