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CASE REPORT

Treatment of theophylline intoxication using continuous venovenous haemofiltration

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Abstract. **Theophylline intoxication can cause serious complications such as seizures, cardiac arrhythmias and eventually cardiac arrest. Because of these potentially life-threatening clinical manifestations of theophylline intoxication, treatment methods that rapidly eliminate the drug are essential. These methods include oral administration of activated charcoal and extracorporeal drug removal. Less life-threatening symptoms like refractory vomiting, that seriously interfere with the oral administration of activated charcoal may necessitate use of extracorporeal methods for drug removal as well. We present a case report on a 77-year-old female patient with theophylline intoxication who was treated by continuous venovenous haemofiltration because of refractory vomiting along with haemodynamic instability.**

Considering the better availability and good clinical efficacy of continuous venovenous haemofiltration in theophylline intoxication, this method may be considered if other methods of drug removal cannot be applied.

Introduction

Theophylline is a drug that is used for the treatment of asthma, chronic obstructive pulmonary disease in adults and apnoea of prematurity in neonates. Like caffeine it is a xanthine derivate, absorbed completely after oral ingestion, subsequently distributed to all tissues and metabolized by CYP iso-enzymes IA2, 2E1 and 3A3 in the liver[1]. In older children and adults, 90% is metabolized in the liver and 10% excreted in the urine[1]. The half life of theophylline is dependent on the patient's age, resulting in a half life that varies between 25 hours for neonates and 10 hours in the elderly[1]. Theophylline intoxication, although previously regularly reported in the literature, has been seen less frequently in recent years due to availability of alternative drugs with a less narrow therapeutic window[2]. Apart from less alarming symptoms and signs, theophylline intoxication can also lead to life-threatening events like seizures, cardiac arrhythmias and eventually cardiac arrest[2-5]. Because of the life-threatening potential of theophylline intoxication, methods to rapidly eliminate the drug are essential. These methods include oral administration of activated charcoal and extracorporeal drug removal. The initial treatment in cases of theophylline intoxication is oral activated charcoal which is started soon after ingestion and administered in multiple, repeated doses [6, 7]. However, problems with its administration often arise because of uncontrollable vomiting. In these cases, extracorporeal drug removal can be an useful alternative. Extracorporeal drug removal treatment can also be used in patients with high theophylline levels or those at risk for serious adverse events, and has been performed by charcoal haemoperfusion[8-10], haemodialysis[11, 12], peritoneal dialysis[13] and continuous renal replacement therapy[14, 15]. We present a case of acute intentional theophylline intoxication which due to refractory vomiting along with haemodynamic instability, was effectively treated by continuous venovenous haemofiltration (CVVH).

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Case report

A 77-year-old female presented at the emergency room five hours after ingestion of 30, 175 mg tablets of extended release formulation of theophylline (a total ingested dose of 5250 mg theophylline) and an unknown number of 500 mg acetaminophen tablets.

Her prior medical history revealed a Billroth II stomach resection, arterial hypertension, cholecystectomy, and appendectomy. She was lonely. No mental disorder had been diagnosed. She had stopped smoking five years previously, drank one glass of wine a day, and was not on any maintenance drug therapy. According to the patient, the family physician had prescribed the theophylline for a previous episode of pulmonary complaints. She was not known with asthma or chronic obstructive pulmonary disease.

On admission she complained of nausea, vomiting and profuse sweating. On initial physical examination her blood pressure was 130/70 mmHg, but 30 minutes later it decreased to 95/50 mmHg. The pulse rate was 140 regular beats per minute, respiration rate 12 per minute, and saturation of 98% without supplemental oxygen. The estimated body weight was 60 kilograms. She was fully conscious. Diaphoresis was present, and the patient vomited continuously. There was a localized systolic murmur audible in the second left intercostal space grade II /VI, radiating to the carotid arteries. Further physical examination revealed no abnormalities. Neither the tablets nor their remains were seen in the vomit. Intravenous N-acetylcysteine was started for the possibility of significant acetaminophen intoxication and she was subsequently admitted to the intensive care unit for further observation and treatment. Laboratory examination yielded the following result: potassium 2.8 mmol/L, sodium 138 mmol/L, creatinine 58 µmol/L (0.65 mg/dl), pH 7.35, bicarbonate 15 mmol/L, lactate 4.4 mmol/L and glucose 11.2 mmol/L (203.6 mg/dl). The theophylline and acetaminophen toxicology levels were 55.5 mg/L

(therapeutic range from 8-20 mg/L) and 81 mg/L (therapeutic range from 10-20 mg/L) respectively. The electrocardiogram showed a sinus tachycardia of 140 beats per minute.

