

TREATMENT OF SEVERE THEOPHYLLINE TOXICITY WITH ORAL ACTIVATED CHARCOAL AND HAEMODIALYSIS – A CASE REPORT

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SYNOPSIS

We describe the management of severe theophylline toxicity in a 41-years-old woman after a massive suicidal overdose of Theo-dur. The serum theophylline levels showed sustained increase for ten hours after admission to hospital. This resulted in delayed onset generalised seizure and supraventricular tachycardia. The theophylline was eventually eliminated with a combined treatment using repetitive doses of oral activated charcoal and haemodialysis. The patient recovered from toxicity without complications.

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INTRODUCTION

Oral theophylline is commonly prescribed for the treatment of obstructive airways disease. It has a narrow therapeutic range (10 to 20 $\mu\text{g}/\text{mL}$.) and may cause death in cases of serious toxicity⁽¹⁾.

Sustained-release preparations of oral theophylline achieve more stable serum levels and are recommended by many authorities for the long term treatment of bronchospasm and in particular for symptoms of nocturnal asthma⁽²⁾. After an overdose of sustained release theophylline the serum levels of the drug may continue to rise many hours after admission to hospital and prolonged toxicity may occur despite prompt treatment⁽³⁾.

Oral activated charcoal enhances the clearance of theophylline and is the treatment of choice for toxicity^(3, 4, 5, 6). Recent reports have described safe and successful treatment of severe theophylline toxicity with repeated doses of oral activated charcoal^(3, 4). In very severe intoxication, however, more aggressive therapy to remove the drug may be indicated particularly if the patient is elderly or if there are significant complications such as cardiac arrhythmias and/or seizures. Charcoal haemofiltration is the modality of choice but its general availability may be limited. Haemodialysis is a more readily available albeit less efficient modality. It is still capable, however, of moving about 40% of the administered dose of theophylline in 3 hours⁽⁷⁾.

In this report we describe the treatment of a patient after a massive overdose of sustained release theophylline. Repeated doses of oral charcoal combined with haemodialysis produced highly effective theophylline elimination.

CASE REPORT

A 41-years-old Chinese woman with a history of depression and chronic asthma was admitted to hospital 2 hours [H.] after ingesting 50 tablets of Theodur-300 mg. in a suicide attempt. The serum theophylline level was 36 $\mu\text{g}/\text{mL}$. on arrival. She complained of nausea, weakness and tremulousness. A gastric lavage with saline was carried out. Treatment with oral activated charcoal in the Medical Intensive Care Unit was commenced 6 H after admission when her serum theophylline had risen sharply to over 80 $\mu\text{g}/\text{mL}$ [figure 1]. Repeated 15 g. doses of oral activated charcoal diluted with distilled water were administered via the naso-gastric tube at hourly intervals. Fifty mg. of intra-venous ranitidine and 10 mg. of intra-venous metoclopramide were also prescribed because of severe nausea and vomiting. The highest level of theophylline, 121 $\mu\text{g}/\text{mL}$, was measured 10H after admission to hospital. This was associated with hypokalemia and a mild metabolic acidosis; the lowest serum potassium level, 2.1 meq/L., coincided with the peak theophylline level. The hypokalemia was corrected with an intravenous infusion of potassium chloride. While preparations were being made for haemodialysis she developed a generalised seizure which lasted for about 1 min., followed by supraventricular tachycardia with a heart rate of 180/min. and blood pressure of 100/80 mmHg. These manifestations of toxicity were controlled by intravenous diazepam 10 mg. and verapamil 2.5 mg. respectively. An intravenous infusion of phenobarbital was also commenced to prevent further seizure activity. For 4 H, when the patient's condition had stabilised, haemodialysis was performed via a double lumen, subclavian catheter using a Gambro GF120m artificial kidney. At the end of haemodialysis the serum theophylline level had declined to 21 $\mu\text{g}/\text{mL}$. Subsequently, her symptoms abated rapidly and she made an unevenful recovery. No complications were noted with either the oral charcoal therapy or haemodialysis.

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DISCUSSION

Oral activated charcoal not only inhibits drug absorption in the gastrointestinal tract, it also enhances the

