

DIFFERENCES IN THE ONSET AND SEVERITY OF SYMPTOMS OF
MALIGNANT HYPERTHERMIA WITH DIFFERENT INHALATIONAL
ANESTHETICS

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14. ABSTRACT Malignant hyperthermia (MH) is an uncommon inherited disorder of skeletal muscle in which commonly used anesthetics can trigger sustained skeletal muscle hypermetabolism in patients who may have had no symptoms previously. The onset and severity of clinical symptoms of MH are variable. Non-clinical studies and case reports have identified differences in the onset and severity of symptoms with the commonly used volatile anesthetics. The purpose of this study was to identify if there is a significant difference in the onset and severity of signs and symptoms of malignant hyperthermia in those MH-susceptible patients who received the different volatile anesthetics. A comparative descriptive research design was used. A retrospective review of the database at the (USUHS) MH muscle biopsy diagnostic center was done. The data collected was used to determine if there was a difference in the onset and severity of signs and symptoms of MH episodes with halothane compared to MH episodes of four other volatile anesthetics. For each of these groups, the following variables were assessed: highest temperature, highest end-tidal carbon dioxide, time from beginning of anesthetic until onset of first MH symptom, time of onset of anesthesia until initial treatment for MH, and the incidence of masseter spasm. Based on results of this study, there was no significant difference among the groups. As much of the pediatric data was excluded, the results may have been skewed. Further studies examining these differences between volatile anesthetics would be extremely valuable in understanding the pathophysiology of malignant hyperthermia.						
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ABSTRACT

Malignant hyperthermia (MH) is an uncommon inherited disorder of skeletal muscle in which commonly used **anesthetics** can trigger sustained skeletal muscle hypermetabolism in patients who may have had no symptoms previously. The onset and severity of clinical symptoms of MH are variable. Non-clinical studies and case reports have identified differences in the onset and severity of symptoms with the commonly used **volatile anesthetics**. The purpose of this study was to identify if there is a significant difference in the onset and severity of signs and symptoms of malignant hyperthermia in those MH-susceptible patients who received the different **volatile anesthetics**. A comparative descriptive research design was used. A retrospective review of the database at the (USUHS) MH muscle biopsy diagnostic center was done. The data collected was used to determine if there was a difference in the onset and severity of signs and symptoms of MH episodes with halothane compared to MH episodes of four other **volatile anesthetics**. For each of these groups, the following variables were assessed: highest temperature, highest end-tidal carbon dioxide, time from beginning of anesthetic until onset of first MH symptom, time of onset of anesthesia until initial treatment for MH, and the incidence of masseter spasm. Based on results of this study, there was no significant difference among the groups. As much of the pediatric data was excluded, the results may have been skewed. Further studies examining these differences between volatile anesthetics would be extremely valuable in understanding the **pathophysiology** of malignant hyperthermia.

Key words: **malignant hyperthermia** **anesthetics** **volatile anesthetics**

DIFFERENCES IN THE ONSET AND SEVERITY OF SYMPTOMS OF
MALIGNANT HYPERTHERMIA WITH DIFFERENT
INHALATIONAL ANESTHETICS

by

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PREFACE AND/OR FOREWARD

This research was conducted to provide information on the pathophysiology of malignant hyperthermia. It was designed to gain further understanding in the differences between the different volatile anesthetics and the presenting signs and symptoms of malignant hyperthermia.

DEDICATION AND/OR ACKNOWLEDGMENT

I dedicate this thesis to Ron, who has been my constant companion and key supporter during this. I never wish to forget the words stated by Paul in Philippians, I thank my God every day for every remembrance of you. Thank you for enduring those long hours and for your patience and guidance. Above all, thank you for being in my life and for encouraging me in this dream. To Major G, I thank you for all those times you kept me on track and focused. Most of all thank you for having the wisdom of knowing when we needed a friend as well as a mentor. To Mom, you demonstrated that anything could be accomplished if one wishes hard enough. I only wish you could have been here to see me reach my dream. To Sonya, never ever give up on your dreams. Your dreams can be obtained if you only wish and try hard enough. All the credit goes to God who not only gave me the opportunity, but also provided me with the strength and patience to fulfill my dream.

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CHAPTER I: INTRODUCTION

Background

Malignant Hyperthermia (MH) is an uncommon inherited disorder of skeletal muscle in which commonly used anesthetics can trigger sustained skeletal muscle hypermetabolism in patients who may have had no symptoms previously (Larach et al. 1994). Denborough and Lovell (1960) published the first known case of MH in a letter written to Lancet. The physicians describe the case of a 21-year old man undergoing anesthesia for repair of compound fractures of the tibia and fibula. In the case described, the patient had expressed great fear of anesthesia as ten of his relatives had died during anesthesia. The case was brought to an early termination by the anesthesiologist when the patient developed profound sweating, fever and extreme muscle rigidity during the early stages of anesthesia. Drastic life support measures were initiated and the patient lived to become the first documented case of MH (Rosenberg, 1996).

Since Denborough and Lovell's letter (1960), a worldwide awareness of the risks of genetic susceptibility to certain drugs and stress has been identified. According to Gronert (1980), earlier reports of perioperative hyperthermia have been documented prior to the case discussed by Denborough and Lovell (1960), but lack sufficient information to relate specifically to MH (Gronert, 1980).

In the years since the case described by Denborough and Lovell (1960), great progress has been made in the identification of MH-susceptible patients, their management under anesthesia, and treatment strategies. Additionally, further research into the pathophysiology of MH has led to a better understanding of the physiology and

biochemistry of skeletal muscle. More recent efforts have been focused on identification of the specific genes responsible for MH and the biochemical characterization of skeletal muscle elements that may be important to triggering MH (Rosenberg, 1996). According to the Malignant Hyperthermia Association of the United States (MHAUS), MH is an uncommon inherited disorder of muscle metabolism that is triggered by potent gas anesthetics and the muscle relaxant, succinylcholine (Rosenberg, 1996). A case was described by Pollock, Hodges, and Sendall (1992) of a patient presenting a probable MH reaction in the absence of any known triggering agents. More recent work by Denborough, Hopkinson, O'Brien, and Foster (1996) has demonstrated that merely overheating or placing MH-susceptible piglets under undue stress can trigger a MH crisis. This syndrome obviously has a wide variability in triggering agents and presenting signs and symptoms.

MH is characterized by MHAUS as a syndrome triggered in susceptible individuals by commonly used general anesthetics (Rosenberg, 1996). Malignant hyperthermia is a medical emergency that is potentially lethal. The incidence of MH in the general population is estimated to be anywhere from 1:4,500 when succinylcholine is used to 1:60,000 anesthetics given to adult patients (Wedel, 1997). Wedel estimates that the reported incidence can range from the previously reported incidence of one in 15,000 to one in 4,500 if succinylcholine is given.

Continuous skeletal muscle rigidity, hypermetabolism, hypercapnea, tachypnea, and tachycardia that can result in cardiac arrest characterize the MH syndrome if left untreated (Dunn, 1997). According to MHAUS consultants, Karan and Greenberg (1997), recent trends from the MH Hotline indicate that more episodes are having a wider

variation in clinical signs and presenting symptoms. Elevated temperature, the more classic and recognized sign of malignant hyperthermia, was not present in over half the cases. Hyperthermia is felt to be a late sign as volatile anesthetics can alter the thermoregulatory responses. Although it is considered a late sign, hyperthermia is still considered one of the classical hallmark signs that help confirm the diagnosis of MH with the presence of other known symptoms (Dunn, 1997). Karan and Greenberg (1997) state that all MH cases do not progress at the same rate or with the same consistent set of symptoms. This finding was confirmed by research conducted by McCarthy (1997). Kaplan (1997) states that the classical signs of MH are rare. He advocates very early treatment before the signs of hyperthermia, tachycardia, fever, and respiratory acidosis are present. According to the author, subtle presentations are more likely the norm. Elevated end-tidal carbon dioxide (CO₂) monitoring is now felt to be the most valuable early sign of malignant hyperthermia (Dunn, 1997; Kaplan, 1997; McCarthy, 1997; Rosenberg, 1996). Kaplan (1997) estimates the incidence of a classic fulminant episode to be approximately one in 200,000 patients not having administration of succinylcholine and one in 50,000 patients with the administration of succinylcholine. The clinical presentation of MH may be mild or severe. The main differences in the presentation lie in the speed of onset, and the number and severity of signs present (Allen, 1994).

Characteristics of the classical fulminant episode as described by Allen (1994, p. 514) include rapid progression, sudden onset, and a wide variety of multiple clinical signs. Other clinical and diagnostic data may include severe hyperkalemia and cardiac arrest. Generalized muscle rigidity, a rapid rise in core body temperature, and a complicated clinical course will be the norm for these episodes. According to the author,

these cases are rare and occur in less than 10% of all MH episodes. Allen also describes a syndrome called *recrudescence* that appears more frequently after severe MH episodes (p. 515). *Recrudescence* refers to the presence of certain signs after survival of the initial episode that herald the return of fulminant MH. Signs of *recrudescence* include evidence of hypermetabolism or rhabdomyolysis. Although the majority of these episodes described had occurred prior to the availability of dantrolene, Allen states that this still remains a significant possibility in up to 25% of MH episodes.

Specific signs listed by Rosenberg (1996) and the Malignant Hyperthermia Association (MHAUS, 1997) include intense muscle rigidity, rapid increase in body metabolism as indicated by increasing carbon dioxide output and increased acidosis. According to Rosenberg (1996), rapid developing fever, although a very specific clinical symptom, is a late sign. Muscle breakdown, as indicated by dark urine or dramatically increased creatine kinase, may also be a confirming sign noted later in the clinical course. Although the classic clinical signs seen in a fulminant MH episode are consistent, the severity of symptoms and presentation can vary with each patient and may vary depending on the triggering agent. In the study conducted by McCarthy (1997), the onset of MH was found to be more rapid in the patients receiving halothane as compared to the other volatile anesthetics. In McCarthy's study, the average temperature for each group was not elevated significantly. The results were felt to be due to the introduction of end-tidal CO₂ monitoring and drug therapy with dantrolene (Rosenberg, 1996).

In a review of 503 cases of MH done by Strazis and Fox (1993), a variety of signs and clinical symptoms were found. Hypermetabolism was again found to be the basis of the various other clinical signs and symptoms. Tachycardia, increased oxygen consumption,

ventricular tachyarrhythmia, unstable arterial blood pressure, cyanosis, mottling, tachypnea, muscle rigidity, and hyperthermia were all clinical signs and symptoms found in the subjects studied by Strazis and Fox. Other diagnostic data found present in a variety of cases were electrolyte abnormalities, myoglobinuria, creatine kinase elevations, impaired coagulation, renal failure, acidosis, and pulmonary edema. Succinylcholine and volatile anesthetics were implicated in this study as the main triggering agents. In this study, fifteen cases reported as MH were not associated with known MH triggering agents. Of the forty deaths in this study, ten percent occurred with dantrolene therapy. There was no relationship of mortality with any anesthetic regimen. Since the signs and symptoms can vary widely among patients and with each anesthetic given, it is difficult for the anesthetic provider to determine the exact onset of clinical MH, although the most common triggering agents are known.

Research Questions

Volatile anesthetics are a known triggering agent in the MH-susceptible individual (Kaplan, 1997; McCarthy, 1997; Rosenberg, 1996). The patient who presents with the classical signs of MH during the early stages is rare. Although these patients are often identified with capnography and close monitoring, a wide variety of clinical symptoms can exist before the classical presentation is evident. (Kaplan, 1997). Prophylactic treatment of patients with dantrolene is controversial because the drug is expensive and can be associated with muscle weakness and respiratory compromise (Van Norman, 1996).

