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Plasma Levels of Dantrolene following Oral Administration in Malignant Hyperthermia-susceptible Patients

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Reports of the lack of protection following oral dantrolene prophylaxis have led some authors to recommend only intravenous administration of dantrolene for prophylaxis against malignant hyperthermia at induction of anesthesia. The authors determined whether a specific regimen of preoperative oral dantrolene would result in protective blood levels at induction of anesthesia, and in the postoperative period. Ten malignant hyperthermia-susceptible (MHS) patients were given a total dose of 5 $mg \cdot kg^{-1}$ of oral dantrolene in three or four divided doses, every 6 h, with the last dose 4 h preoperatively. Plasma dantrolene levels were determined by reverse phase high pressure liquid chromatography at induction of anesthesia and every 6 h thereafter for 48 h. All ten patients had plasma dantrolene levels over 2.8 $\mu g \cdot ml^{-1}$ at induction of anesthesia, for at least 6 h and, in three patients, up to 18 h after induction. Every patient had an uneventful perioperative course. Side effects (drowsiness, weakness) occurred in seven patients. An elimination half-life of 15.8 ± 6.0 h was determined. In contrast to intravenous dantrolene, this specific oral dantrolene regimen resulted in protective plasma levels for 6–18 h after induction of anesthesia. These results were likely due to the relatively high bioavailability of oral dantrolene and, possibly, to continued absorption of dantrolene in the postoperative period. (Key words: Hyperthermia, malignant: prophylaxis. Neuromuscular relaxants, dantrolene: pharmacokinetics; prophylaxis. Pharmacokinetics: dantrolene.)

SINCE 1975, DANTROLENE has been shown to be effective in the prevention and treatment of malignant hyperthermia crisis, such that mortality has dropped from 70% in 1975 to less than 10% today.[1] The efficacy of oral dantrolene prophylaxis has been questioned because of case reports of MH crisis despite oral prophylaxis,[2,3] as well as concern over possible side effects. This has led some authors to recommend only intravenous (iv) dantrolene for prophylaxis at induction of anesthesia.[1,4]

Because of the uncertain efficacy of oral dantrolene prophylaxis, we determined whether a specific regimen of preoperative oral dantrolene would result in blood levels considered protective in the perioperative period.

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Materials and Methods

The study protocol was approved by the hospital research ethics committee, and all subjects provided informed consent.

Patients were included in the study if they were undergoing elective surgery and had a personal or family history of malignant hyperthermia-susceptibility, or a positive muscle biopsy by *in vitro* caffeine-halothane contracture studies.[4] Patients were excluded if pregnant, if hepatic disease was present, or if the study protocol was broken. Demographic data are shown in table 1.

In accordance with FDA recommendations,[5] a total dose of 5 $mg \cdot kg^{-1}$ of oral dantrolene (Dantrium, Norwich-Eaton-Pharmaceuticals, Cambridge, Ontario) was given in three or four divided doses every 6 h, with the last dose administered 4 h preoperatively. The number of doses depended on the time available from the patient's admission to the ward on the afternoon prior to the day of their scheduled surgery, until the scheduled operating room time. Because of possible weakness or dizziness, patients were asked not to get out of bed without assistance. Information regarding side effects was collected from the patients, nursing staff, and attending physicians pre- and postoperatively.

A baseline sample of venous blood was drawn prior to the first dose of dantrolene. Blood samples were then drawn at induction of anesthesia and every 6 h thereafter for 48 h, or until the patient was discharged from hospital. The plasma was separated and frozen at −70° C until assayed.

