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REVIEW ARTICLE

Dantrolene – A review of its pharmacology, therapeutic use and new developments

T. Krause,[1] M. U. Gerbershagen,[2] M. Fiege,[1] R. Weißhorn[1] and F. Wappler[3]

1 Assistant Professor, 2 Staff Anaesthesiologist, 3 Professor of Anaesthesiology, Department of Anaesthesiology, University-Hospital Hamburg-Eppendorf, Hamburg, Germany

Summary

Human malignant hyperthermia is a life-threatening genetic sensitivity of skeletal muscles to volatile anaesthetics and depolarizing neuromuscular blocking drugs occurring during or after anaesthesia. The skeletal muscle relaxant dantrolene is the only currently available drug for specific and effective therapy of this syndrome in man. After its introduction, the mortality of malignant hyperthermia decreased from 80% in the 1960s to < 10% today. It was soon discovered that dantrolene depresses the intrinsic mechanisms of excitation–contraction coupling in skeletal muscle. However, its precise mechanism of action and its molecular targets are still incompletely known. Recent studies have identified the ryanodine receptor as a dantrolene-binding site. A direct or indirect inhibition of the ryanodine receptor, the major calcium release channel of the skeletal muscle sarcoplasmic reticulum, is thought to be fundamental in the molecular action of dantrolene in decreasing intracellular calcium concentration. Dantrolene is not only used for the treatment of malignant hyperthermia, but also in the management of neuroleptic malignant syndrome, spasticity and Ecstasy intoxication. The main disadvantage of dantrolene is its poor water solubility, and hence difficulties are experienced in rapidly preparing intravenous solutions in emergency situations. Due to economic considerations, no other similar drugs have been introduced into routine clinical practice.

Keywords *Dantrolene, malignant hyperthermia. Ecstasy. Neuroleptic Malignant Syndrome. Muscle spasticity.*

Correspondence to: T. Krause
E-mail: tkrause@uke.uni-hamburg.de
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Dantrolene is the only clinically available agent for the specific treatment of malignant hyperthermia (MH). In Europe and North America, MH was the commonest cause of death directly attributable to general anaesthesia in the 1970s. Mortality ranged between 70% and 80% [1], even after therapy with procaine, the first choice treatment in that decade [2, 3]. Apart from an increasing awareness of the syndrome and advance diagnosis of MH susceptibility by the *in vitro* contracture test, the introduction of dantrolene was predominantly responsible for a decrease in mortality to < 10% [1]. This review summarises the pharmacological properties of, and clinical indications for, dantrolene.

History

Dantrolene was originally synthesised by Snyder and his co-workers in 1967 [4]. It was found to have skeletal muscle relaxant properties after intravenous administration in animals. Studies revealed that these relaxant properties are due to depression of excitation–contraction coupling. This complex process enables skeletal muscles to transform a chemical signal at the neuromuscular junction into a muscle contraction [4, 5]. Dantrolene was initially used as a muscle relaxant in the long term treatment of skeletal muscle spasticity [6].

In certain breeds of pigs, a stress-related syndrome was observed that was similar to MH crises induced by general anaesthesia in susceptible humans. Untreated, mortality approached 100% [7]. Since the life-threatening severity of the syndrome prohibited placebo-controlled studies in humans, MH-susceptible (MHS) pigs were used to investigate the pathophysiology and therapy of the condition. The efficacy of dantrolene in treating and preventing MH *in vivo* was first observed in Landrace pigs

in 1975 [8]. Later, these results were confirmed in other MHS breeds such as Poland China pigs and Pietrain pigs [9, 10]. The *in vitro* effects of dantrolene in decreasing and preventing halothane-induced skeletal muscle contractions in MHS pigs were first reported in 1976 [11]. Consequently, the hypothesis was put forward that the efficacy of dantrolene treatment was the result of a direct effect on skeletal muscles [11].

From September 1977 to May 1979, a North American multicentre study involving 65 hospitals was conducted to evaluate the safety and efficacy of dantrolene therapy in MH crises in a large number of patients [12]. This study showed a significant decrease in mortality in patients with a clinical suspicion of MH during anaesthesia [12]. After publication of these results, dantrolene was introduced for the clinical treatment of MH.

