ORIGINAL CLINICAL RESEARCH REPORT

Oral Dantrolene for Myopathic Symptoms in Malignant Hyperthermia–Susceptible Patients: A 25-Year Retrospective Cohort Study of Adverse Effects and Tolerability

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BACKGROUND: Patients susceptible to malignant hyperthermia (MH) may experience disabling manifestations of an unspecified myopathy outside the context of anesthesia, including myalgia, fatigue, or episodic rhabdomyolysis. Clinical observations suggest that oral dantrolene may relief myopathic symptoms in MH-susceptible (MHS) patients. However, high-dose oral dantrolene has been associated with severe hepatotoxicity.

METHODS: In a retrospective database review (1994–2018), we investigated a cohort of patients who were diagnosed as MHS by a positive caffeine-halothane contracture test (CHCT), had myopathic manifestations, and received oral dantrolene. Our aim was to investigate the occurrence of serious adverse effects and the adherence to oral dantrolene therapy. We also explored factors associated with self-reported clinical improvement, considering as nonresponders patients with intolerable adverse effects or who reported no improvement 8 weeks after starting treatment.

RESULTS: Among 476 MHS patients with positive CHCT, 193 had muscle symptoms, 164 started oral dantrolene, 27 refused treatment, and 2 were excluded due to abnormal liver function before starting therapy. There were no serious adverse effects reported. Forty-six of 164 patients (28%; 95% confidence interval [CI], 22%–35%) experienced mild to moderate adverse effects. Twenty-two patients (22/164, 13%; 95% CI, 9%–19%) discontinued treatment, among which 16 due to adverse effects and 6 due to lack of improvement. One hundred forty-two patients (87%; 95% CI, 80%–90%) adhered to therapy and reported improvement of myalgia (n = 78), fatigue (n = 32), or rhabdomyolysis/hiperCKemia (n = 32). The proportion of responders was larger among patients with MH history than among those referred due to a clinical myopathy with nonpertinent anesthetic history (97% vs 79%, respectively; 95% CI of the difference, 8.5–28; $P < .001$). Patients with a sarcoplasmic reticulum Ca2+ release channel ryanodine receptor gene (*RYR1)* variant had higher odds of responding to dantrolene treatment (OR, 6.4; 95% CI, 1.3–30.9; $P = .013$). Dantrolene median dose was 50 (25–400) and 200 (25–400) $mg \cdot day^{-1}$ in responders and nonresponders, respectively.

CONCLUSIONS: We found that oral dantrolene produced no serious adverse effects within the reported dose range, and was well tolerated by most MH-susceptible patients presenting myopathic symptoms. Our study provides dosing and adverse effect data as a basis for further randomized controlled clinical trials to determine the efficacy of oral dantrolene for symptomatic relief in MHS-related myopathies. (Anesth Analg 2023;136:569–77)

KEY POINTS

- **Question:** Is oral dantrolene well-tolerated when prescribed for myopathic symptoms in patients susceptible to malignant hyperthermia (MHS)?
- **Findings:** A 25-year retrospective database review at the Malignant Hyperthermia Investigation Unit in Toronto revealed that MHS patients on oral dantrolene did not have serious adverse effects, while 142 of 164 (87%; 95% CI, 80%–90%) adhered to therapy and reported clinical improvement.
- **Meaning:** MHS patients with clinical myopathy who report improvement after starting oral dantrolene are likely to adhere to therapy without experiencing serious adverse effects within the reported dose range.

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GLOSSARY

CACNA1S = calcium voltage-gated channel subunit alpha1 S gene; **CHCT** = caffeine-halothane contracture test; **CI** = confidence interval; **EMHG** = European Malignant Hyperthermia Group; **FDA** = US Food and Drug Administration; **MH** = malignant hyperthermia; **MHIU** = Malignant Hyperthermia Investigation Unit; **MHS** = malignant hyperthermia–susceptible; ***RYR1*** = sarcoplasmic reticulum Ca^{2+} release channel ryanodine receptor gene; **RyR1** = sarcoplasmic reticulum Ca^{2+} release channel ryanodine receptor protein; ***STAC3*** = SH3 and cysteine rich domain 3 gene; **STROBE** = Strengthening the Reporting of Observational Results in Epidemiology

Malignant hyperthermia (MH) is a hypermetabolic reaction—lethal in about 10% of cases[1]—triggered by halogenated anesthetics and/or depolarizing muscle relaxants in genetically predisposed individuals.

