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A Review on Malignant Hyperthermia

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ABSTRACT

Malignant hyperthermia (MH) is a potentially lethal inherited disorder characterized by disturbance of calcium homeostasis in skeletal muscle. Volatile anesthetics and/or depolarizing muscle relaxant succinylcholine may induce this hypermetabolic muscular syndrome due to uncontrolled sarcoplasmic calcium release via functionally altered calcium release receptors, resulting in hypoxemia, hypercapnia, tachycardia, muscular rigidity, acidosis, hyperkalemia, and hyperthermia in susceptible individuals. Mortality without specific treatment is 80% and decreases to 5% with the use of dantrolene sodium. If it is not recognized and promptly treated, this hypermetabolic state can disturb acid-base balance and produce rhabdomyolysis with hyperkalemia, myoglobinuria, and, consequently, multiorgan dysfunction and death. The treatment requires immediate suspension of the trigger agent, administration of dantrolene, active cooling, and supportive measures. This review is an attempt to provide a summary of malignant hyperthermia and highlight some recent advances.

KEY WORDS: Malignant Hyperthermia, Dantrolene, Anesthesia.

INTRODUCTION

Malignant hyperthermia (MH) is a rare, but life-threatening, autosomal-dominant inherited pharmacogenetic disorder that may lead to metabolic crisis of skeletal muscle in susceptible individuals following exposure to triggering agents, such as volatile anesthetics such as halothane, sevoflurane, desflurane, the depolarizing muscle relaxant succinylcholine, and rarely, in humans, to stresses such as vigorous exercise and heat.[1] The apparent features were, dominated by a progressive pyrexia that usually lead to death.[2] hence the name malignant hyperthermia.[3],[4] The malignant in MH has proved useful in emphasizing the potentially fatal nature of the reaction whereas, hyperthermia is relatively late feature in which early intervention is important.[4] Altered calcium release channels cause dysfunction of intracellular calcium homeostasis and uncontrolled calcium release from the sarcoplasmic reticulum, which may lead rapidly to a fatal hypermetabolic state known as MH crisis.[5] It manifests as a potentially lethal hypermetabolic crisis, which can lead to breakdown of muscle cells, resulting in hyperkalemia, acidosis, increased serum creatine kinase concentration, and myoglobinuria.[6],[7] Complications include cardiac arrhythmia and cardiac arrest s(from acidosis and hyperkalemia), renal failure, compartment syndrome, disseminated intravascular coagulation (DIC), pulmonary edema, and central nervous system injury.[1],[7] Moreover, in everyday life, most MH-susceptible (MHS) individuals do not suffer from muscle symptoms. Nevertheless, MH is still a relevant complication and every anesthesiologist must recognize the symptoms of an MH episode and start appropriate treatment without delay.[8]

EPIDEMIOLOGY

The incidence of MH episodes during anesthesia is between1:10,000 and 1:250,000 anesthetics. The highest incidence is in young people. It has been found that children under 15 years age comprised 52.1 % of all reactions.[9] The estimated prevalence of genetic abnormalities associated with MH susceptibility may be as great as one in 3000 individuals (range 1:3000 to 1:8500), with a more recent estimate being 1 in 400. MH crises develop not only in humans but also in other species, particularly pigs, which have been a valuable source for research. Such reactions have also been described in horses, dogs and other animals.[1],[2] Malignant hyperthermia mortality dropped from 80% to less than 5% after the introduction of a potent MH antidote, dantrolene, in the late 1970s. Nevertheless, in the first decade of the 21st century mortality has risen to 14% and this may be associated with the increased use of MH triggering anesthetics outside conventional hospital settings and possibly the mistaken belief that MH was not triggered by modern inhalation anesthetics.[10] Regardless of the cause, the increase in mortality emphasizes the need for anesthesiologists to have a sound understanding of MH, even though it is rare.

