Review Article

Dantrolene

Beverley A. Britt MD, FRCP(C)

CONTENTS

Dantrolene sodium (Dantrium, Norwich-Eaton Pharmaceuticals) is a lipid soluble hydantoin analogue[1,2] (Figure 1). It relaxes skeletal muscles by acting directly on the muscle. The site of action of dantrolene within the muscle is not yet clearly understood. It is believed, however, that it either directly or indirectly increases calcium uptake into or inhibits calcium release from the sarcoplasmic reticulum (SR). Its relaxant effect is reversed by germine monoacetate.[3] Dantrolene is presently marketed as dantrolene sodium but other dantrolene salts and analogues of dantrolene also have muscle relaxant properties.[4]

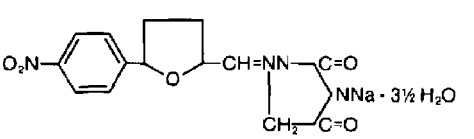
From the Departments of Anaesthesia and Pharmacology, University of Toronto, Toronto, Ontario.

Address correspondence to: Dr. B.A. Britt, Dept. of Anaesthesia, University of Toronto, Medical Sciences Bldg., Room 5271, Toronto, Ontario M5S 1A8.

Mode and site of action of dantrolene

A *Motor nerves*

Extensive *in vitro* studies on the site and mode of action of dantrolene have been done. Ellis *et al.*[5] demonstrated, by crossover circulation experiments of vascularly isolated but neurally intact hind limbs of normal dogs, that the site of action of dantrolene sodium is peripheral and not central. Furthermore, the action of d-tubocurarine (a non-depolarizing neuromuscular blocker) or of edrophonium (an anticholinesterase agent) on twitch tension is not altered by dantrolene.[5] Colton and Colton[6] have shown that, at lobster neuromuscular junctions, dantrolene sodium does not appear to affect either spontaneous or evoked transmitter release nor excitory or inhibitory end plate function. These various actions indicate, therefore, that dantrolene acts at some point distal to the motor nerves. Although Durant *et al.*[7] suggest that dantrolene decreases neuromuscular transmitter mobilization which in turn causes a reduction in the available store of acetylcholine, they suggest that this effect is due to impairment by dantrolene of calcium from bound stores within the nerve terminal. The authors feel, however, that this effect of dantrolene is unlikely to be of physiological consequence *in vivo*



Dantrolene
(Dantrium)

FIGURE 1 Dantrolene Na (Dantrium) is a benzathiazepine derivative which, by inhibiting release of calcium from the sarcoplasmic reticulum, decreases contraction and heat production in skeletal muscle during MH reactions.

since it is only observed at high frequencies of nerve stimulation and does not cause a significant reduction of end plate potential amplitude during trains of stimuli.[7]

B *Skeletal Muscle*

Dantrolene attenuates twitch tensions in skeletal muscle that is being stimulated either directly or indirectly through its nerve.[5,8] Leslie and Part[9] have shown that this inhibition of twitch tension by dantrolene sodium is greater for individual motor units than for muscle.

Microelectrode studies show that a dose of dantrolene which reduces the twitch responses of electrically stimulated skeletal muscle has no effect on either resting or action potentials of the muscle membrane.[1,10] Dantrolene does not change total membrane capacitance or membrane resistance.[11] Electromyograms (EMGs) are not altered by dantrolene. Since, therefore, dantrolene does not affect electrical excitability of the muscle membrane and does not disrupt the transverse tubules, it cannot act by decreasing electrical conduction between the postsynaptic junction and the SR.

1 SARCOLEMMA

Dantrolene has no influence on the resting influx of Ca^{++} from the extracellular fluid to the myoplasm of normal giant barnacle muscle cells.[12] Dantrolene, therefore, probably does not relax barnacle muscle cells by preventing influx of extracellular fluid calcium. Similar studies have not yet been reported on normal or MHS (malignant hyperthermia susceptible) mammalian muscle.

Dantrolene does inhibit potassium induced contractures of normal intact skeletal muscle fascicles.[11–18] On the other hand, Brocklehurst[19] has shown that dantrolene sodium does not alter any aspect of potassium induced contractures of frog muscle fibres regionally (but not completely) skinned by mechanical means. These experiments suggest that dantrolene prevents calcium release from the SR by an indirect action which requires an intact sarcolemma. For instance, dantrolene might inhibit release of regenerative or trigger calcium from the sarcolemma. This postulation is supported by the observation of Oba[20] that extracellular dantrolene sodium always depresses twitch tension of frog skeletal muscle while intracellularly injected dantrolene sodium transiently increases and then decreases frog muscle twitch tension. These effects are more potent at high than at low temperatures.

In MHS, but not in normal swine muscle halothane depolarizes the sarcolemma of skeletal muscle. This depolarization is reduced by dantrolene.[21] At least in MHS pig muscle, therefore, dantrolene sodium might have a primary, though not necessarily exclusive, action on the sarcolemma. Dantrolene might act by displacing regenerative ("trigger") calcium from binding sites on the transverse tubular membrane to the extracellular fluid.[20]

It is of interest that in chicks succinylcholine produces rigid paralysis, hyperpyrexis and death.[22] Dantrolene 2.5 and 5.0 $mg \cdot kg^{-1}$ provides marked protection against these events. The muscle cells of fowls have multiple motor end plates whereas the muscle of normal mammals have only one motor end plate per cell.[22] The adverse response of chicks to succinylcholine might be due to the drug acting on many, rather than one, cholinergic neuromuscular receptor, thereby creating an excessively rapid rise in myoplasmic calcium.[22] Could it be that the sarcolemma of MHS mammals also contains multiple rather than single cholinergic neuromuscular receptors, and perhaps also a greater than normal complement of adrenergic receptors?

2 SARCOPLASMIC RETICULUM (SR)

a Calcium Release

The effect of dantrolene on calcium release from the SR has been studied by several investigators using *in vivo* and *in vitro*, and direct and indirect techniques.

Ellis and Carpenter[23] and Krarup[8] have reported that in the rat diaphragm, dantrolene inhibits direct and indirect electrically induced twitch responses, and antagonizes caffeine potentiation of twitch responses. They have also found that the addition of EDTA increases, while the addition of calcium decreases these various dantrolene effects. These *in vitro* responses, at least in normal muscle, are unaltered by curare.[11,14,15,24] Morgan and Bryant[25] using a voltage clamp technique, have noted that dantrolene makes the action potentials of frog, rat and goat skeletal muscle more positive and increases the steepness of the strength duration curve for mechanical threshold. Desmedt and Hainaut[12,26] have observed that in giant barnacle muscle fibres micro-injected with the photoprotein

aequorin, the resting rate of light emission reversibly decreases upon exposure to dantrolene. Since aequorin emits light only in the presence of calcium this experiment suggests that dantrolene lowers the concentration of calcium in the myoplasm. They postulate that dantrolene reduces the number of Ca^{++} releasing sites at the SR membranes activated by a given depolarization. Other work has demonstrated that dantrolene inhibits electrically[14] induced Ca^{++45} release from the SR to the myoplasm of normal frog skeletal muscle cells. Nelson and Flewellen[27–30] have noted that dantrolene, but not procainamide, inhibits indirectly evoked foretoe twitches of normal and MHS pigs. The addition of halothane augments this dantrolene depression of MHS but not of normal pig foretoe twitches. Anderson and Jones[31] have found that dantrolene pretreatment inhibits *in vitro* twitch amplitude of normal and MHS pig muscle in the absence and in the presence of halothane. In both normal and MHS muscle the twitch inhibition induced by halothane is reversed by caffeine (2.8 mM). Their paper, however, does not compare twitch heights observed in the presence of caffeine alone to those observed in the presence of caffeine with dantrolene. The ability of dantrolene to depress twitch tension is greater in rat extensor digitorum brevis (a fast muscle) than in rat soleus (a slow muscle).[32]

These various *in vivo* and *in vitro* findings suggest that dantrolene, in both normal and MHS muscle, in some way prevents release of calcium from the SR to the myoplasm, either by a direct action or by inhibition of release of "trigger" or "regenerative" calcium from the sarcolemma or by inhibition of the excitation-contraction (EC) step between the transverse tubules and the sarcoplasmic reticulum.