Similar to other sarcoplasmic reticulum Ca2+ release channel ryanodine receptor gene (*RYR1*)–related myopathies, MH-susceptible (MHS) patients may experience myopathic symptoms—outside the context of anesthetics—that affect their quality of life due to frequent myalgia, fatigue, and functional impairments.[2,3] A recent report suggested that a history of strenuous exercise or pyrexia within 72 hours before general anesthesia may increase the risk of developing MH in patients with predisposing genotypes.[4] Exertional myalgia and rhabdomyolysis may be indeed more common manifestations of pathogenic *RYR1* genotypes than MH itself.[5]

MH is caused by calcium dyshomeostasis in skeletal myocytes associated with mutations in the *RYR1*, and—less frequently—in calcium voltage-gated channel subunit alpha1 S gene (*CACNA1S)* and SH3 and cysteine rich domain 3 gene (*STAC3*).[6,7] Dantrolene, a muscle relaxant that reduces intracellular calcium concentration by inhibiting sarcoplasmic reticulum Ca^{2+} release channel ryanodine receptor protein (RyR1*)* gating, is the only available specific MH treatment.

An oral formulation of dantrolene used to treat chronic spasticity may improve myalgia and rhabdomyolysis in *RYR1*-related myopathies, as suggested by several clinical observations.[8] Oral dantrolene bioavailability is 70%, being eliminated in bile and urine after liver metabolism. Common adverse effects include drowsiness, dizziness, weakness, tiredness, pruritus, nausea, and diarrhea. Interaction with verapamil or diltiazem may cause cardiovascular collapse, its coadministration with nondepolarizing muscle relaxants may result in prolonged neuromuscular blockade,[9] and high doses may result in irreversible liver injury.[10]

At our center, oral dantrolene has been prescribed to MHS patients with myopathic symptoms for >25 years, under the rationale that a clinical myopathy originates from RyR1 dysfunction. We previously observed clinical improvement with oral dantrolene in 82% of MHS patients referred for nonanesthetic reasons (eg, exertional rhabdomyolysis, viral-induced fatigue, and hyperCKemia).[11,12]

In the present study, we performed a database review covering a 25-year-period to identify MHS patients prescribed with oral dantrolene for myopathic symptoms. Our primary aim was to investigate the occurrence of serious adverse effects documented in our patient records after starting oral dantrolene, including irreversible liver injury. Our secondary aims were to assess oral dantrolene tolerability within the prescribed dosage range displaying the proportion of patients who adhered to treatment or who discontinued it due to adverse effects, and to search for nongenetic and genetic factors associated with self-reported clinical improvement after treatment. We hypothesized that oral dantrolene did not produce serious adverse effects within the prescribed dose range.

METHODS

Standard Protocol Approvals, Registrations, and Patient Consents

The Research Ethics Board at the University Health Network, Toronto, ON, Canada, approved this database cohort review and waived the informed consent given the retrospective nature of the study. This article adheres to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement applicable to reports of cohort studies.[13] STROBE's checklist is included as supplemental information.

Study Design and Patient Population

The Malignant Hyperthermia Investigation Unit (MHIU) located at Toronto General Hospital is an academic institution affiliated to the Department of Anesthesiology and Pain Medicine of the University of Toronto. The MHIU is the only diagnostic center for MH in Canada and the sole clinic in North America to prescribe oral dantrolene to MHS patients for muscle symptom relief. We receive referrals from primary care physicians and specialists across provinces for genetic screening, counseling, and muscle contracture testing. The MHIU has no commercial interests. Our clinical services are provided by staff anesthesiologists from the Department of Anesthesia and Pain Management at the University Health Network. Our

center is dedicated to perform scientific research concerning MH, to disseminate knowledge about MH among Canadian health practitioners and patients, and to keep a nationwide MH registry. Clinical records, kept in hardcopy archives since the inception of our unit, have been progressively transferred into electronic format in the form of an internal searchable database curated since 2010 and kept up to date. Our database contains clinical, laboratory, and genetic data from all patients referred to our institution because of a personal or family history of an adverse anesthetic reaction, and from patients with chronic or episodic muscle symptoms of uncertain origin, such as idiopathic hyperCKemia and recurrent rhabdomyolysis.

