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Safety of General Anesthesia in Patients Previously Tested Negative for Malignant Hyperthermia Susceptibility

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Anesthetic management and outcome were examined in patients with negative *in vitro* contracture tests for malignant hyperthermia (MH). Contracture testing was performed in a standardized fashion using 3% halothane alone and incremental doses of caffeine alone. Medical records were examined for 54 anesthetic exposures in 42 MH(−) patients who had received anesthesia since their MH testing. Sixteen patients received anesthesia with known MH triggering agents on 23 occasions, all without incident. In six MH(−) patients with previous masseter muscle rigidity, no adverse reactions occurred in response to volatile anesthetic agents. Succinylcholine was avoided in these patients. Eleven MH(−) patients were managed as if MH-susceptible, although it was known that these patients had tested MH(−). Two of these patients also received prophylactic iv dantrolene. These results suggest that "triggering" anesthetic agents may be safely administered to patients who test MH(−) by *in vitro* contracture testing. However, until the anesthetic experience of larger numbers of MH(−) patients is known, these results should be interpreted cautiously. (Key words: Anesthesia: complications. outcome. Anesthetics: inhalation, volatile. Malignant hyperthermia.)

A MEASURE of the utility of a diagnostic test is its ability to alter patient management or outcome.[1] Although the *in vitro* contracture test has been used for 20 yr to determine malignant hyperthermia (MH) susceptibility,[2] there has not been a report of anesthetic challenge of patients previously diagnosed as MH(−).

We therefore determined whether patients with a negative *in vitro* contracture test had any adverse anesthetic outcomes when subsequently exposed to triggering anesthetic agents.

Methods

Following approval of the Human Studies Committee, the records of all patients who tested negative for MH at Hahnemann University from January 1985 to December 1988 were reviewed.

These MH(−) patients were contacted by form letter requesting information regarding anesthetic experiences since their MH testing. We then attempted to contact by telephone all patients who returned the form letter. Patients who had received anesthesia since their MH testing were requested to have their medical records sent to us for review.

From the medical records and the telephone interview, we sought the following details: whether the patient's MH history and biopsy test results were discussed preoperatively, and if this was documented in the preanesthetic note; the anesthetic agents used, and any documented rationale; whether prophylactic dantrolene was administered; the type of surgical procedure and its duration; and the outcome of each patient.

Anesthetic technics were broadly classified as "triggering,"[3] *i.e.*, a halogenated volatile anesthetic agent ± succinylcholine; "nontriggering," *i.e.*, avoidance of known MH triggering agents; "regional," *i.e.*, major conduction anesthesia or nerve blocks.

MH susceptibility was determined in all patients by the caffeine-halothane contracture test. From 1985 to November 1987, patients were tested according to a standardized institutional protocol.[4] After November 1987, contracture testing was performed according to the recently adopted North American MH Group standards.[5] The two protocols are similar, using the *in vitro* response to 3% halothane alone, and the response to incremental caffeine concentrations to determine MH susceptibility. A contracture ≤ 0.7 g to 3% halothane, and <0.2 g to 2 mM caffeine were considered normal responses, *i.e.*, an MH(−) diagnosis.

The *in vitro* contracture test is based upon the observation that muscle fascicles from MH susceptible (MHS) subjects develop contractures on exposure to lower concentrations of halothane or caffeine than do muscle specimens from MH(−) subjects. In a recent study at our institution, MHS and MH(−) swine underwent *in vitro* contracture testing, following the standards of the North American MH Group.[6] The results showed that such standardized testing is highly sensitive (100%) and specific (90–100%) for determining MH susceptibility.

The simultaneous exposure of muscle fascicles to both 1% halothane and increasing concentrations of caffeine has been proposed as an even more sensitive test of MH susceptibility.[7] However, the validity of this test has been questioned because of the high false-positive rates associated with it.[8,9] This test was not used for MH diagnosis at Hahnemann University during the study period 1985–1988. However, it was performed for research purposes in some patients and we report the results that are available.