Confusingly, Nelson[29] has claimed that dantrolene augments, in normal pig and human skeletal muscle fascicles, caffeine potentiated twitch tensions at 2.0 but not at 0.5 or 1.0 mM concentration of caffeine. However, Nelson explains this apparent contradiction of other workers' results by postulating that dantrolene, by improving calcium uptake into the SR has, therefore, made more calcium available for release and so ensuing twitch tensions become correspondingly greater.

b Calcium Uptake

Evidence for acceleration by dantrolene of calcium uptake into the SR is not unequivocal. Some investigators, such as Anderson and Jones,[31,33,34] Nelson[27,35] and Okumura *et al.*[18] have observed that dantrolene does inhibit caffeine and/or halothane induced contractures of MHS swine or human skeletal muscle. Halsall and Ellis found that dantrolene inhibits succinylcholine induced contracture in caffeinated muscle fascicles isolated from MHS and normal humans.[16] Okumura *et al.*[18] reported a statistically non-significant inhibition by dantrolene of caffeine, three per cent halothane and thymol induced contractures of MHS swine muscle. Similarly, Fairhurst *et al.*[17] found that dantrolene inhibits ryanodine induced contractures, both in the presence and in the absence of halothane potentiation. Other workers, however, have claimed that dantrolene sodium has no influence on caffeine induced contractures of normal rat phrenic and frog sartorius muscles.[11,14] These apparent discrepancies might in part be due to non-uniform experimental techniques.

We are aware of at least three MHS patients who have had two skeletal muscle biopsies each – one without and one with *in vivo* dantrolene pretreatment. The skeletal muscle fascicles of one patient reported by Rosenberg[36] developed caffeine and also halothane induced contractures which were not inhibited by prior *in vivo* dantrolene sodium administration. However, the skeletal muscle fascicles of two other patients, one reported by Lambert[37] and the other measured by ourselves,[38] developed caffeine and halothane induced contractures which were substantially less after, than before, *in vivo* dantrolene sodium therapy.

Thus, some but not all studies suggest that dantrolene increases calcium uptake into the SR. Since, however, these studies have been done on intact skeletal muscle fascicles, they do not elucidate whether the action of dantrolene is directly on the SR or is mediated indirectly via the sarcolemma or the E-C coupling step.

Furthermore these caffeine induced contractures may not be due to increased calcium uptake into the SR but rather may be due to continued excessive calcium release from the SR during the intervals between twitches. The extent of this caffeine induced calcium release may be so great that the muscle becomes incapable of complete relaxation between twitches. The influence of the dantrolene on so called "resting tension" therefore may in

reality be an effect on calcium release from the SR rather than calcium uptake into the SR.

c Calcium binding

Studies with (C^{14}) dantrolene have shown that the mitochondria and SR of pig heart and skeletal muscle bind to the drug with low affinity. In addition skeletal muscle SR possesses a separate class of sites which bind dantrolene with high affinity. These high affinity sites suggest a specific site of action for this drug on skeletal muscle SR.[39] However, the isolation technique employed for the SR does not remove the E-C coupling step at the gap junction. The high affinity binding sites, therefore, are in this location rather than in the SR.

3 HEART MUSCLE AND VASCULAR SMOOTH MUSCLE

In the past, dantrolene has been stated to have no significant action on vascular smooth muscle or on heart muscle.[5,40–46] More recent work, however, has shown that dantrolene does alter the function of both vascular and heart muscle. Thus Ally *et al.*[47] have reported that dantrolene blocks intracellular calcium release from the smooth muscle of the superior mesenteric arteries of rats by competitively antagonizing throboxane A_2. Bailey and his colleagues[48] observed that dantrolene inhibits the positive inotropic effects of Anthopleurin-A (a potent cardiostimulant polypeptide) on rat and rabbit atria. Plizga and Hall[49] noted that dantrolene reduces the contractile force of isolated rabbit left atria without altering the effective refractory period, suggesting to them that the inhibitory effect of dantrolene on cardiac muscle is on the SR and not on sarcolemmal excitability.

More recently Hatae *et al.*[50] found that in guinea pig and frog myocardia dantrolene increases twitch tension amplitudes and prolongs action potentials. These workers concluded that dantrolene increases the slow inward calcium current. They also observed that in guinea pigs, but not in frogs, the dantrolene-induced increase in twitch tension is preceded by a transient reduction in myocardial twitch tension. They attributed this to inhibition of calcium release from the SR by dantrolene similar to that postulated for skeletal muscle.

Salata and Jalife[51] described selective effects of dantrolene in dog Purkinje muscle. Thus dantrolene prolongs action potential duration at 90 per cent repolarization and effective refractory period of normally polarized fibre, depresses the plateau phase of the action potential and decreases strength of contraction. Dantrolene, however, has no significant effect on resting membrane potential, upstroke velocity of phase O, conduction velocity or pacemaker activity of Purkinje fibres.[51] Salata and Jalife feel that dantrolene acts in Purkinje fibres by interfering with the slow inward current.

4 OTHER TYPES OF SMOOTH MUSCLE

Dantrolene has been claimed by Harris and Benson[52] to have no significant inhibitory effect on acetylcholine-induced canine detrusor muscle contractions. However, Khalaf *et al.*[53] observed that dantrolene causes dose-dependent depression of maximal canine urethral and bladder pressures. In humans Hackler *et al.*[54] noted that in some spinal cord injured patients dantrolene decreased urethral pressures and lowered residual urine volumes. Dantrolene reversibly reduces the amplitude of calcium induced contractions of rabbit jejunum *in vitro*.[55] Thus dantrolene might act on intestinal and bladder smooth muscle by inhibiting calcium movement across the cell membranes.[55]

In vivo use of Dantrolene in MHS humans and pigs

A *During acute MH reactions*

The efficacy of intravenous dantrolene sodium in the therapy of MH crises was first observed by Harrison.[56] He noted that dantrolene relieved halothane induced MH reactions of susceptible Landrace swine. Other investigators soon reported that intravenous dantrolene was beneficial in the therapy of MH reactions in other strains of pigs, for instance, Pietrain,[57,58] Poland China,[59] and Landrace[60] hogs.

B *Intravenous dantrolene formulations*

Dantrolene began to be used in the treatment of human MH reactions in 1975.[38] As the intravenous lyophilized formulation was not officially approved at that time these early patients were treated with a variety of non-official formulations, in most of which only an infinitesimal fraction of the added dantrolene actually dissolved and became available to the muscle cells. Furthermore, because preparation of these "homemade" dantrolene solutions usually began only after diagnosis of the MH

reactions, the majority of the early patients began to receive their dantrolene only after prolonged delays – often of several hours.

The first intravenous dantrolene formulation was that employed by Harrison to treat MH crises in pigs.[56] It consisted of dantrolene 300 mg, Mannitol 26.64 grams, sodium hydroxide 48 mg and water ad 600 ml. The disadvantage of this formulation was that several hours of stirring was required to achieve solubilization of the dantrolene – and once solubilized the dantrolene remained effective for only about six hours.