The present work aimed to investigate the adverse effects and tolerability of oral dantrolene when prescribed for relief of myopathic symptoms, such as myalgia, fatigue, muscle cramps, heat or exercise intolerance, and recurrent episodic rhabdomyolysis (ie, 2 or more documented episodes of serum creatine kinase increase 5 times above baseline values). For that purpose, we performed an internal database search to identify MHS patients with a positive caffeine-halothane contracture test (CHCT), who had been prescribed oral dantrolene at our center between 1994 and 2018 (Table 1). Adverse effects and tolerability outcomes were established a priori.

Oral Dantrolene Treatment

In general, MHS patients who received oral dantrolene at our center opted for treatment because of muscle symptoms subjectively impairing their quality of life. Patients were prescribed dantrolene by an anesthesiologist at the MHIU. Patients with muscle symptoms who refused treatment or had abnormal baseline liver function tests were not prescribed oral dantrolene.

After starting dantrolene treatment, patients were instructed to keep a diary of symptoms, following explanation of common and often intermittent adverse effects such as drowsiness, dizziness, weakness, tiredness, pruritus, nausea, and diarrhea. Patients were also alerted to potentially persistent or serious adverse effects, including central nervous system depression (eg, persistent drowsiness or weakness interfering with their daily activities), seizures, and biochemical evidence of liver injury.

Patients were started on 25 mg oral dantrolene every night at bedtime followed by increments of 25 mg as required at 6 hourly intervals until achieving symptom relief, until the appearance of undesired effects, or until reaching a maximum dose of 400 $mg{\cdot}day^{-1}$. If there was no clinical improvement after the initial dose, the nighttime dose was increased to 50 mg in the first instance. In case of short-lived symptom relief, 25 mg interval doses were added during the daytime as needed (Figure 1).

Any clinical improvement as judged by the patient was considered a favorable response to dantrolene treatment. Patients who did not report any symptom relief after 6 to 8 weeks despite dose adjustments as outlined above were considered nonresponders. Dose adjustments aimed for the minimal dantrolene dose that would achieve subjective symptom relief with minimal adverse effects. Patients were assessed every 3 months at the MHIU over 1 year after initiating oral dantrolene. Thereafter, follow-up information was received from their family physicians as part of their ongoing treatment. Liver function tests, including aspartate and alanine aminotransferase, alkaline phosphatase, and bilirubin, were checked before starting dantrolene, quarterly during the first year, and annually thereafter.

Table 1. Demographics and Follow-Up Duration of Patient Cohort

Characteristics	Responders, n = 142	Nonresponders, n = 22	*P*
Sex, n (%)			
Male	86 (61)	12 (55)	.64
Female	56 (39)	10 (45)	
Age[a]	59 (24–91)	62 (31–87)	.91
Follow-up duration[a]	8 (2–27)	0.25 (0.1–0.6)	

[a]Median age and follow-up duration are presented in years (range).

Primary Outcome

The occurrence of serious adverse effects after oral dantrolene was determined through a retrospective chart review of patients' clinical notes. Death, liver failure, irreversible liver injury, anaphylaxis, and any life-threatening event; or requiring hospitalization; or resulting in permanent disability, were considered serious adverse responses to oral dantrolene. Any other undesired effects on records after starting therapy, and elevation of liver enzymes above the normal laboratory range or greater than twice the baseline values were considered as adverse effects.

Secondary Outcomes

The proportion of patients who adhered to treatment and who discontinued treatment due to adverse effects or lack of response were calculated to assess oral dantrolene tolerability. Demographic and clinical variables were explored post hoc for associations with clinical improvement. Clinical improvement was defined as a binary outcome, adjudicating patients as "responders" if they reported subjective improvement after initiating oral dantrolene, or "nonresponders" if there was no reported improvement in 6–8 weeks of treatment or in case of treatment discontinuation. Variables extracted from our database to explore associations with clinical improvement