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TABLE 1. Indications for Muscle Biopsy and Contracture Testing in MH(−) Patients Subsequently Receiving Anesthesia

Indication for MH Testing	Subsequent Anesthesia by Group		
	Trigger	Nontrigger	Regional
Masseter muscle rigidity	6	2	1
Positive family history	4	7	6
Other myopathy	2	0	0
Perioperative temperature elevation	4	5	1
Previous suspicious episode during anesthesia*	0	2	2

* Suspicious signs of MH present, but eventually another etiology discovered, *e.g.*, allergic drug reaction, sepsis, or endocrine disorder.

Results

A total of 177 contact letters were sent; 15 were returned because the patients had moved. Of the 82 (51%) who replied, 45 patients (55%) had received anesthesia one or more times since their MH testing. Complete medical records were available for 54 anesthetic exposures in 42 patients. The indications for MH testing in these 42 patients are listed in table 1, while table 2 gives details of the *in vitro* contracture responses.

The characteristics of these 42 MH(−) patients are shown in table 3. None of the 42 patients who had previously tested MH(−) developed any signs of MH during subsequent anesthetic exposures. In 41/42 patients, the MH history and negative test results were discussed with the patients and documented in the anesthesia record. The MH history was not discussed or documented in one patient who received regional anesthesia.

The triggering anesthetic agents received by patients are listed in table 4. Succinylcholine was avoided in six patients in this group where it was considered contraindicated (four patients with previous masseter muscle rigidity, one patient with myotonic dystrophy, one patient who developed increased temperature after succinylcholine), and this was also noted in the records. In four patients, the anesthesiologist who had recommended MH testing subsequently administered anesthesia with a volatile anesthetic agent ± succinylcholine.

We examined the anesthetic experience of MH(−) patients who were subsequently managed as if MHS. Eleven of 26 patients were documented to be managed as if MHS during 15 anesthetic exposures, although the MH test results were known to be negative. In six of these patients, the anesthesiologist who had recommended MH testing subsequently managed the patient as if MHS. Two patients received preoperative iv dantrolene prophylaxis, 2.5 mg/kg in addition to nontriggering general anesthesia.

No documented perioperative complications occurred in patients receiving triggering agents or regional anesthesia. There were six minor complications in patients who received nontriggering general anesthesia. One patient complained of distressing weakness and a feeling of suffocation after a prophylactic dose of dantrolene. One patient suffered from postoperative delirium. Another patient required physostigmine and naloxone for reversal of anesthetic effects; two other patients required naloxone only. The lungs of one patient who underwent abdominal hysterectomy were mechanically ventilated postoperatively "to avoid reversal of neuromuscular blockade in a possibly MHS patient."

In patients receiving regional anesthesia, spinal or epidural anesthesia was used in seven of 11 cases (five cases for labor or caesarean section, two cases for lumbar laminectomy). In six of 11 cases, an amide local anesthetic agent was used; in three cases an ester group agent was

TABLE 2. Results of Caffeine Halothane Contracture Testing for all MH(−) Patients Reviewed

Test	Mean ± SD (n)	Range
3% Halothane (g)	0.33 ± 0.20 (42)	0–0.7
2 mM Caffeine (g)	0.01 ± 0.02 (39)	0–0.1
HCSC* (mM)	1.15 ± 0.82 (8)	0.4–3
	HCSC ≤ 1 mM in 5/8 patients	

* HCSC = halothane-caffeine specific concentration, caffeine concentration combined with 1% halothane required to produce 1-g contracture.

TABLE 3. Characteristics of MH(−) Patients Reviewed by Group

	Trigger	Nontrigger	Regional
Number of patients	16	16	10
Mean age (yr)	25	24	33
Age range	3–64	5–37	23–65
Sex (M:F)	4:12	4:12	4:6
Number of anesthetic exposures	23	20	11
Range of duration of anesthetic exposure (h)	0.6–7.0	0.5–6.0	0.7–3.5
Type of Procedure			
General surgical	5	3	1
Ear/nose/throat	7	4	0
Gynecological	5	4	0
Obstetrical	0	1	5
Plastics	3	1	2
Oral/dental	2	4	1
Spinal surgery	0	2	2
Other orthopedic	1	1	0

TABLE 4. Triggering Anesthetic Agents Received by MH(−) Patients Subsequent to MH Testing

	Isoflurane	Enflurane	Halothane
Number of exposures	11*	5	7
Maximum concentration (range)	0.6–2%	1–3%	1.5–4%
Duration of exposure (range)	1–3.5 h	0.7–7 h	0.6–3 h

* Succinylcholine was administered on four occasions prior to isoflurane.

administered; in two cases the agent used was not documented.