All inhalation anesthetics (e.g., halothane, ether, desflurane, sevoflurane, isoflurane) except nitrous oxide are reported as MH triggers.[5],[6] Confirming previous findings, a recent study showed that the depolarizing neuromuscular blocking agent, succinylcholine, is associated with adverse events graded as ‘‘very likely’’ or ‘‘almost certainly’’ MH, even when inhalation anesthetics were not used.[11] Studies in different populations have indicated that early dantrolene administration drastically reduces the incidence of complications. They revealed that the complication rates increase with delay in administration of dantrolene treatment.[11]

CLINICAL PRESENTATIONS

Clinical symptoms of MH are highly variable, and range from mild or moderate symptoms to fulminant MH crises with severe skeletal muscle hypermetabolism and rhabdomyolysis.[8] Excessive CO2 production presenting with an increase in the end tidal CO2 concentration or hyperventilation while breathing spontaneously is a sensitive and specific early sign of imminent MH. Further early symptoms of an MH crisis may include tachycardia, supraventricular or ventricular arrhythmia, and isolated muscle spasm or generalized muscular rigidity. 50–80% of patients develop arrythmia or muscular reactions.[12] Distinctive cyanosis indicating increased oxygen consumption may occur later in the course of an Malignant hyperthermia episode. A rapid increase in temperature (to .38.8°C) is a relatively late sign. However, a rapid increase of .1°C in 15 minutes is diagnostically more relevant than the peak temperature.[13] In some cases, there is no relevant changes in body temperature, particularly if adequate treatment is started early.[14],[15] Arterial blood gas analyses shows a combination of respiratory and metabolic acidosis with negative base excess, lactemia, hypercapnia, and hypoxemia. Fulminant MH crisis usually presents with paCO2 values more than 60 mmHg and a base excess of more than 8 mVal/L. As the MH episode progresses, rhabdomyolysis leads to increased creatine phosphokinase, hyperkalemia, and myoglobinemia, and might result in acute renal failure. The end stage of a fulminant MH crisis is characterized by multiorgan failure and circulatory collapse.[8]

PATHOPHYSIOLOGY

The exact mechanism by which different substances initiate a MH has not been determined. The defect of intracellular Ca2+ homeostasis plays an important role.[16] Calcium ions are responsible for excitation contraction coupling mechanism of skeletal muscles. Release of Ca2+ is initiated by the

activation of dihydropyridine receptor (DHPR) located in the wall of the transverse tubule.[17] The DHPR is a voltage dependent receptor has 5 subunits: a1,a2, b, c and d with the a1-subunit holding Ca2+ channel activity and binding to Ca2+ antagonists. The other four subunits function as modulators.[18] The DHPR functionally couples the transverse tubule to the ryanodine receptor which is a protein complex built up of four identical monomers and transmits the wave of depolarization from the transverse tubule to the ryanodine receptor. This process is initiated by a voltage-dependent conformational change in the a1 subunit of the dihydropyridine receptor being transmitted to the ryanodine receptor through the protein segment linking motifs II and III that open the ryanodine receptor and induce Calcium release into the myoplasm. Triadin, calmodulin or calsequestrin are proteins located in specialized areas of the sarcoplasmic reticulum, they can modify the interaction of the dihydropyridine receptor and the ryanodine receptor.[19] The myoplasmic part of the ryanodine receptor is additionally equipped with numerous binding sites for proteins and other ligands including Calcium, ATP, Magnesium and various other agents such as volatile anaesthetics, ryanodine or dantrolene.[20] During the normal muscle contraction cycle the free ionized unbound intracellular Calcium within the muscle cell reduces troponin inhibition of the contractile elements and hence results in muscle contraction. The intracellular Calcium pumps rapidly transfer calcium ions back into the sarcoplasmic reticulum, and relaxation occurs when the concentration is less than the mechanical threshold.[34] Susceptibility to MH is clearly based on an abnormal Calcium metabolism within the skeletal muscle most probably caused by a defective Ca2+ release channel in the sarcoplasmic reticulum. Calcium dependent metabolic activities that are provoked by an increased cytoplasmic Ca2+ concentration is being stimulated leading to typical symptoms of MH which include hypercapnia, acidosis and fever.[17]

DIAGNOSIS

The diagnosis of Malignant Hyperthermia is mainly based on clinical presentation or laboratory testing. The principal diagnostic features of MH are unexplained elevation of ETCO2 concentration, tachycardia, acidosis, muscle rigidity, hyperthermia, and hyperkalemia. The variability in the order and time of onset of signs often makes the clinical diagnosis difficult.[1]

A clinical grading scale was developed by Larach and colleagues in order to assist in clinical diagnosis oh MH.[2]