Chemical properties of dantrolene

The molecular structure of dantrolene (hydrated 1-(((5-(4-nitrophenyl)-2-furanyl)-methylene)amino)-2,4-imidazolidine dione sodium salt), a hydantoin derivative, is planar except for the phenol ring, which is rotated approximately 30° out of the plane of the furane ring (Fig. 1) [13]. Dantrolene is highly lipophilic and therefore poorly soluble in water. This created problems for its clinical introduction until the 1980s. Widespread use had to await a suitable intravenous preparation. Today, dantrolene is available for intravenous use in vials containing 20 mg lyophilized dantrolene sodium added to 3 g mannitol to improve water solubility. The contents of the vials have to be dissolved in 60 ml water, yielding a final dantrolene concentration of 0.33 $mg.ml^{-1}$ at pH 9.5. The commercially available package contains 12 vials of dantrolene and 12 vials of distilled water. Before administration, the solution must be clear and without visible particles. The prepared solution should be protected from light and stored at 15–25 °C, and once prepared should be used within 6 h. The resulting alkaline solution is highly irritating to peripheral veins and should therefore be injected into a large vein or a fast running infusion.

Pharmacokinetics

After oral administration, 70% of a dose of dantrolene is absorbed. Significant variations in plasma concentrations are seen, peaking at about 6 h [6]. In healthy conscious volunteers, intravenous administration of dantrolene 2.4 $mg.kg^{-1}$ results in plasma concentrations of 4.2 $\mu g.ml^{-1}$, which blocks up to 75% of skeletal muscle contraction [14]. The subjective feeling of muscle weakness was objectively confirmed by a maximum decrease in grip strength of 42%. However, total paralysis cannot be obtained with dantrolene sodium regardless of the dose, a fact attributed to its poor water solubility. Plasma concentrations remain stable within the therapeutic range for approximately 5 h after administration. The plasma elimination half-life time is estimated to be 12 h. In children, the pharmacokinetic profile is similar, with a half-life of approximately 10 h [15].

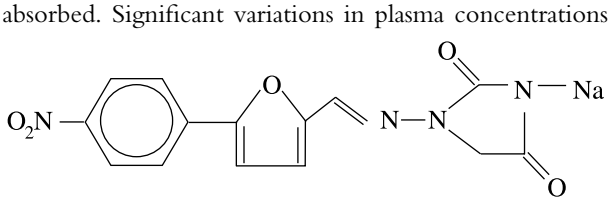

Figure 1 The chemical structure of dantrolene sodium.

Dantrolene is metabolised by liver microsomes to 5-hydroxydantrolene, which itself acts as a skeletal muscle relaxant. Reduction of the nitro moiety of the benzene ring leads to the formation of aminodantrolene, which is metabolized to the reduced acetylated derivative of dantrolene [16]. Dantrolene and its metabolites are excreted mainly via urine and bile [6, 16]. Dantrolene has structural similarities to both hydantoin and some local anaesthetics, but has neither anticonvulsant nor anaesthetic properties [17].

Pharmacodynamics

Voltage changes in the t-tubule membrane regulate conformational changes in the dihydropyridine receptor during normal excitation–contraction coupling of skeletal muscle fibres. Dihydropyridine receptors act as voltage sensors that undergo intramolecular charge movement during depolarization. This phenomenon probably results in a movement of the intracellular loop between the transmembrane domains II and III of the alpha-1 subunit of the dihydropyridine receptor. The alpha-1 subunit and the ryanodine receptor isoform 1 (RYR1), the main calcium-releasing channel of the sarcoplasmic reticulum, are intimate physiological partners. The opening of RYR1 induces the efflux of calcium ions into the myoplasm [18, 19]. Subsequently, calcium ions activate muscle contraction by attenuation of troponin C inhibition of the contractile proteins actin and myosin. Relaxation is achieved by a rapid adenosine triphosphate (ATP)-consuming transfer of calcium ions back into the sarcoplasmic reticulum and is completed when the myoplasmic concentration is less than the mechanical threshold.