There have been few studies documented in the literature to examine the variability in clinical signs and symptoms. A grading scale was developed by Larach et al. (1994) to

objectively define clinical signs and symptoms. An initial study conducted by researchers in Germany demonstrated that this scale does not correlate well with the MH diagnosis utilizing the in vitro contracture test, the established gold standard for diagnosis of MH (Von Richofen, Wappler, Scholz, Fiege, & Kochling, 1997). However this grading scale is presently being utilized by MHAUS to further objectively define the malignant hyperthermia syndrome (Larach et. al., 1994). At present, the differences in clinical presentations and symptoms have not been very well documented in the literature for human subjects and have a very wide degree of variability (McCarthy, 1997).

Therefore the purpose of this study was to identify if there is a difference in the onset and severity of signs and symptoms of MH between MH susceptible patients who receive the volatile anesthetics halothane, enflurane, isoflurane, desflurane, or sevoflurane.

The research questions guiding this study were as follows:

1. Is there a difference in the highest temperature during a MH episode with halothane compared to enflurane, isoflurane, desflurane, and sevoflurane?
2. Is there a difference with the highest recorded end-tidal CO₂ during a MH episode with halothane compared to enflurane, isoflurane, desflurane, and sevoflurane?
3. Is there a difference from the time of the beginning of the anesthetic until time of onset of first symptoms of MH with halothane compared to enflurane, isoflurane, desflurane, and sevoflurane?
4. Is there a difference from the time of the beginning of the anesthetic until the time of initial treatment for MH with halothane compared to enflurane, isoflurane, desflurane, and sevoflurane?

5. Is there a difference in incidence of masseter spasm during a MH episode with halothane, compared to enflurane, isoflurane, desflurane, and sevoflurane?

The halothane-caffeine muscle biopsy database in the department of anesthesiology at the Uniformed Services University of the Health Sciences contains approximately 400 patients. This database has descriptions of MH episodes that have occurred in humans when given volatile anesthetics. To examine this variability in clinical onset and severity of MH symptoms for this study, it was hypothesized that:

1. There are no significant differences among halothane, enflurane, isoflurane, desflurane, or sevoflurane in the highest temperature exhibited during a MH episode.
2. There are no significant differences among halothane, enflurane, isoflurane, desflurane, or sevoflurane in the highest end tidal CO₂ exhibited during a MH episode.
3. There are no significant differences among halothane, enflurane, isoflurane, desflurane, or sevoflurane in the time from the beginning of the anesthetic until the first MH symptom.
4. There are no significant differences among halothane, enflurane, isoflurane, desflurane, or sevoflurane from the beginning of the anesthetic until the initial MH treatment.
5. There are no significant differences among halothane, enflurane, isoflurane, desflurane, or sevoflurane in the incidence of masseter spasm during a MH episode.
- 6.

Conceptual Framework

Malignant hyperthermia is perhaps one of the most widely discussed topics in anesthesiology. In the early stages of identification, it was called malignant hyperpyrexia (Denborough, Forster, Hudson, Carter, & Zapf, 1970, p. 1137). The authors describe malignant hyperpyrexia as a syndrome in which a general anesthetic causes a steep rise in body temperature that is usually considered fatal. Since that time, the term has been changed to malignant hyperthermia. Malignant is a term often meaning poor prognosis and terminal. In the era prior to dantrolene, the mortality rate for patients exhibiting MH was as high as 90%. However since the introduction of dantrolene in 1979, a dramatic decrease in mortality has been seen in patients with MH to less than 10% (Nagelhout & Zaglaniczny, 1997, p.348). Hyperthermia is defined by Rhoades and Tanner (1995, p. 608) as an abnormally high core temperature. Luciano, Sherman, and Vander (1994, p. 642) define hyperthermia as an elevation of body temperature regardless of the cause. Huether and McCance (1994) define hyperthermia more concisely. The definition given by these authors is a marked warming of core temperature that can produce nerve damage, coagulation of cell proteins, and death. According to these authors, hyperthermia is not mediated by pyrogens and there is no resetting of the hypothalamic set point. Malignant hyperthermia is an iatrogenic hyperthermia precipitated by the administration of a volatile general anesthetic in susceptible patients (McCarthy, 1997). Malignant hyperthermia should not be confused with neuroleptic malignant syndrome, a rare but potentially fatal form of drug-induced hyperthermia as a result of antipsychotic drugs. In those patients receiving both anesthetics and neuroleptics, the disorders may be indistinguishable and difficult to assess. Current data indicate that

although these disorders are clinically similar, they are pharmacologically distinct. The likelihood is that the same drugs do not trigger this syndrome (Caroff, Campbell, & Mann, 1994).

The American Association of Nurse Anesthetists (AANA) recognizes the Malignant Hyperthermia Association of the United States as the expert for treatment of MH. The AANA's position statement recognizes the Malignant Hyperthermia Association of the United States (MHAUS) as the experts in establishing protocol for the diagnosis and treatment of malignant hyperthermia. Additionally AANA advocates that all anesthesia providers and healthcare facilities adhere to the recommendations of the Malignant Hyperthermia Association of the United States (MHAUS) (<http://www.aana.com/profinfo/malhyp25.htm.recommendations>). The American Society of Anesthesiologists home page (<http://www.asahq.org>) does not make a position statement although a consultant from MHAUS in an ASA newsletter does discuss the definition and clinical presentations of malignant hyperthermia (Kaplan, 1997). Kaplan defines malignant hyperthermia as a collection of diseases that share a final common pathway, involving the release of intracellular myoplasmic calcium, which causes a hypermetabolic state involving skeletal muscle (p.1). The National Organization for Rare Disorders, Inc. defines malignant hyperthermia as an inherited condition characterized by a rapid rise in body temperature and other serious symptoms after an affected individual has been given general anesthesia (http://www.stepstn.com/nord/org_sum/156.htm).

A pathophysiological model of MH was used as basis for this research study. McCarthy (1997) found that this pathophysiological model had a wide degree of

variability in presenting signs and symptoms. MH is defined by Mickelson (1996) as a disorder of skeletal muscle in which certain anesthetic agents trigger a sustained elevation in myoplasmic calcium concentration that activates biochemical and physiological alterations in the skeletal muscle of MH-susceptible pigs and humans that appear responsible for this inherited disorder. The definition used by this researcher was the one by Hogan (1994). Hogan's definition encompasses the other triggers that are coming to light more recently such as stress, overheating, and other non-anesthetic drugs (Denborough et al., 1996). Hogan defines malignant hyperthermia as acute disorders of skeletal muscle sharing a pathophysiologic cascade initiated by elevation of cytoplasmic calcium requiring an environmental trigger in a genetically predisposed individual (Hogan, 1994, p. 571).

Recent studies have been focused on determining the genetic basis and defining the more specific characteristics of the malignant hyperthermia syndrome. Denborough et al. (1996) stated that previous studies have demonstrated that both MH-susceptible humans and pigs share a common biochemical basis for MH, an elevation of calcium in the myoplasm. These definitions confirm the model used by McCarthy (1997). McCarthy stated in her work that malignant hyperthermia is caused by an increased release of calcium from the sarcoplasmic reticulum of the skeletal muscle cell in the MH susceptible individual. It is apparent that most sources generally agree that MH is an inherited disorder of skeletal muscle where a defect in calcium release is expressed by exposure to certain triggering agents. Nelson (1988) hypothesized that this increased release of calcium is due to the binding of halothane or other volatile anesthetics to the ryanodine receptor that regulates the release of calcium ions from the

sarcoplasmic reticulum in the skeletal muscle cell. During a MH episode, increased ryanodine receptor activation and calcium conductance cause a sustained elevation in intramyoplasmic calcium. Muscle metabolism increases more than two to three times the resting rate, as re-uptake mechanisms attempt to remove excess calcium, depleting adenosine triphosphate (ATP). As the hypermetabolic state continues, further heat, lactic acid and excess carbon dioxide is produced (Allen, 1994). Despite a consistent physiological model to explain the mechanism of malignant hyperthermia, the more recent molecular genetic research has been focused on susceptibility and understanding the genetic changes that occur with malignant hyperthermia. According to Fletcher (1996) the abnormal ryanodine receptor has not been found in many of the MH susceptible families who have been tested for this receptor and its genetic coding. McCarthy (1997) speculated in her research that several receptors regulating the release and uptake of calcium in the skeletal muscle cell with multiple genetic coding may explain the high degree of variability noted in the clinical presentation of the malignant hyperthermia syndrome. Malignant hyperthermia is a syndrome that is associated with a high mortality rate if unrecognized (Kaplan 1997). The variability of clinical signs and symptoms among anesthetics is significant knowledge in early detection and prevention of the more severe, classical episode of malignant hyperthermia that can have a greater than 90% mortality if untreated (Rosenberg, 1996). Malignant hyperthermia as a pathophysiological model can serve as a guide with the ever-changing parameters as new information becomes available on the genetic markers and triggering agents.

Operational Definitions

For the purpose of this study, the following definition of terms and concepts were utilized:

1. Hyperthermia: Inappropriately rapid increase in temperature or inappropriately increased temperature greater than 38.8 degrees centigrade measured via esophageal, skin temperature, rectal, or tympanic (Larach et al., 1994).
2. Malignant Hyperthermia (MH): A rare but potentially lethal type of syndrome that occurs in genetically predisposed patients who are exposed to MH-triggering agents used to induce general anesthesia (Hogan, 1994).
3. Malignant Hyperthermia Susceptibility (MHS): An underlying inherited muscle disorder seen in the person who has the autosomal dominant gene for malignant hyperthermia (Rosenberg, 1996).
4. Malignant Hyperthermia Triggering Agent: An anesthetic, agent, or environmental condition that can cause a MH episode in the MH susceptible individual (McCarthy, 1997).
5. MH Registry: The North American MH Registry located in Hershey, Pennsylvania, which archives MH events reported by anesthesia care providers (Larach & Muldoon, 1997).
6. Malignant Hyperthermia Association of America (MHAUS): A non-profit organization founded in 1981 to conduct research and offer a variety of educational services to reduce the morbidity and mortality of malignant hyperthermia (<http://www.mhaus.org/whatismh.html>).

7. Malignant Hyperthermia Data Base: The data base of the Uniformed Services University of Health Sciences used for MH diagnostic testing of military patients and dependents (MHAUS, 1996).
8. Masseter Muscle Rigidity (MMR): Muscle rigidity or increased muscle tension of the masseter muscle of the face that can occur when a patient is given a triggering agent and indicates the possibility that the patient is MH susceptible (Van Norman, 1996).
9. Trismus: Observed increased tension in the masseter muscles accompanying the administration of a known triggering agent associated with a high probability of malignant hyperthermia. (Stoelting & Miller, 1994).
10. Muscle Rigidity: Observed generalized skeletal muscle spasm or increased skeletal muscle tension in the absence of shivering (Larach et al., 1994).
11. End-tidal carbon dioxide (ETCO₂): The amount of exhaled carbon dioxide measured by capnography when an endotracheal tube is inserted (Stoelting & Miller, 1994).
12. General Anesthesia: Anesthesia used to put the patient to sleep by administration of a volatile anesthetic or intravenous induction agent (Rosenberg, 1996).
13. Muscle Biopsy: The caffeine halothane muscle contracture test (CHCT) for diagnosing malignant hyperthermia susceptibility (Larach, 1993).

