A 64-year old ex-smoker with a 5-year history of chronic obstructive airway disease (COAD), hypertension and heart failure was treated at home with Slow-Theo SR (slow release theophylline) 200 mg twice a day; ipratropium bromide (an anti-muscarinic agent) 40 µg by inhalation four times a day; losartan K (an angiotensin receptor blocker) 50 mg once daily; and hydrochlorothiazide (a diuretic) 12.5 mg once daily. He was brought to hospital following an attack of grand mal seizure. This was an entirely new event.

On arrival in hospital, his Glasgow Coma Scale (GCS) score was 12/15. His blood pressure was 95/52 mmHg, pulse rate 138 beats/min and regular and respiratory rate 24 breaths/ min. He was afebrile and oxygen saturation by pulse oximetry was 93% while breathing room air. There were no signs of congestive heart failure. Examination of the chest revealed barrel-shape chest and generalized wheezes consistent with COAD. Examination of the central and peripheral nervous system revealed no abnormalities.

1. What is the differential diagnosis of his presenting condition?

The new event in this patient was grand mal seizure and the differential diagnosis of convulsion is long and varied. It includes

- Intracranial vascular events: cerebral infarction, subarachnoid hemorrhage, intracerebral hemorrhage.
- Intracranial infections: meningitis, encephalitis, cerebral abscess.
- Intracranial neoplasm: primary or secondary.
- Traumatic head injury.
- Metabolic disturbances: electrolyte abnormalities, hypoxia, hypoglycemia, uremia, hyperpyrexia.
- Drug withdrawal: alcohol or opiates.
- Drug overdose: amphetamine, cocaine, ketamine (ecstasy), antipsychotic drugs, theophylline.

The mild fall in GCS score in this patient would be consistent with his post-ictal state. The absence of abnormal neurological signs would rule out intracranial pathology.

Progress in hospital. This patient’s ECG showed sinus tachycardia; CXR showed hyperinflated lungs consistent with emphysema; CT scan of the brain was normal; complete blood count also normal. Plasma biochemistry results appear below:
<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
<th>Reference range</th>
<th>Units</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium</td>
<td>136</td>
<td>134 – 145</td>
<td>mmol/L</td>
</tr>
<tr>
<td>Potassium</td>
<td>2.9</td>
<td>3.5 – 5.1</td>
<td>mmol/L</td>
</tr>
<tr>
<td>Urea</td>
<td>8.1</td>
<td>3.4 – 8.9</td>
<td>mmol/L</td>
</tr>
<tr>
<td>Creatinine</td>
<td>92</td>
<td>6.2 – 106</td>
<td>µmol/L</td>
</tr>
<tr>
<td>Random glucose</td>
<td>7.8</td>
<td></td>
<td>mmol/L</td>
</tr>
</tbody>
</table>

Shortly after arriving in the ward, he had another convulsion, which was aborted by IV diazepam. According to his wife, the patient had increased dyspnea and was taking extra medication he bought over the counter from a pharmacy. He became housebound in the 2 days before admission and was noted to have vomited twice in the morning of admission.

2. With this new information, what is the most likely diagnosis?

Normal CT scan of the brain confirmed the absence of intracranial pathology and normal plasma biochemistry, except hypokalemia, ruled out metabolic causes of convulsion. The patient was not a known alcoholic or drug addict and there was no history suggesting abuse of street drugs. However, this patient had COAD and was adjusting his medication on his own. Theophylline poisoning should be suspected in all patients with asthma or COAD presenting with nausea, vomiting, tremors, hypokalemia, hypotension, and sinus tachycardia.

3. How does theophylline toxicity manifest itself?

Theophylline toxicity is seen in the following situations:

- Deliberate overdose in suicide attempts.
- Intravenous dose given rapidly.
- Dose increase in patients on chronic therapy.
- Interaction with drugs that inhibit the cytochrome P450 enzymes, such as oral contraceptives, erythromycin, ciprofloxacin, calcium-channel blockers, fluconazole, and cimethidine. (Theophylline is metabolized in the liver by these enzymes).
- Heart failure or liver impairment resulting in decreased clearance.
- Low albumin state. (Theophylline is bound to albumin in the circulation. Low serum albumin increases the active free theophylline fraction.)

The drug has a narrow therapeutic index. Although the therapeutic plasma concentration is 50 – 100 µmol/L (10 – 20 mg/L), mild manifestations of toxicity can occur at the upper end of this therapeutic range. These include anorexia, nausea, vomiting, headache, nervousness, and tremor. The frequency of toxic symptoms and signs increases when therapeutic plasma concentration is exceeded and hypertension, tachycardia, tachypnea, and central nervous system stimulation appear when the plasma concentration surpasses 200 µmol/L (40 mg/L). Hypotension, arrhythmias, and convulsions indicate severe toxicity. Seizures and ventricular arrhythmia can be protracted, resulting in death.
4. Why did our patient develop theophylline toxicity?

Our patient was already on a theophylline preparation for COAD and he was medicating himself at home with drugs bought from a pharmacy because of increasing COAD symptoms. Many of these proprietary drugs contain theophylline. Or he may have increased the dose of prescribed theophylline himself. The plasma theophylline level of our patient was reported to be 195 µmol/L. Cardiac arrhythmias and convulsions tend to occur at a lower plasma theophylline concentrations in patients who are already on theophylline and in patients over 60 years of age.

5. How should theophylline toxicity be managed?

Theophylline toxicity is potentially fatal. Patient requires continuous monitoring of vital signs, cardiac rhythm, and neurological status even when presenting symptoms and signs are mild. Plasma concentration should be measured on admission and repeated every 2 to 4 hours until a declining trend is well established. A single measurement of plasma concentration can be misleading because of continued absorption. The principles of management include:

Gastrointestinal decontamination

Two methods have been reported to be successful in reducing gastrointestinal absorption of ingested theophylline. They are:

- Multiple doses of activated charcoal (MDAC) by mouth.
- Whole-bowel irrigation with polyethylene electrolyte solution. The former is easier to manage and more popular.

Emesis should not be induced in the hope of achieving gastrointestinal decontamination. In fact vomiting, which is a presenting symptom of theophylline toxicity, should be controlled. The act of vomiting is ineffective in removing ingested theophylline and can cause esophageal tear and other complications.

Clearance of theophylline from the circulation

Charcoal hemoperfusion can clear theophylline directly from the circulation. This procedure requires the experience of a nephrologist. It is indicated in

- The presence of life-threatening complications: convulsion, hypotension, arrhythmias, intractable vomiting.
- Patients with very high plasma theophylline level (> 400 µmol/L or > 80 mg/L), even when signs of major toxicity are absent.
- Toxic patients with conditions that can prolong the half-life of theophylline or increase its side-effects.
- Plasma concentration fails to decline with other means of treatment.

Supportive care

- Maintain hydration and correct electrolyte and acid-base disturbance.
- Prescribe anti-emetic drug for nausea and vomiting.
- Treat hypotension with fluid and vasopressor.
- Monitor the patient for cardiac arrhythmias and treat accordingly.
- Convulsion requires aggressive management. While lorazepam and diazepam as well as phenobarbital may be tried, phenytoin is ineffective. In intractable cases of status epilepticus, the patient may have to be paralyzed with a neuromuscular blocking drug and his ventilation controlled in an intensive care unit.

Further Readings


