MALIGNANT HYPERTHERMIA IN CRITICALLY ILL PATIENTS

An Essay

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By

Amr Mohammed Abo-Zahhad

M.B., B.Ch.

Under Supervision of

Prof. Dr. Laila Ali Al-Sayed Al-Kafrawy

Professor of Anesthesiology and Intensive Care

Faculty of Medicine

Ain- Shams University

Prof. Dr. Sameh Michel Hakim

Professor of Anesthesiology and Intensive Care

Faculty of Medicine

Ain- Shams University

Dr. Ahmed Abd Al-Dayem Abd Al-Hak

Lecturer in Anesthesiology and Intensive Care

Faculty of Medicine

Ain- Shams University

Faculty of Medicine

Ain- Shams University

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List of Abbreviations

AI	: Adequate intake
ATP	: Adenosine triphosphate
Ca2+	: Calcium ion
CACNA1S	: Calcium channel, voltage-dependent, L type, alpha 1S subunit
CK	: Creatine kinase
CPK	: Creatine phosphokinase
1,25-$(OH)_2$-D3	: 1, 25-dihydroxyvitaminD
DHP	: Di-hydro-pyridine
DRIs	: Dietary Reference Intakes
ECF	: Extracellular fluid
EMHG	: European Malignant Hyperthermia Group
EtCO2	: End tidal carbon dioxide
FNB	: Food and Nutrition Board
GCs	: Glucocorticoids
GK	: Guanylate Kinase
HEK	: Human embryonic kidney cells
(HVA) Ca^{2+}	: High-voltage-activated Ca2+ Channels
HVGCC	: High voltage gated calcium channel
5-HT	: Serotonin
(LVA) Ca^{2+}	: Low-voltage-activated Ca2+ Channels
ICU	: Intensive care unit
IP3	: Inositol-1,4,5-triphosphate
IVA	: Intermediate-voltage-activated channels
MAGUK	: Intracellular Membrane-Associated Guanylate Kinase
Mg^{2+}	: Magnesium
MH	: Malignant hyperthermia
MHApp	: Malignant hyperthermia application
MHS	: Malignant hyperthermia susceptibility
MMR	: Masseter muscle rigidity
NAMHG	: North American Malignant Hyperthermia Group

NAMHR	: North American Malignant Hyperthermia Registry
NMS	: Neuroleptic malignant syndrome
PTH	: parathyroid hormone
RDA	: Recommended Dietary Allowance
RYR1	: Ryanodine receptor 1
SR	: Sarcoplasmic reticulum
VDCC	: Voltage-gated ion channels
VGCC	: Voltage gated calcium channel

INTRODUCTION

Malignant hyperthermia (MH) is a complex genetic disorder of skeletal muscle typically manifesting clinically as a hypermetabolic crisis when a susceptible individual receives a triggering agent (e.g. succinylcholine). It has become clear that MH is related to uncontrolled release of calcium from the sarcoplasmic reticulum. Other organ systems are involved only secondarily. The consequence of enhanced release of calcium is muscle contraction due to release of inhibition of the actin-myosin interaction ***(Litman et al., 2009)***.

There are special situations associated with malignant hyperthermia in intensive care unit (ICU) in susceptible patients (e.g. endotracheal intubation using succinylcholine, therapeutic hypothermia using isoflurane and other volatile anesthetics, treatment of chemotherapy induced vomiting using ondansetron, treatment of congestive heart failure by phosphodiesterase III inhibitors as enoximone, using statins post myocardial infarction, and treatment of cyanide poisoning by methylene blue) ***(Hellstrom et al., 2014).***

Over the past 50 years, many drugs have been implicated as triggers of MH. The principal triggers are the potent inhalation agents that cause MH reactions whose onset is delayed for several hours. Reports of certain drugs (e.g. ondansteron, methylene blue, phosphodiesterase III inhibitors) that may be used in the intensive care unit have been implicated as additional triggers

of MH over the past 10 years. Thus, health care providers should be well prepared to face this critical complication, in case it occurs ***(Hopkins, 2011).***