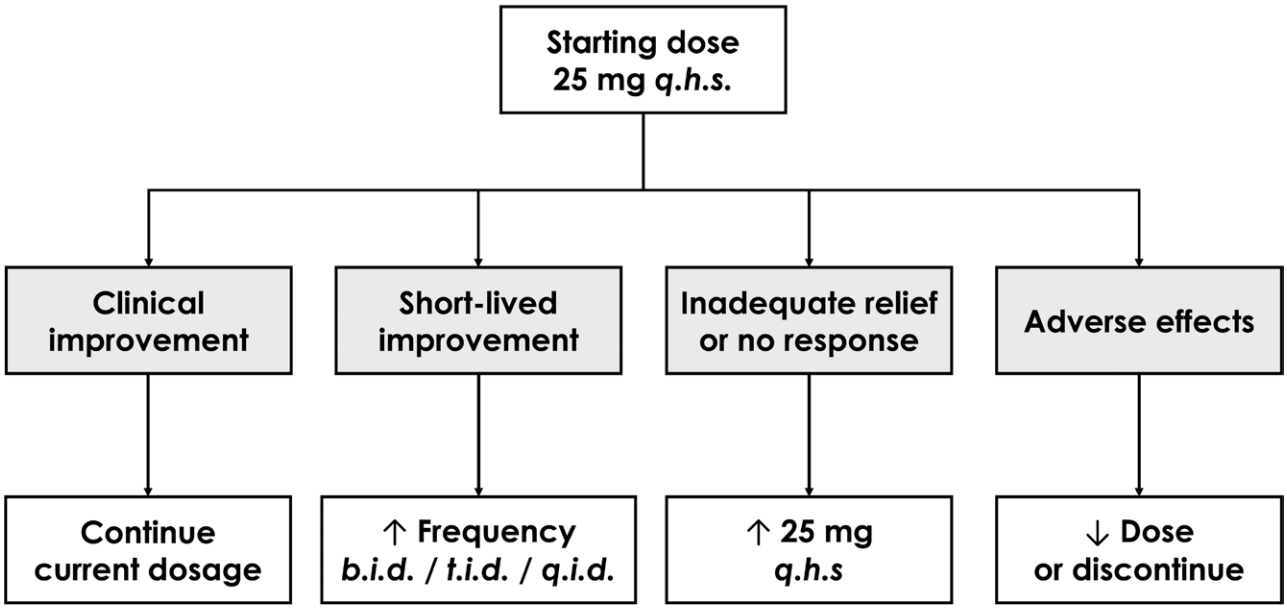

Figure 1. Dantrolene dosing regimen. Starting with a nighttime dose, oral doses of dantrolene were added as needed by increments of 25 mg at 6 hourly intervals, up to 100 mg per dose or 400 mg per day, until achieving the desired effect. *b.i.d. (bis in die)* indicates twice a day; *q.h.s. (quaque hora somni)*, every night at bedtime; *q.i.d. (quater in die)*, 4 times a day; *t.i.d. (ter in die)*, 3 times a day.

were age, sex, personal or family history of adverse anesthetic reaction, the reason for starting dantrolene treatment (ie, the main complaint), dantrolene dose, and results of the CHCT, genotype, and muscle histopathology. Histopathology results were defined as a binary outcome (ie, normal or abnormal), considering any pathological finding as abnormal.

Genotype. Screening of the *RYR1* and *CACNA1S* full-coding regions and exon-intron boundaries is done at our Center as a primary diagnostic alternative to muscle contracture testing for MH susceptibility. Detection of one or more functionally characterized pathogenic variants included in the European Malignant Hyperthermia Group (EMHG) list[14] is considered confirmation of the MHS diagnosis. Genotype data, where available, were extracted from the database to explore associations with clinical improvement.

Statistical Analysis

There was no formal calculation of sample size. Our search was based on all the data available in our database within the specified study period. Clinical data were summarized using descriptive statistics; categorical variables were represented as frequencies and percentages; continuous variables were represented by mean ± SD, or median and range, as appropriate. The association of demographic and clinical variables with clinical improvement was analyzed using Wilcoxon rank sum test (age, follow-up duration) and Pearson χ^2 or Fisher exact test (referral reason, main complaint, histopathology, and genotype), as appropriate. Z-test was used to assess the significance of the difference between independent proportions. A 2-tailed $P < .05$ was used for statistical significance. The data analysis for this article was generated using SAS software (SAS Institute Inc).