Assumptions and Limitations

Assumptions

The following assumptions were used in this study:

1. A positive caffeine halothane contracture test (CHCT) indicates a definitive diagnosis of malignant hyperthermia and is considered a true MH episode in this retrospective study.
2. The temperature and end-tidal carbon dioxide recorded in the MH database are measured with similar methodology and according to professional standards.
3. The interpretation of masseter muscle rigidity, trismus, and muscle rigidity is consistent among all clinicians.
4. The method for recording the time in all documentation is assumed to be the same or similar in all institutions and patients.
5. The North American protocol for muscle biopsy testing is used in all cases.
6. The anesthesia providers involved followed standards for monitoring of anesthesia as stated by the American Association of Nurse Anesthetists and American Society of Anesthesiologists.

Limitations

The following were limitations of this study:

1. The retrospective data are taken from anecdotal clinical cases over several years from a variety of clinical settings in North America during which time the monitoring and vigilance of monitoring, clinical standards, patient treatment and recovery could have varied.
2. Not all cases, which have occurred in the area serviced by the muscle biopsy

center at USUHS, have been reported.

3. The genetic history and key specific data needed may be unknown or unobtainable.
4. Many pediatric patients were excluded from this study, as muscle biopsy is not normally obtained in those patients younger than ten years of age.

Relevance to Nursing

Malignant hyperthermia is a potentially lethal complication of general anesthesia that can prove fatal in otherwise healthy patients if treatment is delayed. A severe MH crisis or delay in treatment or recognition can lead to severe complications such as cerebral hypoxia, cerebral edema, and long term sequelae such as permanent renal damage (Struebing, 1995). With increased awareness, and provider vigilance the mortality of MH has decreased considerably. The information gleaned from this study will continue to expand the body of knowledge regarding the clinical presentation of the malignant hyperthermia syndrome. The diagnosis of MH can be difficult because of the great variability of the many clinical signs and findings (Larach et. al, 1994). The knowledge of the differences in clinical signs and symptoms among the most commonly used anesthetics would assist in further defining the malignant hyperthermia syndrome. The nurse anesthetist can utilize this information to provide much closer monitoring and vigilance so that early intervention in a malignant hyperthermia crisis can be instituted. It is well established that a good outcome and patient prognosis in this potentially lethal syndrome depends very heavily on astute monitoring, accurate assessment, and rapid, appropriate treatment.

Military Relevance

Malignant hyperthermia is an inherited defect that predisposes susceptible patients to a catastrophic cascade of events following certain triggering agents such as volatile anesthetics and depolarizing, muscle relaxants. MH can occur unexpectedly in a young, healthy active duty member undergoing a minor surgical procedure. The possibility that stress can trigger a MH episode also is very relevant in the military environment (Biscardi, Condon, & Muldoon, 1985). Those active duty service members diagnosed as MH susceptible who are based outside of the United States are at increased risk of suffering a serious anesthetic complication as a foreign civilian hospital may not have access to alternative anesthetic techniques or modes of treatment for an MH episode. Additionally, in the combat duty setting, field hospitals may or may not be equipped to prevent or treat the syndrome. According to Biscardi, Condon, and Muldoon, there is a protocol for referral of active duty personnel for MH diagnostic testing. Once the diagnosis is made, decisions are made as to the acceptable levels of risk for those service members. Although rare, the diagnosis of MH does present unusual potential problems to the military medical community.

Summary

Malignant hyperthermia is a syndrome that has a wide variability in presenting clinical signs and symptoms. Hyperthermia, the more classical sign, is not evident until much later in the clinical course. All MH cases do not progress at the same rate or present with the same signs and symptoms. As volatile anesthetics are considered a known trigger, clinical signs and symptoms may also have a wide degree of variability among the specific anesthetics. Elevated end-tidal CO₂ and masseter muscle rigidity are recognized

clinical parameters that can be assessed readily and easily by any anesthetic provider. The purpose of this study was to determine if there is a significant difference in the onset and severity of signs and symptoms of MH among MH-susceptible patients receiving volatile anesthetics. This study utilized the malignant hyperthermia pathophysiological model as a framework to assess the signs and symptoms. The results from this descriptive research will attempt to answer the research questions noted. Chapter Two provides an overview of the literature as it applies to this study of presenting symptoms of MH-susceptible patients exposed to various volatile anesthetics.

CHAPTER II: REVIEW OF LITERATURE

Introduction

The purpose of this study was to examine the variability of clinical responses in those patients with a MH reaction triggered by the volatile anesthetics. The responses to those patients receiving halothane, enflurane, isoflurane, desflurane, and sevoflurane will be described in terms of patterns of end-tidal carbon dioxide, timing of onset and severity of reactions, hyperthermia, and masseter muscle spasm. This chapter reviews the historical framework of malignant hyperthermia, research and additional literature that discuss the variability in the different clinical responses, and data demonstrating the wide variability among the different volatile anesthetics.

Historical Perspective

Between 1915 and 1925, one family experienced three MH deaths featuring rigidity and hyperthermia. MH susceptibility has now been confirmed in three descendents (Gronert & Antognini, 1994). Denborough and Lovell (1960) described the first known case of malignant hyperthermia in 1960. In a letter written to Lancet, a case presentation is given of a young man with a family history of ten anesthetic deaths out of 22 relatives. The young man was very frightened about his own pending surgery for repair of a fractured tibia. During surgery the young man was anesthetized with halothane and developed profound tachycardia, hot sweaty skin, and cyanosis. The surgery was terminated early and the patient is now known as the first documented case of malignant hyperthermia. Denborough and Lovell subsequently reported on this case again in The British Journal of Anesthesia (Denborough, Forster, & Lovell, 1962).

Prior to that case, Dr. G.A. Jones, an anesthesiologist, observed and recorded a fatal

reaction to chloroform anesthesia, but never published his findings so never received credit for the discovery (Harrison & Isaacs, 1992). His letters written in 1919 and earlier regarding the circumstances of two anesthetic deaths in a family are of considerable historical interest. The letters written by Dr. Jones to the surviving family members following the anesthetic deaths of the son and then the mother, indicate that that these are possibly the true first documented cases of MH, although the details are somewhat unclear. The son's death is described following anesthesia where a curious muscular rigidity existed (Harrison & Isaacs, 1992, p. 54). The mother's reaction while under ether and chloroform was also described as a marked tendency to spasm of the muscles of the arms and jaw and apparently those of respiration (p. 55). In 1925, a third member of the family died during an appendectomy, although the clinical details are not documented. A fourth member, the grandfather, died in 1930 also while receiving anesthesia. In this case, specific details are lacking other than the muscular rigidity. According to Harrison and Isaacs, temperature monitoring was not customary during that time, so it is unclear as to whether any other symptoms were present other than the profound muscular rigidity.

In the 1960s other cases of MH began to be reported in larger numbers. A case was reported by Bennike and Jarnum (1964) about a patient who developed rhabdomyolysis and hyperthermia following general anesthesia in which suxamethonium was administered, however this was not directly linked to malignant hyperthermia. Purkis and other colleagues reported of two patients in one family who died of what he referred to as hyperpyrexia following the use of suxamethonium (Purkis, Horreelt, DeYoung, Fleming, & Langley, 1967 p. 901). Relton, Creighton, & Conn (1968) as well as other

researchers in the late 1960 era concluded that a genetic abnormality may be responsible for the syndrome known then as malignant hyperpyrexia (Barlow & Isaacs, 1970).

In 1969, Britt, Locher, and Kalow reported on 115 cases compiled from the literature and from their own experiences (as cited in Barlow & Isaacs, 1970). Between 1955 and 1958, Locher became involved with the anesthetic care of a family in which 30 members had died in conjunction with anesthesia. He then became associated with Britt and Kalow in Canada who were investigating the problem as well (Gronert, 1980). Britt, Locher and Kalow conducted a very systematic study of MH in families in Wisconsin and reported their findings in 1969 on the hereditary aspects of the MH syndrome. Of the 115 cases investigated by Britt and his colleagues, more than 40 per cent gave a positive family history for MH (Britt, Locher, & Kalow, 1969).

Barlow and Isaacs (1970) did further studies to investigate susceptibility for MH. These investigators first recognized the elevated serum creatine phosphokinase (CPK) in the MH-susceptible patients. In their study, serum CPK and aldolase levels were obtained in a MH-susceptible family of 99 members over four generations. It was interesting that although the levels were drawn both at rest and after strenuous exercise, a surprising number of the abnormally high levels of CPK levels were elevated at rest. Direct skeletal muscle involvement rather than a central syndrome regulating temperature was recognized and established by Kalow and colleagues in 1970. In their work, it was discovered that increased muscle metabolism or muscle rigidity occurred early in the MH syndrome (Kalow, Britt, Terreau, & Haust, 1970).

Denborough et al. (1970) did further work to determine the biochemical changes in MH. At that point in time, it was well established that MH was an inherited autosomal dominant

characteristic. Denborough and his associates also helped to further document the elevated serum CPK and elevated potassium levels that occurred with MH-susceptible patients. By that time, well over 120 cases had been reported in the literature. Gronert (1980) speculated that earlier reports of perioperative hyperthermia could possibly have been MH, however these cases all lacked sufficient information to directly link to this specific pathophysiologic entity.

Non-clinical Studies of MH

A specific breed of pig provides an excellent animal model for the study of MH. This model evolved from earlier reports describing unsuitable pork resulting from accelerated metabolism and rapid deterioration of the muscle from the pig. This led to the term porcine stress syndrome (Gronert & Antognini, 1994, p. 1076). Topel and colleagues confirmed that the porcine stress syndrome was actually a specific disorder of muscle (Gronert, Mott, & Lee, 1988). Porcine breeds such as the Landrace, Poland, China, and Pietrain all show the classical signs of MH during anesthesia with volatile anesthetics and succinylcholine and serve as excellent animal models for studies and research of the genetics and pathophysiology of MH (Rosenberg, Fletcher, & Seitman, 1997).

In 1966, Hall reported MH induced by halothane and succinylcholine in stress-susceptible swine. Experiments later demonstrated that the pigs and humans share a common biochemical basis for MH, an elevation of calcium in the myoplasm (as cited in Denborough et al., 1996). The human and porcine forms of MH appear almost identical when the clinical and laboratory changes of anesthesia-induced MH are compared, however there are some differences in the MH syndrome. Stress-induced, awake-triggering, and overheating alone can trigger MH in the MH susceptible swine, but is

relatively rare in humans. (Gronert & Antognini, 1994; Denborough et al, 1996).

Additional work by Roewer, Greim, Rumberger, & Schulte (1995) suggests that halothane produces abnormal alteration in the electrical properties in the ventricle of MH-susceptible pigs. Work done by Iaizzo, Kehler, Zink, Belani, and Sessler (1996) demonstrated that the core hyperthermia from MH results from heat produced in the central organs of the pig model rather than in the skeletal muscle. Additionally, these researchers demonstrated that induction of mild hypothermia impairs triggering in the MH-susceptible pig and slows the progression of MH.

In a recent study, the researchers compared desflurane with isoflurane and halothane in the MHS swine (Wedel, Gammel, Milde, & Iaizzo, 1993). In this study the effects of desflurane, isoflurane, and halothane on twelve MHS swine were studied. There was a statistical difference between the anesthetics in the time required to trigger MH as measured by an elevated arterial carbon dioxide of 70mm Hg. Halothane exposure resulted in the fastest onset of a MH episode at around 25 minute, whereas desflurane took anywhere from 65 to 90 minutes to trigger. All the animals required two minimum alveolar concentrations (MAC) of desflurane to trigger, whereas with halothane, only one MAC was sufficient. Isoflurane took between one and two MAC for individual animals. Desflurane was statistically slower in triggering MH episodes compared to the other two anesthetics.