In the event of MH crisis, early recognition and prompt therapeutic actions are needed, as survival of the patient depends on this. The MH phenotype can be considered as benign until a susceptible individual is exposed to certain triggers, (e.g. depolarizing muscle relaxants, and/or more rarely excessive thermal stress). Although some of the early clinical features of an MH episode are per second, rather unspecific (hyperventilation or hypercapnia, tachycardia), it is the evolving pathophysiological process that leads to more signs, which should alert the knowledgeable practitioner. The pattern of these signs and their temporal relationship in general is fairly typical and consistent and, all in all, should be considered by the clinician as a potential MH event ***(Bandschappa et al., 2012).***

Successful treatment of an MH crisis depends on early diagnosis and aggressive treatment. The onset of a reaction can be within minutes of induction or may be more insidious. Presentation may vary and treatment should be modified accordingly ***(*Glahn *et al., 2010)***.

The aim of the work is to discuss the fairly uncommon event of malignant hyperthermia in critically ill patients as regards its epidemiology, risk factors, pathophysiology, clinical presentation, management and prevention.

Pathophysiology of MH

1.1. CALCIUM

1.1.1. Introduction

Calcium is the fifth most abundant element on earth and the principle extra cellular divalent cation in the human body. A heathly, 70kg adult contains 1-1.25kg of calcium (25-33g/kg of fat –free tissue), while a 3.5-kg newborn contains about 25g of calcium .About 95-99% of body calcium is in the skeleton as hydroxyapatite crystals. The reminder is in the extra cellular fluid and is exchangeable with that in periosteal fluid, bone forming surfaces, and soft tissues. Skeletal calcium is slowly exchangeable with extra cellular fluid calcium, and the skeleton is thus reservoir of calcium ***(Bhagavan N V, 2003)***.

1.1.2. Calcium function in human body:

Calcium (Ca^{2+}) plays a pivotal role in the physiology and biochemistry of organisms and the cell. It plays an important role in signal transduction pathways, where it acts as a second messenger, in neurotransmitter release from neurons, contraction of all muscle cell types, and fertilization. Many enzymes require calcium ions as a cofactor, those of the blood-clotting cascade being notable examples. Extracellular calcium is also important for maintaining the potential difference across excitable cell membranes, as well as proper bone formation ***(Brini et al., 2013)***.

1.1.3. Calcium Recommended Intakes

Intake recommendations for calcium and other nutrients are provided in the Dietary Reference Intakes (DRIs) developed by the Food and Nutrition Board (FNB) at the Institute of Medicine of the National Academies ***(Food and Nutrition Board, Institute of Medicine, 2010)***.

DRI is the general term for a set of reference values used for planning and assessing the nutrient intakes of healthy people. These values, which vary by age and gender, include:

- Recommended Dietary Allowance (RDA): This is defined as the average daily level of intake sufficient to meet the nutrient requirements of nearly all (97%–98%) healthy individuals.
- Adequate Intake (AI): This is established when evidence is insufficient to develop an RDA and is set at a level assumed to ensure nutritional adequacy.

The FNB established RDAs for the amounts of calcium required for bone health and to maintain adequate rates of calcium retention in healthy people. These are listed in Table 1.1 in milligrams per day (mg/day).

1.1.4. Achieving recommended intake:

Knowledge of dietary calcium sources is a first step towards increasing the intake of calcium-rich foods. Table 1.2 shows typical amounts of calcium for some common food sources. The largest source of dietary calcium for most persons is milk and other dairy products. Other

sources of calcium are available that act as important adjuvants, especially for achieving calcium intakes of 1200 to 1500 mg/d. Most vegetables contain calcium, although at low density. Therefore, relatively large servings are needed to equal the total intake achieved with typical servings of dairy products.

***Table 1.1**: Recommended Dietary Allowances (RDAs) for Calcium*

Age	Male	Female	Pregnant	Lactating
0–6 months*	200 mg	200 mg		
7–12 months*	260 mg	260 mg		
1–3 years	700 mg	700 mg		
4–8 years	1,000 mg	1,000 mg		
9–13 years	1,300 mg	1,300 mg		
14–18 years	1,300 mg	1,300 mg	1,300 mg	1,300 mg
19–50 years	1,000 mg	1,000 mg	1,000 mg	1,000 mg
51–70 years	1,000 mg	1,200 mg		
71+ years	1,200 mg	1,200 mg		

* Adequate Intake (AI)

Adapted from Food and Nutrition Board, Institute of Medicine (2010).