The patient was treated with intravenous potassium because of the low potassium level associated with the theophylline intoxication. Anti-emetics were prescribed for the vomiting. In addition, oral activated charcoal 50 grams and sodium-sulfate 15 grams were administered through a nasogastric tube to absorb and eliminate the drug from the gastrointestinal tract. They were prescribed four-hourly but had to be discontinued after one dose because of refractory vomiting, despite the administration of metoclopramide 10mg IV push and ondansetron 8mg IV push. Subsequently, the extracorporeal drug removal option was considered and initiated two hours after admission. CVVH was chosen instead of haemodialysis or haemoperfusion because of a low blood pressure of 95/50 and a tachycardia of 140. CVVH, using a Polyflux 140H filter (Gambro Benelux, Zaventem, Belgium), at a blood flow of 200 ml/min and a substitution flow of 2000 ml/h administered in predilution with a bicarbonate buffer (HF 32 Bic) solution (Dirinco, Rosmalen, the Netherlands), was continued for 10 hours. During the subsequent four hours of CVVH therapy, the patient's vomiting and diaphoresis disappeared completely. Eight hours after initiation of CVVH the theophylline level had decreased to 19.7 mg/L, and two hours later CVVH was discontinued. The estimated elimination half life of the drug during CVVH was around six hours. Three hours after cessation of CVVH, the theophylline level had further decreased to 6.7 mg/L and rebound in neither theophylline levels nor symptoms was observed. The acetaminophen level had decreased to 5 mg/L, and the N-acetylcysteine infusion was discontinued.

After two days she was discharged from hospital in good clinical condition. Further ambulatory evaluation revealed a significant aortic valve stenosis. A year later she had an uncomplicated aortic valve replacement.

Discussion

This case illustrates the potential of CVVH as extracorporeal drug removal therapy in the treatment of intentional intoxication with theophylline with refractory vomiting and haemodynamic instability.

Intoxication with theophylline can easily occur due to the narrow therapeutic window of the drug, and can be classified as chronic overmedication, intoxication on therapeutic use or acute intentional intoxication[4]. Acute intentional intoxication is mostly seen when medication of spouses is ingested. In our case, intoxication was made possible by unjustified prescription for unspecified pulmonary symptoms. The severity of theophylline intoxication can be classified as minor and major intoxication according to clinical presentation and plasma levels. The main symptoms of theophylline intoxication are arrhythmias, tachycardia, hypotension, seizures, vomiting, nausea, abdominal pain, low potassium levels, metabolic acidosis, hyperglycaemia, tremor and agitation[2,4,5]. Serious toxicity symptoms are seizures and severe cardiac arrhythmias, which may lead to death[2-5]. In cases of serious or life threatening clinical symptoms extracorporeal drug removal is the treatment of choice. This is also indicated if serious adverse events are likely to develop. Some authors use the plasma level of theophylline to support their decision, hereby differentiating between an acute(>100 mg/L) or chronic(> 60 mg/L) intoxication to start extracorporeal drug removal therapy[2]. Serious events may be seen at a lower threshold (< 30-40 mg/L) in the elderly patient, the patient with heart failure and the patient with liver disease[2, 4, 10].

The treatment of theophylline poisoning has four components, namely supportive care, gastrointestinal decontamination, pharmacological treatment of manifestations and enhancement of elimination[1]. Multiple doses of oral activated charcoal is the initial therapeutic intervention and is sufficient for minor symptoms[6, 7]. Administration of charcoal prevents the completion of the enterohepatic cycle present during theophylline drug metabolism and disrupts theophylline absorption in the gut. Refractory, untreatable vomiting limits the administration of activated charcoal and may be a reason to use extracorporeal drug removal. Furthermore, extracorporeal drug removal is also advised in patients at risk for, or already experiencing, serious adverse events[4]. According to literature, the extracorporeal drug removal therapy of choice,is charcoal haemoperfusion as this eliminates the drug faster [8-10]. Nowadays haemodialysis is as effective[12]. Other modalities have also been used with success[13-15].

In our patient, oral activated charcoal was the initial choice of therapy. When refractory vomiting impeded this method of administration other modalities for elimination were explored. We decided to start extracorporeal removal therapy with CVVH. Three factors influenced this decision. Primarily, the high dose ingested and the relatively high plasma level in an elderly patient were considered. The first theophylline level was obtained on admission. Considering that the time interval between ingestion and maximal concentration (Cmax) is estimated to be ca. eight hours (http://www.drugs.com/pro/theophylline.html), and blood was taken five hours after ingestion, it is appropriate to assume that the maximum plasma level of theophylline (ingestion of slow release tablets and no tablets seen in the vomit) had not yet been reached when the first blood sample was taken. Secondly, the potential for life-threatening complications is higher in elderly patients and can occur at lower plasma levels. Furthermore, at higher plasma levels the metabolic pathways for theophylline become saturated, favouring CVVH as a strategy for drug removal. Finally, the decreasing blood pressure also favoured the choice of CVVH.

