Fatal theophylline toxicity precipitated by in situ pulmonary artery thrombosis

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Summary: A 57 year old man developed theophylline toxicity in association with acute pulmonary artery thrombosis. The plasma half life of theophylline was prolonged suggesting impaired metabolism secondary to acute right heart failure.

Introduction

Oral theophylline preparations are frequently used in the treatment of chronic obstructive airways disease. Theophylline has a narrow therapeutic index and toxic effects that include agitation, tremor, fits, and cardiac arrhythmias. Metabolism of theophylline by the liver is impaired as a result of liver disease or congestion.

We present a case of theophylline toxicity precipitated by pulmonary artery thrombosis causing acute right heart failure.

Case report

A 57 year old ex-smoker presented to his general practitioner with a 15-year history of progressively increasing breathlessness and obstructive pulmonary function tests without reversibility. He was thereafter treated with steroid and ipratropium bromide inhalers, frusemide 40 mg, and amiloride, 5 mg daily; theophylline slow release, 800 mg, at night; and Nethaprin Dospan one twice daily. Nethaprin Dospan contains bufylline 180 mg, doxylamine 25 mg, ethafedrine 50 mg and phenylephrine 25 mg, in each tablet. This regimen improved his symptoms, caused no side effects, and was unchanged for several weeks before admission.

He was admitted with a 3-day history of increasing breathlessness, falling exercise tolerance, increasing anxiety and sweating. He and his family were certain he had not altered the doses of his medication.

On arrival in hospital he had an atrioventricular (AV) nodal re-entrant tachycardia at 240 beats/minute. This reverted to a sinus tachycardia at 120 beats/minute with intravenous verapamil, 10 mg. Examination showed he was barrel chested with prolongation of expiration and his jugular venous pressure was raised. There were no other abnormal cardiac or respiratory signs. The lungs were hyperinflated on chest X-ray and his electrocardiogram showed right axis deviation and right ventricular hypertrophy. His liver function tests were deranged; (gamma glutamyl transpeptidase 165 IU/l, bilirubin 31 µmol/l, alanine aminotransferase 257 IU/l) and the serum concentration of theophylline (74 mg/l) was at toxic levels (therapeutic range 10–20 mg/l).

Conservative management with oral activated charcoal was adopted and further episodes of supraventricular tachycardia controlled with verapamil and finally disopyramide. His serum theophylline level fell but with a prolonged half life (Figure 1). After two days he suddenly deteriorated, becoming more breathless, hypoxic, disorientated, and shocked. His electrocardiogram showed progressive right axis deviation. Despite anticoagulation and inotropic and fluid support, he developed resistant electromechanical dissociation and died.

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Figure 1. Elimination of theophylline in the case described. The half life of 18.3 hours is calculated from best fit analysis.
Post-mortem examination revealed marked obstructive emphysema with cor pulmonale. The pulmonary trunk and arteries were dilated, thickened and atheromatous, and contained extensive fresh adherent thrombus which appeared to have formed in situ over a few days prior to death. The leg veins were normal with no evidence of thrombosis. The liver was markedly congested.

Discussion

The post-mortem examination in this case suggested that the sudden development of theophylline toxicity was due to acute right heart failure and hepatic congestion caused by an in situ thrombosis in the pulmonary trunk. Such thrombosis is a well recognized but rare complication of cor pulmonale.\(^3\) Despite the administration of oral activated charcoal which partitions theophylline into the gut, reducing the apparent half life,\(^4\) the drug half life in this case was markedly prolonged to 18.3 hours (normal range 3 – 13 hours).\(^5\)

The unique feature of this case is the production of acute theophylline toxicity by pulmonary artery thrombosis complicating chronic airways obstruction and cor pulmonale. Each of these two latter factors impair theophylline metabolism, together reducing average clearance by 38% from normal.\(^6\) The independent significance of chronic right ventricular failure in theophylline dose adjustment has previously been reported.\(^6\) We now emphasize that acute right heart failure can also induce dangerous poisoning. In patients with acute theophylline toxicity without another precipitating factor this diagnosis and its causes should be considered.

References