The plasma dantrolene assay was performed as follows:[6] 50 μl aliquots of plasma were precipitated with 100 μl of acetonitrile, vortexed, and centrifuged for removal of plasma proteins. Twenty-five microliters of the clear supernatant was injected onto a reverse phase high pressure liquid chromatographic column (LiChrosorb RP-18, 10 μ, 250 cm × 4.6 mm ID, Merck, Darmstadt, W. Germany). The isocratic mobile phase consisted of acetonitrile: 20 mM aqueous glycine (35:45, v/v) with a final *p*H of 3.5 at ambient room temperature. Using a flowrate of 2 ml/minute, dantrolene had a retention time of 6.5 min. Detection was by an in-line ultraviolet absorption spectrometer (Waters Assoc., Ontario, Canada, Model 440) at 405 nanometers. Quantitation was by comparison to peak heights to external dantrolene standards in human plasma. Reproducibility of repeated sample injection was

TABLE 1. Demographic Data, Surgical Procedure, and Anesthetic for Patients Receiving Oral Dantrolene

Patient	Age/Sex (Yr)	Weight (kg)	History	Procedure	Anesthesia
1	14/M	70	FH	Arthroscopy, knee	Spinal (tetracaine)
2	29/F	82	FH	Laparoscopy	General (fentanyl, droperidol, STP, N_2O/O_2, atracurium)
3	16/M	61	FH	Shoulder repair	General (fentanyl, droperidol, STP, N_2O/O_2, pancuronium)
4	29/F	83	FH	Cholecystectomy	General (fentanyl, droperidol, STP, diazepam, N_2O/O_2, pancuronium)
5	24/F	52	FH, bx	Hysterectomy	General (fentanyl, droperidol, STP, diazepam, N_2O/O_2, pancuronium)
6	40/F	86	FH	Hysterectomy	General (fentanyl, droperidol, STP, N_2O/O_2, pancuronium)
7	21/F	54	FH, crisis, bx	Septoplasty	General (fentanyl, droperidol, STP, N_2O/O_2, vecuronium)
8	44/F	52	FH, bx	Urethropexy	Epidural (carbonated lidocaine with 1:200,000 adrenalin)
9	22/F	48	FH	Wisdom teeth extraction	General (fentanyl, droperidol, STP, N_2O/O_2, vercuronium)
10	64/F	56	FH, bx	Osteotomy, foot	Spinal (tetracaine)
X ± SD	30.3 ± 14.4	64.4 ± 13.9			

FH = family history of malignant hyperthermia; bx = positive muscle biopsy.

documented by a coefficient of variation less than 5%. Using this method, dantrolene could be quantitated to at least 0.5 $\mu g \cdot ml^{-1}$ in plasma. Storage of plasma standards revealed insignificant drug loss over the time interval between collection and assay. The methodology easily distinguished between dantrolene and its metabolites.[6]

Results

Fourteen patients were initially enrolled into the study. One was excluded because of pregnancy, and three others were subsequently excluded because of significant breaks in the study protocol (incorrect dantrolene dose in two patients, interdose interval greater than 8 h in one patient). Ten patients completed the study, eight of whom were women (table 1). All ten patients had a family history of MH, four patients had a positive muscle biopsy by *in vitro* halothane-caffeine contracture testing,[4] and one patient had an MH crisis in the past. None of the patients were obese or very thin.

All patients underwent elective surgery without major fluid shifts or volume replacement. Patients were admitted to the hospital the afternoon of the day before surgery, unless earlier admission was indicated for a reason not related to the study. All patients were premedicated with oral diazepam and/or intramuscular morphine. Seven patients received general anesthesia not associated with triggering malignant hyperthermia, and three received regional anesthesia (table 1). Intraoperative monitoring included ECG, automated blood pressure cuff, axillary temperature probe, capnography, and pulse oximetry. Residual muscle paralysis was reversed with an anticholinesterase (edrophonium or neostigmine) and atropine.

All ten patients had an uneventful perioperative course, with no evidence of MH crisis. No patient had their admission to hospital prolonged as a result of side effects from oral dantrolene prophylaxis. Three patients (patients 1, 2, and 9) were discharged from hospital on the first postoperative day; the rest were discharged when deemed appropriate by the attending surgeon.

Plasma dantrolene levels for ten patients from induction of anesthesia until 24 h after induction are shown in table 2. All patients had plasma levels of 2.8 $\mu g \cdot ml^{-1}$ or more at, and 6 h after, induction of anesthesia. Three patients had levels of 2.8 $\mu g \cdot ml^{-1}$ or more 18 h after induction of anesthesia. Figure 1 illustrates the change in plasma dantrolene concentration from time of induction until 48 h after induction of anesthesia.