RESULTS

Among 476 MHS patients diagnosed at our center between 1994 and 2018 by a positive CHCT, 193 had muscle symptoms and were offered oral dantrolene treatment. One hundred sixty-four patients started oral dantrolene, 27 patients refused therapy, and 2 patients were excluded due to abnormal liver function tests before treatment (Figure 2). A personal or family history of anesthesia-related MH reactions was the reason for referral in 70 cases (43%; 36 and 24 patients, respectively). Ninety-four patients (57%) were referred by a specialist in neuromuscular disorders for MH risk assessment based on nonspecific myopathic symptoms that have been previously linked to MH susceptibility, such as unexplained hyperCKemia >1000 IU·L^{-1}, exercise intolerance, and/or frequent rhabdomyolysis. Patients' main complaints were muscle pain (90/164; 55%), followed by muscle fatigue (40/164, 24%), and signs of muscle breakdown such as high serum creatine kinase or recurrent rhabdomyolysis (34/164; 21%). Of note, patients often presented with >1 clinical manifestation. There were no patients lost to follow-up.

Adverse Effects and Tolerability

There were no reports of irreversible liver injury or any other serious adverse effect. One hundred

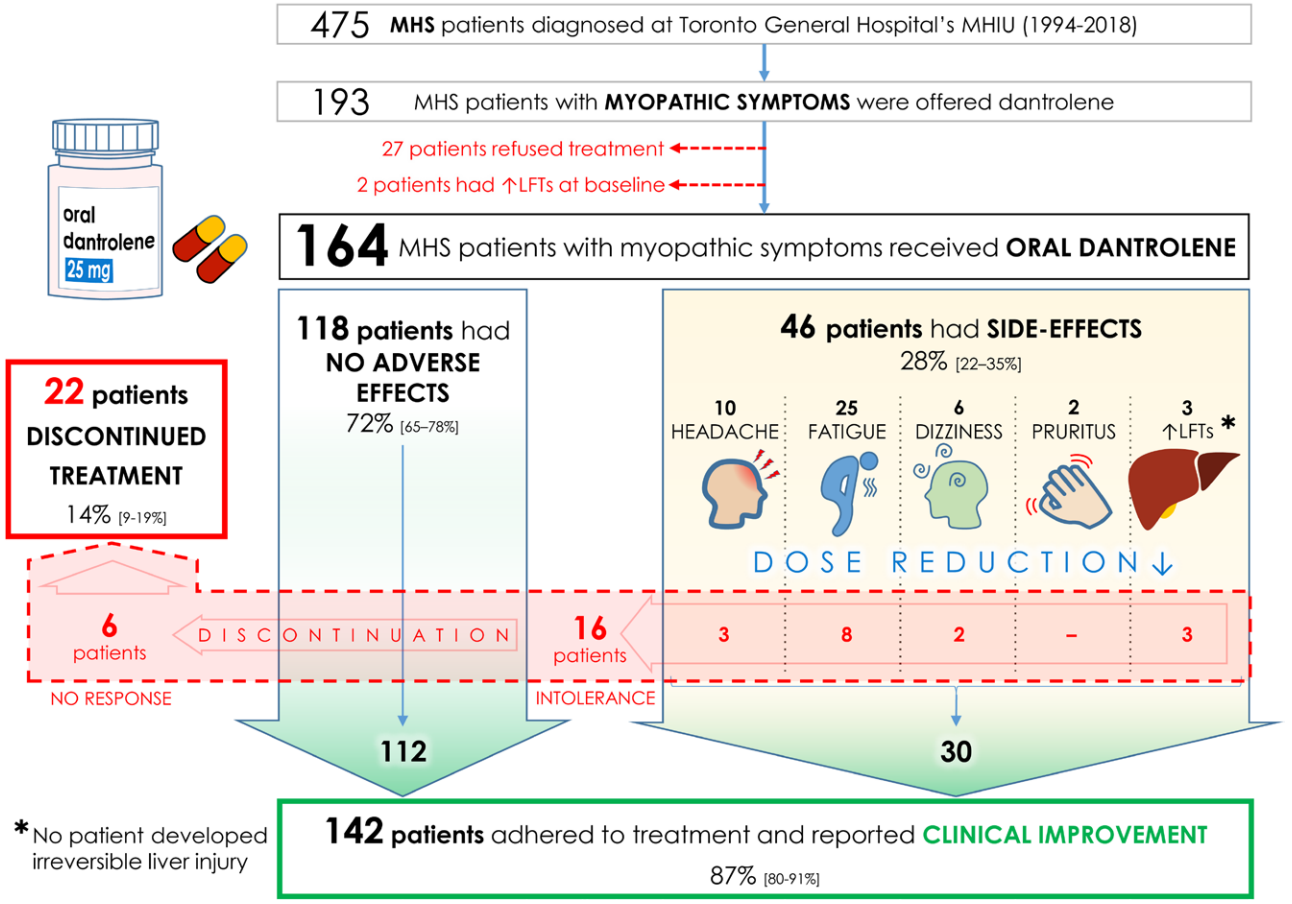

Figure 2. Adverse effects and tolerability of oral dantrolene for myopathic symptom relief in patients susceptible to malignant hyperthermia. LFTs indicates liver function tests; MHIU, Malignant Hyperthermia Investigation Unit; MHS, malignant hyperthermia–susceptible.

