OPEN ACCESS

Use of multiple anticholinergic medications can predispose patients to severe non-exertional hyperthermia

Ahila Manivannan ,[1] Dana Kabbani,[2] Diane Levine[2]

[1]School of Medicine, Wayne State University, Detroit, Michigan, USA
[2]Internal Medicine, Detroit Medical Center/Wayne State University School of Medicine, Detroit, Michigan, USA

Correspondence to
Ahila Manivannan;
fj0752@wayne.edu

Accepted 5 March 2021

SUMMARY

We present a case of a 64-year-old woman who developed severe non-exertional hyperthermia (NEHT) due to excessive anticholinergic effects from her psychiatric medications. The patient was found unresponsive in a non-air-conditioned room where the outside temperature was over 33°C. She presented with altered mental status, hypotension and an oral temperature of 42°C. Drug–drug interactions from her home medications for depression, bipolar disorder and seizures (amitriptyline, cyclobenzaprine, benztropine, topiramate, clonazepam, trazodone) were suspected. Blood cultures grew *Staphylococcus hominis*. The patient quickly returned to baseline with supportive care in the intensive care unit. She was treated for the Staph hominis bacteraemia with a 7-day course of vancomycin. Due to her quick recovery and lack of neurological findings, severe NEHT with associated bacteraemia was determined to have caused her presenting symptoms. This patient's multiple anticholinergic medications increased her susceptibility to develop NEHT by inhibited sweating, this patient's natural cooling mechanism.

BACKGROUND

Severe non-exertional hyperthermia (NEHT) is defined as an elevated core body temperature above 40°C[1] and can initially be difficult to distinguish from other heat illnesses such as neuroleptic malignant syndrome, serotonin syndrome or infection. When the ambient temperature is elevated, the body can only tolerate minor elevations in body temperature before systemic dysfunction begins to occur. Evaporation is the most effective way for the body to dissipate heat and there are serious consequences when that regulatory mechanism is suppressed, either through drug effects or through neural dysfunction. Failure of thermoregulatory mechanisms and exposure to hot ambient temperatures can be a potentially life-threatening combination, and this case demonstrates the need for physicians to be aware of this when prescribing multiple anticholinergic medications.

CASE PRESENTATION

A 64-year-old woman with bipolar depression, diabetes, migraine headaches and known seizure disorder was found unresponsive in a non-air-conditioned room by her husband. The ambient temperature outside was in excess of 90°F (33°C). Her home medications included amitriptyline 175 mg daily, cyclobenzaprine 10 mg daily, lurasidone 80 mg daily, benztropine 1 mg three times a day, topiramate extended release 100 mg daily, clonazepam 0.5 mg daily, trazodone 100 mg daily, sitagliptin 25 mg daily and erenumab 70 mg injected monthly. Emergency medical service was called, and the patient was febrile on initial evaluation. Cool compresses were applied, and the patient was transported to the hospital.

On presentation to the emergency department, she was hypotensive (blood pressure 84/42) and febrile with a rectal temperature of 42°C. Skin was warm and dry. Mucous membranes were also dry. The remainder of the exam was normal with the exception of the neurological examination. The patient was only responsive to painful stimuli. She did not have any focal neurological deficits, hyperreflexia or rigidity. Initial labs were significant for leucocytosis (11 400). Creatine phosphokinase was normal. EKG was normal. The patient was admitted to the intensive care unit (ICU) and started on vancomycin and cefepime for possible sepsis. Blood cultures grew *Staphylococcus hominis*. During her ICU course, her core body temperature decreased to less than 38°C and her mentation returned to baseline. She was then transferred to the medical floor, where she was treated for the Staph hominis bacteraemia with a 7-day course of vancomycin. Toxicology recommended that she discontinue use of cyclobenzaprine on discharge to avoid excess anticholinergic effects. Due to her quick recovery and lack of neurological findings (ie, rigidity, tremors), severe NEHT with associated bacteraemia was determined to be the cause of her presenting symptoms.

DIFFERENTIAL DIAGNOSIS

When the patient first presented to the emergency department febrile with a high temperature, leucocytosis and hypotension, she was initially thought to be severely septic and was immediately started on broad spectrum antibiotics. However, once she was admitted to the ICU, due to her home medications there was concern for drug–drug interactions. Serotonin syndrome was also considered due to the serotonergic actions of trazodone,[2] amitriptyline,[2] lurasidone[3] and cyclobenzaprine.[4] However, there was low suspicion for this as she presented with no neurological deficits others than altered mental status. Blood cultures were obtained, and toxicology was consulted to assist the team in making a final diagnosis. Surprisingly, blood cultures were positive for *S. hominis*, which is part of the skin flora and

Check for updates

To cite: Manivannan A, Kabbani D, Levine D. *BMJ Case Rep* 2021;**14**:e239873. doi:10.1136/bcr-2020-239873

has mainly been found in nosocomial infections.[5] Toxicology's assessment stated that due to the high ambient temperature, NEHT was likely precipitated by the multiple home anticholinergic medications. Once the patient's mentation improved to baseline, she revealed that she had been feeling overheated and fatigued at home for the past 2 weeks. No medication changes had been made in that time period.

OUTCOME AND FOLLOW-UP

In a 2-month postdischarge follow-up call, the patient revealed that her primary care physician advised her to continue her current medication regimen, including the cyclobenzaprine she was advised to stop per toxicology's recommendation. She was encouraged to discuss with her physician if any of her current medications can be weaned due to the risk of a recurrence of NEHT. She was also educated about the risks of polypharmacy and the high likelihood of drug–drug interactions with her current medication regimen.

