



A Rare Case of Drug Interaction Presenting as Perioperative Hyperthermia in a Patient Presenting for Neurosurgery

Sapna Suresh¹ Ajay P. Hrishi¹ Manikandan Sethuraman¹

¹Division of Neuroanesthesia, Department of Anesthesiology, Sree Chitra Tirunal Institute for Medical Sciences and Technology, Trivandrum, Kerala, India

Address for correspondence Ajay P. Hrishi, MD, DM, EDAIC, Division of Neuroanesthesia, Department of Anesthesiology, 7th Floor, C Block, Sree Chitra Tirunal Institute for Medical Sciences and Technology, Trivandrum 695011, Kerala, India (e-mail: drajay@sctimst.ac.in).

J Neuroanaesthesiol Crit Care 2022;9:186–188.

Abstract

Perioperative hyperthermia has many differential diagnoses. This case report describes the rare causation of perioperative hyperthermia in a patient presenting for epilepsy surgery. The patient had two episodes of hyperthermia, initially post-anesthetic induction and later in the immediate post-operative period. The quest for the etiology sheds light on a rare drug interaction between topiramate, an antiepileptic drug, and glycopyrrolate causing intraoperative hyperthermia. However, the literature has not reported drug interaction between topiramate and glycopyrrolate resulting in perioperative hyperthermia. The combination of a glycopyrrolate-induced rise in temperature and oligohydrosis could have resulted in hyperthermia in our patient. Thus, it is prudent to avoid glycopyrrolate in the perioperative period when patients are on topiramate.

Keywords

- ▶ intraoperative hyperthermia
- ▶ neurosurgical settings
- ▶ drug interaction
- ▶ topiramate

Introduction

Perioperative hyperthermia has many differential diagnoses. In addition, hyperthermia in neurologically injured patients can result in adverse outcomes.¹ Systematically excluding the causes of perioperative hyperthermia based on clinical signs and relevant investigations is paramount in identifying the etiology and its effective management. This case report describes a rare drug interaction between antiepileptic drugs and anticholinergic drugs resulting in perioperative hyperthermia.

Case Report

A 6-year-old boy weighing 20 kg of American Society of Anesthesiologists status II presented with complex partial seizures refractory to medical treatment for epilepsy sur-

gery. He was scheduled for anterior temporal lobectomy and amygdalohippocampectomy and was on preoperative anti-epileptic medications, including topiramate, oxcarbazepine, and clobazam. He had no history of fever, weight loss, endocrine dysfunction, or drug allergy.

On the day of surgery, after attaching standard pre-induction monitors, anesthesia was induced with glycopyrrolate 0.1 mg, thiopentone 5 mg/kg, fentanyl 2 µg/kg, and vecuronium 0.1 mg/kg. Following intubation, anesthesia was maintained with sevoflurane in oxygen: air mixture. Additionally, invasive blood pressure, end-tidal carbon dioxide (EtCO₂), nasopharyngeal temperature, and urine output were monitored. The baseline temperature was noted as 36.8°C. A forced-air warmer (3M Bair Hugger Model 775) set at 37°C was used to avoid hypothermia. A few minutes post-induction, we noted a rapid rise in temperature, reaching up to 40°C within the next

article published online
May 5, 2022

DOI <https://doi.org/10.1055/s-0042-1744398>.
ISSN 2348-0548.

© 2022. Indian Society of Neuroanaesthesiology and Critical Care. All rights reserved.

This is an open access article published by Thieme under the terms of the Creative Commons Attribution-NonDerivative-NonCommercial-License, permitting copying and reproduction so long as the original work is given appropriate credit. Contents may not be used for commercial purposes, or adapted, remixed, transformed or built upon. (<https://creativecommons.org/licenses/by-nc-nd/4.0/>)

Thieme Medical and Scientific Publishers Pvt. Ltd., A-12, 2nd Floor, Sector 2, Noida-201301 UP, India

30 minutes. During this episode, there was a marginal increase in the heart rate from 68 to 82 bpm with an increase in blood pressure from 110/72 to 130/80 mm Hg and EtCO₂ from 38 to 40 mm Hg. On examination, the patient did not have any rashes, and the arterial blood gas showed pH: 7.31, paO₂: 174, paCO₂: 39, HCO₃: 20, and lactate: 1.9. The electrolytes and urine output were within normal limits.

