Malignant Hyperthermia Susceptibility in Neuroleptic Malignant Syndrome

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The relationship between neuroleptic malignant syndrome (NMS) and malignant hyperthermia (MH) was investigated using the *in vitro* skeletal muscle contracture test to screen for MH-susceptibility in NMS patients. The maximum contracture tension which developed following exposure to halothane (1–3%), and incremental doses of fluphenazine (0.2–25.6 mM) was measured in muscle obtained from seven NMS, six MH, and six control patients. Comparison of the cumulative responses to fluphenazine revealed no significant differences among the groups. However, the response (mean ± SEM) to halothane in the NMS group (1.7 ± 0.7 g), which was similar to the response in the MH group (1.5 ± 0.2 g), was significantly greater than the response found in controls (0.2 ± 0.1 g). In addition, five of seven NMS patients could be diagnosed as MH-susceptible, based on the development of muscle contractures greater than 0.7 g in response to 1–3% halothane. In contrast, none of the controls were MH-susceptible. These findings appear to correlate with clinical evidence suggesting an association between NMS and MH. (Key words: Ataractics, phenothiazines: fluphenazine. Complications: hyperthermia. Hyperthermia, malignant: neuroleptic malignant syndrome; skeletal muscle rigidity.)

THE NEUROLEPTIC MALIGNANT SYNDROME (NMS) is an uncommon, life-threatening disorder associated with the use of neuroleptics.[1–3] Despite numerous clinical reports, the pathophysiology underlying NMS has yet to be elucidated. In view of clinical similarities between NMS and malignant hyperthermia (MH), several investigators have suggested that these disorders may share common pathogenetic mechanisms.[1–3] Thus, further examination of the nature of the relationship between MH and NMS may enhance understanding of the mechanisms underlying both syndromes.

To further explore etiologic mechanisms in the NMS and to evaluate the association between NMS and MH, we used the halothane contracture test[4–6] to determine MH-susceptibility in skeletal muscle specimens obtained from seven NMS, six MH, and six control patients. Utilizing variations of this procedure, previous investigators have obtained conflicting results regarding the prevalence of MH-susceptibility among NMS patients[7–12] (table 1), and their families.[10,12] In addition, to determine whether NMS, MH, and control patients could be distinguished on the basis of sensitivity to neuroleptic administration, we used the same *in vitro* pharmacologic system to evaluate the contracture response to fluphenazine, a neuroleptic implicated in NMS episodes. We hypothesized that muscle from NMS and MH patients would show increased sensitivity to fluphenazine, as well as to halothane, in comparison to muscle from controls.

Methods and Materials

SUBJECTS

Seven patients with documented NMS episodes were included in the study (table 2). There were five men and two women in this group. Their mean (±SEM) age was 39 ± 6 years. They were drug free at the time of biopsy, except for one patient (case 2) who was taking carbamazepine for seizures. Neuroleptic drugs were discontinued 49.7 ± 14.1 days (mean ± SEM; range 11–90 days) prior to biopsy. Serum levels of creatine phosphokinase (CPK) returned to normal 35.8 ± 10.4 days (range 8–60 days) prior to biopsy. Biopsy results from one of these patients have been previously reported.[13,14]

A second group consisted of six patients referred for biopsy because of signs suggestive of an MH episode during anesthesia or a family history of MH, in whom MH-susceptibility was confirmed by contracture test results. There were two men and four women in this group, and their mean age was 29 ± 3 yr. Specimens of skeletal muscle were also obtained from six control patients undergoing elective surgery for conditions unrelated to MH or NMS. This group consisted of one man and five women, and their mean age was 41 ± 6 years. MH and control patients were also drug free at the time of biopsy, and MH patients were studied at least 90 days after adverse reactions during anesthesia.