A simpler technique was to place five 100 mg capsules of dantrolene in a one litre bottle of warm 15 or 20 per cent mannitol and shake. The resulting dantrolene solution was run through a millipore blood filter placed in the intravenous line. Since no sodium hydroxide was used in this formulation the common ion effect of Harrison's formulation was avoided and so the amount of dantrolene dissolved was greater.[61]

A rather different formulation was that of Fukuchi *et al.*[62,63] who prepared dantrolene by sealing 1400 mg of crystalling dantrolene in an ampoule which was then heat sterilized at 105° C for 60 minutes. Three hundred and fifty ml of aqueous solution of 1.0 M nicotinamide was placed in a separate vial and subjected to autoclave sterilization. When needed these two vials were mixed to give 0.4 W/V per cent of dantrolene at pH 9.0–10.3.

Another Japanese formulation was described by Tomonaga *et al.*[64] They dissolved dantrolene by using cyclodextrin.[64]

In order to achieve a preparation that would dissolve rapidly and which would also remove the starch, talc, magnesium, stearate and lactose present as binding agents in dantrolene capsules, Gronert *et al.*[65] recommended placing thirty-two 100 mg capsules in litres of sterile water and stirring for 30 minutes. They then filtered the resulting liquid through a 201 grade filter paper. The clear orange filtrate was sterilized by passing it through a 0.45 micron millipore filter. Eighty ml of ten per cent citric acid was added to the sterile filtrate to lower its pH to 3.0, thereby inducing precipitation of dantrolene crystals. The crystals were collected by vacuum filtration and dried overnight in a laminal flow hood. The crystals were weighed aseptically into 500 mg lots and placed in sterile 100 ml vials. When desired the crystals were reconstituted with 100 ml of a sterile aqueous solution containing 88 mg of sodium hydroxide. The suspension was immediately added to a sterile 900 ml solution containing 44.5 grams of mannitol to make the solution isotonic. The dantrolene dissolves within two to three minutes. This preparation, like that of Harrison[56] had the disadvantage of a common ion effect with the sodium hydroxide.

TABLE I Relationship between formulation of dantrolene therapy and survival from MH reactions

Dantrolene formulation	*No. of patients*			
	Died	*Survived*	*Totals*	χ^2
Official	9	75	84	9.63*
Homemade	7	8	15	
Totals	16	83	99	

*$p < 0.01$.

Fortunately, these and other[66] tedious "homemade" efforts are now past history. An official intravenous dantrolene sodium formulation was finally approved for use in North American hospitals in 1979.[67] This preparation is lyophilized in combination with sodium hydroxide and mannitol. Thus a 70 ml vial contains 20 mg of dantrolene, 3.0 grams of mannitol and enough sodium hydroxide to raise the pH to 9.5 when the material is reconstituted with 60 ml of water.

c *Epidemiology of* in vivo *Dantrolene use during MH reactions in humans*

The efficacy of dantrolene therapy for MH reactions in humans has now been demonstrated by a large number of published case reports,[68–75] personal communications* and reviews.[45,76–81] This has been done by comparing simultaneous survival rates in countries in which dantrolene has been approved for use with survival rates in countries with similar medical standards in which dantrolene has not been approved for use.

We are now aware of 99 patients who have received dantrolene between 1975 and 1981 (Table I). Seventy-nine of these have received the official formulation before cardiac arrest (Tables I–III). Seventy-two of this latter group survived, giving a

*A listing of these may be obtained by writing to the author.

TABLE II Relationship between dantrolene therapy (official formulation, begun pre arrest) and survival from MH reactions

	No. of patients			
*Dantrolene**	*Died*	*Survived*	*Totals*	χ^2
Used	7	72	79	4.94†
Not Used	76	299	375	
Totals	83	371	454	

*Patients who received homemade formulations of dantrolene or who received first dose of dantrolene post arrest are excluded.
†$p < 0.05$.

TABLE IV Relationship between dose of dantrolene and survival from MH reaction

	*No. of patients**	
Dose of dantrolene $mg \cdot kg^{-1}$	*Died*	*Survived*
<1.0	1	9
1.0–1.99	2	19
2.0–2.99	1	15
3.0–5.99	2	5
6.0–8.99	0	4
≥9.0	0	8

*Data include only patients receiving official formulation prior to cardiac arrest.

mortality rate of 8.86 per cent among patients treated before cardiac arrest with the official formulation. The mortality rate among the 375 patients who have had MH crises, but have not been treated with dantrolene during the same time span has been 25.42 per cent. Dantrolene has therefore been associated with a 16.56 per cent reduction in mortality ($\chi^2 = 4.94$, d.f. = 1, $p < 0.05$) (Table II). This improvement is remarkable in that the data include a number of patients who received inadequate amounts of dantrolene long after the onset of the reaction. Some of the patients who died, therefore, might have expired, not because of true failure of control of MH by dantrolene, but rather because the dantrolene reaching the muscle cells was inadequate in amount and arrived too late in the course of the reaction to prevent death.

The dose of dantrolene employed ranged from less than $1.0\,mg \cdot kg^{-1}$ to $17\,mg \cdot kg^{-1}$.[1,82] The majority of cases received less than $2.99\,mg \cdot kg^{-1}$ (Table IV). All patients who received at least $6.0\,mg \cdot kg^{-1}$ survived (Table IV). In patients not receiving dantrolene, deaths occurred following maximum temperatures as low as 37° C, while in patients receiving dantrolene no patient died whose maximum temperature was under 38.8° C (Table V). In patients who did not receive dantrolene, maximum temperatures tended to be higher than in those patients who did receive dantrolene (Table V). The highest temperature reached in the absence of dantrolene was 46° C while the highest temperature recorded in a dantrolene treated patient was 43° C. As was to be expected, survival was higher when diagnosis was made early and dantrolene infusions were promptly instituted (Table VI).

In patients dying in spite of dantrolene administration, one or more of the following was nearly always present:

1. use of a homemade formulation (which on later analysis nearly always was found to contain much less dantrolene than its creators had thought) (Table II);

2. inordinate delay in starting dantrolene therapy (often due to failure to have the official lyophilized IV dantrolene sodium formulation on hand in the operating theatre) (Table VI);

TABLE III Relationship between giving dantrolene pre vs post cardiac arrest and survival from MH reactions

	No. of patients			
Time given	*Died*	*Survived*	*Totals*	χ^2
Pre arrest	15	76	91	7.02
Post arrest	5	3	8	
Totals	20	79	99	

TABLE V Relationship between dantrolene therapy and maximum temperature attained during MH reaction

	No. of patients			
	Died		*Survived*	
Dantrolene	*Yes*	*No*	*Yes*	*No*
Max. temp. °C				
≤37.9	1	0	53	7
38.0–39.9	10	2	104	3
40.0–41.9	19	4	72	17
42.0–43.9	29	1	26	6
≥44	4	0	0	0

TABLE VI Relationship between time after induction of commencing dantrolene therapy and survival from MH reaction

Time after induction (minutes)	No. of patients*	
	Died	Survived
0–29	0	9
30–59	0	7
60–119	0	12
120–179	2	4
≥180	8	7

3. treatment with an insufficient amount of dantrolene (Table IV);

4. concomitant use of contraindicated remedies, for instance calcium salts, cardiac glycosides, isoproterenol and sympathomimetic vasopressors; and

5. true diagnosis not MH but rather some other fever causing condition.