Clinical Finding	Manifestation
Respiratory acidosis	End-tidal CO2>55 mmHg; PaCO2>60 mm Hg
Cardiac involvement	Unexplained sinus tachycardia, ventricular tachycardia or ventricular fibrillation
Metabolic acidosis	Base deficit >8 m/Eql pH<7.25
Muscle rigidity	Generalized rigidity; severe masseter muscle rigidity
Muscle breakdown	Serum creatine kinase concentration >20,000/L units; cola colored urine; excess myoglobin in urine or serum; plasma [K+] >6 mEq/L
Temperature increase	Rapidly increasing temperature; T >38.8°C
Other	Rapid reversal of MH signs with dantrolene. Elevated resting serum creatine kinase concentration
Family history	Consistent with autosomal dominant inheritance

MANAGEMENT AND TREATMENT

Dantrolene is the only drug known to specifically treat Malignant Hyperthermia. The drug, introduced in 1979, has been responsible for lowering the mortality rate.[1]

Acute MH crisis

The essential points in the treatment of acute MH are the immediate discontinuation of trigger agents, hyperventilation, administration of dantrolene in doses of 2.5 mg/kg repeated to limit MH, cooling by all

routes available and treating hyperkalemia. Calcium blockers should not be used along with dantrolene, since hyperkalemia may occur with such a drug combination The steps in the treatment of acute MH include discontinuation of potent inhalation agents and succinylcholine, Increase minute ventilation to lower ETCO2, Prepare and administer dantrolene 2.5 mg/kg initial dose, Titrate dantrolene to tachycardia and hypercarbia. Begin cooling measures: If hyperthermic, use iced solutions, *i.e*. Ice Packs to groin, axilla, and neck; Nasogastric lavage with iced solution; More aggressive measures as needed and Stop cooling measures at 38.5°C, Treat arrhythmias as needed. Do not use calcium channel blockers, Secure blood gases, electrolytes, creatine kinase, blood and urine for myoglobin, evaluate Coagulation profile every 6–12 hours; Treat hyperkalemia with hyperventilation, glucose and insulin as needed. Once crisis is under control. Further Continue dantrolene at 1 mg/kg every 4–8 hours for 24–48 hours. Ensure urine output of 2 ml/kg/hour with mannitol, furosemide, and fluids as needed. Evaluate need for invasive monitoring and continued mechanical ventilation. Observe patient in Intensive Care Unit for at least 36 hours. Refer patient and family to Malignant hyperthermia Testing Center for contracture or DNA testing.[1],[18]

DANTROLENE

Dantrolene is the only clinically available agent for the specific treatment of malignant hyperthermia. Dantrolene was synthesised by Snyder and his co-workers in 1967. It was found to have skeletal muscle relaxant properties after intravenous administration in animals. Studies revealed that these relaxant properties are due to depression of excitation contraction coupling. This complex process enables skeletal muscles to transform a chemical signal at the neuromuscular junction into a muscle contraction. Dantrolene was initially used as a muscle relaxant in the long term treatment of skeletal muscle spasticity. [21]

Dantrolene is highly lipophilic and therefore poorly soluble in water. Today, dantrolene is available for intravenous use in vials containing 20 mg lyophilized dantrolene sodium added to 3 g mannitol to improve water solubility. The prepared solution should be protected from light and stored at 15^0–25^0C, and once prepared should be used within 6 h. The resulting alkaline solution is highly irritating to peripheral veins and should therefore be injected into a large vein or a fast running infusion.[21],[22]

PHARMACOKINETICS

After oral administration, 70% of a dose of dantrolene is absorbed. Significant variations in plasma concentrations are seen, peaking at about 6 hr. In healthy conscious volunteers, intravenous administration of dantrolene 2.4 mg/kg results in plasma concentrations of 4.2 µg.ml^{-}1, which blocks up to 75% of skeletal muscle contraction.[23] The Plasma concentration remains stable within the therapeutic range for approximately 5 h after administration. Plasma elimination half-life time is estimated to be 12 h. In Paediatric patients, the pharmacokinetic profile is similar, with a half-life of approximately 10 hr.[24]

Dantrolene is metabolised by liver microsomes to 5-hydroxydantrolene, which itself acts as a skeletal muscle relaxant.

