CASE REPORT

Malignant hyperthermia and the dilemma of Dantrolene's unavailability: A case report

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Abstract

Malignant Hyperthermia (MH) is a rare disorder which is triggered in genetically susceptible individuals when exposed to non-depolarising muscle relaxant (Succinylcholine) and inhalational anaesthetics (Isoflurane, Desflurane, Sevoflurance, Halothane, etc.). If not treated promptly, it carries a significantly high mortality rate. The only approved drug for the treatment of MH is Dantrolene, which is not available in Pakistan and its availability in other countries is also limited. We encountered a case of MH on January 3, 2024, in a five-year-old girl during her recovery from general anaesthesia after undergoing Tenotomy of Flexor Digitorum Superficialis (FDS) tendon for her Camptodactyly. Isoflurane was used for the maintenance of anaesthesia. The patient developed high grade fever and muscle rigidity in her limbs during recovery from anaesthesia. Supportive treatment was started promptly and the patient was immediately shifted to the ICU from the recovery room. Unfortunately, due to unavailability of Dantrolene the patient did not survive the event despite rigorous attempts at resuscitation.

Keywords: Malignant Hyperthermia, Dantrolene, Camptodactyly.

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Introduction

Malignant Hyperthermia (MH) is an autosomal dominant disorder that manifests as a hypermetabolic response when the patient is exposed to certain triggers. Well-known triggers of MH are inhalation of anaesthetics (Isoflurane, Sevoflurane, Halothane, Desflurane, etc.) and depolarising muscle relaxant (Succinylcholine). When any of these drugs is given to a patient with underlying genetic mutation, MH is triggered. Type 1 Ryanodine receptors (RYR1) and Voltage-gated calcium channel (CACNA1S) genes are known to be associated with MH causative mutations.[1] Overall prevalence of MH is estimated to be around 1–2 per 100,000 anaesthesia cases. Triggering drugs increase the rate of calcium release from sarcoplasmic reticulum resulting in a sustained increase in intracellular calcium concentration which leads to uncontrolled muscle contraction; as a result the patient develops symptoms such as mixed (metabolic and respiratory) acidosis, hyperthermia, generalised muscular rigidity, and hypoxemia. The only approved drug for the treatment of MH is Dantrolene. If not treated promptly, patients can develop serious complications like rhabdomyolysis, renal failure, pulmonary oedema, arrhythmias, and disseminated intravascular coagulation.[2] A case of MH due to induction and maintenance of anaesthesia with Isoflurane was encountered; unfortunately the patient did not survive despite rigorous efforts because of the unavailability of Dantrolene. The objective of sharing this case is to enhance awareness regarding the diagnosis and early management, and to highlight the issue of the unavailability of Dantrolene countrywide.

Case Report

A five-year-old girl, weighing 20kg, was scheduled for Tenotomy of Flexor Digitorum Superficialis (FDS) tendon for Camptodactyly in Ayub Teaching Hospital, Abbottabad, on January 3, 2024, after conservative measures failed to respond. The patient did not have any significant past medical, surgical, and anaesthesia history. The patient's family also did not have any history of neuromuscular disease. The pre-operative laboratory reports were within the normal values. The pre-operative vital signs were blood pressure: 100/70mmHg, heart rate: 88 beats/minute, respiratory rate: 44/minute, and axillary temperature: 37.0°C. Anaesthesia was induced with injection Propofol 40mg, injection Glycopyrrolate 0.1mg, injection Nalbuphin 4mg and injection Metoclopramide 3mg via IV bolus, meanwhile Laryngeal Mask Airway (LMA) was passed without any interruption. LMA was used as it was a short procedure. General anaesthetic drug for maintenance of anaesthesia used was Isoflurane 1.2mcc, oxygen (FiO_2 0.5), other drugs used were, infusion Paracetamol 250mg IV-stat, infusion R/L 350ml intravenous (IV)- Stat, while no short acting muscle relaxant was used. Two large bore IV lines

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were maintained and Foley's catheter was inserted for checking the hourly urine output. Intra-operatively, the patient remained haemodynamically stable. During the surgery, the surgeon noticed slight muscle rigidity for which 15mg IV Propofol bolus was given. Afterwards the surgery was concluded and the patient was recovered from anaesthesia and LMA was removed uneventfully. After five further minutes in the OT, the patient was shifted to the recovery. The patient experienced a sudden onset of pyrexia, with a reported skin temperature of 103°F measured in the axillary region. The patient also started developing rigidity in her limbs. At that time her Glasgow Coma Scale (GCS) was 15/15,[3] BP of 90/60 mmHg, pulse of 76bpm, SpO_2 97% at room air. Cold sponging and cold IV fluids were started immediately. Infusion Paracetamol 250mg, injection Decadron 4mg, and injection Hydrocortisone 100mg were also given. Serial temperature recordings showed a rising trend i.e. 104.5°F and 105.9°F despite receiving fluids, Paracetamol and cold sponging. She also developed masseter muscle spasm. On the basis of her clinical presentation, anaesthesia and paediatric teams labelled it as a case of malignant hyperthermia. The patient was immediately shifted from the recovery room to the Intensive Care Unit (ICU), where endotracheal intubation was attempted right away but could not be done due to masseter spasm. Immediately, the patient collapsed and ECG showed asystole. Cardiopulmonary resuscitation (CPR) and AMBU (artificial manual breathing unit) bagging was started and continued for 25 minutes, a total of four doses of Epinephrine were given. Despite all these efforts, the patient could not be resuscitated and unfortunately declared dead after 30 minutes.