TABLE 1. Results of Skeletal Muscle Contracture Test in Previous Studies of NMS Patients

Reference	Patients* NMS (Age/Sex)	Patients* Controls	Test Drugs†	Criteria for MH-susceptibility	MH-susceptibility in NMS Cases
Tollefson (1982)[7]	41M	—	Halothane (2%), caffeine (0.25–32 mM)	Contracture at <2 mM caffeine (plus halothane); <4 mM caffeine alone.	Negative
Scarlett *et al.* (1983)[8]	50F	—	Halothane, caffeine, succinylcholine, potassium chloride	—	Negative
Denborough *et al.* (1984)[10]	31M	Two cases with rhabdomyolysis‡	Halothane (1%), caffeine (2mM)	Contracture (>0.2 g) observed at these concentrations	Positive
Merry *et al.* (1986)[9]	14M	—	Halothane, caffeine	—	Negative
Araki *et al.* (1986)[11]	Six cases*	Seven MH cases; plus "control" group*	Caffeine (<30 mM)	Concentration of caffeine to produce 10%, 50% maximum contracture (skinned fibers)	5/6 positive at 10%; 4/6 positive at 50%

* Absent data not available in published reports.
† Concentrations not indicated were not stated in published report.

‡ Rhabdomyolysis secondary to sepsis in one case and exercise and alcohol in the other.

Differences in sex (Fisher's exact test, $P > .05$) and age (Student's t test for independent samples, $P > .05$) between groups were not statistically significant. All patients scheduled for testing were admitted to the Hahnemann University Hospital and had a complete medical and neurological examination prior to biopsy. Informed consent was obtained prior to inclusion in the study as approved by the Hahnemann University Human Studies Committee.

PROCEDURES

According to a standardized protocol,[5,6] muscle specimens were obtained from the vastus lateralis after femoral nerve block anesthesia.[15] Muscle strips were dissected free, attached to a force transducer, and placed in tissue baths containing 5 ml of Krebs solution at 37° C bubbled with 95% O_2:5% CO_2. An equilibration period of at least 10 min was allowed prior to testing.

Testing for the contracture response to fluphenazine was performed as follows: preparations of Krebs solution containing various concentrations of fluphenazine hydrochloride (0.2, 0.4, 0.8, 1.6, 3.2, 12.8, 25.6 mM) were equilibrated with 95% O_2:5% CO_2 at 37° C. Muscle strips were exposed to drug solutions increasing in concentrations at two-fold increments for 2 min at each concentration. Maximum tension achieved during exposure to drugs at each concentration was recorded, and a complete dose-response (concentration-tension) profile was obtained. In separate strips, halothane (1–3%) in 95% O_2:5% CO_2 was bubbled through bath

TABLE 2. Characteristics of Seven Patients with NMS Tested by Muscle Biopsy

Case/Age/Sex	Pre-existing Condition	Neuroleptic Drug*	Major Symptoms	Creatine Phosphokinase† (IU/L)	MH-susceptibility
1/63/M	Alzheimer's Disease	Haloperidol	40° C, rigidity, stupor/mutism, tachycardia	1,130	Positive
2/30/M	Major Depression, seizure Disorder	Thiothixene, haloperidol	40° C, rigidity, stupor/mutism, tachycardia, dyspnea	2,120	Negative
3/22/F	Atypical psychosis	Haloperidol, chlorpromazine	41° C, rigidity, stupor/mutism, tachycardia	16,070	Positive
4/52/M	Bipolar disorder	Trifluoperazine, thioridazine	38° C, rigidity, stupor/mutism, tachycardia	700	Positive
5/26/M	Mental retardation	Haloperidol	42° C, rigidity, delirium, tachycardia, dyspnea	100,000	Positive
6/36/F	Bipolar disorder	Haloperidol, chlorpromazine, thiothixene	40° C, rigidity, stupor, tachycardia, dyspnea	17,240	Positive
7/50/M	Bipolar disorder	Haloperidol	38° C, rigidity, stupor/mutism, tachycardia, dyspnea	381	Negative

* Neuroleptics associated with onset of NMS. Listing reflects sequence of administration.

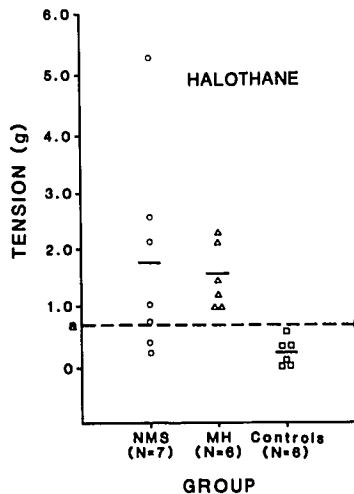† Maximum value reported during NMS episode.

FIG. 1. Between-group comparison of the maximum changes in resting tension from baseline (contracture response) in muscle exposed to halothane (1–3%) *in vitro*. Horizontal bars indicate mean response in each group.

