Severe headache as a chief presentation of theophylline intoxication

LCC Cheung, LCH Tsoi, CCH Chung

We describe a case of acute on chronic theophylline intoxication with severe headache as the chief complaint in a Chronic Obstructive Pulmonary Disease (COPD) patient. Headache is a non-specific symptom. The intensity of headache is unusually severe in our patient, and is much worse than the headache commonly encountered by an experienced emergency physician. (*Hong Kong j.emerg.med.* 2000;7:104-106)

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Introduction

In Hong Kong, theophylline is a commonly prescribed medication for COPD patients. We describe a case of theophylline intoxication presenting with severe headache, which was not previously reported as a chief presentation. The severe headache also heralds the occurrence of a seizure. COPD patients are usually of the elderly age group. Some of them may have problems in understanding the complicated medication regimen and provide accurate information to the emergency physicians.

Case

A 69 years old man presented to the emergency department of a University hospital with exacerbation of COPD and progressive headache for 3 days. He received 5 mg Ventolin nebulisation in the ambulance en route to the hospital.

On examination, he was afebrile, blood pressure was 128/83 mmHg, pulse rate was regular at 128/min, SpO_2 99% on 28% oxygen, peak expiratory flow at 280 L/min. Chest examination revealed bilateral rhonchi. ECG showed sinus tachycardia. Chest radiograph was unremarkable.

He stayed at the observation ward. Information from the patient was that he had past history of COPD, diabetes mellitus, and hypertension and being followed up at the government outpatient clinic. His outpatient clinic card revealed that he was on the following medication: Ventolin MDI, Methyldopa 250 mg daily, Gliclazide 60 mg BD, Terbutaline SR 5 mg nocte, Theodur 200 mg BD. He did not have history of drug allergy. The usual maintenance medication was continued in the observation ward.

Five hours after observation, his dyspnoea improved. However he complaint of severe frontal headache again which was constricting in character. He did not have meningism. There was no nausea nor vomiting. Neurological examination, including the fundi was normal. His blood pressure was normal and pulse rate decreased to 115 per minute. Paracetamol was prescribed for pain relief. Two hours after being given paracetamol, he complained of increase in severity of headache and which had spread diffusely all over the head. He also complained of dizziness. An intramuscular injection of non-steroidal anti-inflammatory drug (NSAID) was given. During the subsequent 12 hours, he asked for regular analgesics. His headache had increased in intensity and was not relieved by treatment. He also developed mild hyperventilation. Arterial blood gas on room air showed pH 7.45, pCO_2 3.7 kPa, pO_2 9.6 kPa.

Correspondence to:
Cheung Chi Chung, Luke, MBBS(HK), FRCS(Edin)
North District Hospital, Accident & Emergency Department, 9 Po Kin Road, Fanling, New Territories, Hong Kong
Email: helenche@netvigator.com

Tsoi Chun Hing, Ludwig, MBChB(CUHK), MRCP(UK)
Chung Chin Hung, Charles, MBBS(HK), FRCS(Glasg), FHKAM (Emergency Medicine)

The emergency physician consulted the medical registrar for suspected theophylline overdose and subarachnoid hemorrhage. While awaiting the laboratory results, he developed a seizure. The results available afterwards showed theophylline at 387 µmol/L, Na 133 mmol/L, K 3.5 mmol/L, urea 3.5 mmol/L, creatinine 116 µmol/L, glucose 8.6 mmol/dL. CT scan of the brain and CSF analysis were normal.

He was treated with multiple dose activated charcoal with steady improvement. He developed rhabdomyolysis with creatinine kinase peak at 5197 I.U.. His relatives later told us that he was a doctor shopper and ingested extra dose of medicine whenever his dyspnoea was not improved.

Discussion

Severe headache as the chief presentation was a striking feature in our case. It has not been previously reported as a chief presentation of theophylline toxicity. This symptom escalated and preceded the occurrence of seizure. Headache is a common and non-specific symptom. However the severity of headache unrelieved with repeated administration of analgesic raised the concern of the emergency physician despite a normal neurological examination.

Life-threatening complications in theophylline intoxication includes seizure and arrhythmia. The development of seizures, especially status epilepticus is associated with a high degree of morbidity and mortality.[1,2] To search for predictors of major toxicity, most consider a level greater than 110 µmol/L as toxic. Level greater than 555 µmol/L is predictive of major toxicity. In acute overdose, serum theophylline correlates with the symptom. This relation is also found in patients over 60 years with chronic overdose.[3] Paracetamol and salicylate are commonly screened in drug overdose patients. In view of the clinical significance of theophylline toxicity, qualitative and quantitative estimation of serum theophylline level for all patient-reported theophylline overdose has been recommended.[4]

In younger adults with chronic overdose, serum theophylline level does not correlate with the clinical feature.[5] Currently, serum theophylline level is readily available in most hospitals in Hong Kong. Infection, hypoxia, smoking and other drugs alter theophylline clearance and make the control of treatment dosage difficult.[6] Clinical features of theophylline intoxication are non specific. Without other predictors, it is only a high index of suspicious and a regular review of the benefits and risk ratio of theophylline in COPD patient that we can prevent this dismay.

The relation of warning clinical features for impending life-threatening complication has not been studied. The mechanism of seizure has been suggested as a manifestation of cerebral vasoconstriction or central adenosine antagonism effect of theophylline. Hyperventilation may be due to direct stimulation of the respiratory centre.[7] Whether the pathogenesis of unexpectedly severe headache share a common pathway with seizure in the central nervous system is an interesting area that needs further study.

Our patient has been maintained on theophylline prior to the exacerbation of COPD. He had increased the medication himself for a few days. The patient continued to receive his maintenance theophylline before the physician suspected intoxication. For patients receiving theophylline chronically, toxicity may occur at a lower serum concentration than patients with acute overdose. The exact mechanism is unknown. It may be due to the increase cellular burdens of theophylline in susceptible tissue.[7]

Seizure resulting from theophylline toxicity may be refractory to conventional drug treatment. Phenytoin is inefficient for status seizure secondary to theophylline toxicity.[8] Induction of general anaesthesia should be considered while pending for treatment to lower the theophylline level.

Theophylline is one of the commonest implicated drug poison fatalities in the American elderly. While children under 6 years of age are involved in the majority of poisoning, the elderly are more likely to require hospitalisation and to die from poisoning.[9] COPD patients receiving theophylline are usually of the elderly age group.

In a 10 year prospective cohort study at a poison

centre in Boston, the result shows that there is no improvement in clinical outcome despite different treatment strategies.[10] The bronchodiator effect of theophylline is only modest in COPD. The non-bronchodilator effects which include stimulation of the respiratory centre, positive inotropic and chronotropic cardiovascular effect and enhanced diaphragmatic contractility are questionable. Over the last five years, there is a resurgence in theophylline at lower dose because of its anti-inflammatory and steroid sparing effect.[11] However theophylline has a narrow therapeutic index and side effects occurs within therapeutic range.[12] With safer alternative options available, the current indication for theophylline should be rigorously evaluated with a goal towards minimal use of this agent until quality evidence is available.

The behaviour of doctor shopping, self-medication and lack of a family doctor in our patient is not uncommon. Alertness on theophylline intoxication and a model of preventive measure for poisoning should be established for the elderly COPD patients on theophylline.

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