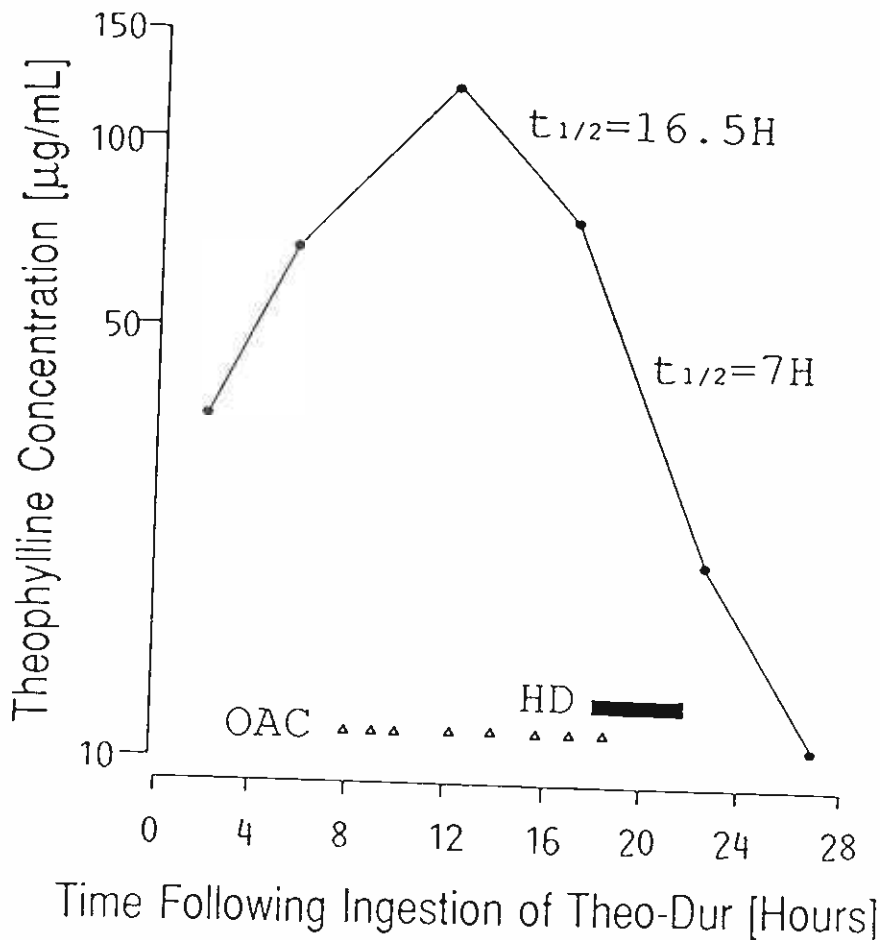


Figure 1:

This is a semi-logarithmic plot of serum theophylline concentration [$\mu\text{g/mL}$] vs. time following drug ingestion [Hours]. The open triangles indicate 15 g. doses of oral activated charcoal [OAC] and the solid bar indicates the duration of haemodialysis [HD].

elimination of drugs which are already in the systemic circulation by "gastrointestinal dialysis". This is a very effective treatment for overdose with drugs such as phenobarbital and theophylline⁽⁵⁾. Moreover, as in the case of this patient, the use of oral activated charcoal did not preclude the concurrent use of other techniques such as haemoperfusion or haemodialysis to further enhance drug clearance⁽⁶⁾. As early treatment is essential for success, doctors in emergency departments and junior house staff should be aware of this very simple and inexpensive therapeutic modality. Ideally the oral activated charcoal should be administered via the nasogastric tube in the emergency department immediately following gastric lavage.

Sustained-release theophylline preparations have been reported to cause delayed peak levels and prolonged toxicity despite prompt treatment with oral activated charcoal⁽³⁾. The extremely high dosage ingested by our patient and the delay in starting oral charcoal must have contributed to the development of severe toxic manifestations of seizures and arrhythmias twelve hours after admission to hospital. The most common problem encountered during treatment is severe nausea and vomiting which can cause intolerance to repeated dosing with oral charcoal. Reduction of gastric secretions with ranitidine in combination with an anti-emetic [metoclopramide] provided partial relief in our patient⁽⁸⁾. Ranitidine is preferred to cimetidine because it does not influence the metabolism of theophylline. We also maintained an infusion of phenobarbital to prevent recurrence of seizures which tend to be very refractory when they are precipitated by theophylline.

The hypokalemia noted in this patient probably resulted from the direct kaliuretic action of theophylline and from its action in elevating serum catecholamine levels⁽⁹⁾. The hypokalemia was rapidly corrected as it constituted an important pro-arrhythmic factor. In this

patient, the very high levels of serum theophylline and the presence of serious complications mandated the use of haemodialysis to achieve more rapid elimination of the drug. The serum half life [$t_{1/2}$] for theophylline was substantially reduced from 16.5 hours, when oral charcoal alone was administered, to 7 hours when haemodialysis was also in progress [figure 1]. Charcoal hemoperfusion is even more efficient than haemodialysis in removing theophylline and is the modality of choice. It was unfortunately not available.

In less clear cut situations of theophylline toxicity, however, the selection of patients for these aggressive treatments remain problematic. It has been suggested that haemoperfusion should be performed in patients with severe acute theophylline toxicity who have a serum level greater than 80 $\mu\text{g/mL}$ even in the absence of serious complications⁽⁷⁾. This is because the occurrence of seizures and serious cardiac arrhythmias may be associated with a high mortality rate as well as with permanent neurological damage.

In conclusion, this paper describes the effective use of repeated oral doses of activated charcoal combined with haemodialysis in the treatment of a patient with severe theophylline toxicity.

The linear regression analysis of the log-theophylline concentration vs. time gives the slope which is equal to the elimination rate constant [K]. The serum half-life [$t_{1/2}$; in hours] was determined from $t_{1/2}$ equals $0.693/K$.

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