CASE REPORT

A 45-year-old woman with an anticholinergic toxidrome

N.A.F. Verheijden[1]*, B.C. Koch[2], Z. Brkic[2], S.C.E. Schuit[1], J. Alsma[1]

Department of [1]Internal Medicine and [2]Hospital Pharmacy, Erasmus Medical Centre, Rotterdam, the Netherlands, *corresponding author: tel.: 06-14305243, fax: 010-704 01 15, email: n.verheijden@erasmusmc.nl

ABSTRACT

Intentional or accidental intoxications are common in the emergency department, but are not always sufficiently recognised. When intoxication is suspected, the causative agent or combination of agents often remain unclear, making these patients a diagnostic challenge. We present here a 45-year-old woman who was admitted due to altered consciousness. The clinical presentation fitted the anticholinergic toxidrome and an intoxication with venlafaxine (her known prescribed medication) was suspected. Plasma venlafaxine concentrations, however, were very low. After 24 hours the patient recovered completely. Further testing after discharge revealed high concentrations of promethazine, confirming the suspected diagnosis. This case illustrates the importance of knowledge of toxidromes and good collaboration with the hospital pharmacist. Because of the thorough testing the patient could receive proper treatment.

What was known on this topic?
Intentional or accidental intoxications with antihistamines can cause an anticholinergic toxidrome.

What does this add?
This case is a reminder of an important clinical lesson in recognition of an anticholinergic toxidrome. Also, this case illustrates that an appropriate diagnostic work-up and good collaboration between the physician and hospital pharmacist is important and leads to the proper diagnosis and treatment for your patient.

INTRODUCTION

Intentional or accidental intoxications are common in the emergency department, but they are not always sufficiently recognised. Approximately 11,000 patients with intentional intoxications are seen each year in Dutch emergency departments.[1] Statistics concerning morbidity and mortality are incomplete. When intoxications are suspected, the causative agent or combination of agents often remains unclear, making these patients a diagnostic challenge.[2]

CASE REPORT

A 45-year-old woman presented to the emergency department by ambulance because of altered consciousness. Medical history revealed hypertension, depression and alcohol abuse. Her known prescribed medications were venlafaxine 150 mg once daily, omeprazole 20 mg once daily and irbesartan 150 mg once daily. The patient also used approximately ten tablets of acetaminophen with caffeine 500/50 mg, and xylometazoline 1 mg/ml on a daily basis, which she acquired over the counter. Until recently, she had overused bisacodyl for weight loss.

The patient's partner found her behaving abnormally. No signs of intentional intoxication were found. In the previous days she had no fever or illness.

At physical examination the patient was confused and disoriented in time and place. Also, she spoke with slurred speech. Her blood pressure was 160/112 mmHg, pulse rate 110 beats/min, temperature 36.7 °C and oxygen saturation was 95% at ambient air. She had dilated pupils, a dry tongue, red skin, and urinary retention of more than 1 litre. The Glasgow Coma Score was E4M6V3 and the patient was suspected to have visual hallucinations, since she was talking to imaginary people. Further neurological examination was unremarkable.

Additional testing, including routine laboratory analysis, an electrocardiogram and a CT scan of the cerebrum showed no abnormalities.

The clinical presentation fitted the anticholinergic toxidrome. At that moment it was unclear what medication the patient could have taken and a possible co-intoxication with non-prescribed medication was expected. Therefore, we decided to measure plasma concentrations of drugs that we know were available to the patient (venlafaxine and acetaminophen), as well as to perform screening for drugs of abuse in the urine. Plasma venlafaxine concentrations were very low: < 25 μg/l venlafaxine and < 80 μg/l desvenlafaxine (the therapeutic range of the sum of venlafaxine and desvenlafaxine plasma levels is 250-750 μg/l). The acetaminophen plasma concentration was also low (< 2.8 mg/l). The test for drugs of abuse was negative for amphetamines, barbiturates, benzodiazepines, cannabis, cocaine, methadone and opiates. The patient was admitted for observation and treated with intravenous fluids.

In 24 hours of observation the patient recovered without sequelae. She denied taking any drugs and was discharged, initially without follow-up. However, despite her denial of taking any medication, we performed further diagnostics to find a causative agent for her strongly suspected anticholinergic poisoning.

Further testing using liquid chromatography-mass spectrometry (LC-MS) (multiple reaction monitoring (MRM) and full-scan mass spectrometry (MS) data) revealed high concentrations of promethazine, confirming our suspected diagnosis. There was also a semi-quantitative high level of tramadol found, proving a co-intoxication. Both concentrations were above the therapeutic range. We informed the patient's general practitioner, who confronted the patient and she admitted the intoxication was an attempted suicide. Subsequently, she was referred for psychiatric treatment. The tramadol she used belonged to her partner; the promethazine was prescribed six months previously by a locum general practitioner.