ᵃResponses ≥0.7g=MH susceptibility.

solutions. The concentration of halothane in the gas phase was checked by gas chromatography. The maximum contracture tension developed during 5 min of halothane exposure was recorded.

While all patients were tested with halothane, decreased amounts or viability of tissue obtained at biopsy precluded testing all patients with fluphenazine. Thus, insufficient muscle strips were available to test one NMS, one MH, and three control patients with fluphenazine.

The contracture response to test drugs is expressed as the change in resting tension (grams) from baseline following drug administration. MH-susceptibility was defined by the development in any strip of a contracture
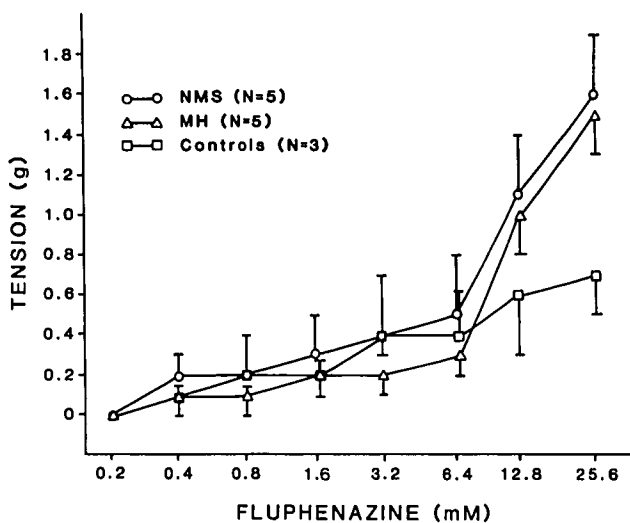

FIG. 2. Between-group comparison of the mean (±SEM) change in resting tension from baseline (contracture response) in muscle exposed to fluphenazine *in vitro*.

≥ 0.5 g in response to halothane (1%) or ≥ 0.7 g in response to halothane (3%). These criteria were based on dose-response data from our laboratory[5,6] and from other investigators,[16,17] which suggest that they may be valid for discriminating between MH-susceptible subjects and normal controls. In this study, the results did not change when a contracture ≥ 0.7 g in response to either 1% or 3% halothane was used as a measure of MH-susceptibility (fig. 1).

Since our objective was to compare NMS patients with a sample of known MH and control patients, we analyzed differences between group means for age, muscle strip weight, halothane concentration, baseline muscle tension, and maximum contracture response to halothane obtained in each patient using Student's t test (two-tailed) for independent samples at a level of significance of $P = .05$. The contracture response to increasing doses of fluphenazine was analyzed by dose and patient group using analysis of variance with repeated measures. Fisher's exact test was used to test the significance of differences in proportions between groups, and Pearson's coefficient of determination was used to analyze the variance in the halothane response with respect to rhabdomyolysis and neuroleptic exposure in NMS patients.

Results

Based on the response to halothane, 5 NMS patients could be diagnosed as MH-susceptible (fig. 1). The proportion of MH-susceptible patients in the NMS group (five of seven) was significantly greater than that in the control group (zero of six; $P < .05$). In addition, the halothane response (mean ± SEM) of NMS (1.7 ± 0.7 g) and MH (1.5 ± 0.2 g) groups was similar ($t = 0.3$, df $= 11, P > .05$), and both NMS ($t = 2.2$, df $= 11, P < 0.5$) and MH ($t = 5.5$, df $= 10, P < .001$) responses were greater than that of controls (0.2 ± 0.1 g). Among NMS patients, there was no correlation between the maximum halothane response and time since neuroleptic exposure ($r^2 = 0.1$), maximum reported CPK ($r^2 < 0.1$), or recovery time following normalization of CPK ($r^2 = 0.1$). Also, concentrations of halothane, and the weights and baseline tension of muscle strips used in analyses of the contracture response to halothane, did not differ significantly between groups.

There were no statistically significant differences between NMS, MH, and control groups in the cumulative response to fluphenazine ($F = 1.77$, df $= 14, 63, P > .05$) (fig. 2).

Discussion

In this study, we found that five of seven patients who recovered from NMS episodes could be diagnosed as MH-susceptible based on the *in vitro* response of skeletal

muscle to halothane. In contrast, no control patients had responses in the MH-susceptible range.

