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Challenges in the management of malignant hyperthermia in Colombia: Case report

Desafíos del manejo de la hipertermia maligna en Colombia. Reporte de caso

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Abstract

Malignant hyperthermia is a potentially life-threatening pharmacogenetic disorder characterized by a hypermetabolic response triggered by exposure to halogenated anesthetics, succinylcholine, and other agents. This is a case of a 40-year-old woman who developed masseter muscle spasm, bronchospasm, hypercapnia, muscle stiffness, and hyperthermia upon the administration of general anesthesia at a clinic in the capital of Colombia. This resulted in a high clinical suspicion of malignant hyperthermia and hence the institutional protocol for management of this condition was activated. It should be highlighted however that the drug used to treat this condition—dantrolene—is not readily available at most clinical institutions in Colombia and in this case a special emergency line must be used in order for the drug to be delivered. Once the drug was received and administered, the patient experienced clinical and hemodynamic recovery, with satisfactory postoperative response. She was discharged on day five without any sequelae. This case report reviews the pathophysiology, diagnosis, and treatment for malignant hyperthermia, as well as the challenges in accessing pharmacological treatment in Colombia.

Key words: Case report; Hyperthermia; Anesthetics; Calcium channels; Bronchospasm.

Resumen

La hipertermia maligna es un desorden farmacogenético potencialmente mortal, manifestado por un estado hipermetabólico desencadenado por la exposición a anestésicos halogenados, succinilcolina y otros agentes. Se presenta el caso de una mujer de 40 años, quien después de recibir anestesia general en una clínica en la capital de Colombia cursó con espasmo del músculo masetero, broncoespasmo, hipercapnia, rigidez muscular e hipertermia, con alta sospecha diagnóstica de hipertermia maligna, por lo que se activó el protocolo de manejo de dicha entidad. Cabe mencionar que en Colombia el fármaco para atender esta situación, el dantroleno, no se encuentra disponible en las instituciones clínicas, por lo que se debe informar a una línea específica para su obtención; una vez recibido y administrado, la paciente tuvo recuperación clínica y hemodinámica. La evolución posoperatoria fue satisfactoria y se dio egreso al quinto día sin secuelas. En este reporte de caso se revisa la fisiopatología, diagnóstico y tratamiento de la enfermedad, así como la dificultad en la obtención del manejo farmacológico en Colombia.

Palabras clave: Reporte de caso; Hipertermia; Anestésicos; Canales de calcio; Broncoespasmo.

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INTRODUCTION

Malignant hyperthermia is one of the potentially life-threatening complications associated with anesthesia. It is a neuromuscular disorder characterized by a hypermetabolic state of the skeletal muscle, with a rapid increase in body temperature and the onset of acidosis due to the acute loss of intracellular calcium control. This condition is triggered by the administration of volatile halogenated anesthetics and/or depolarizing muscle relaxants. (1)

The first case of malignant hyperthermia was described in 1960 in a family with a history of eight deaths following the administration of general anesthesia. However, there is evidence of letters written in 1915 and 1919 describing the circumstances surrounding the deaths of two family members after undergoing general anesthesia. Later in 1966, the first symposium on malignant hyperthermia was held in Toronto, when the term for the disease was coined. Then, in 1975 Harrison described the effectiveness of dantrolene in preventing and treating porcine malignant hyperthermia, which was later confirmed in humans. (2)

The syndrome may develop during the first exposure to anesthesia; however, it is a rare condition compared to other anesthesia-associated perioperative complications. Notwithstanding the difficulty to establish its incidence due to its variable clinical presentation, reports estimate an incidence ranging between 1:10,000 and 1:250,000, with a higher frequency in men as compared to women. (3) Regarding mortality, a report from the North American Malignant Hyperthermia Registry of the Malignant Hyperthermia Association of the United States revealed that between 1987 and 2006, there were 291 episodes, including eight cardiac arrests (2.7%), four of which (1.4%) resulted in death. (4) In the United Kingdom, mortality began to decline around the 1970s and is currently estimated at approximately 4%. (5)

According to the literature reviewed, the most recent data available in Colombia come from Bogotá between 1988 and 1990, showing an incidence of 1 in 65,190 cases. (6) However, since reporting malignant hyperthermia cases is not mandatory, national statistics may be underreported.