D *Recommended route and dosage of dantrolene*

Reconstituted lyophilized dantrolene should ideally be administered at the rate of 1.0 mg (2.5 ml) per kg per minute under EKG control until the temperature begins to fall, muscle stiffness starts to subside and/or the heart rate begins to decline. A maximum of 10 mg per kg may be given over a fifteen minute period. This loading dosage may be repeated every 15 minutes if the reaction recurs. Even in the absence of recurrence of the reaction, the loading dose(s) of dantrolene should be followed by a maintenance infusion of 1.0–2.0 $mg \cdot kg^{-1}$ during each three- to four-hour period until all evidence of an active MH crisis has disappeared. As soon as possible intravenous dantrolene should be replaced with oral dantrolene as intravenous dantrolene induces thrombophlebitis of peripheral veins.

E *Dantrolene before elective anaesthesia of MHS patients*

In the management of porcine MH reactions dantrolene has proved effective not only in the therapy of established crises but also prophylactically when given before anaesthesia. Harrison,[83] Kerr *et al.*,[84] Gronert *et al.*[59] and Flewellen and Nelson[85] observed that pretreatment with dantrolene prevents the initiation of MH reactions in susceptible pigs. The total preanaesthetic dose of dantrolene sodium in these studies ranges from $5 mg \cdot kg^{-1}$ [83] to 24 $mg \cdot kg^{-1}$.[84] The number of doses varies from one to four. The time of start of treatment extends from two days to four hours before anaesthesia. Kerr[84] found that a single oral dose of $8 mg \cdot kg^{-1}$ four hours before halothane challenge is as effective as smaller but multiple doses of dantrolene. Gronert[59] has shown that pretreatment with $5 mg \cdot kg^{-1}$ intravenously prevents, $1–3 mg \cdot kg^{-1}$ attenuates and $0.1 mg \cdot kg^{-1}$ has no effect on induction of reactions in MHS swine by halothane and succinylcholine. Flewellen and Nelson[85,86] reported that the intravenous dose of dantrolene which produced 95 per cent of maximal muscle relaxation (i.e. reduction of toe twitch tension) is sufficient to prevent effectively MH crises in swine. They determined that this dose is $3.5 mg \cdot kg^{-1}$. They also discovered that this same dose corrects already established MH reactions.

Oral dantrolene has also been used extensively in preanaesthetic prophylaxis of MHS patients.[45,87–92] However, the true value of dantrolene pretreatment in patients remains largely unknown since for ethical reasons no one has ever been given any potent inhalational anaesthetic or depolarizing skeletal muscle relaxant following a course of dantrolene. Rather patients have been anaesthetized with drugs known to be safe for MHS patients. Therefore, even without dantrolene pretreatment, an MH reaction would have been unlikely. However, we are aware of one patient who was treated with only $3.0 mg \cdot kg^{-1}$ per day for two preoperative days and developed a MH reaction during anaesthesia with droperidol, fentanyl and thiopentone, pancuronium and cocaine.[90,93] On the other hand, no human pretreated with at least $4.0 mg \cdot kg^{-1}$ of dantrolene has been known to have developed evidence of MH during anaesthesia.

At present the choice between use of prophylactic dantrolene or reliance only on administration of "safe" anaesthetics is a difficult one.[94] Unfortunately, the effective prophylactic dose of dantrolene is similar to that at which adverse side effects occur.[94,95] In a recent study, Flewellen *et al.*[96] have found that neostigmine does not reverse dantrolene-induced depression of muscle function. They warn that this might contribute to respiratory inadequacy in the postoperative period.[94] In our hospital prophylactic dantrolene is given to known or suspected MHS patients only in the following situations:

1. if the patient is very apprehensive;

2. if the operation is to be prolonged and injurious to muscles;

3. if the anaesthesia or the operation is likely to be associated with a fall in blood pressure, and a reduction in oxygen or a rise in carbon dioxide or lactic acid in the blood;

4. if the operating room and/or gas machine are not absolutely free of inhalational anaesthetic vapours;

5. if the patient is going to have awake dental or obstetrical anaesthesia with local or conductive anaesthesia using amide agents.

F *Other uses of dantrolene*

In addition to emergency and elective use of dantrolene in MHS patients this drug is at present used in a number of other situations. For instance, dantrolene is employed to relieve muscle pains and spasms in MHS and in non-MHS patients. Dantrolene is also used to lower body temperature due to causes other than MH.

1 DANTROLENE TO CONTROL SKELETAL MUSCLE PAIN ASSOCIATED WITH THE MH TRAIT

Oral dantrolene has been used to alleviate skeletal muscle cramps, aches, pains and spasms which occasionally afflict MHS patients. We have carried out a double blind study to test the value of dantrolene for this purpose (unpublished data). In essence dantrolene appears to lower serum CPKs (creatine phosphokinase) and to attenuate partially, but not completely muscle discomfort in some, but not all MHS humans.

Gronert *et al.*[97] reported their experience with a muscular patient who during periods of extreme physical or emotional stress suffered from episodes of fever, sweats and aching joints. A skeletal muscle biopsy was positive for MH. The serum CPK was elevated. All his distressing symptoms were relieved by administering 2.2 $mg \cdot kg^{-1}$ of oral dantrolene over a period of 15 hours. We have had similar experiences with a number of our own patients.[38]

2 DANTROLENE IN SKELETAL MUSCLE DISEASES OTHER THAN MH

An oral preparation of dantrolene has been used for some years to relieve muscle spasms associated with such conditions as cerebral palsy, Parkinson's disease, chorea, athetosis, spinal cord injury, multiple sclerosis and myotonia.[98–116] The advantage of dantrolene for these conditions is that even at very high doses it causes only slight reduction in skeletal muscle power. Moreover, it does not adversely affect the frequency of epileptic seizures which afflict many patients suffering from spastic disorders.[117] Meyler *et al.*[116] have, however, found that high doses (above 200 mg/day) are not more effective than low doses ($\leq$ 200 mg/day) in the long-term management of chronic muscle spasticity.

3 DANTROLENE BEFORE ELECTIVE ANAESTHESIA OF NORMAL PATIENTS WITH SUCCINYLCHOLINE

Dantrolene (3.0 $mg \cdot kg^{-1}$) pretreatment has been used successfully to attenuate succinylcholine induced fasciculations, muscle pains and rises in serum potassium.[118] Furthermore, Plotz *et al.*[119] have shown that preanaesthetic treatment of twenty children with oral dantrolene not only significantly reduces the incidence of post-succinylcholine skeletal muscle fasciculations but also significantly inhibited pre- and postoperative serum CK levels.