The results of the combined 1% halothane/caffeine test are shown in table 2. Five of eight patients had "abnormal" responses,[7] *i.e.*, ≤1.0 mM. All five of these patients received triggering anesthetic agents without incident. Three of the five patients received such anesthesia on two separate occasions.

Discussion

In this study, we have documented 23 uneventful administrations of general anesthesia with MH triggering agents to 16 patients previously tested MH(−) by caffeine halothane contracture testing. Seven of 16 patients were exposed to MH triggering anesthetic agents on two separate occasions. No episodes of MH were documented in any patient. These cases support our belief that triggering anesthetic agents can be used safely in patients who have tested negative for MH susceptibility.

Our study is limited by the small number of patients surveyed, although the response rate to our contact letters was high. To our knowledge, this is the first reported follow-up study of anesthesia in MH(−) patients. A larger sample size can only be provided by a multicenter study, perhaps in collaboration with the Malignant Hyperthermia Association of the United States (MHAUS), or the North American Malignant Hyperthermia Registry.[5]

Although an uneventful exposure to triggering anesthetic agents does not rule out MH susceptibility,[10] none of the 23 patients who received triggering agents developed clinical signs suspicious of MH during subsequent anesthetic exposure. Our impression from the records was that the index of suspicion for early MH was high among anesthesiologists managing these patients. Therefore, it seems unlikely that early or aborted MH was overlooked.

One cannot ethically challenge an MHS patient with triggering anesthetic agents in order to validate a positive contracture test result. This has been done in swine, where a clear discrimination can be made between MHS and MH(−) animals. MH(−) swine did not develop even subtle signs of MH during exposure to halothane and succinylcholine.[11] In our own studies of known MHS and MH(−) swine,[6] the results of *in vitro* contracture testing were in agreement with the *in vivo* response to challenge with halothane and succinylcholine.

Eleven patients with a negative contracture test were managed as if MMH. Some clinicians seem reluctant to rely on contracture testing to rule out MH susceptibility. Such management may have led to the higher number of complications noted in these patients, as clinicians opted for less-familiar anesthetic techniques. In addition, dantrolene prophylaxis is controversial even in known MHS patients.[12,13] It is questionable if the two MH(−) patients who received prophylactic iv dantrolene derived any benefit from it; one patient had distressing side effects.

Of interest are the results of the combined 1% halothane/caffeine test in patients who received triggering anesthetic agents (table 2). This test was performed on eight patients, five of whom had a result considered abnormal by those who rely on this test for MH diagnosis.[7] Three of five of these patients received anesthesia twice with known MH-triggering agents without incident. The validity of this test has been questioned by others[8,9] because of high rates of false-positive diagnoses. In our experience with known MHS and MH(−) swine, the results of the combined 1% halothane/caffeine test overlapped to the extent that diagnosis was impossible.[6]

Six MH(−) patients who were tested after developing masseter muscle rigidity (MMR) with succinylcholine had received anesthesia nine times with volatile anesthetic agents since they had their MH testing. Neither MH nor MMR occurred in any of these patients. This is to be expected, since over 50% of patients with MMR are MH(−).[14] None of these patients have subsequently received succinylcholine. We continue to recommend that succinylcholine be avoided in all patients with previous MMR.

In conclusion, we observed that 16 MH(−) patients received anesthesia with known MH triggering agents without incident. Although the number of patients reported is quite small, these findings support the diagnostic accuracy of a negative contracture test for MH when testing is conducted using widely accepted standards. However, cautious interpretation of these results is recommended until larger numbers of patients have been studied. We encourage clinicians to report their experiences with such patients through such agencies as MHAUS.

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