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Clinical experiences of malignant hyperthermia encountered by Thai anesthesiologists

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Objective : *To survey the clinical memorable experiences, which were suggested to intraoperative malignant hyperthermia (MH) among Thai anesthesiologists.*

Material and Method : *Questionnaires for a national survey of dantrolene requirement were sent by the Royal College of Thai Anesthesiologists (RCAT) to all Thai anesthesiologists (855 members) in 2007. One hundred and two (11.93%) questionnaires were returned. There were 25 anesthesiologists (24.51%), who had experiences of suspected MH events. All of them were later included for an interview by phone. The questions consisted of which part of the region the hospital is located in, the number of MH events, clinical manifestations, problems in the diagnosis and management, the outcomes in terms of mortality and medico-legal aspect, and preventive strategy for MH.*

Results : *The most frequent clinical signs of MH were inappropriate sinus tachycardia (100%), masseter spasm (84%), rapid increase in body temperature (64%), and generalized muscular rigidity (44%). Only*

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half of the suspected MH patients were monitored with capnogram. About one-third (32%) of the patients received dantrolene. Acidosis was corrected in nearly two-thirds (60%) of the suspected MH patients. The mortality rate of MH was 36%. One anesthesiologist (4%) encountered litigation problem from a fatal case. Family counseling was conducted in 84% of cases. Suggestions from anesthesiologists, who experienced MH were expansion and publicity of dantrolene-stored hospitals, and more education programs on MH.

Conclusion : *Although MH is a rare condition, it induces high mortality which potentially brings in the litigation. Earlier detection and shorten the time until the initial dantrolene administration should be acquired.*

Keywords : *Malignant hyperthermia, Dantrolene, Thai.*

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วัตถุประสงค์ : *เพื่อศึกษาขนาดของปัญหา MH จากประสบการณ์การทำงานของวิสัญญีแพทย์ไทย ความสามารถในการตรวจวินิจฉัยด้วยอาการทางคลินิก การดูแลรักษาผู้ป่วย การเสียชีวิต และการให้คำแนะนำแก่ญาติสายตรง*

วิธีการ : *หลังจากที่ราชวิทยาลัยวิสัญญีแพทย์แห่งประเทศไทย ได้ส่งแบบสำรวจการบริหารจัดการ dantrolene ไปยังสมาชิกวิสัญญีแพทย์ทั่วประเทศ จำนวน 855 คน แล้วได้รับการตอบแบบสอบถามกลับมาทั้งสิ้น 102 คน ในจำนวนนี้มี 25 คน เคยพบผู้ป่วยที่มีอาการแบบ MH ผู้วิจัยจึงทำการศึกษาเชิงพรรณนาโดยสัมภาษณ์แพทย์ทั้ง 25 คน ทางโทรศัพท์ถึงประสบการณ์ที่เคยพบอาการแบบ MH ในระหว่างการดมยาสลบ โดยครอบคลุมถึงลักษณะอาการ การรักษาภาวะแทรกซ้อน ปัญหาการวินิจฉัยและการรักษา ผลลัพธ์ของการรักษา และ การเฝ้าระวัง*

ผลการศึกษา : *อาการผิดปกติที่ตรวจพบในผู้ป่วยทุกรายที่สงสัยว่าเป็น MH คือ อัตราการเต้นของหัวใจเพิ่มขึ้นโดยอธิบายสาเหตุไม่ได้ (ร้อยละ 100) ซึ่งพบร่วมกับอาการเกร็งของกราม ร้อยละ 84 อุณหภูมิร่างกายเพิ่มขึ้นอย่างรวดเร็ว ร้อยละ 64 อาการกล้ามเนื้อลายแข็งเกร็ง ร้อยละ 44 โดยมีการตรวจวัด End-tidal carbon dioxide เพียงร้อยละ 50 สำหรับการตรวจค่าทางห้องปฏิบัติการ (ระดับโปตัสเซียมและ creatinine phosphokinase ในเลือด และระดับ myoglobin ในปัสสาวะ) พบว่ามีความผิดปกติประมาณร้อยละ 40 - 60 ส่วนทางด้านการดูแลรักษาผู้ป่วยพบว่ามีการให้ dantrolene เพียงร้อยละ 32 และมีการแก้ไขภาวะ acidosis เพียงประมาณร้อยละ 60 โดยระหว่างการดูแลรักษามีผู้ป่วยเสียชีวิต ร้อยละ 36 ซึ่งพบปัญหาเรื่องการฟ้องร้องจากญาติผู้ป่วย 1 ราย ส่วนการให้ความรู้เกี่ยวกับโรคและการถ่ายทอดทางพันธุกรรมแก่ผู้ป่วยและญาติ คิดเป็น ร้อยละ 84 สำหรับข้อเสนอแนะโดยรวมพบว่าสมาชิกราชวิทยาลัยวิสัญญีแพทย์ส่วนใหญ่ต้องการให้มีการสำรองยา dantrolene ในปริมาณเพิ่มขึ้น และมีการประชาสัมพันธ์ว่าจะขอยาใช้รักษาเบื้องต้นได้จากโรงพยาบาลใดบ้าง รวมถึงจัดให้มีการฝึกอบรมเพื่อเพิ่มพูนความรู้แก่วิสัญญีแพทย์และพยาบาลให้มากขึ้น*