eighteen patients (118/164, 72%; 95% confidence interval [CI], 65%–78%) reported no adverse effects after initiating oral dantrolene. In total, forty-six patients (46/164, 28%; 95% CI, 22%–35%) experienced one or more adverse effects, including headache, dizziness, weakness, pruritus, and/or elevated liver enzymes (Table 2; Figure 2). One hundred forty-two patients (142/164, 87%; 95% CI, 80%–91%) adhered to treatment. Twenty-two patients (22/164, 13%; 95% CI, 9%–19%) discontinued oral dantrolene: 6 (3.7%; 95% CI, 2%–8%) due to lack of response in the administered dose range (25–400 mg·day^{-1}), and sixteen (10%; 95% CI, 6%–15%) because of intolerable adverse effects, including 3 patients who had elevated liver enzymes 3 to 4 times above the upper normal limit. Liver enzymes returned to normal values 1 month after cessation of dantrolene treatment in all affected patients.

Patients who experienced adverse effects had 2.67 higher odds of discontinuing treatment compared to those without adverse effects (odds ratio, 9.9; 95% CI, 3.6–27.6).

The median dantrolene dose taken by patients reporting adverse effects was 150 mg·day^{-1}, within a range of 25–300 mg·day^{-1}. Reducing dantrolene dosage eliminated undesired effects in 70% (32/46; 95% CI, 55%–81%) of the affected patients, who after adjustments received a final median dose of 50 mg·day^{-1}, within a range of 25–200 mg·day^{-1}.

Factors Associated With Clinical Improvement After Oral Dantrolene

Reason for Referral. One hundred forty-two patients (142/164, 87%; 95% CI, 80%–90%) reported clinical improvement, including 68 of 70 (97%) patients with personal or family history of MH, and 74 of 94 (79%) with nonpertinent anesthetic history referred for an unspecified myopathy (Table 3).

The latter group included 34 CHCT-positive probands with no history of adverse anesthetic reaction, meeting the inclusion criteria of the current study, whose clinical response to dantrolene was reported in a previous publication.[11] Of note, the proportion of responders was significantly higher in patients with a history of MH (95% CI of the difference, 8.5–28; Fisher exact test mid, $P < .001$). The median daily dose of dantrolene was 50 (25–400) and 200 (25–400) mg·day^{-1} in responders and nonresponders, respectively.

Table 2. Adverse Effect Profile and Oral Dantrolene Dose

Adverse effects	Had adverse effects	Discontinued dantrolene	Withdrawal likelihood [a]
Abnormal LFTs	3 (1)	3 (2)	1
Headache	10 (6)	3 (2)	0.3
Fatigue/weakness	25 (15)	8 (5)	0.32
Dizziness	6 (4)	2 (1)	0.33
Pruritus	2 (1)	0	0
Subtotal (adverse effects)	46 (28)	16 (10)	0.35[b]
No adverse effects	118 (71)	6 (4)	0.05[b]
Total	164	22	0.13
Dantrolene-tolerated dose (mg)[c]	50 (25–300)		

Results from a 25-year span database search, presented as "n" number of patients (% of study total, N = 164).

Abbreviation: LFTs, liver function tests.

[a]Patients with adverse effects were more likely to discontinue oral dantrolene that those without adverse effects.

[b]Odds ratio, 9.9 (95% confidence interval, 3.6–27; 2-tailed Z-test, 5.013; $P < .001$).

[c]Median dantrolene dose (range) in patients with no reported adverse effects.