4 DANTROLENE DURING NEUROLEPTIC MALIGNANT HYPERTHERMIA

Malignant hyperthermia-like crises have occasionally occurred following the use of tranquillizers.[38,120] On at least one occasion such a reaction has been reversed with dantrolene.[121]

5 DANTROLENE DURING HEAT STROKE

Intravenous dantrolene has been used successfully to treat acute heat stroke induced by working in an excessively hot environment.[122]

G *Side effects of dantrolene*

Consistent side effects of dantrolene therapy, which largely subside after a few days include: dizziness, diplopia, dysarthria, a sensation of swelling of eyeballs and tongue, a feeling that limb muscles are rubbery, spaghetti-like and weak (not confirmed on objective management), uncertainty of location of feet when ascending or descending stairs, nausea, epigastric discomfort and diarrhoea.[45,123] Dantrolene elevates serum potassium.[124]

Rarely, after prolonged very high dosage, hepatic dysfunction has been reported.[105,107,125] In all cases liver function studies have returned to normal

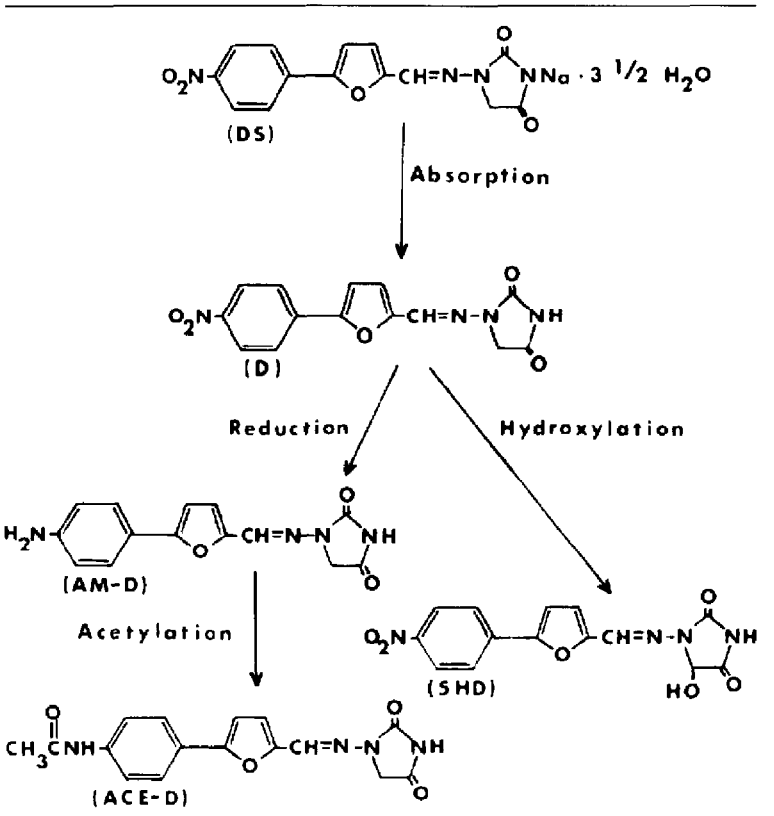


FIGURE 2 Proposed metabolic scheme of dantrolene sodium (DS) and dantrolene (D), based on identified metabolites: 5-hydroxy-dantrolene (5HD), aminodantrolene (AM-D), and acetylated dantrolene (ACE-D).

Reprinted with the permission of Dr. K.O. Ellis, Scientific Affairs Department, Norwich-Eaton Pharmaceuticals, Norwich, New York.

after withdrawal of the drug. Experiments on rats have shown that:

1. the action of dantrolene is on the bile acid-independent rather than the bile acid-dependent fraction of the bile;[126]

2. dantrolene inhibits the hepatic mixed function oxidase (MFO) system activity and cytochrome P_{450} content.[127,128] The dose required to induce these changes is in the range of 25 to 400 $mg \cdot kg^{-1}$ for five days. This dose range is, however, far in excess of the known effective dose required for humans. Nevertheless, if therapy of patients continues over several days, liver function studies should be performed.

In a recent report Petusevsky *et al.*[129] record that long-term dantrolene therapy was followed by chronic pleural effusion in three patients, one of whom also developed acute pericarditis. A fourth patient manifested both pleural and pericardial effusions. After the dantrolene was discontinued, resolution of the pleural process was prolonged. This report does not prove a causal relationship between dantrolene therapy and pleural and pericardial reaction, but it should alert one to search for such a possibility in all patients on chronic dantrolene treatment.

Lymphocytic lymphoma has been reported in one patient on long-term high-dose dantrolene.[130]

Whether the lymphoma was a coincidental finding or was induced by the dantrolene therapy cannot of course be determined on a clinical sampling of one. Nevertheless, the report should make one cautious about the prolonged administration of large amounts of dantrolene.

Long-term high-dose dantrolene therapy rather consistently causes a fine cuneiform rash over the face and back.[38,131]

A claim that dantrolene has induced asystole during MH reactions in two susceptible swine cannot be accepted, as the arrest in each case was likely due to the MH crisis itself rather than to the effects of dantrolene.[132]

H *Metabolism of dantrolene*

Metabolism of dantrolene (as measured by high performance liquid chromatography[133] or spectrofluorometry[134,135] occurs through both reductive and oxidative pathways.[136–138] The nitro group of dantrolene is reduced to aminodantrolene. In some animals, including man, the amine is acetylated.[136,137] Oxidation of dantrolene produces 5-OH dantrolene[136,137] (Figure 2). Ellis and Wessels have shown that 5-OH dantrolene is able to relax skeletal muscle as well as dantrolene.[138] On the other hand they each discovered that aminodantrolene and acetylated dantrolene had minimal relaxing properties.[138]

References

1 Norwich-Eaton Pharmaceuticals (Division of Norwich-Eaton, Ltd.). 1979. Dantrium Intravenous (Dantrolene Sodium Intravenous). Product Monograph.

2 *Snyder HR Jr, Davis CS, Bickerton RK, Halliday RP.* 1-[(5-Arylfurfurylidine)]amino hydantoins. A new class of muscle relaxants. J Med Chem 1967; 10: 807–10.

3 *Lee C, Durant NN, Au E, Katz RL.* Reversal of dantrolene sodium-induced depression of skeletal muscle in the cat. Anesthesiology 1981; 54: 61–5.

4 *Ellis KO, White RL Jr, Wright GC, Wessels FL.* Synthesis and skeletal muscle relaxant activity of quaternary ammonium salts of dantrolene and clodanolene. J Pharm Sci 1980; 69: 327–31.

5 *Ellis KO, Castellion AW, Honkomp LJ, Wessels FL, Carpenter JF, Halliday RP.* Dantrolene, a direct acting skeletal muscle relaxant. J Pharm Sci 1973; 62: 948–51.

6 *Colton CA, Colton JS.* The action of dantrolene sodium on the lobster neuromuscular junction. Comp Biochem Physiol 1979; 64C: 153–6.

7 *Durant NN, Lee C, Katz RL.* The action of dantrolene on transmitter mobilization at the rat neuromuscular junction. Eur J Pharmacol 1980; 68: 403–8.

8 *Karup C.* The effect of dantrolene on the enhancement and diminution of tension evoked by staircase and by tetanus in rat muscle. J Physiol 1981; 311: 389–400.

9 *Leslie GC, Part NJ.* Effect of dantrolene sodium on twitch contractions of individual motor units in the rat. J Physiol 1981; 318: 24.

10 *Nott MW, Bowman WC.* Actions of dantrolene sodium on contractions of the tibialis anterior and soleus muscles of cats under chloralose anaesthesia. Clin Exp Pharmacol Physiol 1974; 1: 113–22.

11 *Ellis KO, Bryant SH.* Excitation-contraction uncoupling in skeletal muscle by dantrolene sodium. Naunyn-Schmiedeberg's Arch Pharmacol 1972; 274: 107–9.

12 *Desmedt JE, Hainaut K.* Inhibition of the intracellular release of calcium by dantrolene in barnacle giant muscle fibres. J Physiol 1977; 265: 565–85.

13 *Ellis KO, Carpenter JF.* Studies on the mechanism of action of dantrolene sodium: A skeletal muscle relaxant. Naunyn-Schmiedeberg's Arch Pharmacol 1972; 275: 83–94.

14 *Putney JW Jr, Bianchi CP.* Effect of dantrolene in E-C coupling in skeletal muscle. FEBS 1973; 32. 772.

15 *Moulds R.* Comparison of the effect of sodium thiocyanate and dantrolene sodium on a mammalian isolated skeletal muscle. Br J Pharmacol 1977; 59: 129–33.