In a more recent study conducted by Sigg, Censier, and Urwyler (1997), the effects of commonly used volatile anesthetics were tested on rat skeletal muscles. The anesthetics, halothane, enflurane, isoflurane, desflurane, and sevoflurane were used. All volatile anesthetics except isoflurane increased the myoplasmic calcium concentration. Halothane

and enflurane were the most potent drugs in this research. Sevoflurane and desflurane also increased myoplasmic calcium but to a lesser degree.

Few other species are considered true MH-susceptible. Stress-induced MH has been reported to occur in the horse, cat, dog, deer, birds, and wild animals during capture. Capture myopathy is a syndrome characterized by temperature elevation, rhabdomyolysis, acidosis, and death in wild animals. It has been suggested that this also is a MH variant (Rosenberg et al, 1997). According to Gronert (1980), it is not known whether these episodes occur in species that have some form of recombinant or other genetic susceptibility or whether this is due to environmental or drug-related factors.

There is a colony of greyhounds being investigated by Dr. Thomas Nelson at Bowman Gray, but much research remains to be done. Dr. Nelson reported at the third international symposium for malignant hyperthermia that his colony of MH-susceptible dogs appears to have inherited MH as a dominant trait. Additionally, he discovered that the dogs did not develop the classical skeletal muscle rigidity or lactic acidosis exhibited by the many MH-susceptible pigs (MHAUS, Spring, 1996). Cosgrove, Eisele, Martucci, and Gronert (1992) evaluated greyhounds for susceptibility to MH and found that this particular group of greyhounds was not MH-susceptible, although other anecdotal reports in the literature suggested that it is a probability. This study was very small with a group of only fourteen dogs, seven of which were greyhounds. The researchers suggested further studies involving specifically the greyhound colonies to study MH susceptibility.

According to Hogan (1994), the canine model aside from the pig, is the best-defined animal model. In his work, Hogan describes a strain of Labrador retrievers that present

with classical symptoms consistent with MH that can be reversed with dantrolene.

Rosenberg and Fletcher (1995) state that some aspects of the canine MH episode differ from porcine MH such as lack of muscle rigidity or lactic acidosis. However, the canine MH is autosomal dominant, making it an interesting model to study genetic aspects.

At present, the pig animal model has helped pinpoint the major metabolic defect now recognized as being in the skeletal muscle. In the 1970s, Kalow and colleagues proposed an in vitro muscle biopsy as a diagnostic test for MH in humans based on animal studies. Studies performed then showed that muscle biopsies from MH-susceptible pigs contracted abnormally when exposed to caffeine and halothane (Kauss & Rockoff, 1994).

Further work done by Ellis and colleagues demonstrated increased sensitivity of muscle strips obtained from MH patients to halothane. The combination of these tests became the caffeine halothane contracture test (Gronert & Antognini, 1994). Isaacs and Bedenhorst (1993) recently reinvestigated the muscle biopsy by demonstrating that occasionally false-negative results are obtained, but the incidence is very low. In their retrospective study of 350 patients, four false negative results were obtained out of 350 patients.

At present, the muscle biopsy remains the gold standard diagnostic test for MH, however further research is being conducted for more non-invasive tests. Presently there are several protocols for the muscle biopsy testing. Physicians from eight European countries in Sweden established the European Protocol in 1983 (The European Malignant Hyperpyrexia Group, 1984). The North American Protocol is being used in the United States and was established shortly after the European protocol in the late 1980s (Fletcher, 1994). Active biopsy programs now exist in Australia, New Zealand, South Africa,

Brazil, and the United States. Additionally, twenty laboratories in twelve European countries are performing in vitro contracture tests using the European protocol (<http://www.medana.unibas.ch/emhghome.htm>). In Japan, testing of single muscle fibers is also now being done (MHAUS, 1996).

Consolidation of the biochemistry of MH took place in the 1980s. A major step was accomplished in 1985 when Lopez and colleagues demonstrated an increased intracellular concentration of calcium ion in the muscle from MH-susceptible pigs and humans. It was demonstrated that the intracellular calcium concentration dramatically increased during a MH crisis and was reversed by the administration of dantrolene (Rosenberg et al, 1997). Lynch and colleagues began first defining the MH phenotype in a patient and 17 family members. These investigators first tested the hypothesis that an alteration in the skeletal muscle ryanodine receptor gene was responsible for inheritance of MH (as cited in Hogan, 1997). In the 1990s, molecular biologic techniques were applied to identify the gene or genes for MH. In 1991, a point mutation in the skeletal muscle calcium release channel, the ryanodine receptor, was found to be co-inherited with predisposition to MH in the pig model (Hogan, 1994). Further identification has been done to identify the ryanodine receptor gene on chromosome 19 as being responsible for MH susceptibility. Although this is present in many cases, it is not present in all cases of MH so further work to identify other genes responsible is still needed.

Levitt first reported that more than one gene could cause MH. This observation has since been confirmed by a number of groups internationally. Currently additional genes linked to chromosomes 3, 7, 17, as well as 19 have been found that could cause MH. Presently, eight mutations in the ryanodine receptor and one mutation in the sodium channel have been described in the literature as possibly causal of MH (Wallace et. al,

1996). Recent work by French investigators have discovered a mutation in human skeletal muscle that is thought to represent the first genetic evidence of a mutation affecting a calcium channel of the skeletal muscle and is associated with MHS (Monnier, Procaccio, Stieglitz, & Lunardi, 1997). However further work is still needed to specifically localize the mutations and determine if they are truly the cause of MH

Pathophysiology and Clinical Presentation

The onset of MH can be acute and rapid, particularly during the induction of anesthesia with a volatile agent or succinylcholine. However the onset can also be delayed and not as evident until the patient is in the recovery room. Regardless of the time of onset, once initiated, the course of MH can be extremely rapid. When clinical signs such as increased end-tidal carbon dioxide, muscular rigidity, tachycardia, or fever suggest MH, the association with MH is not strong unless more than one abnormal sign is noted (Gronert & Antognini, 1994).

The volatile anesthetics and succinylcholine can cause MHS patients to undergo a profound increase in metabolism, both aerobic and anaerobic, resulting in intense production of heat, carbon dioxide, and lactate. Additionally, there is a marked respiratory and metabolic acidosis (Gronert, 1980). In MH, lactic acidosis is a very prominent feature as well as hypercarbia. The acidemia and hypercarbia stimulate the sympathetic nervous system and heart rate and cardiac output increase. Additionally, compensatory mechanisms such as an increase in minute ventilation (tachypnea), peripheral vasodilation (flushing), and tachycardia occur (Allen, 1994). Since many surgical patients are receiving neuromuscular blocking agents, the tachypnea may not be evident (Rosenberg et al., 1997).

Early in the MH episode, due to the effect of ATP depletion, acidosis, and hyperthermia, the sarcolemma become leaky and potassium is lost with a resultant hyperkalemia (Allen, 1994). The increased permeability of the muscle also results in an increased creatine phosphokinase, myoglobin, and serum sodium. Generalized body rigidity occurs in about 75% of MHS patients (Gronert & Antognini, 1994). Desaturation of the blood in the operative field and then an increase in body temperature at a rate of 1-2 degrees centigrade every five minutes will usually occur (Rosenberg, Fletcher, & Seitman, 1997). Cardiac signs are prominent throughout the whole episode. Initially tachycardia and increased myocardial contractility is seen. However, the increase in circulating catecholamines leads to myocardial irritability, impaired cardiac contractility and dysfunction (Allen, 1994).

With metabolic exhaustion, cellular permeability will continue to increase with accompanying generalized edema and intravascular coagulopathy. Accompanying these deficits, cardiac and renal failure may also develop. MH is considered a disorder of increased metabolism that does not necessarily involve an increased temperature if heat loss is greater than production or if cardiac output falls early on (Gronert & Antognini, 1994). Cerebral injury may occur as a complication of MH. It is thought that this is due to the combination of hyperthermia, hypoperfusion, acidosis, and electrolyte imbalance. Additionally, it has been found that the electroencephalogram has showed slowing and decreased total power early in the MH episode. It is felt that this may account for the fact that intraoperative awareness has not been reported among MH survivors (Allen, 1994).

The classical lab findings of MH are hyperkalemia, hypercalcemia, lactic acidosis, and myoglobinuria. An increase in the serum creatinine kinase level is very dramatic, often

exceeding 20,000 units in the first 12-24 hours. Death will result unless the syndrome is promptly treated. Even with proper treatment, the patient is at risk for renal failure, coagulopathies, and further organ dysfunction.

Another significant problem in the evolution of the MH crisis is the reoccurrence of the syndrome within the first 24-36 hours (Allen, 1994). According to Allen, recrudescence is more likely after the fulminant more classical presentation of MH. Recrudescence refers to the present of signs of hypermetabolism after survival of the initial episode that may herald the return of fulminant MH. Allen states that recrudescence may occur in about 25% of all MH episodes, however he does not differentiate which volatile anesthetics that this is most likely to occur. Review of case reports indicates that the MH syndrome is most apparent shortly after anesthesia induction and on emergence, however differences among the different anesthetics are not noted (Rosenberg et al,1997).

According to Kaplan (1994), masseter muscle rigidity (MMR) or trismus accounts for one-third of all MH hotline calls and referrals to MH biopsy centers. In an article written by Larach (1994), masseter muscle rigidity is associated with a 61% incidence of other additional signs of MH in those patients registered in muscle biopsy centers in the United States. According to Larach, masseter muscle rigidity is a controversial issue in which further research is needed to determine the morbidity and mortality of MMR when it is an early sign of a MH event. Barlow and Isaacs (1970) first identified MMR as an abnormal response to succinylcholine and were the first to describe its association with MH. Donlon and associates first associated MMR with MH susceptibility in 1978 (Byers & Green, 1992). Subsequent studies over the years have been flawed by lack of agreement on the definition of masseter muscle rigidity. According to Allen

(1994), the incidence of MMR in MH susceptible patients ranges from approximately 50% in the pediatric population to approximately 25% in the adult population. Karan and Greenberg (1997) state that the incidence of MMR in pediatric patients is declining due to practice changes in the use of succinylcholine in children.

Allen's research (1994) indicates that of those children who receive halothane and succinylcholine and present with masseter muscle rigidity, over 50% tested positive for MHS. In contrast, the work done by Smith and colleagues indicate that increases in muscle tension may be a normal response to suxamethonium in children. Smith suggested that this might be considered an exaggerated form of the normal pharmacological effect of suxamethonium (Smith, Saddler, Bevan, Donati, & Bevan, 1990). In the work done by Van Der Spek and associates, a spring gauge was used to monitor resistance to mouth opening after the administration of succinylcholine in apparently healthy children. In all of these patients, jaw muscle tone increased but was generally sub-clinical and not always detectable (Van Der Spek et al, 1990). In research done by Shi, Storella, Keykhah, and Rosenberg (1997), it was demonstrated that pre-treatment with low-dose vecuronium decreased suxamethonium-induced MMR clinically in rats anesthetized with halothane. Smith and his colleagues (Smith, Saddler, Bevan, Donati, & Bevan, 1990) discovered that utilizing tubocurarine was ineffective in preventing the increase in suxamethonium-induced masseter muscle tension in children. Four researchers from Italy determined that the preservative, chlorocresol added to a commercial preparation of succinylcholine made available in Europe was able to cause muscle contracture in MHS muscles (Tegazzin, Scutari, Treves, & Zorzato, 1996). The researchers speculated that the trismus might not be due to the effect of succinylcholine but to the preservative. As this is a preliminary

study, much further research is needed to generate this conclusion.