Table 3. Variables Explored for Associations With Clinical Improvement

Characteristics	Responders, n = 142	Nonresponders, n = 22	*P*
Sex			
Male	86 (61)	12 (55)	.64
Female	56 (39)	10 (45)	
Age[a]	59 (24–91)	62 (31–87)	.91
Referral reason			
Personal or family history of MH	68 (48)	2 (9)	<.001
Myopathy (no MH history)[b]	74 (52)	20 (91)	
Main complaint			
Cramps/myalgia	78 (55)	12 (55)	.22
Fatigue	32 (22.5)	8 (36)	
Rhabdomyolysis/ HyperCKemia	32 (22.5)	2 (9)	
Histopathology			
Abnormal[c]	46 (32)	4 (18)	.22
Normal	96 (68)	18 (82)	
Genetic testing	**Responders, n = 96**	**Nonresponders, n = 12**	
RYR1 variant	54 (56)	2 (17)	<.0001
pathogenic[d]	16	0	

Results from a 25-year span (1994–2018) database search, presented as "n" number of patients (% per response group). Associations between patient characteristics and response to treatment were explored post hoc (2 tailed $P < .05$, by Wilcoxon's rank, Fisher, or Z-test, as appropriate).

Abbreviations: CHCT, caffeine-halothane contracture test; EMHG, European Malignant Hyperthermia Group; MH, malignant hyperthermia; *RYR1*, ryanodine receptor type 1 gene.

[a]Median age is presented in years (range).

[b]28 responders and 6 nonresponders included in a previous publication.[10]

[c]Cores, fiber size variation, type 2 fibers atrophy, increased internal nuclei, and interstitial fibrosis.

[d]MH-diagnostic variants included in EMHG list.[13]

Genotype. Genetic testing results were available for 108 patients (96/142 responders and 12/22 nonresponders). MH-diagnostic *RYR1* mutations included in the EMHG list[14] were found only among responders (16/96, 17%), whereas both responders (38/96, 40%) and (2/12, 17%) nonresponders had *RYR1* variants of uncertain significance (Table 3). The following 5 MH diagnostic *RYR1* mutations were found in 16 patients who responded to oral dantrolene: p.Arg614Cys in 3 patients, p.Gly2434Arg in 5 patients, p.Arg2454His in 6 patients, p.Val2168Met in 1 patient, and p.Val4849Ile in 1 patient. There were no patients in the study sample with *CACNA1S* gene variants. Patients who had an *RYR1* variant had 6.4 times higher odds of responding favorably to dantrolene treatment compared to those who had no confirmed genetic variant(s) (95% CI, 1.3–30.9; 2-tailed, $P = .013$).

Clinical improvement after oral dantrolene was not associated with patient's age, sex, type of muscle symptoms (pain, decreased function, or muscle breakdown), or abnormal histopathology findings. Reported pathological abnormalities were nonspecific and included increased presence of central nuclei, type 2 fibers atrophy, and the presence of cores. Apart from 56 patients with no available genetic testing, there were no missing data.

DISCUSSION

Our retrospective analysis of MHS patients with positive CHCT, referred to our clinic over 25 years due to MH history or to an unspecified myopathy, provides evidence that oral dantrolene prescribed for myopathic symptom relief did not produce serious adverse effects and was well-tolerated, as judged by the observed adherence to treatment. Although our study might be underpowered to detect rare life-threatening reactions to oral dantrolene, no patient developed serious adverse effects within the prescribed dose range.

Oral dantrolene is approved by the FDA for the treatment of chronic muscle spasticity.[15] Dantrolene has also been used off license for treating muscle spasms and hyperthermia unresponsive to conventional therapies in neuroleptic malignant syndrome,[16] MDMA intoxication,[17] and heat stroke,[9,18] and for treating muscle symptoms or recurrent rhabdomyolysis in MHS patients carrying pathogenic *RYR1* variants.[19–21] However, a black box warning of liver failure was included in the package insert after 2% of patients (19/1044) who received dantrolene developed liver injury and 3 patients died.[10,22] Liver failure occurred in patients taking doses >500 mg·day^{-1}, with preexisting disease or with concomitant use of medications affecting liver function. Nevertheless, in a recent study using oral dantrolene doses <100 mg·day^{-1}, only 1 of 243 patients developed mild hepatic dysfunction.[23]