CLINICAL CASE

A 40-year-old female patient was scheduled for open reduction of temporomandibular joint dislocation plus condylectomy. Her medical history included thrombocytosis which was being followed by hematology, and a previous appendectomy under general anesthesia without complications. The pre-operative assessment classified the patient as ASA II, Lee I, with no difficult airway predictors.

Upon admission to the operating room, her vital signs were: heart rate 75 bpm, blood pressure 133/60 mmHg, and oxygen saturation 97%. General anesthesia was induced with 60 mg IV lidocaine 2% without epinephrine, 1 mg IV midazolam, remifentanil via Target Controlled Infusion (TCI) at 5 ng/mL, 100 mg IV propofol, and 70 mg IV succinylcholine for neuromuscular relaxation. Following the administration of succinylcholine, the patient developed masseter muscle spasm, prompting the administration of an additional 40 mg IV propofol, which improved the situation. Nasotracheal intubation was performed through the right nostril using a 6.5 mm tube after applying lidocaine gel. Symmetrical chest expansion and capnography were confirmed. The patient was connected to the anesthesia machine under volume-controlled ventilation with protective parameters, ensuring ocular, thermal, electrical, and pressure point protection. Anesthesia was maintained with balanced general anesthesia using titrated remifentanil via TCI and 2 vol% sevoflurane.

After intubation, the patient exhibited desaturation, an obstructive capnography pattern, and bilateral rhonchi, which was interpreted as severe bronchospasm. Management included 400 µg salbutamol via metered-dose inhaler (MDI), 80 µg ipratropium bromide via MDI, 200 mg IV hydrocortisone, 1 g IV magnesium sulfate, and 100 mg ketamine, resulting in gradual oxygen saturation improvement. Pulmonary auscultation revealed wheezing in the left hemithorax and diminished breath sounds in the right hemithorax. The differential diagnosis was anaphylaxis, and 100 µg IV epinephrine was administered. Despite treatment, the patient developed hypercapnia ($EtCO_2$ 50–60 mmHg) and a rising temperature of 38.3°C, prompting the decision to suspend the surgical procedure.

Supportive measures were initiated with epinephrine infusion at 0.05 µg/kg/min and norepinephrine at 0.05 µg/kg/min. A right internal jugular central venous catheter was placed under ultrasound guidance, along with a right radial arterial line and a urinary catheter, which collected 100 mL of cola-colored urine. Basic cardiac and pulmonary POCUS was performed, showing preserved right and left chamber mobility, no indirect signs of pulmonary hypertension, no pulmonary edema or pneumothorax, and preserved pleural sliding.

The patient experienced persistent hypercapnia, with progressive increases from 70 mmHg to 90 mmHg and up to 110 mmHg confirmed by arterial blood gas analysis. Her temperature rose to 39.9°C, accompanied by generalized muscle rigidity and cola-colored urine. Given the high suspicion of malignant hyperthermia, laboratory tests were ordered, revealing a creatine kinase (CK) level of 18,000 U/L, indicating significant muscle damage; hyperglycemia (serial glucose readings of 117–148–140–161 mg/dL); thrombocytosis with platelet count of 930,000; and progressive hyperkalemia (4.9–5.7–5.3–6.1 mEq/L), suggesting possible secondary rhabdomyolysis. The clinical grading scale for malignant hyperthermia scored over 50 points (7) (Table 1), indicating a high probability of the condition. Due to the unavailability of dantrolene at the institution, the malignant hyperthermia emergency protocol was activated.

Table 1. Clinical grading scale for malignant hyperthermia.