According to Allen (1994) and Van Der Spek (1991), it is helpful to classify whether or not the masseter spasm occurs with rigidity of other muscle groups. Rosenberg (1996) states that the most specific sign of MH is generalized total body rigidity, although not the most specific indicator. Littleford and colleagues (Littleford, Patel, Bose, Cameron, & McKillop, 1991) determined that the masseter spasm that occurred in isolation without other clinical symptoms of body rigidity did not usually progress to MH. Their recommendation based on research done on 57 children with isolated MMS indicated that anesthesia did not necessarily have to be discontinued in those cases, provided careful monitoring accompanied diagnostic evaluation. In the study conducted by O Flynn, Shutack, Rosenberg, & Fletcher (1994), a high incidence of patients with masseter muscle rigidity (MMR) tested positive for MHS. This particular study evaluated 70 pediatric patients being seen for muscle biopsy based on evidence of MMR after succinylcholine. Out of the 70 patients being seen, 59% tested positive for MH. In five of these patients, clinical MH developed within ten minutes of MMR. According to this study, 83% of the anesthetics given to the 70 patients were halothane-succinylcholine.

Other Findings

Other findings in the patients in the study conducted by O Flynn and associates (O Flynn et al., 1994) was that a significant number of patients developed arterial carbon dioxide tension greater than 50 mm Hg with adequate controlled ventilation, arterial pH less than 7.25 and a base deficit of greater than 8 meq/L. From these studies it seems apparent that hyperthermia is a very late sign in MH, whereas increased carbon dioxide production seems to occur very early. Byers and Green (1992) discuss the variability in clinical signs and presenting symptoms and discuss

the controversies present about how to treat some of these presenting clinical symptoms such as masseter muscle rigidity.

In pediatric patients, the elevated carbon dioxide may not be such a clear-cut indicator of MH. Patel, Leith, and Hannallah (1996) state that an elevation of end-tidal CO₂ is the most sensitive sign of MH in children. However, the authors state further that the beginning of some MH episodes may not be associated with an elevated end-tidal CO₂ due to hyperventilation and inaccuracy in measurement of carbon dioxide levels in children. The authors did not discuss what these inaccuracies were, but advocate looking at additional signs and symptoms such as unexplained tachycardia or hyperthermia. MHAUS consultants, Karan and Greenberg (1997), state that end-tidal carbon dioxide levels will rise within one to two hours into an uneventful anesthetic in a child under 5 years of age. Dantrolene and discontinuation of the triggering anesthetics usually results in improvement. Early intermittent increases in minute ventilation can prevent the early elevation of carbon dioxide, thus masking a MH episode. If the triggering agent is continued, other clinical signs of MH such as tachycardia, temperature elevation, and acidosis will manifest. An elevated end-tidal carbon dioxide is felt to be the most valuable early sign of malignant hyperthermia based on multiple studies (Byers & Green, 1992; Dunn, 1997; Kaplan, 1997; Rosenberg, 1996).

Researchers in Australia analyzed the first 2000 incidents reported to the Australian Incident Monitoring Study (AIMS) and state that in the cases of malignant hyperthermia reported, 50% were first detected by capnography (Williamson, Webb, Cockings, & Morgan, 1993). In a case reported in New Zealand, arterial carbon dioxide monitoring was the only means used to measure carbon dioxide levels (Hodges, Pollock, Couchman,

Hall, & Spiers, 1990). In this case a patient had an uneventful two hours of surgery when the heart rate suddenly increased and the oxygen saturation fell precipitously from 98% to 88%. The first blood gases demonstrated a profound acidosis with a pH of 6.86 and a carbon dioxide of 170 mm Hg. The patient was eventually stabilized and discharged home. In this case, had capnography been used, perhaps it could have detected the MH crisis much earlier and the cardiac arrest that occurred could have been prevented.

Clinical studies of MH With different volatile anesthetics

The individual described by Denborough and Lovell (1960), underwent anesthesia with halothane and manifested symptoms within ten minutes after the operation began. His symptoms ranged from tachycardia to profound diaphoresis and a drop in blood pressure. The study conducted by McCarthy (1997) demonstrated that with halothane, MH triggers very early within 30 minutes. In her study, a retrospective analysis of a MH database demonstrated a wide variability of onset and severity of clinical signs and symptoms with the different volatile anesthetics, including halothane. McCarthy's study also demonstrated that the incidence of masseter muscle spasm was greatest in the halothane and enflurane group compared to the isoflurane group.

Caropreso, Gittleman, Reilly, & Patterson (1975) reported one of the earliest documented cases associated with enflurane. In this case a young woman underwent a cholecystectomy with succinylcholine and enflurane. Within thirty minutes of induction of anesthesia, a tachycardia of 130 was noted. Over the next 20 minutes, the pulse rate increased up to 160 and the anesthetic was discontinued. This patient manifested with a rapid rise in body temperature of 104.4 degrees Fahrenheit. The authors discuss previous reports in which MHS patients can manifest temperatures as high as 110 degrees Fahrenheit. The authors also state that tachycardia has

occurred in 75% of the patients with MH currently reported in the literature as of the time of the article. In the patient presented, there was an initial normal reaction to anesthesia with only a gradual onset of muscular rigidity.

Thomas, Dev, and Whitehead (1987) reported a case in which isoflurane was used and end-tidal carbon dioxide measurements were successful in detecting the signs of MH prior to profound changes were evident. In this patient, the temperature did not go to 38.5 degrees Centigrade while the patient manifested with a gradual but subtle increase in his end-tidal carbon dioxide concentration. The end-tidal carbon dioxide concentration never did elevate beyond ten percent of baseline. The triggering anesthetic, isoflurane, was discontinued and the patient later tested positive on a muscle biopsy for MHS. Prior to this case, few reports had been received in the literature regarding MH with isoflurane. Although the creatine kinase increased to a level of 1360 international units per liter, no myoglobin was ever detected in the urine. Additionally, this patient did not develop a profound metabolic acidosis. The author discussed an earlier case of MH reported in 1982 that discussed the possibility of isoflurane as a triggering agent. The case reported, however, also used succinylcholine and it was difficult to determine which was the triggering agent.

The two cases reported by McGuire and Easy (1990) showed that patients could be exposed during previous anesthetics that are known triggering agents and may not necessarily manifest symptoms. In one case, the patient had undergone four prior surgical procedures, two of which involved both halothane and suxamethonium. In the case discussed by McGuire and Easy, isoflurane was used as the anesthetic. The patient did not develop trismus with suxamethonium again and was intubated readily without

difficulty. His end-tidal carbon dioxide was not monitored due to a faulty capnograph. The earliest symptoms were cyanosis of the upper trunk and ear lobes in the absence of tachycardia. Within the next twenty minutes, the temperature increased to 39.2 degrees centigrade and the heart rate increased to 138 beats per minute. The isoflurane anesthetic was discontinued and dantrolene was given after blood gases demonstrated metabolic acidosis. After discharge from the hospital, the patient continued to have a significant degree of muscle discomfort. A subsequent muscle biopsy confirmed the diagnosis of MHS. The second case discussed by the authors was very similar in presentation and history in that the patient also had undergone two previous surgeries with halothane and the sequence of events was similar. This patient had an uneventful recovery and was discharged home 10 days after surgery. A muscle biopsy later also confirmed the diagnosis of MHS. In both of these cases, the classical signs were evident early, however what is atypical is the fact that both patients had undergone previous surgical procedures with halothane, a known triggering agent. Neither patient had developed MH clinical symptoms during any previous surgical procedures, yet developed a classical MH episode when exposed to isoflurane.

There seems to be a wide variability in the time of onset even among the same agent. In a case reported by Karan, Crawl, and Muldoon (1994), a patient did not manifest obvious signs of MH until approximately six hours into the isoflurane anesthetic. The retrospective chart review did demonstrate a subtle change in carbon dioxide. In this case, however the carbon dioxide change was misleading as small increases of end-tidal carbon dioxide were treated successfully with increases in minute ventilation.

Isoflurane not only seems to be associated with delayed triggering, but a case reported by

DeRuyter, Wedel, and Berge (1995), indicate that isoflurane may also be associated with prolonged dantrolene treatment. In this case report the patient had undergone two prolonged anesthetics prior to the exposure to isoflurane. During the eight-hour procedure, the end-tidal carbon dioxide never did rise above 32 mm Hg. The heart rate remained within normal limits. The patient was transferred to the post-anesthesia care unit where the first arterial blood gases obtained demonstrated a metabolic acidosis. The temperature began to rise from 37.1 degrees centigrade intraoperatively to 38.6 degrees centigrade postoperatively. A tentative diagnosis of MH was made and dantrolene treatment was started. This patient required a total of 39 mg/kg of dantrolene over a period of five days. Approximately three months later, the patient underwent muscle biopsy testing which confirmed the diagnosis of MH susceptibility.

In a case reported by Smith, Carvill, and Eckert (1997) isoflurane was used as the anesthetic. An early slight elevation of the end-tidal carbon dioxide was noted with values in the 40mm Hg range. The perioperative course was unremarkable and the surgical procedure was completed within two hours after induction. Approximately ten minutes after termination of the surgical procedure, the patient developed tachycardia and a sudden, abrupt increase in end-tidal carbon dioxide to greater than 80 mm Hg. Hyperthermia manifested and the patient developed profound metabolic acidosis. Dantrolene was given and the patient survived.

Struebing (1995) describes a patient undergoing surgery with isoflurane who had an elevated end-tidal carbon dioxide of 38mm Hg. In this case, the patient's temperature and heart rate remained normal. After the first 90 minutes, the heart rate increased, the temperature spiked suddenly to 38 degrees centigrade, and the patient a sudden increase of end-tidal CO₂ to 60 mm Hg. A diagnosis of probable MH was made and the anesthetic

agents were discontinued and dantrolene treatment was initiated. Ten minutes after discontinuation of the anesthetics and the dantrolene treatment, the patient's heart rate dropped to normal and the end-tidal carbon dioxide went back down to the original baseline. (Caroff et al., 1994).

A recent case reported (Medina & Mayhew, 1998) discussed a case of generalized muscle rigidity occurring in a pediatric patient receiving isoflurane and halothane when succinylcholine was not used. This patient developed jaw rigidity but not true masseter spasm upon induction with halothane and was intubated successfully. Halothane was switched to isoflurane and the patient continued to develop more profound rigidity. Capnography demonstrated an end-tidal carbon dioxide of 67 mm Hg and the isoflurane was discontinued. The blood gases did not demonstrate acidosis. The rectal temperature never elevated beyond 36.8 degrees centigrade. The surgery was completed with propofol and the patient did well postoperatively. In this case, the increased end-tidal carbon dioxide and the muscular rigidity were the only two symptoms. The carbon dioxide was corrected by controlled ventilation and the rigidity improved quickly after cessation of the volatile anesthetic.

McCarthy's study (1997) of a comparison of onset and severity of clinical signs and symptoms among the various volatile anesthetics demonstrated that the onset of MH with isoflurane and enflurane was significantly slower than that of the other groups. The average time from the onset of the anesthetic until the initial treatment was much slower in the isoflurane group (107.3 minutes) and enflurane group (72.4 minutes) compared to the halothane group (31.5 minutes). Isoflurane, however, had the lowest incidence of masseter muscle spasm (0.38) compared to the halothane group (0.66). McCarthy's

research supports the other cases previously discussed that demonstrate delayed triggering with isoflurane as well as a wide variability of clinical signs and symptoms that occur in MH episodes with different volatile anesthetics.