DISCUSSION

The combination of medications with anticholinergic medications taken by this patient (amitriptyline, trazodone, cyclobenzaprine and benztropine) increased her susceptibility to develop NEHT by inhibited sweating; this patient's natural cooling mechanisms. Topiramate further increased the risk of NEHT by causing hypohydrosis.[6] NEHT has been reported in patients being treated with antipsychotic medications,[7 8] and in at least one elderly patient on oxybutynin.[9] One case report described the fatal outcome of NEHT in a patient with schizophrenia who was prescribed risperidone and biperiden hydrochloride.[10] Despite the long history of the use of medications with anticholinergic effects by patients, reports of NEHT due to medications are few and physicians may not be aware of the risk of this complication.

The current guidelines for NEHT management include initial stabilisation, rapid cooling and measurement of rectal temperature. We suspect that if her core temperature had remained elevated beyond her initial presentation, NEHT would have been diagnosed earlier in her hospital course.

Our patient's medication regiment put her at high risk for hyperthermia. It is important to note that many of her home medications were high dosages, which may have further increased her risk for NEHT, although no literature could be identified that correlated NEHT with medication dosage. The Anticholinergic Risk Scale, developed by Randoph *et al*, was used to quantify this patient's anticholinergic burden. A score of 3 or more increases the risk of central anticholinergic side effects.[11] Using their scoring system, our patient had a score of 9, well above their cut-off (amitriptyline=3; benztropine=3; cyclobenzaprine=2; trazodone=1; lurasidone=0; topiramate=0; clonazepam=0). The Naranjo Scale was also used to quantify the likelihood that the reaction our patient experienced was due to an adverse drug reaction.[12] Our patient scored a 4, which denotes a possible adverse drug reaction related to the medications prescribed.

Patients who require multiple medications with anticholinergic effects should receive extensive counselling about the risks of NEHT and medicine reconciliation must be done periodically to prevent recurrence of heat-related illness and its sequelae. Physicians must be aware of the vulnerability of these patients with psychiatric disorders prescribed multiple anticholinergic medications. An increase in emergency department visits for psychiatric emergencies has been associated with periods of heatwaves; this has thought to be partially due to the maladaptive effects of certain psychiatric medications.[13] Further, a thorough history including a detailed medication history is necessary to make this diagnosis. Communication with the patient's physician and pharmacy may be necessary to obtain all relevant information. Additionally, newer electronic health records with integrated pharmacy fill histories are invaluable.

Learning points

- Severe non-exertional hyperthermia (NEHT) can be caused by anticholinergic medication use and is associated with serious sequelae, including death.
- Patients with multiple psychiatric disorders and older adults are particularly vulnerable and may be at increased risk for adverse drug events. Patients on multiple anticholinergic medications should be counselled on the risk of NEHT, particularly during hot summer months. They should be advised to remain hydrated and avoid high temperature environments.
- This case highlights the importance of a medication reconciliation with each patient encounter to avoid the adverse effects associated with polypharmacy.

Contributors All authors have contributed to conception and design; contributed to acquisition, analysis and interpretation; drafted the manuscript; critically revised the manuscript; gave final approval; agree to be accountable for all aspects of work ensuring integrity and accuracy.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

ORCID iD

Ahila Manivannan http://orcid.org/0000-0001-6757-7048

REFERENCES

1 Peiris AN, Jaroudi S, Noor R. Heat stroke. *JAMA* 2017;318:2503.
2 Volpi-Abadie J, Kaye AM, Kaye AD. Serotonin syndrome. *Ochsner J* 2013;13:533–40.
3 Racz R, Soldatos TG, Jackson D, *et al*. Association between serotonin syndrome and second-generation antipsychotics via pharmacological Target-Adverse event analysis. *Clin Transl Sci* 2018;11:322–9.
4 Keegan MT, Brown DR, Rabinstein AA. Serotonin syndrome from the interaction of cyclobenzaprine with other serotoninergic drugs. *Anesth Analg* 2006;103:1466–8.
5 Piette A, Verschraegen G. Role of coagulase-negative staphylococci in human disease. *Vet Microbiol* 2009;134:45–54.
6 Cheshire WP, Fealey RD. Drug-induced hyperhidrosis and hypohidrosis. *Drug Saf* 2008;31:109–26.
7 Lee C-P, Chen P-J, Chang C-M. Heat stroke during treatment with olanzapine, trihexyphenidyl, and trazodone in a patient with schizophrenia. *Acta Neuropsychiatr* 2015;27:380–5.
8 Kwok JSS, Chan TYK. Recurrent heat-related illnesses during antipsychotic treatment. *Ann Pharmacother* 2005;39:1940–2.
9 Adubofour KO, Kajiwara GT, Goldberg CM, *et al*. Oxybutynin-induced heatstroke in an elderly patient. *Ann Pharmacother* 1996;30:144–7.
10 Gómez Ramos MJ, Miguel González Valverde F, Sánchez Álvarez C, *et al*. Fatal heat stroke in a schizophrenic patient. *Case Rep Crit Care* 2012;2012:1–5.
11 Rudolph JL, Salow MJ, Angelini MC, *et al*. The anticholinergic risk scale and anticholinergic adverse effects in older persons. *Arch Intern Med* 2008;168:508–13.
12 Naranjo CA, Busto U, Sellers EM, *et al*. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther* 1981;30:239–45.

13 Lõhmus M. Possible biological mechanisms linking mental health and Heat—A Contemplative review. *Int J Environ Res Public Health* 2018;15:1515.