16 *Halsall PJ, Ellis FR.* A screening test for the malignant hyperpyrexia phenotype using suxamethonium-induced contracture of muscle treated with caffeine, and its inhibition by dantrolene. Br J Anaesth 1979; 51: 753–5.

17 *Fairhurst AS, Hamamoto V, Macri J.* Modification of ryanodine toxicity by dantrolene and halothane in a model of malignant hyperthermia. Anesthesiology 1980; 53: 199–204.

18 *Okumura F, Crocker BD, Denborough MA.* Site of the muscle cell abnormality in swine susceptible to malignant hyperpyrexia. Br J Anaesth 1980; 52: 377–83.

19 *Brocklehurst L.* Dantrolene sodium and 'skinned'

muscle fibres. Nature 1975; 254: 364.
20 *Oba T.* Influence of temperature and external Ca^{2+} concentration upon dantrolene action on excitation-contraction coupling in frog skeletal muscle. Can J Physiol Pharmacol 1981; 59: 358–63.
21 *Gallant EM, Godt RD, Gronert GA.* Role of plasma membrane defect of skeletal muscle in malignant hyperthermia. Muscle and Nerve 1979; 2: 491–4.
22 *Korczyn AD, Shavit S, Schlosberg I.* The chick as a model for malignant hyperpyrexia. Eur J Pharmacol 1980; 61: 187–9.
23 *Ellis KO, Carpenter JF.* The effect of dantrolene sodium (F440) on skeletal muscle. Fed Proc 1971; 30: 670.
24 *Flewellen EH, Nelson TE, Bee DE.* Effect of dantrolene on neuromuscular block by d-tubocurarine and subsequent antagonism by neostigmine in the rabbit. Anesthesiology 1980; 52: 126–30.
25 *Morgan KG, Bryant SH.* The mechanism of action of dantrolene sodium. J Pharmacol Exp Therap 1977; 201: 138–47.
26 *Desmedt JE, Hainaut K.* Dantrolene and A23187 ionophore: specific action on calcium channels revealed by the aequorin method. Biochem Pharmacol 1979; 28: 957–64.
27 *Nelson TE, Flewellen EH.* Does prior dantrolene affect the in vitro diagnosis of malignant hyperthermia susceptibility? Can Anaesth Soc J 1979; 26: 484–8.
28 *Nelson TE, Flewellen EH.* Rationale for dantrolene vs. procainamide for treatment of malignant hyperthermia. Anesthesiology 1979; 50: 118.
29 *Flewellen EH, Nelson TE, Bee DE.* Porcine malignant hyperthermia – failure of dantrolene dose response to diagnose susceptibility (halothane effect). Can Anaesth Soc J 1980; 27: 16–21.
30 *Flewellen EH, Nelson TE.* A comparison of dantrolene and procainamide on in vivo muscle twitch of malignant hyperthermia susceptible pigs. FEBS 1978; 37: 331.
31 *Anderson IL, Lipicky RJ, Jones EW.* Dantrolene sodium in porcine malignant hyperthermia: studies on isolated muscle strips. *In*: Second International Symposium on Malignant Hyperthermia (eds. Aldrete, J.A. and Britt, B.A.), Grune & Stratton, New York, p. 509–34 (1978).
32 *Leslie GC, Part NJ.* The action of dantrolene sodium on rat fast and slow muscle in vivo. Br J Pharmac 1981; 72: 665–72.
33 *Anderson IL, Jones EW.* Porcine malignant hyperthermia: effect of dantrolene sodium on in-vitro halothane-induced contraction of susceptible muscle. Anesthesiology 1976; 44: 57–61.
34 *Anderson IL, Rawstron RE, Dunlop DJ.* Screening for malignant hyperthermia susceptibility. NZ Med J 1980; 91: 417–9.
35 *Nelson TE.* Excitation-contraction coupling: a common etiologic pathway for malignant hyperthermia susceptible muscle. *In*: Second International Symposium on Malignant Hyperthermia (eds. Aldrete, J.A. and Britt, B.A. Grune & Stratton, New York, p. 23–36 (1978).
36 *Rosenberg H.* Dantrolene and caffeine contracture test (letter to the editor). Can Anaesth Soc J 1980; 27: 303–4.
37 *Lambert W.* Dantrolene and caffeine contracture test (letter to the editor). Can Anaesth Soc J 1980; 27: 304.
38 *Britt BA.* Unpublished data. (1981).
39 *Sengupta C, Meyer UA, Carafoli E.* Binding of dantrolene sodium to muscle intracellular membranes. FEBS 1980; 117: 37–8.
40 *Butterfield JL, Ellis KO.* Effects of dantrolene sodium, a skeletal muscle relaxant, on the contractility of cardiac and smooth muscle. Fed Proc 1973; 32: 772.
41 *Ellis KO, Wessels FL, Carpenter JF.* Effects of intravenous dantrolene sodium on respiratory and cardiovascular functions. J Pharmaceut Sci 1976; 65: 1359–63.
42 *Ellis KO, Butterfield JL, Wessels FL, Carpenter JF.* A comparison of skeletal, cardiac, and smooth muscle actions of dantrolene sodium – a skeletal muscle relaxant. Arch Int Pharmacodyn Ther 1976; 224: 118–32.
43 *Gollan F, McDermott J.* Effect of the skeletal muscle relaxant dantrolene sodium on the isolated, perfused heart (40384). Proc Soc Exp Biol Med 1979; 160: 42–5.
44 *Bowman WC, Houston J, Khan HH, Rodger IW.* Effects of dantrolene sodium on respiratory and other muscles and on respiratory parameters in the anaesthetised cat. Eur J Pharmacol 1979; 55: 293–303.
45 *Gronert GA.* Malignant hyperthermia. Anesthesiology 1980; 53: 395–423.
46 *Ellis RH, Simpson P, Tatham P, Leighton, M, Williams J.* The cardiovascular effects of dantrolene sodium in dogs. Anaesthesia 1975; 30: 318–22.

47 *Ally AI, Horrobin DF, Manku MS et al.* Dantrolene blocks intracellular calcium release in smooth muscle: competitive antagonism of thromboxane A_2. Can J Physiol Pharmacol 1978; 56: 520–3.

48 *Bailey LE, Shibata S, Seriguchi DG, Dresel PE.* Inhibition of the positive inotropic effect of anthopleurin-A (AP-A) by dantrolene. Life Sciences 1980; 26: 1061–8.

49 *Plizga A, Holl JE.* Myocardial depression associated with effective refractory period prolongation after pentobarbital and procainamide but not after dantrolene. Res Comm Chem Pathol Pharmacol 1980; 28: 13–26.

50 *Hatae J, Ohba M, Kawata H.* Effects of dantrolene sodium on the excitation-contraction coupling of the mammalian and amphibian cardiac muscle. J Mol Cell Cardiol 1980; 12: 857–67.

51 *Salata JJ, Jalife J.* Effects of dantrolene sodium on the electrophysiological properties of cacine cardiac Purkinje fibers. J Pharmacol Exp Ther 1982; 220: 157–66.

52 *Harris JD, Benson GS.* Effect of dantrolene sodium on canine bladder contractility. Urology 1980; 16: 229–31.

53 *Khalaf IM, Foley G, Elhilali MM.* The effect of dantrium on the canine urethral pressure profile. Investigative Urology 1979; 17: 188–90.

54 *Hackler RH, Broecker BH, Klein FA, Brady SM.* A clinical experience with dantrolene sodium for external urinary sphincter hypertonicity in spinal cord injured patients. J Urol 1980; 124: 78–81.