Prior to induction of anesthesia, three patients described a feeling of weakness, especially in their legs. Five patients felt drowsy or sedated, and three patients had no apparent side effects. Similar, but milder, side effects were

TABLE 2. Plasma Dantrolene Levels, n = 10

Patient	Total Dose (mg/kg)	Preoperative Side Effects	Induction Level (μg/ml)	6 h Level (μg/ml)	12 h Level (μg/ml)	18 h Level (μg/ml)	24 h Level (μg/ml)	T 1/2B (h)
1	5.0	Drowsy	5.4	4.9	3.2	2.8	1.9	14.1
2	4.9	Drowsy/weakness	4.1	2.9	2.7	2.1	1.8	25.2
3	4.9	Drowsy	4.1	3.2	—	1.1	0.9	8.8
4	5.4	Drowsy	10.2	—	4.3	3.6	2.5	—
5	4.8	None	3.3	2.9	2.5	1.4	1.2	22.6
6	4.6	None	5.5	4.6	4.4	2.8	1.9	—
7	4.6	Weakness	6.3	5.0	3.6	2.7	1.3	12.7
8	4.8	Weakness	3.9	2.9	2.5	2.0	1.1	15.7
9	5.2	Drowsy	5.5	3.1	2.0	1.5	0.9	11.4
10	4.0	None	6.8	3.6	2.0	0.9	0.5	—
X ± SD	4.8 ± 0.4		5.5 ± 1.9	3.7 ± 0.9	3.0 ± 0.9	2.1 ± 0.8	1.4 ± 0.6	15.8 ± 6.0

reported postoperatively, but did not prevent ambulation of these patients. No patient suffered from choking or swallowing difficulties, nausea, vomiting, or diarrhea, nor was there any clinical evidence of cardiorespiratory depression. Plasma dantrolene concentrations were not related to the presence of side effects.

The elimination half life was determined to be 15.8 ± 6.0 h, with a range of 8.8–25.2 h (table 2).

Discussion

In the present study, we found that this specific regimen of preoperative oral dantrolene produced plasma levels that would be considered protective at induction of anesthesia, and for as long as 18 h after induction of anesthesia. This would imply that protection carried over into the immediate postoperative period, when MH crisis most often presents.[4] Patients did not suffer major side effects; in particular, gastrointestinal upset was not seen. Finally, hospitalization was not prolonged by oral dantrolene prophylaxis.

Our protocol was consistent with the way we routinely manage MHS patients. Such patients are not eligible for same-day surgery requiring general or major regional anesthesia. They are usually admitted to the hospital on the afternoon prior to the day of their scheduled surgery. Postoperatively, MHS patients are kept in the Recovery Room for at least 4 h and temperature, heart rate, and ECG are continuously monitored. They are not discharged from the hospital before 24 h following surgery. An alternate approach would have been to admit the patients on the same day of surgery and give iv dantrolene immediately prior to induction of anesthesia, or to have patients begin oral dantrolene prophylaxis at home 1 day prior to their surgery.

We chose a total oral dantrolene dose of 5 $mg \cdot kg^{-1}$ because it met the current FDA recommendations,[5] and minimal side effects were anticipated with this dose. The