DISCUSSION

Anticholinergic poisoning can be the result of medication and plants, and more than 600 compounds with anticholinergic properties are known. These compounds competitively inhibit binding of acetylcholine to muscarinic acetylcholine receptors. These receptors are found on peripheral postganglionic cholinergic nerves in smooth muscle, the ciliary body of the eye, the central nervous system and secretory glands. Symptoms of an anticholinergic poisoning, therefore, include both central and peripheral effects. Central effects manifest as agitation, psychosis and seizures. Peripheral effects manifest as tachycardia, cutaneous vasodilation, leading to a red skin, mydriasis, anhidrosis, hyperthermia, urinary retention and gastrointestinal dysmotility.[3,4] These symptoms are collectively described as 'Blind as a bat, mad as a hatter, red as a beet, hot as Hades, dry as a bone, the bowel and bladder lose their tone, and the heart runs alone'.[5]

In the Netherlands, 60% of reported intoxications concern medication. Antihistamines, such as promethazine, currently form the sixth most commonly reported drugs and the frequency of antihistamine abuse has increased.[6,7] Treatment of antihistamine overdose is mainly supportive and consists of intravenous fluids and urinary catheterisation, and in some cases, gastrointestinal decontamination and administration of activated charcoal in combination with a laxative. Gastrointestinal decontamination is appropriate within two hours of ingestion. Severe agitation and seizures should be treated with benzodiazepines. Physostigmine, a short-acting anticholinesterase with a half-life of approximately 15 minutes, is the treatment of choice in case of a central anticholinergic syndrome.[8] Dexmedetomidine, an alpha-2 agonist with sedative, analgesic, anxiolytic, and sympatholytic effects, is considered to be an adjunctive treatment option.[9] Clonidine may be an equal and cheaper alternative for dexmedetomidine, but to our knowledge the use of clonidine in intoxications with antihistamines has not been described before. For our patient, we chose supportive care with fluids. Because the causative agent was unclear at the moment of presentation, no further treatment was given. Gastrointestinal decontamination was contraindicated because of the altered mental state of our patient. Besides, the time of ingestion was unclear. Agitation was mild and therefore the use of benzodiazepines was not necessary.

In our patient, the screening for drugs of abuse, including opiates, was negative and serum venlafaxine concentrations were low. After close collaboration with the patient's physician and the hospital pharmacist, we decided to perform further testing with LC-MS (MRM and full -scan MS data) because proving an intoxication would have consequences for the further follow-up and psychiatric treatment of our patient. Additional testing should be considered per individual case. LC-MS revealed not only promethazine, but also high concentrations of tramadol. Tramadol does not have anticholinergic effects itself, but can lead to depression of the central nerve system and therefore probably contributed to the clinical presentation in this case. Tramadol is not detected by the general screening for opioids (the immunoassay analyser Architect Abbott; a particle enhanced turbidimetric inhibition

immunoassay). The intoxication was without long-term physical harm for the patient, but the diagnosis led to referral for psychiatric counselling.

In conclusion, we present a patient with an anticholinergic toxidrome, and where thorough additional diagnostic testing revealed the causative agent and led to additional psychiatric treatment of the patient. This case illustrates the importance of knowledge of toxidromes, and the value of good collaboration between physicians and hospital pharmacists for patient care.

DISCLOSURES

The authors declare no conflict of interest. No funding or financial support was received.

REFERENCES

1. Kerkhof AJFM, Mulder S, Draisma JA. Suïcidepogingen behandeld in Nederlandse ziekenhuizen. Tijdschrift voor Gezondheidswetenschappen. 2007;85;37-42.
2. Fabbri A, Ruggeri S, Marchesini G, Vandelli A. A combined HPLC-immunoenzymatic comprehensive screening for suspected drug poisoning in the emergency department. Emerg Med J. 2004;21:317-22.
3. Rinder CS, D'Amato SL, Rinder HM. Survival in complicated diphenhydramine overdose. Crit Care Med. 1988;16:1161-2.
4. Erickson T, Ahrens W, Aks S, Baum C, Ling L. Pediatric toxicology (1st ed). New York, NY: McGraw-Hill; 2005. http://www.r2library.com/Resource/Title/0071417362.
5. Stead LG, Stead SM, Kaufman MS. First Aid for the Emergency Medicine Clerkship (2nd ed.). New York, NY: McGraw-Hill; 2006; p. 395-6.
6. Van Gorcum TF, van Velzen AG, Brekelmans PJAM, Van Riel AJHP, Meulenbelt J, de Vries I. Acute intoxications among humans and animals: National Poisons Information Centre Annual Report, 2007. Bilthoven: National Institute for Public Health and the Environment; 2008.
7. Mowry JB, Spyker DA, Cantilena LR Jr, Bailey JE, Ford M. 2012 Annual Report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 30th Annual Report. Clin Toxicol. 2013;51:949-1229.
8. Burns MJ, Linden CH, Graudins A, Brown RM, Fletcher KE. A comparison of physostigmine and benzodiazepines for the treatment of anticholinergic poisoning. Ann Emerg Med. 2000;35:374-81.
9. Walker A, Delle Donne A, Douglas E, Spicer K, Pluim T. Novel Use of Dexmedetomidine for the treatment of anticholinergic toxidrome. J. Med Toxicol. 2014;10:406-10.