Two cases of MH triggered by desflurane have been reported in humans. Of the two case reports, one of the patients had also received succinylcholine (Fu, Scharf, Mangar & Miller, 1996; Michalek-Sauberer, Fricker, Gradwohl, & Gilly, 1997). The case reported by Fu and associates is very different than the animal studies conducted by Wedel (Wedel, Iaizzo, & Milde, 1991; Wedel et al, 1993) in that the patient triggered within ten minutes of induction (Fu et al., 1996). However in this case reported by Fu and colleagues, the patient had also received succinylcholine. This pediatric patient developed tachycardia and an elevated end-tidal carbon dioxide within ten minutes of induction with no further symptoms initially. In the next few minutes, the temperature increased to 38.4 degrees centigrade and blood gases revealed profound metabolic acidosis. The anesthetic with desflurane was discontinued and dantrolene therapy was started. The patient recovered with no further incident although his serum creatine kinase level peaked to 28,314 international units/liter. Due to the patient's age, muscle biopsy was not done succinylcholine (Fu et al., 1996).

In the case reported by Michalek-Sauberer and colleagues (1997), a pediatric patient received desflurane. After 90 minutes of surgery, the patient's respiratory rate increased and the end-tidal carbon dioxide suddenly climbed to 85 mm Hg. At the same time, temperature increased to 38.8 degrees centigrade and profuse sweating was noted. Blood gases were obtained that revealed a metabolic acidosis. The anesthetic was discontinued and dantrolene was given. The patient had an uneventful recovery. Due to his age, the patient was not tested for MH, however his parents were tested with a muscle biopsy. The

mother was diagnosed as MH-susceptible. Less than one mean alveolar concentration (MAC) of desflurane was used whereas in the animal studies more than one MAC was required to trigger MH. Severe hypercarbia was the main symptom along with an increase in temperature.

Two MHS cases with sevoflurane have been reported in 1992 by anesthesiologists in Japan. However the cases were not confirmed as MHS by muscle biopsy (Ochiai et. al., 1991). These two cases involved a pediatric and an adult patient. The pediatric patient underwent a prolonged surgical procedure with sevoflurane anesthesia with no significant changes within the first four hours other than a rectal temperature of 36.5 degrees centigrade. At approximately four hours into the surgery, the heart rate increased to 120/minute, the rectal temperature increased to 39.8 degrees centigrade, and blood gases demonstrated a profound metabolic acidosis. Dantrolene was given and the surgery was terminated. Postoperatively the patient developed myoglobin in the urine and high concentrations of serum creatine kinase. The second patient underwent two hours of surgery with isoflurane. The isoflurane was switched to sevoflurane due to a malfunctioning vaporizer at about the two-hour mark. Approximately thirty minutes later, the rectal temperature increased to 40 degrees centigrade and the patient developed a sinus tachycardia and ventricular dysrhythmias. The operation was terminated and dantrolene was administered after receiving a blood gas report demonstrating profound metabolic acidosis. This patient died on the fourth postoperative day. These two cases are the first documented cases in the literature of MH triggered by sevoflurane, although the picture is somewhat clouded in the second case due to the use of isoflurane. What is interesting about these two cases is that the temperature elevation seemed to have

occurred earlier and more rapidly than some of the other anesthetics, although the other clinical signs are very similar.

In a case described by Ducart and colleagues (Ducart, Adnet, Renaud, Riou, & Krivosic-Horber, 1995), the patient underwent muscle biopsy fifteen days after the MH episode that confirmed the patient's MHS. This patient had undergone two prior surgical procedures under a general anesthetic with no problems, although the anesthetics given were not known. Approximately 90 minutes into the procedure using sevoflurane anesthesia, the end-tidal carbon dioxide increased to 60 mm Hg despite increases in minute ventilation. The temperature elevated to 36.8 degrees centigrade and no other clinical symptoms were noted. Muscle tone remained normal. This case is the first found in the literature of sevoflurane-induced MH confirmed by a positive in vitro test.

Additionally, in this case, no other known MH-triggering agents were used. According to the authors, prior to this case, three other pediatric cases of MH had been reported using sevoflurane anesthesia but no muscle biopsy had been obtained. In this case, the initial symptoms were an increase in end-tidal carbon dioxide.

Summary

MHAUS was founded in 1981 by a small group of individuals with a personal interest in treating MH. In 1995, MHAUS merged with the North American Malignant Hyperthermia registry to bring together MH data in one organization and allow for focus in critical research and clinical initiatives. Presently MHAUS is the only association in the United States dedicated specifically to the research and treatment of malignant hyperthermia (MHAUS, 1997). Internationally there are six MH associations and eight dedicated international hot lines for the consultation and treatment of MH (Wald, 1993).

In 1971, the first international symposium on MH was held in Toronto (Rosenberg et al., 1997). Then in 1996, the field of MH had progressed to the point to where the third international symposium on MH was held in Hiroshima, Japan and involved 21 countries (MHAUS, 1996).

Research in the last three decades not only has increased our knowledge of malignant hyperthermia, but also has generated many questions about the wide variability of presenting signs and symptoms, triggering-agents and factors, as well as the genetic differences. Episodes of MH have been reported in certain patients with a history of multiple uneventful triggering anesthetics. The study conducted by Strazis and Fox (1993) of 503 cases of MH emphasized that a wide variability exists in the presentations of MH, the triggering agents, and epidemiology. Individual case reports have shown that the clinical presentations of MH can be different depending on the volatile anesthetic used. Non-clinical studies have shown that MHS swine as well as the results of muscle biopsy demonstrate a wide variability when exposed to different anesthetics. McCarthy's study (1997) comparing the clinical differences among the different anesthetics demonstrated that there is a wide variability in time of onset and clinical symptoms among the different anesthetics. In this study, a comparison will be done using the newer anesthetics as well as the older ones currently in use. By looking at end-tidal carbon dioxide levels, this information may provide a better understanding of the pathophysiology of MH, the presenting signs and symptoms, and the variations among the different volatile anesthetics.

CHAPTER III: METHODOLOGY

Introduction

Variability exists in clinical signs and symptoms as well as onset of the MH episode. The purpose of this retrospective descriptive study was to identify if there is a difference in the onset and severity of signs and symptoms of malignant hyperthermia in patients who received halothane, enflurane, isoflurane, desflurane, and sevoflurane. Necessary measures were taken to ensure complete confidentiality of human subjects.

Research Design and Procedure

This study used a comparative descriptive research design. A retrospective review of records obtained from the muscle biopsy center at the Uniformed Services University of the Health Sciences anesthesiology department was done. The data collected was used to determine if there was a difference in onset and severity of signs and symptoms of MH episodes with halothane compared to MH episodes of four other volatile anesthetics. The investigator reviewed all records of patients who were confirmed as MH susceptible by the muscle biopsy center starting in alphabetical order. The investigator reviewed only those patients who tested positive by the caffeine halothane contracture test. Only those patients who had a volatile anesthetic with halothane, enflurane, isoflurane, desflurane, or sevoflurane were included in the sample. A total of 47 patients were included in the sample.

A data collection sheet was used to obtain descriptive and scientific data and will be kept by the investigator for five years (see Appendix A). A separate data sheet was used for each patient. The variables of highest temperature, highest end-tidal carbon dioxide, time from beginning of the anesthetic until the initial MH treatment, time of onset of first

symptoms, and the incidence of masseter spasm for the MH episodes that were reported was described in this study. The use of succinylcholine was recorded, as it is a known MH trigger that increases incidence of masseter spasm (Gronert & Antognini, 1994). However, this drug was not included in this descriptive study other than for statistical purposes and additional data.

Records from the database at the MH muscle biopsy diagnostic center in the Uniformed Services University of Health Sciences (USUHS) anesthesiology department was used. The medical director of the muscle biopsy center reviewed all patient records and muscle biopsies. Personnel at this database maintain patient records, and gather data specific to the muscle biopsy center. Reports were sent to the muscle biopsy center and the North American Malignant Hyperthermia Registry by anesthesia care providers following a suspected MH episode on a standardized form. The original form is sent to the MH Registry and a copy is kept at the USUHS muscle biopsy diagnostic center. Other pertinent patient information including anesthetic records, narrative summary, and the results of the skeletal muscle biopsies are included in the USUHS database.

Permission was granted from the director of the muscle biopsy center to proceed with the study. A proposal was sent to and approval for this study was obtained from the Uniformed Services University of the Health Sciences Institutional Review Board.

Sample

The study population was derived from the MH muscle biopsy diagnostic center at the Uniformed Services University of Health Sciences (USUHS). The investigator reviewed all USUHS muscle biopsy center records. The following patients were excluded from the study:

- Patients who did not receive a muscle biopsy
- Patients with no recorded exposure to volatile anesthetics
- Patients with incomplete muscle biopsies due to various factors such as surgical technique or age
- Patients with a muscle biopsy not reviewed and validated by medical director or designee
- Patients who had a nonstandard MH test (European protocol, different caffeine dose)

Measurement

From those identified in the sample, five groups of patients exposed to halothane, enflurane, isoflurane, desflurane, and sevoflurane were identified. For each of the five groups, the following were identified:

- Date of occurrence of MH episode
- Age
- Sex
- Highest recorded temperature during MH episode
- Highest recorded end-tidal carbon dioxide
- Time from beginning of anesthetic until first MH symptom as identified by the clinical indicators used in the MH grading scale (Larach et al., 1994)
- Time from beginning of anesthetic until initial MH treatment as determined by discontinuation of the volatile anesthetic
- Presence of masseter spasm as determined by anesthesia provider caring for patient and recorded on anesthetic record or patient record

These data were put into table form with the variables listed vertically and the volatile anesthetics listed starting at the top horizontally for statistical analysis. The research data collection tool was minimally modified from the instrument used by McCarthy (1997) and was used with permission of the investigator of McCarthy's study. Modifications of the data collection tool were done to accommodate this study information such as end-tidal carbon dioxide in lieu of arterial blood gases and to add a space for comments and a space for the administration of succinylcholine. The investigator in McCarthy's study reviewed the additional information and modified tool for content and construct validity. According to Burns and Grove (1997), validity of an instrument is a determination of the extent to which the instrument actually reflects the abstract construct being examined (P. 330). As this tool was previously used by an investigator in a similar study (McCarthy, 1997), validity has previously been established. For this study a reliability coefficient of .80 is used. According to Burns and Grove (1997), this score is considered an acceptable coefficient for a well-developed instrument. For a newly developed instrument, a coefficient of .70 is also considered acceptable.

Any other pertinent information such as use of other medications and the administration of succinylcholine was included in the comments section of the data collection tool used for this study (see Appendix A). The administration of succinylcholine was included as it is a well-known trigger of not only MH but of masseter spasm (Rosenberg, 1996). Although the effects of this agent is not included in this study, whether or not this drug was utilized may affect the degree or presence of masseter spasm (Gronert, 1995).

Protection of Human Rights

A proposal was developed and submitted to the Uniformed Services University of Health Sciences Institutional Review Board for review and approval prior to beginning the investigation. The data collection tool contained no identifying data. Only demographic data such as age or the variables were used in any published or non-published work regarding this study. The data collection tool will be kept in a secured file at USUHS according to protocol.

Statistical Analysis

A power analysis was performed prior to the study. According to Kraemer and Thiemann (1987) at a .01 significance level, 80% power, it was determined that the minimal sample needed was a sample size of 40. According to Goodwin (1984), power analysis is appropriate when a one-way analysis of variance (ANOVA) is used. In this study the t-test and ANOVA were utilized for statistical analysis. A preliminary review of the muscle biopsy data records prior to starting the study determined that at least 42 records would be available for this study.