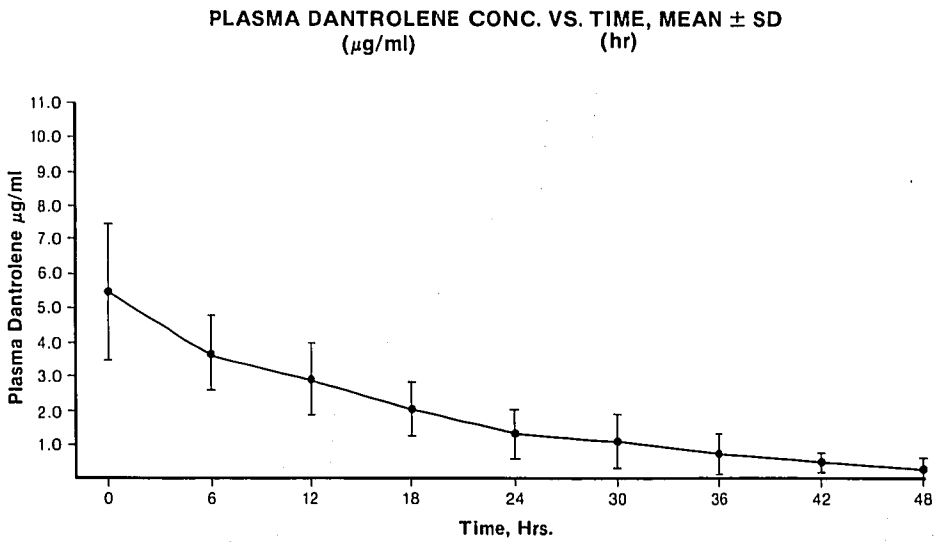

FIG. 1. Plasma dantrolene concentration (mean ± one standard deviation) following induction of anesthesia (time 0 h) until 48 h postoperatively.

dosing schedule used for each patient was individualized and reflected the time available preoperatively (usually 12–16 h), from time of admission to the booked OR time. The necessity for this regimen to be practical was always kept in mind.

What constitutes a blood level of dantrolene consistent with protection against malignant hyperthermia is not clear, but some guidelines are available. In MHS swine, Flewellen and Nelson have shown that a dose of iv dantrolene that is at least 95% of the maximal muscle depressant dose proved both prophylactic and therapeutic for MH triggered by halothane-succinylcholine challenge.[7]

Assuming a similar relationship in humans, these investigators theorized that the same level of muscle twitch depression would also provide protection in human subjects.[8] Ninety-five percent of maximal twitch depression was produced by an iv dantrolene dose of 1.6 $mg \cdot kg^{-1}$, resulting in a blood level of 2.8 $\mu g \cdot ml^{-1}$. Using an iv dose of 2.4 $mg \cdot kg^{-1}$ of dantrolene produced 100% of maximal twitch depression, and a blood level of 4.2 $\mu g \cdot ml^{-1}$. Other investigators have found a similar correlation between blood dantrolene level and twitch depression.[9]

Thus, Flewellen and Nelson recommended 2.4 $mg \cdot kg^{-1}$ as the prophylactic iv dantrolene dose in humans. Blood levels greater than 4.2 $\mu g \cdot ml^{-1}$ would not seem to be more protective as twitch depression plateaus at that blood level. The lower safe blood level of dantrolene is unknown, but it would seem prudent to maintain levels of at least 2.8 $\mu g \cdot ml^{-1}$.

The clinical efficacy of iv dantrolene prophylaxis has not been studied intensively.[9] In one abstract where six patients received 2.4 $mg \cdot kg^{-1}$ of iv dantrolene prior to induction of anesthesia, only three patients had blood dantrolene levels over 2.5 $\mu g \cdot ml^{-1}$ 6 h after induction of anesthesia.[10] The authors concluded that the minimal effective blood level of dantrolene is not known. In addition, the infusion rate of dantrolene was faster than that used in the previous non-clinical study,[8] but the elimination half-time was the same, 12 h.

The major reason for the plasma levels seen in our patients may have been the relatively high bioavailability (70%) of oral dantrolene.[9] In addition, the initial portion of the plasma dantrolene concentration *versus* time curve (fig. 1) is less steep than that seen with iv dantrolene.[10] This was likely due to continued absorption of dantrolene from the GI tract.

Side effects appear to be a more significant problem following iv dantrolene prophylaxis than were seen in this study. Nelson and Flewellen reported altered sensorium and muscle weakness lasting up to 48 h in their 12 non-MHS subjects associated with difficulty in walking, especially down stairs.[8] Four subjects complained of "disequilibrium," one was nauseated and vomited, and one had difficulty swallowing and a choking episode. All 12 subjects complained of fatigue 24 h after the last dose. Such effects might delay the discharge of a patient from the hospital. It is possible that our patients had some of their side effects masked by preoperative sedation, anesthetic, and analgesic medications, although one might expect more side effects in patients who are exposed to a larger number of drugs.