The patient was immediately exposed to ambient room temperature (21°C), and the forced-air warmer was turned off. As we suspected malignant hyperthermia (MH), anesthesia was switched to total intravenous anesthesia (TIVA) with propofol. Intravenous paracetamol of 15 mg/kg and 250 mL of cold saline (4°C) were administered to address the hyperthermia, following which the temperature slowly returned to 37°C over the next 30 minutes. Since it was an isolated episode of transient hyperthermia with normal hemodynamic parameters, it was decided to proceed with the surgery after discussion with the surgical team. Post-craniotomy, the brain was lax as there was no underlying pathology causing raised intracranial pressure and the body temperature remained at 37°C till extubation. The rest of the surgery was uneventful, and the reversal of muscle relaxation was done with neostigmine and glycopyrrolate before extubation. Five minutes post-extubation, the patient developed a similar episode of a rapid rise in temperature up to 40°C, which returned to the baseline of 36.9°C after 30 minutes. Hyperthermia episode was managed with inj. paracetamol of 15 mL/kg, 250 mL of cold saline, and cooling blanket with the forced-air warmer set at 32°C. The drug chart was reviewed, and the patient was found to be on topiramate, and we suspected interaction with glycopyrrolate. The patient was shifted to the intensive care unit and had no further episodes of hyperthermia.

Discussion

Hyperthermia, defined as an elevation of body temperature >37.5°C, is due to failed thermoregulation (heat generated greatly exceeds heat dissipated) and should be differentiated from fever with an alteration hypothalamic set point.¹ The common causes of intraoperative hyperthermia are drug reaction, sepsis, thyroid storm, transfusion reaction, increased heat delivery by patient warmers, MH, and neuroleptic malignant syndrome.^{1,2} Sellar suprasellar pathologies, hypothalamic injuries, intraventricular hemorrhages, and strokes are the common causes of central fever encountered in neurosurgical settings.^{2,3}

In our case, the child was afebrile preoperatively, did not have any features of sepsis, as evidenced by normal blood counts. There was no history of endocrine dysfunction with a normal thyroid function test. Since there was a malignant rise in temperature in the perioperative period with MH, it was considered the first differential. MH is a genetic disorder of skeletal muscle cells which predisposes a genetically susceptible patient to develop a hypermetabolic response on exposure to depolarizing muscle relaxants and halogenated inhalational anesthetics. MH is usually associated with tachycardia, dysrhythmias, hypertension, elevated EtCO₂, muscle rigidity, and metabolic acidosis on arterial blood gas.⁴ However, there was

no associated hypertension, muscle rigidity, or rhabdomyolysis in our case, and ABG showed borderline metabolic acidosis with normal electrolytes.^{4,5} Moreover, we switched over to TIVA to preclude MH. Neuroleptic malignant syndrome presents a similar picture as MH. It occurs due to withdrawal from neuroleptic agents, anti-Parkinson's drugs, and other dopamine-depleting agents.⁶ Pathognomonic features of neuroleptic malignant syndrome include hyperthermia, muscle rigidity, and elevated creatinine phosphokinase.⁶ Our patient did not have a history of consumption of these medications. Central causes of fever were ruled out as the operative site was distant from the hypothalamus, and the initial hyperthermia episode occurred before the onset of surgery.

Intraoperative febrile non-hemolytic transfusion reaction (FNHTR) requires a high index of suspicion and close vigilance. It manifests with a temperature rise of >1°C above 38°C and produces only a subtle change in hemodynamics.⁷ In our case, the patient did not receive any intraoperative transfusion; hence, FNHTR was ruled out. Drug-induced fever is a manifestation of an adverse drug interaction wherein the administration of the medication results in a hypermetabolic state resulting in fever.^{1,7} Drug-induced fever under anesthesia is challenging to diagnose and is usually a diagnosis of exclusion wherein the fever is associated with relative bradycardia (Faget's sign).^{1,7} In this case, there was no history of consumption of drugs commonly implicated in causing drug fever, and the episode was not associated with bradycardia.