The precise pathological mechanisms by which certain substances trigger MH crises are not fully understood. However, susceptibility to MH is clearly associated with abnormal calcium metabolism within the skeletal muscle fibre, most probably caused by an altered RYR1 in the

sarcoplasmic reticulum. It has been shown that in MH-susceptible subjects, the RYR1 receptor shows a prolonged duration in the open state and thus has a higher affinity to radioligands [20]. This results in an enhanced efflux of calcium from the sarcoplasmic reticulum into the myoplasm, followed by a prolonged and intensified interaction of actin and myosin. The clinical symptomatology of hypercapnia, hyperthermia and acidosis is aggravated by the activation of other calcium-dependent cytoplasmic metabolic processes. The initially enhanced aerobic metabolism of the skeletal muscle cell cannot be maintained. The ensuing excessive anaerobic metabolism is the cause of the lactic acidosis and the accumulation of intramitrochondrial calcium. Finally, the deconjugation of oxidative phosphorylization results in cytolysis [21].

To date, the underlying molecular mechanisms and the exact mode of dantrolene's action have been incompletely understood. Dantrolene is a direct-acting skeletal muscle relaxant blocking calcium release from intracellular storage in the sarcoplasmic reticulum. Muscle contraction is decreased without an effect on the action potential patterns of the neuromuscular junction [17]. A detailed knowledge of the mechanisms regulating intracellular calcium balance under physiological and pathological conditions would be of particular interest and undoubted help in developing new therapeutic strategies.

Investigations focus on the RYR1 receptor of the skeletal muscle cell as a potential direct or indirect site of dantrolene action [22–24]. Experiments with radioactive ligands could localise [^{3}H]dantrolene and [^{3}H]ryanodine binding sites closely associated to sarcoplasmic reticulum membrane fractions from porcine skeletal muscle [25, 26]. Single-channel measurements of RYR1 have revealed a high affinity activating and a lower affinity inhibiting binding site on the sarcoplasmic reticulum membrane [27]. These results were confirmed in a similar experimental setting in which dantrolene inhibited both [^{3}H]ryanodine binding to and calcium release from sarcoplasmic reticulum vesicles directly [28]. Additionally, [^{3}H]azidodantrolene, a photo-affinity analogue of dantrolene, was used to identify the molecular target of dantrolene action. Photo-cross-linking experiments analysed by sodium-dodecylsulphate-polyacrylamide gel electrophoresis and tritium fluorography revealed a 160-kDa protein as the putative skeletal muscle dantrolene receptor [23]. However, the same authors were able to specify this 160-kDa protein as the N-terminal region of the RYR1, indicating that this is not the true dantrolene receptor [29]. Further animal studies indicate that amino acids 590–609 of the RYR1 represent the binding site for dantrolene [30].

Another recently published study, in which purified RYR1 was incorporated into an artificial planar lipid bilayer, contradicts these results [31]. The aim of the purification process was to prevent the transfer of other proteins to the new lipid bilayer. The exposure of 50 μM dantrolene did not reveal any change in channel activity or pharmacology, which led to the conclusion that the RYR1 is not the molecular target of dantrolene. Methodological concerns about the validity of this study focus on the purification process. On the one hand, the binding site could have been lost or destroyed as a result of the purification process. On the other hand, it is speculated that the binding site requires additional elements of RYR1, which either might have been removed during the purification process or cannot sufficiently interact in the new lipid bilayer [30]. In addition to the yet unknown binding site of dantrolene, even the mechanism of inhibition of the RYR1-mediated calcium efflux is still a subject of experimental work. Possibilities include voltage, current or calcium dependence of inactivation [31, 32]. Moreover, the discussion focusses on the interaction of dantrolene or its binding site with the dihydropyridine receptor [31], and a retrograde effect from the binding site or from the altered gating of RYR1 [33]. Another option is the stabilization of RYR1 interdomain interaction [34].