A recent case report of the use of prophylactic iv dantrolene described similar adverse effects.[11] The patient, a healthy 19-yr-old male, received 2.5 $mg \cdot kg^{-1}$ of iv dantrolene 30 min prior to the induction of anesthesia. He subsequently developed marked fatigue associated with impaired swallowing. Spinal anesthesia was then induced, producing a T-3 block, whereupon the patient developed respiratory difficulty. This was presumed to be due to the combination of dantrolene and a high level of spinal anesthesia.

Another disadvantage of iv dantrolene is its cost. At our hospital, 5 $mg \cdot kg^{-1}$ of oral dantrolene for a 70-kg patient (350 mg) costs $1.67. Intravenous dantrolene, 2.5 $mg \cdot kg^{-1}$ (175 mg), would cost $239.00. Patient care was, therefore, less expensive using oral dantrolene. It is true, however, that patients scheduled for same-day surgery and who receive iv dantrolene would benefit from a greater cost reduction than that afforded by oral dantrolene, because 2.5 $mg \cdot kg^{-1}$ of iv dantrolene is less expensive than an additional day of hospitalization. Not all patients are candidates for same-day surgery; in our case, only four patients (patients 1, 2, 7, and 9) would otherwise have been candidates for same-day surgery at our hospital.

In addition to 175 mg of iv dantrolene, a 70-kg patient would also receive 27 gm (0.38 $gm \cdot kg^{-1}$) of mannitol. Mannitol is added to the dantrolene powder to make the solution isotonic.[4] This dose of mannitol is sufficient to produce an osmotic diuresis, with loss of fluids and electrolytes. For this reason, it is recommended that patients receiving intravenous dantrolene also have a urinary catheter in place.[8] Furthermore, patients with poor left ventricular function may not tolerate an increased intravascular volume. Patients with poor renal function may also be at additional risk.[12]

Other disadvantages of iv dantrolene include phlebitis and tissue necrosis due to its alkaline pH of 9.5 if extravasation occurs.[9] It is recommended that dantrolene be given into a large vein, through a free-flowing, large-bore iv catheter. This may be difficult in some patients, particularly pediatric patients.

Can oral dantrolene prophylaxis fail to prevent MH crisis? There have been two reported cases of "failure" following the use of oral dantrolene.[2,3] In the first case, the patient received only 3.3 $mg \cdot kg^{-1} \cdot day^{-1}$ for 2 days; the time interval from the last dose was not reported.[2] The patient received a "non-triggering" general anes-

thetic with thiopental, fentanyl, droperidol, N_2O in O_2, and pancuronium. The diagnosis of MH crisis was made 60 min into the procedure. In the second case, the patient received 4 $mg \cdot kg^{-1}$ orally 1 day preoperatively, then 1 $mg \cdot kg^{-1}$ iv dantrolene at induction of anesthesia.[3] The authors did not describe the details of their dosing schedule, nor the time interval between the last dose and the beginning of anesthesia. The patient received no preoperative sedation. A "non-triggering" general anesthetic of thiopental, fentanyl, N_2O in O_2, and pancuronium was administered; MH crisis was diagnosed 25 min intraoperatively.

Wingard, in commenting on the first case, stated that the problem may have been related to the time that the dantrolene was given, not the quantity.[13] In addition, the total dose given was less than the FDA recommendation.[5] Gronert has concluded that no anesthetic regimen can ensure absolute patient safety.[14] Despite preoperative sedation, perioperative dantrolene (oral or iv), and a nontriggering general anesthetic, MH crisis can still occur.

In summary, we found that using a specific regimen of preoperative oral dantrolene, plasma levels greater than 2.8 $\mu g \cdot ml^{-1}$ were achieved at induction of anesthesia, and for 6–18 h after induction of anesthesia. Side effects were minor, and hospitalization was not unnecessarily prolonged. Preoperative oral dantrolene prophylaxis appears to be safe, effective, and is relatively inexpensive. It should be kept in mind that no anesthetic regimen will entirely remove the risk of MH crisis. Known triggering agents must be avoided even when dantrolene prophylaxis (oral or iv) is used.

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