Process	Clinical criteria	Points
Muscle rigidity	Generalized muscle rigidity	15
	Succinylcholine-induced masseter muscle stiffness	15
Muscle breakdown	Creatine kinase >20,000 U/L after anesthetic including succinylcholine	15
	Creatine kinase >10,000 U/L after anesthetic without succinylcholine	15
	Cola-colored urine in the perioperative period	10
	Myoglobin in urine >60 µg/L	5
	Serum myoglobin >170 µg/L	5
	Blood/plasma/serum K^+ >6 mEq/L (in the absence of renal failure)	3
Hypercapnia	End-tidal CO_2 >55 mmHg or $PaCO_2$ >60 mmHg with adequately controlled ventilation	15
	End-tidal CO_2 >60 mmHg or $PaCO_2$ >65 mmHg with spontaneous ventilation	15
	Inappropriate tachypnea	10
Hyperthermia	Rapidly increasing temperature	15
	Inappropriate temperature >38.8 °C	10
Cardiac involvement	Unexplained sinus tachycardia	3
	Ventricular tachycardia or fibrillation	3
Family history	First-degree relative with malignant hyperthermia	15
	Non–first-degree relative with malignant hyperthermia	5
	Base excess >8 mEq/L	10
	pH <7.25	10
	Rapid reversal of malignant hyperthermia signs with dantrolene therapy	5

Score range	Probability
0–2	Almost never
3–9	Unlikely
10–19	Less than likely
20–34	More than likely
35–49	Very likely
>50	Almost certain

Source: Authors.

Simultaneously, inhaled agents were discontinued, the anesthesia machine was replaced with another machine not exposed to inhaled agents for the past 24 hours, and anesthesia was switched to sedation with midazolam and fentanyl. Ventilator settings were adjusted, and cooling measures were initiated using local ice packs, cooling blankets, room cooling, orogastric tube placement, and administration of 200 mL of cold saline, which reduced the temperature to 36.7°C.

The patient received 160 mg of dantrolene. After stabilization, she was transferred to the Intensive Care Unit, where medical management continued. She was discharged five days after the event with orders for a muscle biopsy for caffeine-halothane contracture test, follow-up labs, and appointments with anesthesiology and physical medicine.

Pathophysiology of the disease

The pathophysiology of this condition involves a defect in the ryanodine receptor in the calcium channels of the sarcoplasmic reticulum, leading to uncontrolled calcium release and impaired reuptake. It follows an autosomal dominant inheritance pattern. There are three isoforms of the ryanodine receptor: RYR1, predominantly expressed in skeletal muscle; RYR2, found in cardiac muscle; and RYR3, present in the central nervous system and smooth muscle. (8) Since the 1990s, mutations in the RYR1 gene (ryanodine receptor) on chromosome 19 have been identified as the cause for most cases of malignant hyperthermia, with fewer cases associated with mutations in the CACNA1S gene, which encodes the α1 subunit of the dihydropyridine receptor. (9–11)

The condition may develop at any time during anesthesia or in the early postoperative period. In a study of 255 cases, the initial signs observed were hypercapnia (38%), hyperthermia (19.6%), sinus tachycardia (31%), and masseter muscle spasm (20.8%) (12). Due to the challenges in identifying malignant

hyperthermia caused by its diverse clinical presentations, an international panel of experts developed a clinical grading scale to estimate the likelihood that an adverse event is associated with the condition. (7)

DISCUSSION

Timely identification and management of the condition are essential in reducing mortality. Triggering agents must be immediately discontinued, and anesthesia should be continued using intravenous opioids, sedatives, and, if necessary, non-depolarizing muscle relaxants. (13) If it is not possible to replace the anesthesia machine with one that has not been exposed to volatile agents for at least 24 hours, alternatives include placing activated charcoal filters at the inlet and outlet of the circuit, changing the breathing circuit and CO_2 absorber, administering high oxygen flows (≥10 L/min) for at least 90 seconds to reduce contamination with volatile anesthetics, or using an ICU ventilator with Total Intravenous Anesthesia (TIVA) to completely avoid exposure to anesthetic gases. (14)

Regarding mechanical ventilation, 100% oxygen should be administered with maximum fresh gas flow, and minute ventilation should be increased 2 to 3 fold in an attempt to achieve a normal $EtCO_2$ range. (15) Other strategies described for managing associated conditions include treating hyperkalemia with a polarizing solution or calcium gluconate; reducing temperature with physical methods and intravenous fluids; ensuring adequate urine output; and evaluating the need for blood products if there is a risk of progression to disseminated intravascular coagulation (DIC). (16,17)