Three distinct genes encode for the three known isoform ryanodine receptors. The gene expression does not appear to be tissue specific, but ryanodine receptors are expressed primarily in skeletal muscle (RYR1), heart muscle (RYR2) and brain tissue (RYR3). Mutations of these receptors are associated with different channelopathies. Malignant hyperpyrexia and Central Core Disease are associated with various mutations of the RYR1 [35–37]. *RYR2* gene mutations encode for the catecholaminergic and familiar polymorph ventricular tachycardias [38, 39] as well as for the arrhythmogenic right ventricular dysplasia type 2 [40]. Recently, Gurrera suggested that the neuroleptic malignant syndrome might be caused by a genetic alteration of RYR3 [41].

Porcine MH susceptibility is based on a point mutation of the *RYR1* gene, resulting in the exchange of arginine to cysteine at position 615 of the receptor protein [42]. However, human MH syndrome is genetically heterogeneous. To date, >25 mutations are thought to be implicated; nine encoding for the extreme N-terminal region, 16 for the central and one for the extreme C-terminal region [35, 43–46]. Furthermore, a single amino acid deletion in the central region of the RYR1 might also be associated with MH susceptibility [47].

In spite of the homogeneity of the isoform ryanodine receptors, especially between RYR1 and RYR2, calcium efflux from the sarcoplasmic reticulum of the heart muscle is not inhibited by dantrolene [48]. It has been hypothesized that the recently identified amino acid area

590–609 of the RYR1 might be the molecular target of dantrolene. However, the question of why dantrolene has less affinity for RYR2 in spite of having exactly the same amino acid sequence (601–619) and also less afinity for RYR3, which has a nearly identical sequence (577–597), can still not be explained. RYR3 differs from RYR2 by a single amino acid substitution (valine to leucine) at position 596 [49, 50]. The *in vivo* sensitivity of RYR3 to dantrolene has not yet been clarified. Nevertheless, *in vitro* experiments have demonstrated an inhibition of calcium efflux from the inner storage of the neurone [51], and various other effects of dantrolene on smooth muscle cells and immune cells have been described [52, 53]. From the clinical point of view, knowledge of the interaction of RYR3 and dantrolene would be very interesting [54]. If the hypothesis of an underlying *RYR3* gene mutation could be proven [41], dantrolene administration might be a reasonable drug therapy for neuroleptic malignant syndrome.

Side-effects

Side-effects may occur after acute or chronic parenteral administration of dantrolene. In a retrospective analysis, 164 patients suffering from MH crises were treated with dantrolene. The most frequently observed side-effects were muscle weakness in 22%, phlebitis in 10%, respiratory failure in 3% and gastrointestinal discomfort in 3% of the patients [55].

Healthy volunteers reported muscle weakness 48 h after intravenous administration of dantrolene 2.4 $mg.kg^{-1}$. Neither impairment of ventilation nor coughing occurred in these subjects [14]. However, studies of pulmonary function have not been performed in patients after MH crises, dantrolene therapy and intensive care management. Dantrolene-associated muscle relaxation might cause prolonged respiratory insufficiency, especially in patients with neuromuscular disease. The second most common side-effect, local inflammatory phlebitis at the infusion site, is caused by the highly alkaline solution [55]. Accidental extravascular infusion causes severe tissue necrosis. Therefore, it is recommended that dantrolene is given into large peripheral veins or via central venous lines.

Additional adverse symptoms of dantrolene treatment include drowsiness, dizziness and confusion [14, 16]. It is not yet clear whether these central nervous symptoms are mediated by altered neuronal calcium homeostasis. Nausea and vomiting are associated with dizziness, confusion and drowsiness after parenteral and oral administration; diarrhoea often occurs after oral therapy [6].

Chronic oral therapy has been associated with liver dysfunction, yet dantrolene was not the only potentially hepatotoxic substance administered to the patients in whom this complication was reported. *In vivo* experiments in mice have not revealed any toxicity to hepatocytes [56, 57]. Nevertheless, routine liver function tests should be performed in all cases of chronic administration. Rare symptoms of chronic dantrolene treatment are anorexia, gastric irritation, abdominal cramps, constipation, dysphagia, enuresis, visual disturbances and an acne-like rash [17, 58].

Neonates are at risk of 'floppy child syndrome' when dantrolene is administered to the mother during Caesarean section [59]. Dantrolene plasma levels of up to 65% of maternal levels were measured in these newborns. Postpartum uterine atony has been described after dantrolene therapy [60].