55 *Mahmoudian M, Dehpour AR, Mofakham S.* Effect of dantrolene sodium on the contractility of rabbit jejunum in vitro. Eur J Pharmacol 1981; 70: 287–92.

56 *Harrison GG.* Control of the malignant hyperpyrexic syndrome in MHS swine by dantrolene sodium. Br J Anaesth 1975; 47: 62–5.

57 *Hall GM, Lucke JN, Lister D.* Treatment of porcine malignant hyperthermia. The successful use of dantrolene in the Pietrain pig. Anaesthesia 1977; 32: 472.

58 *Hall GM, Lucke JN, Lister D.* Malignant hyperthermia – pearls out of swine? Br J Anaesth 1980; 52: 165–71.

59 *Gronert GA, Milde JH, Theye RA.* Dantrolene in porcine malignant hyperthermia. Anesthesiology 1976; 44: 488–95.

60 *Hall LW, Trim CM, Woolfe N.* Further studies on porcine malignant hyperthermia. Br Med J 1972; 2: 145.

61 *Ellis KO.* Personal communication. Norwich Eaton Pharmaceuticals, Norwich, N.Y. (1981).

62 *Fukuchi H, Kuwata N, Seki Y, Morio M.* Preparation and stability of parenteral solution of 0.4W/V% dantrolene sodium. Hiroshima J Anesthesia 1979; 15: 21–4.

63 *Fukuchi H, Morio M.* Preparation of dantrolene sodium for intravenous use. Hiroshima J Anesthesia 1977; 13 (Suppl.): 119.

64 *Tomonaga F, Kobayashi T, Yago K, et al.* Pharmaceutical studies of dantrolene sodium. Hiroshima J Anesthesia 1979; 15 (Suppl.): 101–8.

65 *Gronert GA, Mansfield E, Theye RA.* Rapidly soluble dantrolene for intravenous use. *In*: Second International Symposium on Malignant Hyperthermia (eds. Aldrete, J.A. and Britt, B.A.), Grune & Stratton, N.Y., p. 535–6 (1978).

66 *Drechsler H.* Zur therapie der malignen hyperthermie. Anaesthesist 1981; 30: 257–8.

67 Editorial. Dantrolene sodium approved for malignant hyperthermia. FDA Drug Bulletin 1979; 9: 27.

68 *Ryan JF.* Treatment of acute hyperthermia crises. *In*: International Anesthesiology Clinics: Malignant Hyperthermia. (ed. Britt, B.A.). 1979; 17: 153–68.

69 *Mathieu A, Bogosian AJ, Ryan JF, Crone, RK, Crocker D.* Recrudescence after survival of an initial episode of malignant hyperthermia. Anesthesiology 1979; 51: 454–5.

70 *Faust DK, Gergis SD, Sokoll MD.* Management of suspected malignant hyperpyrexia in an infant. Anesth Analg 1979; 58: 33–5.

71 *Friesen CM, Brodsky JB, Dillingham MG.* Successful use of dantrolene sodium in human malignant hyperthermia syndrome: a case report. Can Anaesth Soc J 1979; 26: 319–21.

72 *Liebenschutz F, Mai C, Pickerodt VWA.* Increased carbon dioxide production in two patients with malignant hyperpyrexia and its control by dantrolene. Br J Anaesth 1979; 51: 899–903.

73 *Jones SEF, Thomas CH.* Malignant hyperthermia in a patient with an ankylosed jaw. Anaesthesia 1980; 35: 987–90.

74 *Hoff B, Taylor C, Kruel J.* Dantrolene therapy for malignant hyperthermia (letter to the editor). Crit Care Med 1980; 8: 699–700.

75 *Harrison GG.* Dantrolene sodium in the treat-

ment of MH: a case report. S Afr Med J 1981; 60: 909–10.

76 *Denborough MA.* Etiology and pathophysiology of malignant hyperthermia. *In*: International Anesthesiology Clinics: Malignant Hyperthermia. (ed. Britt, B.A.) 1979; 17: 11–26.

77 *Britt, BA.* Malignant hyperthermia – a review. *In*: Handbook of Experimental Pharmacology, Pyretics and Antipyretics (ed. Milton, A.S.), Springer-Verlag, Heidelberg. 1982; p. 547–615.

78 *Sedwick LA, Romano PE.* Malignant hyperthermia. Considerations for the ophthalmologist. Surv Ophthalmol 1981; 25: 378–82.

79 *Schvaneveldt JA, Stankiewicz JA.* Malignant hyperpyrexia: an update for the otolaryngologist. The Laryngoscope 1981; 81: 918–26.

80 *Landauer B.* Zur Behandlung der malignen Hyperthermie mit Dantrolen. Der Anaesthesist 1980; 29: 507–8.

81 *Dohlman LE.* Malignant hyperthermia: a consideration for plastic surgeons. Plastic and Reconstructive Surgery 1982; 69: 547–51.

82 *Hopkins S.* Dantrolene sodium. Nursing Mirror 1980; 151: 30.

83 *Harrison GG.* The prophylaxis of malignant hyperthermia by oral dantrolene sodium in swine. Br J Anaesth 1977; 49: 315–7.

84 *Kerr DD, Wingard DW, Gatz EE.* Prevention of porcine malignant hyperthermia by oral dantrolene. *In*: Second International Symposium on Malignant Hyperthermia (eds. Aldrete, J.A. and Britt, B.A.), Grune & Stratton, New York, 1978; 499–507.

85 *Flewellen EH, Nelson TE.* Dantrolene dose response in malignant hyperthermia-susceptible (MHS) swine: method to obtain prophylaxis and therapeusis. Anesthesiology 1980; 52: 303–8.

86 *Flewellen EH, Nelson TE.* Porcine malignant hyperthermia: a method to produce dantrolene prophylaxis and therapeusis. Anesthesiology 1978; 51: 1001.

87 *Gallagher DM, Hyer RL.* Effective use of dantrolene in a patient susceptible to malignant hyperthermia. J Oral Surgery 1980; 38: 438–40.

88 *Free CW, Jaimon MPC.* Pre-anaesthetic administration of dantrolene sodium to a patient at risk from malignant hyperthermia: case report. NZ Med J 1978; 88: 493–4.

89 *Bronstein SL, Ryan DE, Solomons CC, Mahowald MC.* Dantrolene sodium in the management of patients at risk from malignant hyperthermia. J Oral Surgery 1979; 37: 719–24.

90 *Fitzgibbons DC.* Malignant hyperthermia following preoperative oral administration of dantrolene. Anesthesiology 1981; 54: 73–5.

91 *Jardon OM, Wingard DW, Barak AJ, Connolly JF.* Malignant hyperthermia. A potentially fatal syndrome in orthopaedic patients. J Bone and Joint Surgery 1979; 61-A: 1064–70.

92 *Relton JES.* Anesthesia for elective surgery in patients susceptible to malignant hyperthermia. *In*: International Anesthesiology Clinics: Malignant Hyperthermia. (ed. Britt, B.A.). 1979; 17: 141–51.

93 *Gronert GA.* Puzzles in malignant hyperthermia. Anesthesiology 1981; 54: 1–2.

94 *Hall GM.* Editorial. Dantrolene and the treatment of malignant hyperthermia. Br J Anaesth 1980; 52: 847–9.

95 *Pandit SK, Kothary SP, Cohen PJ.* Orally administered dantrolene for prophylaxis of malignant hyperthermia. Anesthesiology 1979; 50: 156–8.