The bioavailability of calcium from vegetables is generally high. An exception is spinach, which is high in oxalate, making the calcium virtually non bioavailable. Some high-phytate foods, such as whole bran cereals, also may have poorly bioavailable calcium ***(National Nutrient Database for Standard Reference, 2011).***

Table 1.2: *Approximate Calcium Contents of Some Common Food.*

Food	Serving Size		Calcium Content
Milk	1 cup	240 mL	300 mg
White beans	1/2 cup	110 g	113 mg
Broccoli cooked	1/2 cup	71 g	35 mg
Broccoli raw	1 cup	71 g	35 mg
Cheddar cheese	1.5 oz	42 g	300 mg
Low-fat yogurt	8 oz	240 g	300-415 mg
Spinach cooked	1/2 cup	90 g	120 mg
Spinach raw	11/2 cup	90 g	120 mg
Calcium-fortified orange juice	1 cup	240 mL	300 mg
Orange	1 medium	1 medium	50 mg
Sardines or salmon with bones	20 sardines	240 g	50 mg
Sweet potatoes	1/2 cup mashed	160	44 mg

Adapted from National Nutrient Database for Standard Reference (2011).

1.1.5. Intestinal calcium absorption

Intestinal calcium (Ca^{2+}) absorption is an important process involved in the maintenance of Ca^{2+} homeostasis. It occurs by two main mechanisms: active transcellular pathway and a passive route, called the paracellular pathway. These mechanisms are regulated by hormones, nutrients and other factors, which have been studied for many years due to their enormous relevance in the prevention of osteoporosis and other abnormalities related to the Ca^{2+} metabolism ***(Balesaria et al., 2009)***.

Under physiological conditions, Ca^{2+} ions are absorbed mainly in the small intestine that is responsible for about 90% of overall Ca^{2+} absorption. Minor amounts of Ca^{2+} ions are absorbed from the stomach and large intestine. The colon accounts for less than 10% of the total Ca^{2+} absorbed ***(Wasserman, 2004)***.

1.1.6. Hormonal regulation of intestinal calcium absorption:

a) Calcitriol:

Calcitriol induces changes in the structure and function of intestinal epithelial cells, which results in an increased intestinal Ca^{2+} absorption. Calcitriol primarily stimulates the transcellular Ca^{2+} movement. Calcitriol enhances intestinal Ca^{2+} absorption through binding to calcium channel ***(Akhter et al., 2007)***.

b) Parathyriod hormones:

It is well known that parathyroid hormone (PTH) plays an important role in the maintenance of the extra cellular Ca^{2+} concentration, sensing minute by minute changes in the blood Ca^{2+}. At the intestinal level, PTH seems to act indirectly on intestinal Ca^{2+} absorption by stimulation of renal 1α-hydroxylase and, thereby, increasing 1, 25-$(OH)_2$-D3 dependent absorption of Ca^{2+} from the intestine. However, direct effects of PTH on Ca^{2+} uptake by enterocytes from duodenum have been demonstrated. PTH stimulates enterocytes Ca^{2+} influx (***Gentili et al., 2003)***.

c) Glucocorticoids:

Glucocorticoids (GCs) are extensively used as anti-inflammatory drugs. Osteoporosis is one of the most important side effects after long-term GC treatments. Reduced intestinal Ca^{2+} absorption seems to be part of the pathogenesis of GC-induced osteoporosis ***(Gourlay M et al., 2007)***.

1.1.7. Control of Calcium Homeostasis:

The serum level of calcium is closely regulated with normal total calcium of 2.2-2.6 mmol/l (9-10.5 mg/dl) and normal ionized calcium of 1.1-1.4 mmol/l (4.5-5.6 mg/dl). Approximately 99% of total body calcium is found in the skeleton, with only small amounts found in the plasma and extra vascular fluid. Serum calcium exists in 3 fractions: ionized calcium (approximately 50%), protein-bound calcium (approximately 40%), and a small amount of calcium that is complexed, primarily to citrate and phosphate ions ***(Balesaria et al., 2009)***.