สรุป : *จากการสอบถามประสบการณ์ของวิสัญญีแพทย์ไทย พบว่ามีจำนวนผู้ป่วยที่มีอาการแบบ MH สูงกว่าอัตราการเกิด MH ที่เคยรายงานและเริ่มเป็นปัญหาการฟ้องร้อง จึงควรมีการพัฒนาและปรับปรุงระบบการดูแลรักษาผู้ป่วยที่เกิด MH และจัดระบบการบริหารจัดการยา dantrolene ให้ได้มาตรฐาน รวมถึงการอบรมให้ความรู้แก่บุคลากรทางวิสัญญีและผู้เกี่ยวข้องให้มากขึ้น*

คำสำคัญ : *Malignant hyperthermia, Dantrolene, ไทย.*

Malignant hyperthermia (MH) is a rare but potentially fatal pharmacogenetic disorder of skeletal muscles that presents as a hypermetabolic crisis following an exposure to commonly-used volatile anesthetics and depolarizing muscle relaxants.[1,2] MH causes abnormal intracellular calcium regulation which is characterized by clinical signs of hypermetabolic responses including tachycardia, hyperthermia, acidosis and muscular rigidity.[1,2]

MH is caused by an autosomal dominant disorder that can also occur from spontaneous mutation.[3-5] To identify the episode a specific laboratory diagnosis involving special series of tests is required. This is possible only in some sophisticated medical centers which do not exist in Thailand. Therefore, the suspected patients are predominantly diagnosed by clinical signs and symptoms during or after anesthesia such as an abrupt change of cardiovascular system, acidosis and sudden rise of body temperature, and muscle breakdown that leads to multiple organs failure.[4-6]

Treatment of MH is often problematic due to the lack of anesthetic personnel's experience, inadequate monitoring and the lack of dantrolene storage. It is the only available specific medication nowadays. Nevertheless, the drug is costly and has short shelf life. Moreover, transferring dantrolene from the available source usually takes too much longer time. All together, these problems are potential to make the patients deteriorate shortly from their ongoing disease.[5-7]

The incidence of MH in Thailand is unclear, although there were a few case reports.[14-19] In 2003, the Royal College of Anesthesiologists of Thailand conducted the Thai Anesthesia Incidences Study (THAI Study)[8,9] of adverse outcomes in 20 hospitals and found only one MH event out of 163,403 patients undergoing anesthesia. However, this low incidence might occur from the limited number of studied hospitals which did not truly represent the entire national MH events.

This study was aimed to survey the clinical experience related to MH among anesthesiologists in Thailand in order to closely achieve the real magnitude of MH problems, and to recognize Thai anesthesiologists' problems in clinical diagnosis and treatment during a malignant hyperthermia crisis.

Material and Method

Questionnaires from the Royal College of Anesthesiologists of Thailand were sent to all Thai Anesthesiologists (855 members) in 2007 for a national survey of dantrolene requirement. As a result, 102 (11.93%) questionnaires were returned. After receiving an approval of the ethics committee of the Faculty of Medicine, Chulalongkorn University, we conducted telephone interviews of 25 anesthesiologists (24.51%) who had encountered MH in their practices. The items of the questionnaires consisted of the part of the region which the hospital is located in, the number of MH events, clinical manifestations, problems in diagnosis and management, the outcome in terms of mortality and medico-legal aspects, and preventive strategies for encountering MH. These answers were based on their first recalls of their clinical experiences from the beginning of their professional career up to the interview. Descriptive statistic was used for data analysis.

Results

Twenty-five anesthesiologists (24.51%) were interviewed. For the question about the first person who noticed and made the presumptive diagnosis of MH, 14(56%) appeared to be anesthesiologists while the rests were anesthetic nurses. However, of the 25 suspected cases, 15 cases (60%) did not report to the Royal College of Anesthesiologists of Thailand.

Regarding clinical indicators, inappropriate sinus tachycardia was the most common MH clinical sign which appeared in all cases (100%). Masseter spasm was found in 21(84%) cases and was the second most frequent clinical sign in our study. Inappropriately rapid increase in temperature (>38.8°C) were reported at 64% and 52%, respectively (Table 1).

As for muscular breakdown, elevated creatine kinase >20,000 IU after anesthetic with succinylcholine, myoglobin in urine > 60 μg/L, and serum potassium > 6 mEq/L (in absence of renal failure) were positive in 14 (52%), 12 (48%), and 15 (60%) suspected cases, respectively. In patients suspected of MH and being monitored, capnogram was used in only 11 (44%) cases, while body temperature was further continuously monitored in only 8 (32%) cases.

Table 1. Clinical indicators of malignant hyperthermia (n = 25)

Indicators	Number (%)	Not evaluated/ Not monitored (%)
Respiratory acidosis		
End-tidal CO_2 > 55 mmHg with appropriately controlled ventilation	11 (44%)	13 (52%)
Cardiac involvement		
Inappropriate sinus tachycardia	25 (100%)	0 (0%)
Ventricular tachycardia or ventricular fibrillation	4 (16%)	0 (0%)
Rigidity		
Masseter spasm	21 (84%)	1 (4%)
Generalized skeletal muscle rigidity	11 (44%)	2 (8%)
Temperature increase		
Inappropriately rapid increase in temperature	16 (64%)	2 (8%)
Inappropriately increased temperature > 38.8 ^{0}C in perioperative period	13 (52%)	18 (32%)
Muscle break down		
Serum K^+ > 6 mEq/L in absence of renal failure	15 (60%)	5 (20%)
Elevated CK > 20,000 IU after anesthetic that included succinylcholine	14 (52%)	5 (20%)
Myoglobin in urine > 60 mcg/L	12 (48%)	7 (28%)

During the acute phase of suspected clinical signs of MH, dantrolene was given to only 8 (32%) cases. All of which were supplied from the university hospitals. Almost all of the suspected cases (92%) received 100% oxygen at the flow rate of >10 L/min. Changing of the circle system and CO_2 absorber, switching volatile agents to intravenous agents, and increasing minute ventilation two times were completed in 76%, 64%, and 64%, respectively. Other supportive treatments are shown in table 2.

Concerning the problems in the diagnosis and treatment, most anesthesiologists replied they (96%) had the knowledge of the clinical diagnosis and treatment of MH. Nevertheless, only 17 (68%) of the suspected cases received intensive care treatment for closed observation after the occurrence. Late diagnosis was reported in 6 (24%) patients. Among these, two patients were given a repeated dose of succinylcholine and 4 patients were managed by nurse anesthetists without immediate supervision by any medical staff. Given that MH episodes occur, 13 (52%) suggested capnometry would be helpful and 1 (4%) answered that temperature monitoring would also be beneficial. As for the help accessibility including MH treatment protocol during the acute phase, university hospitals remained their principal source (100% answers). General hospitals could also be an alternative option (16% answers). Most anesthesiologists 23 (92%) could access the MH information website provided by the Royal College of Anesthesiologists of Thailand for emergency situations. Other available options were the Internet (72%), textbooks (68%), consulting colleagues (26%), and hospital MH guidelines (4%). Six (24%) responded questionnaires showed that the possibility and severity of MH did not receive enough concern from the hospital administrators. Therefore, they had no dantrolene prepared in the hospital stock in advance.

Table 2. Acute phase treatment of suspected cases (n = 25).

Treatment	Number of patients (%)
Prepare and administer dantrolene	8 (32%)
Change the circle system and carbondioxide absorber	19 (76%)
Discontinue volatile agents and use intravenous agents instead	16 (64%)
Administer 100% oxygen at flow of 10 L/min	23 (92%)
Increase minute ventilation two times	16 (64%)
Correct metabolic acidosis	15 (60%)
7.5% sodium bicarbonate 1-2 mEq/kg	
Correct hyperkalemia	
10 units regular insulin iv and 50 ml 50% glucose	11 (44%)
Calcium choloride 10 mg/kg or calcium gluconate 10-50 mg/kg	7 (28%)
Induce diuresis to 1-2 mL/kg/hr	7 (28%)
Cool the patients	21 (84%)

Mortality was found in 9 (36%) suspected MH cases. Two died in the operating room while the rest died later in the intensive care units. Legal problem was found in one case among the 9 patients who died. Prolonged hospitalization occurred in 2 (8%) of suspected patients who survived. Both encountered acute renal failure which finally led to hemodialysis.

For prevention of unpredictable MH occurrence, family counseling on MH knowledge was held in 21 cases (84%). Most respondents (88%) have become more confident in anesthetic management to the susceptible patients and their relatives ever since the events. The rest remained unconfident because of questioning in the personnel's ability and lack of dantrolene storage in the hospital. Suggestions from most repliers for MH management were: increase of dantrolene storage suppliers (44%), publicity for dantrolene-stored hospitals (24%) and more education programs for all involved personnel (48%).

Discussion

The hypermetabolic response of MH results in muscle rigidity, hyperthermia, and life threatening metabolic acidosis. [1,2] The mortality rate is high if undetected or without appropriate treatment. [1,7,10] So far, dantrolene is the only specific mainstay treatment commercially available which should be rapidly administered, while other supportive measures, such as cooling, correction of hyperkalemia and metabolic acidosis should also be promptly initiated.

Dantrolene has an important role in decreasing mortality rate since the US Food and Drug Administration approval in 1980. Before that, the mortality rate was as high as 70%.[1] A report from Austria[11] revealed 51 suspected cases of MH from 1975 to early 1986 with 16.4% mortality. Fifteen percent of the dead cases received dantrolene. Moreover, a study from Japan[7] reported 383 cases of fulminant MH from 1961 to 2004, with decreased the mortality rate over time from 42.3% (1981 - 1984) to 15.0% (1995-2004). They concluded that the decrease might be related to the release of dantrolene. A recent study from the North American Malignant Hyperthermia Registry (NAMHR) [12] demonstrated 4 of 291 MH events resulted in death (1.4%). However, they stated this significantly low mortality rate maybe due to underreporting or bias reporting (withholding sensitive cases). Another recent study from the United States[10] reported the mortality rates decreased from 16.9% in 2001 to 6.5% in 2005. In our study, we found 36% of mortality rate (9 of 25 cases) in which dantrolene was given to 33% of the patients. Dantrolene storage in hospital is still a major problem in our country due to economical unavailability. Therefore, most of the questionnaire responders pointed out that obtaining pre-arrangement of dantrolene by regional hospital connections should be encouraged to accelerate the process of medical treatment.

The most frequent and earliest clinical sign of MH in this study is inappropriate tachycardia along with inappropriate increase of end tidal CO_2. Therefore, capnogram is particularly beneficial for early detection of MH.[7,12] Moreover, a longer period of time between the induction of anesthesia and the maximum end-tidal CO_2 was related to increased risk of cardiac arrest/death, according to a study of NAMHR.[12] This corresponds with this study because more than half of the replies did not mention the

monitoring of end-tidal CO_2 and more than half agreed monitoring capnogram would be helpful for earlier diagnosis. Moreover, monitoring of capnogram and the body temperature were also important in clinical grading[6] scale recommended to aid the anesthesiologist's judgment, in case that there is a confusion with resemble medical conditions such as insufficient depth of anesthesia, hypoxia, hypercarbia, iatrogenic hyperthermia, thyrotoxicosis, pheochromocytoma, sepsis and neuroleptic malignant syndrome.[6]

Litigation is also an important issue. Fatal complication makes profession in anesthesia susceptible to cases of legal punishment. Our study reported 1 litigation that entailed death of a patient wherein financial compensation was given to the family by the hospital.

Limitations of our study included the limited number of the returned questionnaires. Other limitations include inconsistencies of the anesthesiologist to recall the event and lack of certain anesthetic details, records and other supporting laboratory results.

In summary, our study revealed a high MH mortality of 36%, which involved litigation (4%). Therefore, we strongly recommend more sufficient patient monitoring methods such as capnometry for early detection and every effort to shorten the time until the initial administration of dantrolene.

References

1. Denborough M. Malignant hyperthermia. Lancet 1998 Oct; 352 (9134):1131 - 6
2. Rosenbaum HK, Miller JD. Malignant hyperthermia and myotonic disorders. Anesthesiol Clin North America 2002 Sep; 20 (3): 623 - 64
3. Levitt RC. Prospects for the diagnosis of malignant hyperthermia susceptibility using molecular genetic approaches. Anesthesiology 1992 Jun; 76 (6): 1039 - 48
4. Rosenberg H, Davis M, James D, Pollock N, Stowell K. Malignant hyperthermia. Orphanet J Rare Dis 2007;2:21
5. Ali SZ, Taguchi A, Rosenberg H. Malignant hyperthermia. Best Pract Res Clin Anaesthesiol 2003 Dec;17(4):519 -33
6. Larach MG, Localio AR, Allen GC, Denborough MA, Ellis FR, Gronert GA, Kaplan RF, Muldoon SM, Nelson TE, Ording H, et al. A clinical grading scale to predict malignant hyperthermia susceptibility. Anesthesiology 1994 Apr; 80(4): 771 - 9
7. Migita T, Mukaida K, Kawamoto M, Kobayashi M, Yuge O. Fulminant-type malignant hyperthermia in Japan: cumulative analysis of 383 cases. J Anesth 2007; 21(2): 285 - 8
8. Charuluxananan S, Suraseranivongse S, Punjasawadwong Y, Somboonviboon W, Nipitsukarn T, Sothikarnmanee T, Vasinanukorn M, Werawatganon T, Tanudsintum S, Lekprasert V, et al. The Thai Anesthesia Incidents Study (THAI Study) of anesthetic outcomes: I. Description of methods and populations. J Med Assoc Thai 2005 Nov; 88 Suppl 7:S1-13
9. Charuluxananan S, Punjasawadwong Y, Suraseranivongse S, Srisawasdi S, Kyokong O, Chinachoti T, Chanchayanon T, Rungreungvanich M, Thienthong S, Sirinan C, et al. The Thai Anesthesia Incidents Study

(THAI Study) of anesthetic outcomes: II. Anesthetic profiles and adverse events. J Med Assoc Thai 2005 Nov; 88 Suppl 7: S14 - S29

10. Rosero EB, Adesanya AO, Timaran CH, Joshi GP. Trends and outcomes of malignant hyperthermia in the United States, 2000 to 2005. Anesthesiology 2009 Jan; 110 (1): 89 - 94
11. Mauritz W, Sporn P, Steinbereithner K. Malignant hyperthermia in Austria. I. Epidemiology and clinical aspects. Anaesthesist 1986 Nov; 35(11): 639 - 50
12. Larach MG, Brandom BW, Allen GC, Gronert GA, Lehman EB. Cardiac arrests and deaths associated with malignant hyperthermia in north america from 1987 to 2006: a report from the north american malignant hyperthermia registry of the malignant hyperthermia association of the United States. Anesthesiology 2008 Apr; 108 (4): 603 - 11
13. Suyama H, Kawamoto M, Yuge O. Prevention and treatment of malignant hyperthermia in certified training hospitals in Japan: a questionnaire. J Anesth 2002; 16(3): 207 - 10
14. Tantisirin O, Prasertchuang C. Malignant hyperthermia: a case report. Thai J Anesthesiol 1979 May; 6(2): 78 - 85
15. Sirivanasandha P, Tontisirin O, Chantharojsiri T, Srichinthai P, Veeranghabutr T. Malignant hyperthermia in Ramathibodi Hospital. Thai J Anesthesiol 1990 Apr; 16(2): 71 - 9
16. Poonyathaworn S, Mullikamas S, Singhapreecha S, Limuthaithip S. Malignant hyperthermia. Thai J Anesthesiol 1997 Jan - Mar; 23(1): 54 - 5
17. Vorakitpokaton P, Kongsayreepong S, Areewatana S, Suchichantararat P. Malignant hyperthermia in Siriraj Hospital. Thai J Anesth 1999 Jan - Mar; 25 (1): 63 - 8
18. Ithiapirak P. Malignant hyperthermia: a case report. Thai J Anesth 2003 Oct-Dec; 29 (4): 227 - 30
19. Sirichotvithyakorn P. Suspected malignant hyperthermia during the 6th general anesthesia: A case report. Chula Med J 2006 Sep; 50 (9): 657 - 62
20. Annas GJ. Medicine, death, and the criminal law. N Engl J Med 1995 Aug; 333(8): 527 - 30