Our finding of MH-susceptibility in some NMS patients is consistent with the reports by Denborough et al.[10] and Araki et al.,[11] and in contrast to results obtained by Tollefson,[7] Scarlett et al.,[8] and Merry et al.[9] One possible explanation for these differences is that patients diagnosed as having NMS may represent a heterogeneous group in terms of response to test drugs and, possibly, etiology as well. From a clinical standpoint, NMS does appear to represent a heterogeneous syndrome with considerable variability in clinical presentation, duration, and response to treatment.[1-3] However, as indicated in table 1, differences between our findings and previous studies are difficult to compare in view of the limited clinical and laboratory data in some prior reports, the variations in procedures, e.g., timing of biopsy and choice of drugs, the lack of uniform criteria for diagnosing MH-susceptibility, and the lack of control data with which to compare the specificity of the test as performed in each laboratory. To facilitate comparisons, given the continued lack of standardization of procedures, reports of studies employing the contracture test in NMS patients should include control data and details of methods, diagnostic criteria, and results obtained.

Nevertheless, the finding of responses consistent with MH-susceptibility in skeletal muscle from NMS patients in this study and others[10,11] provides support for an association between the two syndromes. Clinically, MH and NMS are similar, both presenting as hypermetabolic episodes, usually with pronounced muscle rigidity, rhabdomyolysis, and hyperthermia. Patients developing either MH or NMS episodes may have been exposed, in the past, to triggering drugs without incident, suggesting that the offending drugs may be necessary, but not sufficient, to precipitate hyperthermic episodes. Other as yet unidentified risk factors may be involved in the development of both syndromes.[1-4,18] In addition, dantrolene sodium, a direct acting muscle relaxant, is effective in treating MH[4] and some cases of NMS as well,[2,3] although this drug may be effective in any disorder involving rigidity and hyperthermia.[19,20] At present, the mortality rate for both MH[4,21] and NMS[1-3] ranges from 10–30%.

The clinical and laboratory similarities between MH and NMS raise the possibility that some patients with a history of NMS may be clinically at risk for MH, and suggest that a conservative approach utilizing appropriate precautions, e.g., avoiding known triggering agents, should be taken in managing NMS patients during anesthesia. Such precautions may be worthwhile, even though some NMS survivors have tolerated anesthesia with triggering drugs,[22] since not all NMS patients appear to be MH-susceptible, and since MH does not uniformly develop during anesthesia even in patients with subsequently documented MH episodes.[18]

However, there are also apparent differences between MH and NMS. MH episodes are triggered by inhalational anesthetics, such as halothane, and depolarizing muscle relaxants, whereas, by definition, NMS is associated with neuroleptic drugs. These pharmacologic differences are underscored by the fact that episodes of MH during anesthesia have not been reported in NMS patients, nor has sensitivity to neuroleptic drugs been demonstrated in MH patients. Also, in swine susceptible to MH, neuroleptic drugs may actually delay the onset and attenuate the severity of the syndrome when administered prior to halothane.[23] The incidence of suspected MH episodes has been estimated to be 1/16,000 anesthetic procedures,[4,21] whereas NMS may occur as frequently as 1/200 neuroleptic-treated patients.[1-3] MH episodes can develop in minutes, while the development of NMS is usually less precipitous.

Finally, in contrast to MH, relaxation of muscle rigidity has been achieved in some NMS patients using neuromuscular blocking agents[24,25] or benzodiazepines.[2,3] This suggests that rigidity in NMS, which results in heat production, acidosis, and rhabdomyolysis, is neurogenic in origin. Evidence emerging from clinical reports[26] and pharmacologic studies of thermoregulation[27,28] lends increasing support to the hypothesis that NMS episodes result from primary abnormalities in central nervous system function, most likely due to antagonism by neuroleptics of dopaminergic systems in the brain.