Less than one-third of our study cohort experienced undesired symptoms—predominantly fatigue and excessive muscle weakness, followed

in frequency by headache, dizziness, and pruritus—most of which improved after dose reduction (Figure 2). Although a majority of patients (142/164, 86%) adhered to therapy, one-third of patients with adverse effects (16/46) discontinued treatment. Whether keeping them on therapy longer at a lower dose would result in symptom improvement remains an unresolved question. Three patients developed elevated liver enzymes 3–4 times above the upper normal limit, which normalized after discontinuing dantrolene. None in the studied cohort developed fulminant liver failure or any other serious adverse effect, even at the highest (400 mg·day^{-1}) prescribed dose. Recent experiments in high-fat-diet-fed mice suggest that appropriate oral dantrolene dosage may prevent liver steatosis by reducing endoplasmic reticulum stress.[24] Nevertheless, reports of severe liver injury with oral dantrolene should prompt close monitoring of liver enzymes. Responders received a lower median daily dose of dantrolene compared to nonresponders (50 mg vs 200 mg, respectively), suggesting that dose increases may not be beneficial in patients who do not respond to the initial dose adjustments.

We also found that patients with MH history were more likely to report clinical improvement after oral dantrolene (68/70, 97%) than MHS patients referred for nonanesthetic reasons (74/94, 79%). Clinical improvement was not associated with other nongenetic factors, such as age, sex, type of main complaint (ie, myalgia, muscle cramps, fatigue, or rhabdomyolysis), or abnormal histopathology. Of note, the histopathological findings seen in our cohort were compatible with nonspecific myopathic changes previously reported in MHS.[25]

Patients without MH history are referred to us after a thorough neurological work up to rule out MH susceptibility in the context of *RYR1*-related myopathies. Patients with any *RYR1* variant had 6-fold increased odds of responding favorably to dantrolene treatment. Several *RYR1* genotypes predispose to MH in an autosomal dominant manner with incomplete penetrance,[14,26] causing calcium disturbance in skeletal muscle (ie, the MHS phenotype)[27] ameliorable by dantrolene through RyR1-modulation.[28,29]

The MHS phenotype defined by CHCT positivity as in the present cohort is also associated with a spectrum of other myopathic manifestations (eg, myalgia, recurrent rhabdomyolysis, and hyperCKemia) that may potentially be treated with oral dantrolene. A study by Figueroa et al[30] showed a positive correlation between a severity index of muscle involvement and the level of cytosolic calcium increase in myotubes derived from MHS patients. Those findings support the rationale for prescribing dantrolene in MHS patients with clinical myopathy—presuming that their phenotype originates from chronic RyR1 dysfunction—to restitute myoplasmic calcium homeostasis.[31]

Our study has several limitations. First, we were unable to account for confounding factors when assessing predictors of clinical improvement after oral dantrolene, as this study was limited to the available clinical data. Therefore, our results should be carefully interpreted as hypothesis generating rather than as conclusive evidence. We cannot conclude whether there is a direct causal relationship between the therapy and the observed effects. Second, although none of our patients developed irreversible liver failure, our study might be underpowered to detect serious adverse effects of oral dantrolene in low to moderate doses. However, our series includes substantially more patients than most samples required for phase I-II dose-finding trials,[32] and—except for genetic testing not being uniformly available to all patients at different time points of the study period—we had no missing data. Third, we based our definition of responders on subjective clinical improvement, a shortcoming that may be addressed in a future prospective randomized controlled trial utilizing validated instruments. The challenge of achieving an appropriate sample size for an efficacy drug trial in a rare condition may be addressed by adopting an N-of-1 design, in which a single patient undergoes a series of treatment pairs, consisting of 1 active and 1 placebo per pair, allocated randomly.[33,34]

Although our study was exclusively focused on MHS patients, the relevance of our findings is wider, considering that *RYR1*-related myopathies are one of the most common nondystrophic neuromuscular disorders.[35] There is a clinical continuum between *RYR1*-related congenital myopathies, exertional myalgia, rhabdomyolysis, and MH, emphasizing the need for a common treatment approach.[4,5] Moreover, the use of dantrolene for these conditions in isolated cases has shown promising results.[8]

In conclusion, we provide evidence that oral dantrolene in appropriate doses is tolerated by MHS patients and might provide relief from myopathic symptoms such as myalgia, fatigue, and rhabdomyolysis. We did not observe serious adverse effects in our study sample. Our observations provide initial dosing data for designing a randomized clinical trial ultimately warranted for assessing the efficacy of oral dantrolene therapy for MHS patients with a clinical myopathy. The finding of a large nonanesthetic disease burden strengthens previous reports that MH susceptibility has implications for patients beyond the operating room.

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DISCLOSURES

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