96 *Flewellen EH, Nelson TE, Bee DE.* Porcine malignant hyperthermia – failure of dantrolene dose response to diagnose susceptibility (halothane effect). Can Anaesth Soc J 1980; 27: 16–21.

97 *Gronert GA, Thompson RL, Onofrio BM.* Human malignant hyperthermia: awake episodes and correction by dantrolene. Anesth Analg 1980; 59: 377–8.

98 *Chyatte SB, Birdsong JH.* The use of dantrolene sodium in disorders of the central nervous system. Southern Med J 1971; 64: 830–4.

99 *Gelenberg AJ, Poskanzer DC.* The effect of dantrolene sodium on spasticity in multiple sclerosis. Neurology 1973; 23: 1313–5.

100 *Chyatte SB, Birdsong JH, Roberson DL.* Dantrolene sodium in athetoid cerebral palsy. Arch Physical Med Rehab 1973; 54: 365–8.

101 *Chyatte SB, Birdsong JH, Bergman BA.* The effects of dantrolene sodium on spasticity and motor performance in hemiplegia. Southern Med J 1971; 64: 180–5.

102 *Mayer N, Mecomber SA, Herman R.* Treatment of spasticity with dantrolene sodium. Am J Physical Med 1973; 52: 18–29.

103 *Basmajian JV, Super GA.* Dantrolene sodium in the treatment of spasticity. Arch Physical Med Rehab 1973; 54: 60–5.

104 *Chyatte SB, Basmajian JV.* Dantrolene sodium: long-term effects in severe spasticity. Arch Physi-

cal Med Rehab 1973; 54: 311–5.

105 *Wilkinson SP, Portmann B, Williams R.* Hepatitis from dantrolene sodium. Gut 1979; 20: 33–6.

106 *Molnar GE, Evangelista LA, Kathirithamby R.* Dantrolene sodium in spasticity. Long-term administration in children. New York State J Med 1978; 78: 1233–7.

107 *Faling LJ, Petusevsky ML, Snider GL.* Nitrofurantoin and dantrolene; liver and lung. Ann Int Med 1980; 93: 151.

108 *Mai J, Pedersen E.* Mode of action of dantrolene sodium in spasticity. Acta Neurol Scandinav 1979; 59: 309–16.

109 *Weiser R, Terenty T, Hudgson P, Weightman D.* Dantrolene sodium in the treatment of spasticity in chronic spinal cord disease. The Practitioner 1978; 221: 123–7.

110 *Feit H.* A form of chorea that responds to dantrolene sodium. Neurology 1979; 29: 1631–2.

111 *Eberstein A, Goodgold J.* Relief of myotonia by dantrolene in experimental myotonia. Exper Neurol 1978; 62: 804–9.

112 *Glass A, Hannah A.* A comparison of dantrolene sodium and diazepam in the treatment of spasticity. Report prepared from study being completed for publication. Kaiser Foundation Hospital, Terra Linda, California.

113 *Joynt RL, Leonard, JA Jr.* Dantrolene sodium suspension in treatment of spastic cerebral palsy. Develop Med Child Neurol 1980; 22: 755–67.

114 *Herman R, Mayer N, Mecomber SA.* Clinical pharmaco-physiology of dantrolene sodium. Am J Physical Med 1972; 51: 296–311.

115 *Chipman M, Kaul S.* The efficacy of dantrolene sodium in the treatment of spasticity. Neurology 1972; 22: 401.

116 *Meyler WJ, Bakker H, Kok JJ, Agoston S, Wesseling H.* The effect of dantrolene sodium in relation to blood levels in spastic patients after prolonged administration. J Neurol Neurosurg Psychiat 1981; 44: 334–9.

117 *Nogen AG.* Effect of dantrolene sodium on the incidence of seizures in children with spasticity. Child's Brain 1979; 5: 420–5.

118 *Collier CB.* Dantrolene and suxamethonium. The effect of pre-operative dantrolene on the action of suxamethonium. Anaesthesia 1979; 34: 152–8.

119 *Plotz J, Braun J, Stallenberger R.* The inhibitory effect of dantrolene on the rise of serum-creatine-kinase activity after combined use of halothane and suxamethonium in man. Anaesthesist 1981; 30: 338–42.

120 *Hackl JM, Engl J, Hofstadter F et al.* Possible malignant hyperthermia as reaction to an overdose of myotonolytic, antidepressive and sedative drugs. Wien Klin Wochenschrift 1981; 93: 475–9.

121 *Delacour JL, Daoudal P, Chapoutot JL, Rocq B.* Traitement du syndrome malin des neuroleptiques par le dantrolene. La Nouvelle Presse Medicale 1981; 10: 3572–3.

122 *Lydiatt JS, Hill GE.* Treatment of heat stroke with dantrolene. Letter to the Editor. JAMA 1981; 246: 41–2.

123 American Hospital Formulary Service, Published by the American Society of Hospital Pharmacists, Bethesda, Md. 20814.

124 *Agoston S.* Dantrolene and suxamethonium. Letter to the editor. Anaesthesia 1980; 35: 1012–3.

125 *Cornette M, Gillard C, Borll-Hermans G.* Hépatite toxique mortelle associée a l'usage du dantrolene. Acta neurol belg 1980; 80: 336–47.

126 *Abernathy CO, Utili R, Zimmerman HJ, Ezekiel M.* The effects of dantrolene sodium on excretory function in the isolated perfused rat liver. Toxicol Appl Pharmacol 1978; 44: 441–52.

127 *Roy S, Francis KT, Born CK, Hamrick ME.* Interaction of dantrolene with the hepatic mixed function oxidase system. Res Comm Chem Pathol Pharmacol 1980; 27: 507–20.

128 *Francis KT, Hamrick ME.* Dantrolene inhibition of the hepatic mixed function oxidase system. Res Comm Chem Pathol Pharmacol 1979; 23: 69–80.

129 *Petusevsky ML, Faling LJ, Rocklin RE, et al.* Pleuropericardial reaction to treatment with dantrolene. JAMA 1979; 242: 2772–4.

130 *Wan HH, Tucker JS.* Dantrolene and lymphocytic lymphoma. Postgrad Med J 1980; 56: 261–2.

131 *Pembroke AC, Saxena SR, Kataria M, Zilkha KD.* Acne induced by dantrolene. Br J Dermatology 1981; 104: 465–8.

132 *Chapin JW, Lou CG, Wingard DW.* Asystole after intravenous dantrolene sodium in pigs. (Letter to the Editor) Anesthesiology 1981; 54: 527–8.

133 *Hackett LP, Dusci LJ.* Determination of dantrolene sodium in human plasma using high-performance liquid chromatography. J Chromatography 1979; 179: 222–4.

134 *Hollifield RD, Conklin JD.* A spectrophotofluoro-

metric procedure for the determination of dantrolene in blood and urine. Arch Int Pharmacodyn 1968; 174: 333–41.

135 *Hollifield RD, Conklin JD.* Determination of dantrolene in biological specimens containing drug-related metabolites. J Pharm Sci 1973; 62: 271–4.

136 *Ellis KO, Wessels FL.* Muscle relaxant properties of the identified metabolites of dantrolene. Naunyn-Schmiedeberg's Arch Pharmacol 1978; 301: 237–40.

137 *Cox PL, Heotis JP, Polin D, Rose GM.* Quantitative determination of dantrolene sodium and its metabolites by differential pulse polarography. J Pharmaceutical Sci 1969; 58: 987–9.

138 *Hollifield RD, Conklin JD.* Determination of dantrolene in biological specimens containing drug-related metabolites. J Pharmaceutical Sci 1973; 62: 271–4.