We noted that the temperature rise had temporal profiling with the administration of glycopyrrolate. A review of drug interactions revealed that patients, especially the pediatric age group on topiramate, administered anticholinergic or carbonic anhydrase inhibitors are known to develop hyperthermia.⁸ The exact causation of hyperthermia is still debatable and is attributed due to oligohydrosis.⁸ Although the mechanisms of thermoregulation such as vasoconstriction and nonshivering thermogenesis are impaired under anesthesia, sweating remains a well-preserved thermoregulatory defense.⁹ The sweating threshold is only slightly increased, in contrast to shivering and vasoconstriction, wherein the thresholds are markedly reduced.⁹ A study by Kim et al showed that premedication with glycopyrrolate could lead to the increased incidence of perioperative fever in patients receiving ketamine anesthesia.¹⁰

The scientific literature has not reported drug interaction between topiramate and glycopyrrolate resulting in perioperative hyperthermia. Drug interactions due to pharmacodynamic mechanisms can happen due to direct effects on receptor function, interference with a biological or physiological control process, or additive/opposed pharmacological effect. In our case, it could have been due to interference with a biological or physiological control process and additive/opposed pharmacological effect. The combination of factors such as glycopyrrolate-induced rise in temperature and oligohydrosis could have resulted in a rapid temperature increase in our patient. The average onset time for intravenous glycopyrrolate is 1 to 2 minutes, with the peak effect around 3 to 7 minutes and an elimination half-life of approximately 50 minutes.^{11,12} This could explain the delayed onset of the hyperthermia episode

approximately 10 to 15 minutes after the administration of glycopyrrolate. The hyperthermia episode lasted approximately 30 minutes plausibly due to decreasing plasma levels and the physiological response to the therapeutic management. Anesthesiologists must consider this as one of the differential diagnoses during the evaluation of perioperative hyperthermia, especially in the context of glycopyrrolate administration in pediatric epilepsy patients on topiramate.

Conclusion

Our case highlights a rare drug interaction that can occur between topiramate, an antiepileptic drug, and glycopyrrolate causing intraoperative hyperthermia. Thus, it is prudent to avoid glycopyrrolate in the perioperative period when patients are on topiramate.

Conflict of Interest

None declared.

References

- Herlich A. Perioperative temperature elevation: not all hyperthermia is malignant hyperthermia. *Paediatr Anaesth* 2013;23(09):842–850
- Luthra A, Dube SK, Kumar S, Goyal K. Intraoperative hyperthermia: can surgery itself be a cause? *Indian J Anaesth* 2016;60(07):515–517
- Hrishi AP, Lionel KR. Intraoperative hyperthermia: a harbinger of hypothalamic injury. *J Neurosurg Anesthesiol* 2017;29(03):379–380
- Gulabani M, Gurha P, Ahmad S, Dass P. Intra-operative post-induction hyperthermia, possibly malignant hyperthermia: anesthetic implications, challenges and management. *J Anaesthesiol Clin Pharmacol* 2014;30(04):555–557
- Sharma A, Karnik H, Kukreja S, Jagger K. Malignant hyperthermia: dantrolene sodium—a must have. *Indian J Anaesth* 2012;56(02):212–213
- Adnet P, Lestavel P, Krivosic-Horber R. Neuroleptic malignant syndrome. *Br J Anaesth* 2000;85(01):129–135
- Cohen R, Escorcía A, Tasmin F, et al. Feeling the burn: the significant burden of febrile nonhemolytic transfusion reactions. *Transfusion* 2017;57(07):1674–1683
- Kristen S, Rebecca S. Neuropharmacology. In: Torbey MT, ed. *Neurocritical Care*. 2nd ed. New York, NY: Cambridge University Press; 2010:104
- Bindu B, Bindra A, Rath G. Temperature management under general anesthesia: compulsion or option. *J Anaesthesiol Clin Pharmacol* 2017;33(03):306–316
- Kim KW, Choe WJ, Kim JH, et al. Anticholinergic premedication-induced fever in paediatric ambulatory ketamine anaesthesia. *J Int Med Res* 2016;44(04):817–823
- Mirakhur RK, Jones CJ, Dundee JW. Effects of intravenous administration of glycopyrrolate and atropine in anaesthetised patients. *Anaesthesia* 1981;36(03):277–281
- Gallanosa A, Stevens JB, Quick J. Glycopyrrolate. [Updated 2021 Oct 11]. In: StatPearls [Internet]. Treasure Island, FL: StatPearls Publishing; 2021 Jan