With regards to pharmacological treatment, the only drug available to reverse the condition is dantrolene, a hydantoin derivative that acts as a specific ryanodine receptor antagonist and inhibits calcium release from the sarcoplasmic reticulum. Prior to the introduction and approval of Dantrolene in 1975, the mortality from malignant hyperthermia was 64%, with a notable reduction following its use. (4,5) The conventional formulation is available in 20 mg vials that require 60 mL of sterile water for reconstitution. Therefore, an average adult weighing 70 kg who requires dantrolene at a dose of 2.5–3 mg/kg, repeated every 10–15 minutes, may need 8 to 10 vials for initial treatment. Since additional doses may be required, this quantity should be available in all institutions where triggering agents are used. However, the high cost hinders the availability of the drug during malignant hyperthermia episodes. (18)

As a result, the availability of a well-structured kit is of the essence for the immediate initiation of supportive measures while the medication is being acquired. This not only optimizes response times but also improves patient safety, significantly reducing morbidity and mortality associated with this condition. Each kit shall include four vials of sodium bicarbonate and calcium gluconate, four arterial blood gas syringes, one 250 mL bag of 20% dextrose, ten 60 mL syringes, ten 18-gauge hypodermic needles, one bag of mannitol, three vials of furosemide, one vial of amiodarone, blood sample tubes (purple, yellow, blue), two pairs of activated charcoal filters, arterial and central line placement kits, a Foley catheter, anesthesia circuit hoses, and a checklist for managing malignant hyperthermia. (19)

The shortage of this medication has been reported in other Latin American countries and even in Germany. (18,20) In Colombia, despite the critical role of dantrolene in the practice of anesthesia, its availability is not mandatory in all institutions. A 2020 study published in the Colombian Journal of Anesthesiology used a simulation to estimate the annual cost of having dantrolene vials in stock, with a view to assess the cost-benefit ratio of having the drug available in operating rooms. The study found that the annual cost of maintaining a full supply of dantrolene was estimated at 6.6 million Colombian pesos, whereas the estimated cost of a single death resulting from the unavailability of the drug was 18.5 million pesos. (20) This suggests that having the medication available in response to a crisis of malignant hyperthermia could have a positive socioeconomic impact. However, its generalized implementation across all healthcare institutions is uncertain because of the lack of data on the incidence of this condition in all regions of the country.

In response to this issue, some governments have created protocols for the management of malignant hyperthermia and for the distribution of the medication through public or private healthcare providers. Such is the case in Antioquia (21) and Bogotá, the latter under the responsibility of the District Health Secretariat, which developed a guide outlining the steps to follow for managing and obtaining the medication. The guide includes phone numbers to report the event, request the kit, and arrange for its replacement. The kit includes twelve dantrolene vials, sterile water, and the necessary medical devices to administer the medication. (22)

CONCLUSIONS

This case report highlights that early diagnostic suspicion, combined with prompt and specific treatment, can lead to favorable outcomes and reversal of signs and symptoms.

Moreover, notwithstanding the lack of incidence data for Colombia, the report emphasizes the importance of dantrolene availability, showing that timely administration significantly reduces mortality. Although there is an established protocol and a telephone line for emergencies, not having the medication available hinders its timely administration in a condition where appropriate medical management can substantially reduce mortality.

ETHICAL DISCLOSURES

Protection of humans and animals

The authors declare that no experiments involving humans or animals were conducted for this research. All procedures followed adhered to the ethical standards of the responsible human experimentation committee and with the World Medical Association and the Declaration of Helsinki.

Data confidentiality

The authors declare that they followed their institution's protocols regarding the disclosure of patient data.

Right to privacy and informed consent

The authors declare that no patient data are disclosed in this article. The authors obtained the informed consent from the patient mentioned in the article. This document is in the possession of the corresponding author.

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Contributions by the authors

WCR: Article planning and data collection.
CALR: Article planning, data collection, and final approval of the manuscript.
LACA: Article planning, data collection, drafting, and final approval of the manuscript.

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