Descriptive statistics were performed for the demographic data of ages and number of cases and are discussed further in chapter four. An analysis of variance (ANOVA) was performed to determine if there is a statistically significant difference between the halothane group and each of the other groups. The variables of highest temperature, highest end-tidal carbon dioxide, time from onset of anesthetic until first MH symptom and time from onset of anesthetic until initial treatment for MH were used in the statistical testing. The data collected were coded and processed. An analysis of variance (ANOVA) was performed to determine if there is a statistically significant difference

among the different groups for the incidence of masseter spasm. The appropriate statistical significance level chosen for this study is $p < 0.05$ (Rankin & Esteves 1996). According to Burns and Grove (1997) the ANOVA is flexible in that it can examine data from two or more groups and is considered a much more rigorous approach to statistical analysis than other tests such as regression analysis.

Summary

This study was conducted using a retrospective chart review to determine the influence of volatile anesthetics on incidence and severity of MH episodes. The study consisted of all patients receiving a volatile anesthetic with a positive muscle biopsy. According to Allen, Larach, and Kunselman (1998), the caffeine halothane contracture test is the only generally recognized test for the laboratory diagnosis of malignant hyperthermia (p. 579). Only those patients referred to the MH muscle biopsy diagnostic center at the Uniformed Services University of Health Sciences were included in the sample. Although it is well established that the incidence of MH is much higher in children (Allen, 1994), those pediatric patients who did not receive a muscle biopsy were not included in the sample. Further information and discussion relating to the findings of this study will be presented in chapter four.

CHAPTER IV: DATA ANALYSIS

Introduction

In this retrospective study, 298 charts were reviewed to determine the effects of different volatile anesthetics on the onset and severity of signs and symptoms of malignant hyperthermia in MH-susceptible patients. The original study design included the volatile anesthetics, halothane, enflurane, isoflurane, desflurane, and sevoflurane. Of the charts reviewed, a sample of 47 patients was obtained. These patients were first identified by referral to the Anesthesiology Department of the Uniformed Services University of the Health Sciences (USUHS). The USUHS muscle biopsy center is one of ten diagnostic laboratories in the United States for the evaluation of potential MH susceptible patients (Biscardi et al., 1985). A standardized form is submitted from The North American Malignant Hyperthermia Registry. These 47 patients were identified as MH susceptible as confirmed by a positive caffeine halothane skeletal muscle contracture test (CHCT). As discussed in chapter three, the CHCT is the only recognized laboratory test to diagnose malignant hyperthermia (Allen et al., 1998). Many of the other charts reviewed had the classical signs of MH as listed by Rosenberg (1996) and the Malignant Hyperthermia Association (MHAUS, 1997) such as intense muscle rigidity, rapid increase in metabolism, hyperthermia, tachycardia, and elevated end-tidal CO₂. However, due to the absence of the CHCT, these charts had to be excluded.

The original goal of the study was to obtain a sample of at least 10 patients in each group that received the volatile anesthetics, halothane, enflurane, isoflurane, desflurane, and sevoflurane. Unfortunately, the data bank at USUHS did not contain any muscle biopsies from patients receiving the volatile anesthetics, desflurane or sevoflurane. Several consults and narrative

summaries regarding patients receiving these two anesthetics had been obtained, but no muscle biopsies had been done to confirm the diagnosis of MH. As discussed, it was necessary to exclude these records from the study. Of the charts reviewed, 21 patients (45.7%) were in the halothane group, 21 patients (45.7%) were in the isoflurane group, and 4 patients (8.7%) were in the enflurane group. The first record reviewed was used as a pilot study to assess the data collection tool. This record data was discarded and results were not used in the study. Of the patients in the enflurane group, all four patients (100%) had received mask induction anesthesia using halothane. Post-induction, the patients were switched to enflurane. For purposes of this study, the patients who received two different anesthetics were grouped into the type of anesthetic received post mask-induction and for the primary anesthetic. A significantly larger sample of pediatric patients receiving volatile anesthetics and documented clinical symptoms suggestive of MH was observed in preliminary chart review of the data bank. However these patients were excluded from this study due to the absence of a muscle biopsy confirming the diagnosis of MH.

Study Sample Demographics

For data analysis, the groups were labeled numerically: (1) Isoflurane, (2) Halothane, and (3) Enflurane. The isoflurane and halothane groups were similar with respect to age and age ranges (See Table 1). The enflurane group had the lowest mean age (17.0 years), but this group consisted of only a small sample of four patients, so this is not statistically significant (Kraemer & Thiemann, 1987).

Table 1.**Average Patient Age When Malignant Hyperthermia Episode occurred**

	Isoflurane	Halothane	Halothane/Enflurane
N	21	21	4
Age (years)	23.7	19.9	17.0
Range	10-40	10-44	12-19

The gender results were relatively similar (see Table 2). The isoflurane group had three females (14.28%) and 18 males (85.72%). The halothane group had four females (19.0%) and seventeen males (81%). The enflurane group had one female (25%) and three males (75%).

Table 2**Gender Data Breakdown of Percentages in Each Group**

	Isoflurane	Halothane	Halothane/Enflurane
N	21	21	4
Males	18	17	3
Females	3	4	1

Analysis of Data

As there were no patients to include in a desflurane or sevoflurane group, these anesthetics were not included in the comparative data analysis. A complete data analysis presentation of all variables is included (see Table 3). As discussed previously, a comparison was done with halothane compared to isoflurane and as compared to enflurane. Although multiple comparisons were done using several different ANOVA, only the Bonferroni is presented here. The Tukey HSD, Scheffe, LSD, Sidak, Gabriel, and Hochberg tests were all run using the SPSS system. However despite the wide variability of tests used to analyze data, the results are relatively the same.

Table 3

Analysis of Data Using ANOVA

Variable	Anesthetic	Anesthetic	Mean Diff.	Std. Error	Significance
Temperature	Halothane	Isoflurane	(-) .4905	.350	.505
	Halothane	Enflurane	.8738	.619	.495
ETCO2	Halothane	Isoflurane	(-) 6.9524	3.804	.224
	Halothane	Enflurane	(-) 6.6548	6.725	.984
First S/S	Halothane	Isoflurane	(-) 32.8571	35.861	1.000
	Halothane	Enflurane	9.3810	63.393	1.000
Treatment	Halothane	Isoflurane	(-)59.8571	42.771	.507
	Halothane	Enflurane	(-) 15.5000	75.608	1.000

Of the 47 patients included in the sample, 46 were used for data analysis. The mean recorded highest temperature for all groups was 38.27 degrees centigrade (see Table 4). The range for all groups as a whole was 36.7 degrees centigrade to the highest temperature of 40.7 degrees centigrade. The highest temperature recorded was in the isoflurane group (40.7 degrees centigrade). The enflurane group had the least variation of temperature ranges (37.00 to 37.70 degrees centigrade). The isoflurane group had the widest temperature ranges recorded (36.70 to 40.7 degrees centigrade). The mean temperature for the isoflurane group was 38.61 degrees centigrade compared to the halothane group (38.12 degrees centigrade) and the enflurane group (37.25 degrees centigrade). The mean temperature of the halothane group was found not to be statistically significant as compared to the other two groups (Scheffe ANOVA).

Table 4

The Mean Highest Recorded Temperature (⁰C) During MH Episodes

Anesthetic	N	Mean	S.D.	Std. Error	Minimum	Maximum
Isoflurane	21	38.61	1.34	.2912	36.70	40.70
Halothane	21	38.14	.9859	.2151	36.80	40.00
Enflurane	4	37.25	.3109	.1555	37.00	37.70

The highest mean recorded end tidal CO₂ for all of the groups was from 52.85 mm Hg with a range of 35.0mm Hg to 91.0 mm Hg. The mean highest end tidal carbon dioxide for the isoflurane group was 56.04 mm Hg with a range of 39.0 to 91 mm Hg.

The isoflurane group had the widest variability of range. The mean highest end tidal CO₂ for the halothane group was 49.09 with a range of 35.0 to 84.0. The enflurane group had the least amount of variability with a mean end tidal carbon dioxide of 55.75 and a range of 38.0 to 65.0. The mean highest recorded end tidal CO₂ was found to be not statistically significant in any of the groups (see Table 5).

Table 5.

Mean Highest Recorded End Tidal CO₂ During MH Episodes

Anesthetic	N	Mean	S.D.	Std. Error	Minimum	Maximum
Isoflurane	21	56.04	13.26	2.89	39.00	91.00
Halothane	21	49.09	11.38	2.48	35.00	84.00
Enflurane	4	55.75	12.07	6.03	38.00	65.00

The mean time from the beginning of the anesthetic until the time of the first recorded MH symptom in all groups was 98.56 minutes with the mean time of treatment of 130.67 minutes. The minimum time recorded was two minutes from the beginning of the anesthetic until the start of symptoms (Equally divided between the halothane and isoflurane group) and the maximum-recorded time was 480 minutes (halothane group). The minimum time recorded for time of treatment in all groups was three minutes with a prolonged time of 650 minutes (isoflurane group). The mean time from the beginning of the anesthetic until the time of the first recorded MH symptom for the isoflurane group

was 117.24 minutes, 84.38 in the halothane group, and 75.0 minutes in the enflurane group (see Table 6). The time from the beginning of the anesthetic until the appearance of the first MH symptom was found to be not statistically significant in any of the groups.

Table 6.

Time in Minutes (Mean) from the Beginning of the Anesthetic Until the Appearance of the First Malignant Hyperthermia Symptom

Anesthetic	N	Mean	S.D.	Std. Error	Minimum	Maximum
Isoflurane	21	117.24	118.27	25.81	2.00	395.00
Halothane	21	84.38	121.27	26.46	2.00	480.00
Enflurane	4	75.00	47.44	23.72	30.00	135.00

The time from the beginning of the anesthetic until the initial treatment for MH was documented in all records reviewed (46 records). The time until the initial treatment for MH was 102 minutes for the halothane group, 117.5 minutes for the enflurane group, and 107.3 minutes for the isoflurane group (see Table 7). The time from the beginning of the anesthetic until the time of initial treatment for MH (as identified as discontinuation of the volatile anesthetic) was found to be not significant statistically for the halothane group compared to the enflurane group and the isoflurane group.

Table 7.

Time (Minutes) from the Beginning of the Anesthetic Until the Initial Treatment for Malignant Hyperthermia

	Halothane	Isoflurane	Halothane/Enflurane
N	21	21	4
Time	102.0	161.8	117.0
Range	3 — 480	14 — 650	35 - 165

The overall incidence of masseter muscle spasm during and MH episode was 37.0 %.

The incidence of masseter muscle spasm during a MH episode was 0.33 % for the isoflurane group, 0.47% for the halothane group, and no occurrences in the enflurane group. The incidence of masseter muscle spasm was found to be not statistically significant in the halothane group compared to the isoflurane and the enflurane group.

Summary

Of the 46 MH episodes reported to the USUHS data bank, the majority of the patients received either halothane or isoflurane. Patients that were given enflurane were younger on the average than the other two groups. The mean age for the enflurane patients was 17 years old. The halothane group means age was 19.9 and the isoflurane group was 23.7 years old. Each null hypothesis was accepted based on utilization of the ANOVA. Based on the results of this study, there were no significant differences in the highest temperature, highest recorded end-tidal CO₂,

time of onset of symptoms, time of treatment, nor the incidence of masseter muscle spasm in any of the groups. As there is a tremendous variability in presenting signs and symptoms (Larach et al., 1994), the results of this study are puzzling and can only be explained in light of the same equal variability of statistical tests used in some of the studies. Additionally, as this was a relatively small sample size with only three of the volatile anesthetics, this researcher suggests that this study be duplicated in the future with a larger sample size utilizing all five of the volatile anesthetics.