On a theoretical basis, CVVH could be expected to be an effective alternative for theophylline removal because of the continuous nature of this treatment modality, in which blood passes along a highly permeable membrane allowing substances up to a molecular weight of 20,000 Da to pass across this membrane and be eliminated. Theophylline has a molecular weight of 180 Da, is 40% reversibly bound to plasma proteins and has a volume of distribution between 0.4-0.6 L/kg, thereby facilitating its removal by CVVH. Based on a mean elimination half-life without CVVH of 9.8 h for elderly non-smoking individuals (as mentioned in the FDA approved drug information on theophylline: http://www.drugs.com/pro/theophylline.html), the elimination half-life could be reduced by at least 40% by means of CVVH. However, so far CVVH as extracorporeal treatment of choice for theophylline intoxication has not been studied extensively and, to our knowledge, only a few case reports have emerged in the medical literature[15].

It is unclear whether the initiation of CVVH contributed to the elimination of acetaminophen and the N-acetylcysteine. Because of the uncertainty about the time of acetaminophen intoxication in our patient, we treated the patient with N-acetylcysteine. Retrospectively, however, the toxic plasma level nomogram showed that treatment with the antidote was not necessary.

Conclusion

In cases of theophylline intoxication where it may not be possible to administer activated charcoal, for example due to refractory vomiting, other treatment modalities for drug elimination may be considered. CVVH, as suggested by this case, may be a suitable alternative method of extracorporeal drug removal in this category of patients. In cases of saturation of the metabolic pathway occurring after ingestion of a very high theophylline dose, CVVH can be useful in selected patients.

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Key words: theophylline, poisoning, haemofiltration, dialysis, refractory vomiting

References

1. Perry H, Shannon M. Theophylline and other methyl xanthines. In: Brent, J, editor. Critical Care Toxicology - Diagnosis and Management of the Critically Poisoned Patient: Elsevier Mosby; 2005. p. 457-64.
2. Shannon M. Life-threatening events after theophylline overdose: a 10-year prospective analysis. Arch Intern Med 1999;159(9):989-94.
3. Robertson NJ. Fatal overdose from a sustained-release theophylline preparation. Ann Emerg Med 1985;14(2):154-8.
4. Shannon M. Predictors of major toxicity after theophylline overdose. Ann Intern Med 1993;119(12):1161-7.
5. Paloucek FP, Rodvold KA. Evaluation of theophylline overdoses and toxicities. Ann Emerg Med 1988;17(2):135-44.
6. Park GD, Radomski L, Goldberg MJ, Spector R, Johnson GF, Quee CK. Effects of size and frequency of oral doses of charcoal on theophylline clearance. Clin Pharmacol Ther 1983;34(5):663-6.
7. Radomski L, Park GD, Goldberg MJ, Spector R, Johnson GF, Quee CK. Model for theophylline overdose treatment with oral activated charcoal. Clin Pharmacol Ther 1984;35(3):402-8.
8. Ehlers SM, Zaske DE, Sawchuk RJ. Massive theophylline overdose. Rapid elimination by charcoal hemoperfusion. Jama 1978;240(5):474-5.
9. Russo ME. Management of theophylline intoxication with charcoal-column hemoperfusion. N Engl J Med 1979;300(1):24-6.
10. Park GD, Spector R, Roberts RJ, Goldberg MJ, Weismann D, Stillerman A, et al. Use of hemoperfusion for treatment of theophylline intoxication. Am J Med 1983;74(6):961-6.
11. Lee CS, Marbury TC, Perrin JH, Fuller TJ. Hemodialysis of theophylline in uremic patients. J Clin Pharmacol 1979;19(4):219-26.
12. Shannon MW. Comparative efficacy of hemodialysis and hemoperfusion in severe theophylline intoxication. Acad Emerg Med 1997;4(7):674-8.
13. Miceli JN, Clay B, Fleischmann LE, Sarnaik AP, Aronow R, Done AK. Pharmacokinetics of severe theophylline intoxication managed by peritoneal dialysis. Dev Pharmacol Ther 1980;1(1):16-25.
14. Okada S, Teramoto S, Matsuoka R. Recovery from theophylline toxicity by continuous hemodialysis with filtration. Ann Intern Med 2000;133(11):922.
15. Henderson JH, McKenzie CA, Hilton PJ, Leach RM. Continuous venovenous haemofiltration for the treatment of theophylline toxicity. Thorax 2001;56(3):242-3.