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Case Report

Theophylline Toxicity – A Forgotten Entity

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Introduction

It is often forgotten that smoking inducescytochrome P450 (CYP) 1A2, resulting in altered concentrations and required doses of drugs metabolized by this route. Conversely, upon cessation of smoking, concentrations of these drugs can rise to toxic levels unless appropriate dose adjustments are made. Medical staff, and others involved with smoking cessation counselling, need to be aware of this if potential harm to patients is to be avoided. Here, we describe a patient who developed tonic clonic seizures due to Theophylline toxicity, having ceased smoking 2 weeks earlier.

Case Report

Our patient is a 76-year-old lady who presented to A&E feeling generally unwell, with a two day history of dizziness. Her medical history included atrial fibrillation, which was treated with Digoxin 62.5mcg, and Chronic Obstructive Pulmonary Disease, for which she took a combination inhaler of 25mcg Salmeterol Xinafoate and 250mcg Fluticasone Propionate, 2 puffs twice a day, plus Theophylline MR 175mg twice daily. She had successfully given up smoking 2 weeks prior to admission, having smoked 100 cigarettes per day over the previous 40 years. On admission, she was in atrial fibrillation, well controlled with a heart rate of 90 beats per minute, and normotensive, with no evidence of postural hypotension. Respiratory system examination revealed prolonged expiration, in keeping with COPD, but the rest of the examination was unremarkable. Routine blood investigations, including full blood count, urea, creatinine and electrolytes, liver function tests and C-reactive protein, were all normal apart from a serum potassium level of 3.0mmol/l (NR 3.5-5.0mmol/l). Theophylline concentrations were not tested at this point. A chest X-ray showed hyper-inflated lung fields in keeping with Chronic Obstructive Pulmonary Disease.

The patient was admitted for observation, and treated with Trimethoprim for a presumed urinary tract infection on the basis of urinalysis, which was positive for leukocytes and nitrites.

Two days following admission, the patient developed facial spasms and twitching of her muscles of her upper limbs. Over the next 24 hours, the patient had two witnessed tonic-clonic seizures, which were terminated with intravenous Lorazepam. An urgent CT (Computed Tomography) scan of the brain was performed. This showed changes in keeping with small vessel disease only, nothing to account for new onset of seizures. Following a post-ictal period, the patient recovered, but then the following day had a further two tonic-clonic seizures. It was at this point that a blood Theophylline concentration was requested.

The Theophylline concentration was reported as 41.6mcg/ml (NR 10-19.9mcg/ml), more than twice the upper safe therapeutic concentration. A search of the laboratory system revealed that this patient's Theophylline concentration had been within the therapeutic range when last checked 2 months prior to admission, while she was still smoking.

The Theophylline was immediately stopped and the patient closely monitored at the Medical High Dependency Unit for further fits, arrhythmias or electrolyte disturbances. Other causes of seizures had been investigated and excluded.

The patient's neurological symptoms improved dramatically following cessation of Theophylline, with no further twitching, muscle spasms or seizures. Within three days her Theophylline concentration returned to a safe level, but the drug was not recommenced. Unfortunately, however, the patient died from sepsis two weeks following her admission without having left hospital.

Discussion

Theophylline has largely fallen out of favour as a treatment for airways disease due to its very narrow therapeutic index. Even within the therapeutic range, side effects frequently occur. These side effects range from mild, including tremor and gastrointestinal disturbance, to serious and potentially life threatening, such as seizures and cardiac arrhythmias. Following acute overdose, hypokalemia, hyperglycemia, hypercalcemia, hypophosphatemia, and acidosis commonly occur.

Theophylline is mainly metabolised in the liver by demethylation or oxidation using the cytochrome P450 system.

The 8-hydroxylation of Theophylline to 1,3-dimethyluric acid (1,3-DMU) via cytochrome P450 1A2 is the major pathway.

The cytochrome P450 enzyme CYP1A2 mediates the rate-limiting step in the metabolism of Theophylline[1], andthe polycyclic aromatic hydrocarbons found in cigarette smoke are potent inducers of this enzyme[2]. For this reason, smokers may need up to double the dose of Theophylline to achieve therapeutic effect compared with non-smokers[3].

The relationship between smoking cessation and Theophylline has also been the subject of many studies. Lee et al demonstrated that stopping smoking for 1 week resulted in a 37.6% decrease in clearanceand a 35.8% increase in the half-life of Theophylline, and that the dose needs to be reduced by one fourth to one third after brief abstinence from tobacco to prevent potentially toxic concentrations[4]. For this reason, careful monitoring of plasma Theophylline concentration should be considered essentialfor optimal dosing in patients following smoking cessation. The study by Faber et al recommends that the dose of CYP1A2 substrates such as Theophylline should automatically be reduced by 10% on cessation of heavy smoking and thereafter be guided by plasma concentration monitoring[5].

We found one report in which Theophylline toxicity resulted in a patient's death following a similar presentation to the one described above[6]. This highlights the close attention that must be paid to drug concentration monitoring by physicians when advising patients to quit smoking.

Theophylline is not the only drug which needs to be considered when patients stop smoking. Other examples are Clozapine, Olanzapine, Haloperidol and Flecanide to name a few. These drugs are also substrates for CYP1A2[7].

Conclusion

When advising patients to stop smoking, it is essential that physicians routinely review the drugs that the patient is taking to look for those that may require dose adjustments. In the case of Theophylline, careful monitoring of Theophylline concentrations, for instance weekly in the first few weeks following smoking cessation, is essential to avoid potentially life-threatening complications.

Competing Interests
None Declared
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REFERENCES

1. Faber M.S.,Jetter A.,Fuhr U. Basic and Clinical Pharmacology and Toxicology, Sep 2005, vol./is. 97/3(125-134), 1742-7835
2. American Journal of Health-System Pharmacy, Sep 2007, vol./is. 64/18(1917-1921), 1079-2082
3. Montalto N.J.,Farid P. Consultant, Feb 1997, vol./is. 37/2(259-262), 0010- 7069
4.Lee B.L.,Benowitz N.L.,Jacob III P. Ann Intern Med April 1, 1987 106:553-555;
5. Faber M.S.,Fuhr U. . Clinical Pharmacology and Therapeutics, Aug 2004, vol. /is. 76/2(178-184), 0009-9236
6. Rao J.K. P and T, 1996, vol./is. 21/8(432-434+448), 1052-1372
7. Kroon L.A. American Journal of Health-System Pharmacy, Sep 2007, vol. /is. 64/18(1917-1921), 1079-2082