Discussion

Malignant Hyperthermia (MH) is a rare disorder which is triggered in susceptible individuals when exposed to certain inhalational anaesthetics (Halothane, Isoflurane, Sevoflurane, Desflurane, etc.) and depolarising muscle relaxant Succinylcholine. A case of Malignant Hyperthermia in a five-year-old girl was seen on January 3, 2024, in Ayub Teaching Hospital, Abbottabad, when the patient was recovering from anaesthesia. The drugs used for induction and maintenance of anaesthesia were Propofol and Isoflurane, respectively. The only approved drug for the treatment of Malignant Hyperthermia is Dantrolene. A retrospective study conducted in Japan on established cases of MH during January 1995 to December 2020 showed that mortality of MH in cases who did not receive Dantrolene was 30.8% and in those who received the drug was 9.6%.[2] Overall mortality rate of MH has decreased from 80% to 1.4% in developed countries after the introduction of IV Dantrolene.[4] The diagnosis of malignant hyperthermia in the present patient was based on clinical grading scale

Table: MH Raw score in our Patient.

Patient's Clinical and Laboratory Indicators	Score
Generalised muscular rigidity	15
$PaCO_2$>60mmHg	15
Inappropriately increased temperature	15
Arterial pH<7.25	10
Arterial base excess more negative than -8	10
Total score	65

developed by Larach et al.[5] The raw score in the present patient was 65 based on the basis of clinical and laboratory indicators cited in Table. Larach et al. established that raw score greater than 50 means MH is almost certain.[5] The gold standard test used for the diagnosis of MH is Caffeine Halothane Contracture Test (CHCT) which is done on biopsied muscle specimen of the patient. Studies have shown that patients with MH raw scores of 50 or more are significantly correlated with positive CHCT,[6] hence in the absence of CHCT clinical grading score developed by Larach et al. can be used to make the diagnosis of MH. A case of malignant hyperthermia was noticed in the literature from Pakistan in 2016, which was triggered by Isoflurane. Remarkably, the patient made a successful recovery even in the absence of Dantrolene.[6] The Malignant Hyperthermia Association of the United States (MHAUS) has recommended that Dantrolene should be injected into suspected patients within 10 minutes of the onset of the symptoms[7] but unfortunately its availability is very limited worldwide and is totally unavailable in Pakistan. The main reasons of its limited availability are its low demand, and high cost. Before 2015, Dantrolene sodium was available in the market with the name Dentrium and it needed almost 36 vials for a complete dose for one patient and each vial costed $65. Newer formulation Ryanodex was introduced in 2015 which solved the high dose demand, as it only needed three vials per patient[8] but still it was priced at $3,450 per year to stock.[9] The prevalence of MH is so low that stored Dantrolene is wasted and it imposes huge financial burden, hence, it is not available in most places. It is important that once an event of MH happens, the family should be counselled and encouraged to undergo genetic testing to confirm the susceptibility of MH.[10] Unfortunately, our patient did not survive the syndrome despite rigorous efforts as Dantrolene was not available. Another case report from 2020 was noticed, originating from the Affiliated Hospital of Gui Zhou Medical University in China. In this instance, the patient received Isoflurane and subsequently developed MH, but unfortunately, she did not survive due to the unavailability of Dantrolene.[11]

Conclusion

In developing countries, like Pakistan, where there is no facility for CHCT or genetic testing, suspected individuals

or individuals with positive family history should carry a warning card which will ensure that anaesthetists use safe drugs if they need general anaesthesia at any point in their life. Moreover, anaesthetists should be aware of the clinical signs and symptoms related to MH, and if any signs develop they should be readily picked and prompt symptomatic treatment, early intubation, and cardiac stabilisation with monitoring should be started. Efforts should also be made to locally produce Dantrolene in order to reduce the cost so that it is readily available when needed.

Informed consent: Informed written consent was taken from the patient's guardian for the publication of this case report.

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Author Contribution:
AM: Data collection, writing and literature review.
MFA: Informed consent, literature review and data analysis.
LS: Induction and maintenance of anaesthesia, patient resuscitation and provision.
SK: Literature review and approval from Head of department.
MM: Literature review.
SMK: Manuscript review.