CHAPTER V: SUMMARY

Introduction

Malignant hyperthermia (MH) is an uncommon inherited disorder of skeletal muscle in which commonly used anesthetics can trigger sustained skeletal muscle hypermetabolism in patients who may have had no symptoms previously (Larach et al., 1994). Since the first case described by Denborough and Lovell (1960), great progress has been made in the identification of MH-susceptible patients and the methods of treatment. Clinically there is a high degree of variability in both the signs and symptoms and presentation of MH. The purpose of this study was to examine the variability of clinical responses in those patients with a MH reaction triggered by the volatile anesthetics. The original goal was to describe the responses of patients receiving halothane, enflurane, desflurane, isoflurane, and sevoflurane. Although sevoflurane is now being used very commonly in pediatric patients, most of this data was not used in this study due to the absence of a skeletal muscle biopsy. Additionally, desflurane data was not utilized due to the absence of patients in this data bank receiving this volatile anesthetic.

Conclusions

From the data bank at USUHS, 298 records of MH-susceptible patients who had received a volatile anesthetic, a positive CHCT and a documented MH episode were reviewed. These records were used to determine the effects of the different volatile anesthetics on the onset and severity of signs and symptoms of MH. The original study design included all five of the volatile anesthetics. However as mentioned previously, only the anesthetics halothane, enflurane, and isoflurane were used due to lack of

subjects. From the 298 records reviewed, a sample of 47 patients was obtained. Although halothane is typically used in the pediatric age group due to inhalation inductions (Miller, 1994), the enflurane group had the lowest mean age (17.0 years). However since the majority of the pediatric patients had to be excluded due to absence of a caffeine-halothane contracture test (CHCT), the data is skewed from what is normally used in clinical practice. The CHCT is the only generally recognized test for the laboratory diagnosis of MH (Allen et al., 1998). As was expected, the enflurane group was the smallest as it has been used less frequently now with the introduction of newer anesthetics (McCarthy 1994). Although there were no records that were used in the sevoflurane and desflurane group, additional data may be available for future studies as both of these agents are used very commonly now compared to other volatile anesthetics (Miller, 1994).

The gender results were all relatively similar and reflected what would be expected in a data bank consisting of active duty personnel and dependents. According to Biscardi et al.,(1985), the population at greatest risk for MH is young males, having a reported incidence of 1:10,000 to 1:50,000. The gender results are also very similar to the study performed by Allen et al, (1988). In this study, more than 51% were male. However the mean age was much higher (53 years) in Allen s 1998 study.

The average highest temperature was not statistically significant among the three groups. The highest temperature recorded was in the isoflurane group (40.70). This group also had the highest mean temperature (38.61). This correlated well with the data found in McCarthy s study (1997). As discussed by McCarthy, the likely explanation is with the advent of end-tidal CO₂ monitoring and the drug dantrolene. Elevated end-tidal CO₂ is

now considered the earliest and most valuable symptom of MH (Kaplan, 1997). With this advent, dantrolene is started much earlier and temperature elevations are typically not seen as much. This also correlates well with the study conducted by Karan and Greenberg (1997) in which hyperthermia was considered to be a late sign of MH. In the study conducted by O Flynn and colleagues (1994) hyperthermia was not observed in any of the 70 patients studied. Karan and Greenberg (1997) hypothesized that the volatile anesthetics can alter the thermoregulatory responses. Rosenberg (1996) also stated that hyperthermia is considered a very late sign, although would be a very specific clinical symptom. According to Kaplan (1997) early treatment can prevent the signs of hyperthermia and acidosis from occurring.

The highest mean recorded end tidal CO₂ for the groups was highest in the isoflurane group. However with statistical analysis, although clinical significant, was not statistically significant ($p < .005$). The mean highest end tidal carbon dioxide was highest in the isoflurane group (56.04) and lowest in the halothane group (49.09). The highest end tidal CO₂ recorded was in the isoflurane group (91.00). These results also correlate with McCarthy's study (1997) in which there were no significant differences. The researcher in McCarthy's study suggested that end tidal CO₂ values rather than arterial carbon dioxide values might yield a different result when studied. The results of this study indicate that there are no significant differences when using end tidal carbon dioxide rather than arterial carbon dioxide. This correlates with the results of McCarthy's study as well.

The onset of MH is faster in the enflurane group (75.0 minutes) compared to the halothane (84.38 minutes) and the isoflurane (117.24 minutes) group. This, as discussed

previously, was measured by the time from the beginning of the anesthetic until the first MH symptom. The MH symptoms were identified by the clinical indicators used in the MH grading scale (Larach et al., 1994). However when using statistical tests, this was not statistically significant through one-way ANOVA. These results do not support the study conducted by McCarthy (1997). However the differences in the two studies may relate to differences in statistical tests used. In this study as well as the one conducted by McCarthy different statistical tests were used. This study used one-way ANOVA whereas the researcher in McCarthy's study used unpaired t-test. Additionally, this does not correlate with the study conducted by O Flynn et al. (1994). In that study, all of the 70 patients developed clinical signs of MH within ten minutes. However that data may have been skewed as the researchers were specifically targeting subjects and looking for specific signs and symptoms of MH.

The time from the beginning of the anesthetic until the initial treatment for MH was shortest in the halothane group (102 minutes) and longest in the enflurane group (117.5) minutes. The longest time of treatment was in the isoflurane group (650 minutes). The results possibly correlate with the fact that the halothane group may have had more pediatric patients. The threshold to treat this population may possibly have been lower as compared to an adult population.

The overall incidence of masseter muscle rigidity (MMR) or (trismus) was 37.0% for all groups. The enflurane group did not have a patient developing MMR and the halothane group had the highest percentage (47.0%). According to O Flynn et al. (1994), the overall incidence of masseter muscle rigidity occurs in 0.3-1.0% of all pediatric patients receiving halothane and succinylcholine. The incidence here is much higher than

those statistics and may reflect the fact that no distinction was made as to whether or not the patient received succinylcholine versus a group of patients not receiving succinylcholine. Additionally as discussed previously, this population consisted of very few pediatric patients. Only six subjects in this study were twelve years of age or younger. The youngest subject was ten years old. The results of this study correlated well with the results in McCarthy's study (1997) in which the incidence of MMR was highest in the halothane group there as well (66%). As most of the subjects in this study were over the age of twelve, the data here may be skewed. According to Littleford et al. (1991), the incidence of MMR is most common in the children of age group 8-12 years of age. Since most of this age group was excluded from this study due to absence of muscle biopsy, much of this data was not collected.

Limitations of Study

This study was a retrospective study of a preexisting database in various clinical settings in North America. As the database consisted of most active duty personnel and few dependents, the age and gender may reflect the population demographics seen in the military rather than a random sample population. Additionally, although pediatric data was available, most of this had to be excluded due to the absence of a CHCT. This study did not correlate MMR with the use of succinylcholine. A future study should be conducted to determine if this correlates and is statistically significant. Patients receiving the volatile anesthetics sevoflurane and desflurane were not used in this study. Although there were several patients referred to the muscle biopsy center, the absence of a CHCT warranted that these patients were excluded. More recent studies in humans indicate that desflurane has been implicated. However the episodes were not validated with a muscle

biopsy (Fu et al., 1996; Michalek-Sauberer et al., 1997). In both case reports, there was a wide variability of clinical signs and symptoms. This study was not able to validate or compare results due to the absence of any patients with a positive CHCT receiving this anesthetic. In the case report done by Ochiai et.al, 1991) sevoflurane has also been implicated. As there were no patients in this database with a positive CHCT receiving sevoflurane, this study was not able to confirm or study the clinical signs and symptoms of these patients.

Additionally, this study made assumptions that clinical signs and symptoms such as MMR are interpreted the same among all anesthesia providers. According to Kaplan (1997), there are three various clinical presentations of MMR. This study made no distinction among any of these nor was there a notation to document this. Other assumptions made in this study was that the time of onset and time of treatment was recorded accurately. In many cases, during the clinical crisis, factors such as time are extrapolated and may not accurately reflect the reality. This study assumes that the times used are completely accurate. During a crisis, such as MH, times recorded may be assumed or merely extrapolated from the sequence of events.

Implications for Nursing

Based on the results of this study, the time of onset of MH may be delayed in those patients receiving isoflurane. As discussed in a previous study, the time of onset may be delayed as much as six hours or more (DeRuyter et al., 1995). Other studies such as those conducted by Smith et al., (1997) suggest that patients receiving isoflurane may not manifest fulminant MH until much later in the clinical course. Although the findings in the study conducted by this researcher are not statistically significant, they do have

clinical implications. With delayed triggering such as that which occurs with isoflurane, the anesthesia provider can be more alert to subtle signs and symptoms even later on in the case. With the knowledge that halothane may manifest much earlier than isoflurane, the anesthesia provider can be more alert to the possibility of a wide variation in time of onset or other clinical symptoms. This study validated other previous studies that suggest that a wide variability of clinical signs and symptoms exist. Additionally, hyperthermia may not be evident until much later in the pathophysiological pathway. With the knowledge that such a wide variability exists in the patient with MH, the anesthesia provider can utilize the more reliable earlier sign of elevated end tidal carbon dioxide. This study validates once again that end tidal carbon dioxide is an early and reliable symptom even in the absence of hyperthermia.

Suggestions for Future Studies

The malignant hyperthermia data bank at the Uniformed Services University of Health Sciences contains a wealth of information within the 400 records reviewed preliminarily. As discussed previously, much of the pediatric data was not utilized. This study could be replicated again at a future time frame with the hopes of obtaining not only additional pediatric data, but also inclusion of the newer volatile anesthetics. A descriptive study using the pediatric data would be useful and may include a larger amount of variability affecting the findings than seen in this study. Since this study used different statistical tests than some of the previous studies, this study should be replicated using a bigger population, all five of the volatile anesthetics and the same statistical tests as used by this researcher.

A future study might be performed using the different volatile anesthetics and

comparing the results among different age groups and gender. The age distribution of findings such as highest temperature, end tidal carbon dioxide, and masseter spasm would be useful information. This study should be replicated with the larger malignant hyperthermia database incorporating all muscle biopsy centers. The study should utilize only end tidal carbon dioxide rather than arterial blood gases.

While reviewing the data at the muscle biopsy center at USUHS, many episodes of unexplained significant temperature increases and rhabdomyolysis were referred to the center. A future study might focus on a description of these incidents and correlation of any variables or family history.

Summary

This is not the first study to describe the variability of MH episodes among the volatile anesthetics. Several studies have been conducted using a variety of statistical tests. Since multiple statistical tests have been used, it is difficult to correlate the results of this study with any previously. Additionally, only three volatile anesthetics were used due to the lack of sample population. Although much of the results here were not statistically significant, there are clinical implications for the anesthesia provider. This study does demonstrate that a wide variability does exist in signs and symptoms. Additionally, this study correlates very well with the recommendations previously stated by MHAUS regarding end tidal carbon dioxide. Although the null hypothesis was not disproved in this study, hopefully further research studies will help anesthesia providers better understand not only the pathophysiology and cellular mechanisms of malignant hyperthermia, but will provide a clearer insight into the clinical signs and symptoms.

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APPENDIX

Data Collection Sheet

APPENDIX

Data Collection Sheet

Case Number:	Halothane	Enflurane	Isoflurane	Desflurane	Sevoflurane
Type of Anesthetic					
Age/Sex:					
Highest Temperature					
Highest ETCO ₂					
Time of First MH symptom					
Time from beginning anesthetic until initial treatment					
Masseter Spasm					
Succinylcholine given					

Comments: