Anesthesiology 2007; 106:901–6

Analysis of the Clinical Variables Associated with Recrudescence after Malignant Hyperthermia Reactions

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Background: **Some patients develop recrudescence after a malignant hyperthermia (MH) reaction, but it is not clear which patients are at risk. The authors analyzed clinical variables associated with recrudescence after a clinical MH episode.**

Methods: **Data were obtained from Adverse Metabolic Reaction to Anesthesia reports in the North American Malignant Hyperthermia Registry. Patients who underwent general anesthesia and with an MH clinical grading score of 20 or greater, indicating a likely MH reaction, were included in this analysis. Patient characteristics, anesthetic agents, MH reaction clinical details, and postoperative outcomes were compared in the recrudescence and no recrudescence groups using chi-square tests and Z tests for categorical variables and the Student *t* test for continuous variables. Associations of clinical variables with recrudescence were assessed with univariate and multivariate logistic regression.**

Results: **Of 308 patients, 63 (20%) had recrudescence. The mean time from initial reaction to recrudescence was 13 h (SD = 13 h). Patients with recrudescence were more likely to have a muscular body type ($P < 0.01$), malignant hyperthermia score of 35 or greater ($P < 0.01$), a temperature increase ($P < 0.01$), and more than 150 min from induction to adverse reaction ($P < 0.05$). Muscular body type, a temperature increase, and a longer time from induction to initial malignant hyperthermia reaction were associated with recrudescence on multivariate logistic regression analysis.**

Conclusions: **Recrudescence occurred in 20% of patients. Muscular body types had a higher rate of recrudescence, perhaps associated with increased muscle mass. The risk of recrudescence increased as time from induction to the initial MH reaction increased, perhaps as a result of greater muscle exposure to triggering agents.**

This article is accompanied by an Editorial View. Please see: Hopkins PM: Recrudescence of malignant hyperthermia. ANESTHESIOLOGY 2007; 106:893–4.

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Received from the Department of Anesthesiology, University of Washington School of Medicine, Seattle, Washington. Submitted for publication April 26, 2006. Accepted for publication December 19, 2006. Support was provided solely from institutional and/or departmental sources.

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MALIGNANT hyperthermia (MH) is an uncommon pharmacogenetic clinical syndrome of hypermetabolism triggered by certain anesthetic agents.[1] MH occurs as a result of abnormally increased intracellular release of calcium from the sarcoplasmic reticulum.[1–3] The pathophysiology is generally believed to involve prolonged opening of the ryanodine receptor, isoform R1 (RyR1).[4] Ryanodine receptor mutations are found in 25% of known MH-susceptible individuals in North America.[2,5] Dihydropyridine receptor mutations have also been identified in MH patients,[2,6] implicating abnormal skeletal muscle excitation–contraction coupling as the main molecular link to MH.

Dantrolene sodium, the treatment for MH, inhibits calcium release *via* RyR1 antagonism.[7,8] Although most patients with MH can be treated successfully with dantrolene,[9] recrudescence or return of the signs and symptoms of MH can occur hours after resolution of the initial event. Although recrudescence has been reported in case reports,[10–14] no formal study of clinical factors associated with recrudescence of MH has been performed. Therefore, we conducted a case–control study of data from patients in the North American Malignant Hyperthermia Registry (NAMHR) to investigate clinical variables associated with recrudescence of MH.

Materials and Methods

After approval of the University of Washington Institutional Review Board (Seattle, Washington), de-identified data were obtained from the Adverse Metabolic Reaction to Anesthesia (AMRA) reports for all 528 patients in the NAMHR database as of January 1, 2005. The NAMHR is a nonprofit, privately supported foundation established in 1987 to investigate the epidemiology of MH to improve diagnosis, treatment, and prevention of MH episodes.[15] Data for AMRAs are collected in a voluntary fashion. An anesthesiologist will call the MH Hotline to request help with management of a patient with suspected MH. If the Hotline consulting anesthesiologist is impressed that a case may be a real MH episode, the MH consultant requests that an AMRA be sent to the caller. In general, there is no record of the date of the episode and date of receipt of the AMRA (personal written communication, Barbara W. Brandom, M.D., Director, NAMHR, University of Pittsburgh, Pittsburgh, Pennsylvania, July 2006).

Reliability for submitted AMRAs is assessed in part by calls from the Registry office to the anesthesiologist if that person has put his or her name on the AMRA. There

is no attempt to obtain original source documents to support the reliability and validity of the AMRA data because it was designed to protect the confidentiality of the patient. Reliability of data entry is assessed by a double-entry system. Validity of the AMRA is demonstrated by the blinded Delphi process by MH experts used in three iterations to produce the MH clinical grading score (CGS), which indicates a suspected clinical MH event.[16] However, this represents a clinical diagnosis, and to secure the definitive diagnosis of MH susceptibility, the patient should obtain a contracture test or a genetic test to confirm his or her MH susceptibility status.

Patients were eligible for inclusion in the current analysis if they had received general anesthesia for a procedure during which the suspected MH event occurred and had an MH CGS of 20 or greater (n = 370), indicating a likely MH reaction.[16] Patients with an AMRA report code of "not applicable for MH" (n = 21) or "not MH" (n = 31) were excluded from the study. Patients who did not survive the initial MH reaction (n = 6) were also excluded, as were patients reported as not applicable for recrudescence (n = 3). We also excluded one patient with an event before 1979, the year in which dantrolene became available for treatment of MH in the United States.

Recrudescence was defined as the development of additional signs of MH after adequate treatment of the initial MH event in the opinion of the anesthesiologist on the AMRA report. Clinical signs of recrudescence included increasing heart rate, increasing minute ventilation (doubling to tripling) to maintain end-tidal carbon dioxide, and increasing temperature. A time period of 2 h after the initial MH event was used to define recrudescence. Patients who had recurrence or continuance of MH signs or symptoms within the 2-h postevent window (n = 3) were assigned to the nonrecrudescence group. The resulting data set included 308 patients, 63 with recrudescence (cases) and 245 with no recrudescence (controls).

We compared year of event, age, sex, weight, body habitus, family medical history, surgical procedures, anesthetic duration and agents, muscle relaxants, MH signs and symptoms, timing of the MH event, and dantrolene dose (single *vs.* multiple administration and initial/total dose) between patients in the recrudescence and nonrecrudescence groups. Body habitus was defined as normal, lean, muscular, obese, or other by the anesthesiologist on the AMRA report and were cross-verified with body weights by the Registry staff. Patients with normal or lean body habitus were grouped together for analysis due to overlap in weights. Patients coded as other or unknown body type on the AMRA reports were excluded from body type analysis.

Malignant hyperthermia signs and symptoms included in the analysis ("muscle rigidity," "muscle breakdown," "respiratory acidosis," "temperature increase," and "cardiac involvement") were grouped according to the MH CGS.[16] *Temperature increase* was defined as an inappropriate temperature greater than 38.8°C in the perioperative period or an inappropriately rapid increase in temperature in the anesthesiologist's judgment. Although subjective in nature, the inappropriate increase of temperature is one of the elements of the CGS that came out of the blinded Delphi process by MH biopsy center directors around the world.[16]

Organ failure after the MH reaction was defined by outcomes recorded on the AMRA reports: cardiac dysfunction, cognitive dysfunction, disseminated intravascular coagulation, hepatic dysfunction, pulmonary dysfunction, and renal dysfunction. Stroke was included in the cognitive dysfunction group. The pulmonary dysfunction group included pulmonary edema, prolonged intubation due to respiratory insufficiency, and pleural effusion. Elevated protime or partial thromboplastin time was included with hepatic dysfunction. Miscellaneous outcomes not relevant to MH (*e.g.*, lower extremity joint infection) or not indicative of primary organ failure (*e.g.*, muscle soreness) were not counted as organ failure.

Univariate statistical comparisons were made using the chi-square test or the Z test for proportions for categorical variables and *t* test for continuous variables. Odds ratios for recrudescence were calculated by binary logistic regression. Variables with statistically significant differences on univariate analysis were included in forward stepwise (likelihood ratio) multivariate logistic regression. Muscular body habitus was compared with normal/lean body habitus for the logistic regression analysis. Statistical significance was accepted at $P < 0.05$. Statistical calculations were made using SPSS 12.0.1 for Windows (SPSS Inc., Chicago, IL).

Results

Recrudescence of MH signs and symptoms occurred in 63 (20%) of the 308 patients. Recrudescence occurred between 2.5 and 72 h after the initial MH reaction (mean 13 h, SD 13 h). Half of the patients showed signs or symptoms of recrudescence within 9 h of the initial event (median time 8.7 h), and the vast majority (80%) did so within 16 h.

There were no differences in year of event or type of surgery between recrudescence and nonrecrudescence groups. Most cases (n = 222, 72%) occurred in the 1990s, with approximately 20% of each group occurring in 2000–2004. Age, sex, and body weight were similar between the groups (table 1). Orthopedic; ears, nose, and throat; and general surgery procedures accounted for 60% of all patients, with no significant differences in surgical procedures between the recrudescence and no

Table 1. Patient Characteristics

	No Recrudescence (n = 245)	Recrudescence (n = 63)	Total (n = 308)
Age, yr			
Median	17	21	18
Range	0–75	1–69	0–75
n (%) < 12 yr	89 (39%)	17 (29%)	106 (37%)
Male sex	176 (73%)	46 (73%)	222 (73%)
Weight, mean (SD), kg	56 (33)	61 (31)	57 (32)
Body type*			
Muscular	52 (22%)†	24 (39%)†	76 (26%)
Obese	26 (11%)	9 (15%)	35 (12%)
Normal/lean	156 (67%)‡	28 (46%)‡	184 (62%)
Medical history			
Any previous GA	112 (46%)	34 (54%)	146 (47%)
No. of previous GA, mean (SD)	2 (3)	2 (2)	2 (3)
Range	0–30	0–13	0–30
Family history MH	14 (6%)	3 (5%)	17 (6%)
Surgical procedure			
Orthopedic	62 (25%)	12 (19%)	74 (24%)
ENT	54 (22%)	7 (11%)	61 (20%)
General surgery	37 (15%)	14 (22%)	51 (17%)
Other	92 (38%)	30 (48%)	122 (40%)

Missing data excluded.

* $P < 0.01$, no recrudescence *vs.* recrudescence for all body types (chi-square). † $P = 0.012$, no recrudescence *vs.* recrudescence (Z test). ‡ $P = 0.003$, no recrudescence *vs.* recrudescence.

ENT = ears, nose, and throat; GA = general anesthetic; MH = malignant hyperthermia.

recrudescence groups (table 1). Recrudescence patients were more likely to have muscular body habitus compared with patients without recrudescence ($P < 0.01$; table 1). There was no difference in family history of malignant hyperthermia or previous anesthetic exposure between the two groups, with approximately half of patients having undergone previous general anesthesia (table 1).

Most anesthesia agent details were similar between the two groups (table 2). Approximately half of the patients in each group received succinylcholine, and approximately half received nondepolarizing neuromuscular blocking agents (table 2). Patients who did not recrudesce were more likely to have received sevoflurane than patients who did recrudesce (18% *vs.* 10%; $P < 0.05$; table 2). Other volatile agents were used in similar proportions in the no recrudescence and recrudescence groups (table 2).

Characteristics of the MH episode differed between patients who recrudesced and those who did not. The MH CGS was more likely to be greater than 35 in the recrudescence group ($P < 0.01$), and the recrudescence group was more likely to exhibit a temperature increase during the MH episode ($P < 0.01$; table 3). Time from induction to adverse event was longer in the recrudescence group (mean, 136 min) compared with the nonrecrudescence group (mean, 86 min; $P < 0.05$) (table 3). Of note, 35% of patients who recrudesced had an MH episode that occurred more than 151 min after induction, compared with only 16% of those who did not recrudesce ($P < 0.01$; table 3). Where known (n = 244), the initial dantrolene dose administered was similar between the two groups. Approximately half of patients received 2.5 mg/kg or more, and approximately half received a lower dose (table 3). The total dantrolene dose was greater in the recrudescence group ($P < 0.05$; table 3).

Patients who recrudesced were more likely to experience postoperative organ failure than patients in the control group ($P < 0.01$; table 4). In particular, cognitive

Table 2. Anesthetic Agents

	No Recrudescence (n = 245)	Recrudescence (n = 63)	Total (n = 308)
Succinylcholine	144 (59%)	31 (49%)	175 (57%)
Nondepolarizing muscle relaxant	114 (47%)	32 (51%)	146 (47%)
Volatile agents	233 (95%)	57 (90%)	290 (94%)
Isoflurane	129 (53%)	37 (59%)	166 (54%)
Halothane	58 (24%)	12 (19%)	70 (23%)
Sevoflurane	45 (18%)*	6 (10%)*	51 (17%)
Desflurane	24 (10%)	9 (14%)	33 (11%)
Enflurane	3 (1%)	1 (2%)	4 (1%)

* $P < 0.05$, no recrudescence *vs.* recrudescence groups (Z test).

Table 3. MH Reaction and Treatment

	No Recrudescence (n = 245)	Recrudescence (n = 63)	Total (n = 308)
MH clinical grading criteria			
Muscle rigidity*	123 (50%)	28 (44%)	151 (49%)
Muscle breakdown	82 (33%)	20 (32%)	102 (33%)
Respiratory acidosis	223 (91%)	58 (92%)	281 (91%)
Temperature increase	158 (64%)†	53 (84%)†	211 (69%)
Cardiac involvement	171 (70%)	51 (81%)	222 (72%)
CGS > 35	160 (65%)†	51 (81%)†	211 (69%)
Induction to adverse reaction, min			
Mean (SD)	86 (117)‡	136 (162)‡	97 (129)
Median	45	77	51
Range	0–685	0–830	0–830
Induction to adverse reaction, min			
≤ 30	109 (44%)	20 (32%)	129 (42%)
31–60	31 (13%)	8 (12%)	39 (13%)
61–90	30 (12%)	4 (6%)	34 (11%)
91–120	15 (6%)	7 (11%)	22 (7%)
121–150	22 (9%)	2 (3%)	24 (8%)
≥ 151	38 (16%)†	22 (35%)†	60 (19%)
Initial dose dantrolene			
< 2.5 mg/kg	104 (56%)	34 (59%)	138 (57%)
≥ 2.5 mg/kg	82 (44%)	24 (41%)	106 (43%)
Total dantrolene dose, mg/kg	6.8 ± 8.5‡	9.4 ± 7.6‡	7.4 ± 8.4

Missing data excluded for percentages.

* Muscle rigidity was either generalized or masseter. † $P < 0.01$, no recrudescence *vs.* recrudescence (Z test). ‡ $P < 0.05$ (*t* test).

CGS = clinical grading score[16]; MH = malignant hyperthermia.

dysfunction and pulmonary dysfunction were more common in the recrudescence group.

Factors associated with recrudescence included muscular body habitus (odds ratio, 2.57; $P = 0.003$), longer time between induction and MH reaction (odds ratio, 1.003 per minute; $P = 0.009$), and a temperature increase (odds ratio, 2.918; $P = 0.004$) (table 5). Multivariate logistic regression showed similar relations (table 5).

Discussion

Recrudescence of MH occurred in 20% of study patients, with 80% occurring within 16 h of the initial MH reaction. Factors associated with recrudescence included muscular body type, longer duration of onset of MH reaction after induction of anesthesia, and a temperature increase. These findings are particularly important to critical care physicians to help pinpoint patients at higher risk for recrudescence after what seems to be initially successful treatment of an MH reaction.

Study Limitations

As data were used from AMRAs reported to NAMHR, study results are limited by reporting and recall bias, subjectivity of definitions (*e.g.*, MH event, recrudescence, temperature, body habitus), geographic distribution, changes in anesthetic techniques over time, and retrospective data entry into a standardized database that may lack specific details of anesthetic and clinical courses.

Selection bias may be present because our inclusion criteria included a high likelihood of an MH reaction, indicated by an MH GCS of 20 or greater,[16] and the most severe cases in which the patient died upon the initial episode (n = 6) were excluded. The manifestations of an MH episode can resolve in a few minutes if treated

Table 4. Postoperative Outcomes

	No Recrudescence (n = 245)	Recrudescence (n = 63)	Total (n = 308)
Any organ failure	29 (12%)*	20 (32%)*	49 (16%)
Cardiac dysfunction	7 (3%)	4 (6%)	11 (4%)
Cognitive dysfunction	10 (4%)*	12 (19%)*	22 (7%)
Disseminated intravascular coagulation	5 (2%)	3 (5%)	8 (3%)
Hepatic dysfunction	6 (2%)	4 (6%)	10 (3%)
Pulmonary dysfunction	7 (3%)†	7 (11%)†	14 (5%)
Renal dysfunction	6 (2%)	5 (8%)	11 (4%)

Cognitive dysfunction included change in consciousness or stroke. Pulmonary dysfunction included prolonged intubation, pulmonary edema or pleural effusion.

* $P < 0.01$ (Z test), no recrudescence *vs.* recrudescence. † $P < 0.05$ (Z test), no recrudescence *vs.* recrudescence.

Table 5. Clinical Variables Associated with Recrudescence

Factor	n	Univariate OR (95% CI)	*P*	Multivariate OR (95% CI)	*P*
Body type*					
Normal or lean	184	Reference		Reference	
Muscular	76	2.57 (1.37–4.82)	0.003	2.00 (1.04–3.86)	0.038
MH reaction after induction, min†	308	1.003 (1.001–1.004)	0.009	1.002 (1.000–1.004)	0.054
Temperature increase					
Absent	97	Reference		Reference	
Present	211	2.92 (1.41–6.02)	0.004	2.34 (1.01–5.41)	0.046
Sevoflurane					
Absent	257	Reference			
Present	51	0.47 (0.19–1.15)	0.099	NA	

Multivariate model: Nagelkerke $R^2 = 0.102$.

* Body type analysis excluded obese subjects (n = 35). † Minutes: continuous variable.

CI = confidence interval; MH = malignant hyperthermia; NA = not applicable; OR = odds ratio.

before the patient becomes acidotic, and the patient therefore does not meet entry criteria.[16] The assigned MH rank may underestimate the likelihood of MH if triggering anesthetic agents were discontinued immediately after the development of masseter spasm, if important monitors or relevant blood tests were not obtained, or if the family history was not obtained.[16] In addition, these cases represent a clinical diagnosis of MH, not proven genetic susceptibility to MH as determined by a caffeine–halothane contracture test or genetic analysis. Hence, the AMRAs represent a clinical database for an uncommon syndrome.

A major limitation of the study is that detailed information was not available regarding dantrolene dosage and timing. The AMRAs give information regarding initial and total dose, with limited information regarding timing of the doses. Hence, we cannot determine whether intermittent or continuous infusions of dantrolene were administered.

Because we compared clinical characteristics of cases who had recrudescence after an episode of MH to those cases who did not recrudesce, this was not the classic case–control study in which controls were disease free, and results should be interpreted accordingly. As in any case–control study, confounding is present, and it must be remembered that associations do not imply causation.

Recrudescence of MH

The pathogenesis of and genetic predisposition of recrudescence are not known. From a clinical standpoint, some episodes of MH are more difficult to treat than others. This study helps to pinpoint clinical factors associated with recrudescence of suspected MH, after what seemed to be successful treatment of the initial episode.

The odds of recrudescence doubled with muscular body types (table 5), perhaps due to increased muscle mass and a proportionally larger amount of hypermetabolic tissue. The odds of recrudescence also increased as time from induction to initial MH reaction increased (table 5). This reaction might occur as a direct result of exposure to larger quantities of triggering agent within the muscle. The longer the anesthetic is continued, the more inhalation agent there will be in the muscle and the longer it will take to remove the inhalation agent from the muscle. Several case reports also describe recrudescence after a slower development of MH.[11,13] However, a slower onset of symptoms with increased likelihood of recrudescence may reflect a different subset and etiology of MH than the rapid fulminant course. Pharmacogenetic epidemiologic studies may help to pinpoint specific mutations associated with differences in clinical courses.

Recrudescence was associated with a temperature increase (tables 3 and 5) but not the other signs of MH (muscle rigidity, muscle breakdown, respiratory acidosis, and cardiac involvement) from the MH CGS.[16] Case reports had previously suggested persistent rigidity,[10] hyperkalemia and oliguria,[10] shivering,[14] and persistent tachycardia[11,13] as clinical signs that may predict recrudescence of MH. Elevated temperature may make it easier to trigger an MH episode.[17–21] Mild hypothermia (35°C) attenuated MH and moderate hypothermia (33°C) completely prevented MH in susceptible swine.[17] As the temperature of a calcium release channel is decreased, the probability of that channel opening abnormally is decreased.[18] Hyperthermia caused exaggerated increases in oxygen consumption and blood lactate in susceptible but not normal swine muscle[19] and triggered MH in susceptible piglets.[20] Data in humans are lacking, although cases of MH were reported after systemic rewarming after hypothermic cardiopulmonary bypass despite a nontriggering anesthetic[21] and after heat stroke.[22]

A smaller proportion of patients with recrudescence received sevoflurane; however, sevoflurane was not associated with statistically significant reduced odds of recrudescence, perhaps because of the small sample size. Sevoflurane may be somewhat less triggering than older volatile anesthetics such as halothane, although there have been a few case reports of MH with sevoflurane.[23,24] Kunst *et al.* [25] found that sevoflurane induced smaller Ca^{2+} release from the sarcoplasmic reticulum of

skeletal muscle than equimolar halothane and isoflurane. Desflurane is an even weaker trigger of MH and induces only minor Ca^{2+} release from the sarcoplasmic reticulum of mammalian skeletal muscle compared with sevoflurane.[26] Desflurane did not affect recrudescence in our study, although few patients received desflurane.

The initial dose of dantrolene was not associated with the development of recrudescence, with a similar proportion of recrudescence occurring with initial dantrolene doses of less than and greater than 2.5 mg/kg, the recommended initial dantrolene dose.[27,28] Not surprisingly, the total dose of dantrolene was greater in the recrudescence group. The timing of recrudescence (mean of 13 h) corresponded roughly to dantrolene's elimination half-life of 10–12 h.[27,29,30] Unfortunately, the AMRAs did not provide detailed dosage information, and we cannot determine whether intermittent or continuous infusions of dantrolene were administered.

Dantrolene in therapeutic concentrations binds to the RyR1 receptor to block Ca^{2+} release.[7,8] However, in low concentrations, it may activate the RyR1 receptor producing Ca^{2+} release and possibly recrudescence of MH.[8] Some RyR1 receptor mutations may be more susceptible to low-dose dantrolene-induced calcium release.[31]

In summary, recrudescence occurred in 20% of patients surviving after a clinical MH episode in the NAMHR, with a mean of 13 h after successful treatment of the initial MH reaction. Clinical variables associated with recrudescence included muscular body habitus, longer duration of induction to MH event, and the presence of a temperature increase.

Data for the manuscript were received from The North American Malignant Hyperthermia Registry (NAMHR) (Pittsburgh, Pennsylvania). The authors thank Barbara W. Brandom, M.D. (Director of NAMHR and Professor of Anesthesiology, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania), and Michael Young, C.H.P. (Technical Manager, NAMHR). The authors also thank Lynn Akerlund (Program Coordinator, Department of Anesthesiology, University of Washington, Seattle, Washington) for assistance with manuscript preparation.

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