While theories implicating neurogenic mechanisms in MH have also been proposed,[4] the weight of evidence suggests that MH is a disorder affecting skeletal muscle in which the concentration of calcium in the myoplasm rises uncontrollably during exposure to triggering drugs. Therefore, laboratory confirmation of MH-susceptibility in NMS patients provides support for the hypothesis that the development of rigidity in NMS is a function of similar skeletal muscle abnormalites triggered by neuroleptics. In fact, several investigators have reported that muscle contractures are produced in vitro by phenothiazines, and that they appear to be mediated by an increase in myoplasmic calcium resulting from drug effects on intracellular calcium storage structures.[29-31]

The clinical and etiologic significance of our findings, however, depends on the specificity of the association between abnormal in vitro halothane contracture responses and MH-susceptibility. In other words, positive contracture test results in NMS patients may be falsely positive and reflect coincidental changes in muscle resulting from rather than causing NMS. For example, Gallant et al.[32] reported recently that muscle cell injury during biopsy and in vitro testing procedures enhances halothane sensitivity and, conceivably, could contribute

to false positive contracture test results. Also, Denborough *et al.*[10] reported positive test results in two patients who recovered from non-drug related episodes of rhabdomyolysis. This implies that nonspecific muscle damage secondary to metabolic factors, drug exposure, abnormalities in central nervous system activity, or testing procedures may have contributed to abnormal responses observed *in vitro* in muscle obtained from survivors of NMS episodes. But, in the present study, abnormal responses were not observed in control muscle, and we found that the variance in the halothane response among NMS patients did not correlate with the temporal proximity of neuroleptic exposure or the magnitude and proximity of NMS-related rhabdomyolysis as determined by recorded serum CPK levels.

Moreover, the *in vitro* contracture response to halothane appears to be sensitive and specific for MH-susceptibility.[4–6,12,16,33–38] False negative test results have never been confirmed clinically,[39] and significant contracture responses to halothane rarely occur in normal muscle.[4,12,16,33,34,37,38] The contracture test also appears to be specific when used to screen for MH-susceptibility among patients with pre-existing neuromuscular disorders. Positive test results, which have been reported in patients with central core disease,[12,40,41] muscular dystrophy,[12,41–43] myotonia congenita,[44] and in parents of children with sudden infant death,[12,45] have been found to correlate with clinical MH episodes in some of the patients with these conditions.[40–42,44,45] Thus, the possibility remains that positive contracture test results in muscle from NMS patients may reflect true clinical MH-susceptibility,[46] and, thereby, indirectly implicate neuroleptic-induced alterations in skeletal muscle in the pathophysiology of NMS.

In contrast to our findings using halothane, we observed no significant differences in the response to fluphenazine between NMS, MH, and control patients. This suggests that the *in vitro* contracture response to fluphenazine does not correlate with clinical evidence of NMS or MH-susceptibility, and is, therefore, nonspecific. However, it may be premature to forego further investigation of neuroleptic-induced contractures in relation to the pathogenesis of NMS, since there was a trend for NMS and MH patients to show greater responses compared to controls at 12.8 and 25.6 mM of fluphenazine, one NMS patient developed contractures at unusually low concentrations of fluphenazine,[13,14] and since Imaeda *et al.*,** in a previous study, observed contractures in response to haloperidol (.05–0.3 mM), a butyrophenone neuroleptic, in muscle from three NMS

patients, but not in muscle from controls. Our negative findings in a small sample of patients may simply indicate that the fluphenazine contracture test, as a pharmacologic model, may not be sensitive enough to detect relevant neuroleptic effects, or may be insufficient in simulating conditions *in vivo*. For example, compared to serum levels of fluphenazine in patients, high concentrations are required to induce a contracture response. In addition, certain factors present *in vivo*, such as neuroleptic metabolites, circulating catecholamines, and neuronal innervation, may be important to consider in developing more precise pharmacologic or biochemical models to explore neuroleptic-skeletal muscle interactions pertinent to NMS.

In conclusion, the precise mechanisms underlying NMS are unknown. While impairment of central heat loss mechanisms by neuroleptic drugs surely must contribute to thermoregulatory dysfunction,[28] hyperthermia, as the core feature of NMS, is most likely a consequence of excessive heat production derived endogenously from skeletal muscle rigidity and hypermetabolism.[27] While substantial clinical evidence suggests that NMS is related to acute inhibitory effects of neuroleptic drugs on dopaminergic activity in the brain, the clinical and laboratory association between NMS and MH suggests that hypermetabolism, in some NMS patients, may be due in part to neuroleptic-related dysfunction in skeletal muscle. Alternatively, NMS and MH may be separate disorders with distinct pharmacologic mechanisms culminating in a similar disturbance of membrane properties, which functions as a final common pathway affecting calcium movement and energetic processes in skeletal muscle.

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