Reduction of the nitro moiety of the benzene ring leads to the formation of aminodantrolene, which is metabolized to the reduced acetylated derivative of dantrolene.[28],[41] Dantrolene and its metabolites are excreted mainly via urine and bile.[3] Dantrolene has structural similarities to both hydantoin and some local anaesthetics, but has neither anticonvulsant nor anaesthetic properties.[22]

PHARMACODYNAMICS

Voltage changes in the t-tubule membrane regulate conformational changes in the dihydropyridine receptor during normal excitation–contraction coupling of skeletal muscle fibres. Dihydropyridine receptors act as voltage sensors that undergo

intramolecular charge movement during depolarization. This phenomenon probably results in a movement of the intracellular loop between the transmembrane domains II and III of the alpha-1 subunit of the dihydropyridine receptor.[33] The alpha-1 subunit and the ryanodine receptor isoform 1 (RYR1), the main calcium-releasing channel of the sarcoplasmic reticulum, are intimate physiological partners. The opening of RYR1 induces the efflux of calcium ions into the myoplasm.[26],[27] Subsequently, calcium ions activate muscle contraction by attenuation of troponin C inhibition of the contractile proteins actin and myosin. Relaxation is achieved by a rapid adenosine triphosphate (ATP)-consuming transfer of calcium ions back into the sarcoplasmic reticulum and is completed when the myoplasmic concentration is less than the mechanical threshold.

the underlying molecular mechanisms and the exact mode of dantrolene's action have been incompletely understood. Dantrolene is a direct-acting skeletal muscle relaxant blocking calcium release from intracellular storage in the sarcoplasmic reticulum. Muscle contraction is decreased without an effect on the action potential patterns of the neuromuscular junction.[25],[41]

ADVERSE DRUG REACTION

Adverse reaction may occur after acute or chronic parenteral administration of dantrolene. A retrospective analysis showed, 164 patients suffering from MH crises were treated with dantrolene. The most frequently observed side-effects were muscle weakness in 22%, phlebitis in 10%, respiratory failure in 3% and gastrointestinal discomfort in 3% of the patients. Dantrolene-associated muscle relaxation might cause prolonged respiratory insufficiency, especially in patients with neuromuscular disease. The second most common side-effect, local inflammatory phlebitis at the infusion site, is caused by the highly alkaline solution. Accidental extravascular infusion causes severe tissue necrosis. Therefore, it is recommended that dantrolene is given into large peripheral veins or via central venous lines. Other ADRs include drowsiness, dizziness and confusion. Chronic oral therapy has been associated with liver dysfunction, yet dantrolene was not the only potentially hepatotoxic substance administered to the patients in whom this complication was reported. Neonates are at risk of 'floppy child syndrome' when dantrolene is administered to the mother during Caesarean section. Postpartum uterine atony has been described after dantrolene therapy.[38]

SYMPTOMATIC TREATMENT

The metabolic acidosis can be corrected by administering 1±2 mmol L^{-1} sodium bicarbonate is important. Repeated administration of sodium bicarbonate might be necessary because of a continuous efflux of lactate from cells as lactate crosses through cell membranes slowly.[12] The treatment of metabolic acidosis and elevated potassium concentration requires forced diuresis and a continuous infusion of glucose and insulin.[31]

Mechanical ventilation with 100% oxygen at a flow of more than 10 L/min is essential. End-tidal carbon dioxide concentration should be kept within the normal range with the aid of hyperventilation of the lungs.

Antidysrhythmic therapy using lidocaine and b-adrenoceptor blocking agents should be initiated. In animal experiments, the administration of channel blockers did not improve survival.[29] Indeed, they might even induce elevated serum potassium concentrations by interfering with dantrolene and this might ultimately lead to another MH crisis or the development of further severe dysrhythmias and low cardiac-output syndrome.[30]

To avoid acute renal failure that might result from hypotension and rhabdomyolysis, sufficient volume replacement and fluid balance is required. Diuresis should be promoted by the administration of loop diuretics until urine production reaches 1±2 mL kg^{-1} body weight.[32]

Once the vitals are stable, the patient should be transferred to the intensive care unit in order to monitor vital functions and to continue dantrolene administration. In addition, laboratory variables should be observed closely, i.e. blood-gas analysis, electrolytes, blood coagulation, blood count and renal function. Low-dose heparin should be initiated as early as possible.[12],[36]

CONCLUSION

Malignant Hyperthermia remains a serious risk factor for susceptible individuals undergoing general anesthesia using volatile agents. A good outcome in MH depends on a combination of factors. Initially, an accurate and a complete preanesthetic evaluation and the anesthesiologist needs to be aware of the pathology, correctly identify and manage it, starting administration of dantrolene as soon as possible. Dantrolene is the key in the treatment hence, it must be available and easily accessible in every hospital that uses trigger agents.

Declaration by Authors

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