Drug interactions

While dantrolene itself has no apparent myocardial effects in humans, in combination with verapamil its use is associated with a significant decrease in cardiac function in swine and dogs [61, 62]. Even though this effect has never been described in humans, the simultaneous administration of both drugs in the management of MH-induced cardiac tachyarrhythmias should be avoided.

Dantrolene depresses excitation–contraction coupling without interfering with neuromuscular transmission or electrical properties such as resting or action potentials. However, since dantrolene decreases the force of skeletal muscle contraction, some synergistic effects with drugs blocking neuromuscular transmission have to be expected. A marked prolongation of the neuromuscular junction recovery has been reported after vecuronium has been given in combination with dantrolene [63]. This may be caused by decreased transmitter release at the neuromuscular junction as a result of attenuated calcium release from the cholinergic terminal calcium storage sites.

New developments

Azumolene is an approximately 30-fold more water-soluble analogue of dantrolene (Fig. 2). The para-nitrophenole group of dantrolene sodium is replaced by a para-bromo-phenyl group. Azumolene is equipotent to dantrolene in the treatment and prevention of the clinical manifestations of an MH crisis after administration of halothane or succinylcholine to MHS swine [64]. Moreover, azumolene has the same potency as dantrolene in inducing relaxation in porcine skeletal muscle *in vitro*. *In vivo*, azumolene was even more potent than dantrolene in inhibiting gastrocnemius muscle twitches [65]. The excitability and contractility of cardiac muscle were not

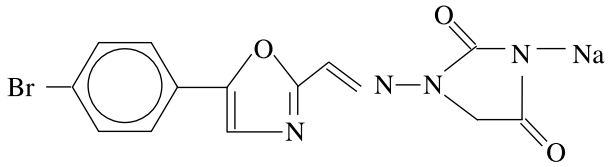

Figure 2 The chemical structure of azumolene sodium.

affected by either dantrolene or azumolene when given in therapeutic doses [65, 66].

New preparations such as lyophilized lecithin-coated microcrystal formulations of sodium dantrolene and neutral dantrolene (which can be reconstituted in water at 200 $mg.ml^{-1}$ within 1 min with high water solubility) were described in 1996, and the therapeutic efficacy of this preparation has been demonstrated in mice, swine and dogs [67]. However, *in vivo* administration of these preparations was sometimes accompanied by marked pulmonary hypertension, a problem that could be solved by filtering before administration. Hence, these preparations might be useful for MH treatment in the future. However, because of economic considerations, none of these new agents has been introduced into clinical practice.

Therapeutic uses of dantrolene

Malignant hyperthermia

Early MH symptoms include tachycardia, supraventricular and ventricular arrhythmias, and even cardiac arrest. In ventilated patients, an increase in $F_{\acute{E}CO_2}$ can be seen, whereas spontaneously breathing patients tend to hyperventilate. Masseter spasm and generalised rigidity after succinylcholine administration are additional early warning signs of MH. Skin discoloration includes initial redness followed by cyanosis and profuse sweating. The sum of these clinical signs is sufficient to justify the diagnosis of MH and the immediate initiation of MH treatment. Treatment guidelines for MH crisis of the German Society of Anaesthesiology and Intensive Care Medicine recommend the following procedure [68]:

A suspicion of MH must result in the immediate withdrawal of all trigger agents. Volatile agent vaporisers should be removed from the anaesthetic machine. Patients' lungs should be ventilated with 100% oxygen and minute volume should be increased. Anaesthesia should be maintained with opioids and hypnotic drugs, and muscle relaxation should be produced with non-depolarizing neuromuscular blockers only. Surgery should be terminated as soon as possible. Repeated analysis of central venous blood for gases, electrolytes, creatine kinase, transaminases, lactate and myoglobin should be performed to confirm the diagnosis of MH and to aid management. Rapid dantrolene preparation and administration are of the highest priority. Therapy is started with a dantrolene bolus of 2.5 $mg.kg^{-1}$ and should be repeated at 5-min intervals until normalisation of the hypermetabolic state and the disappearance of all MH symptoms. If >20 $mg.kg^{-1}$ dantrolene is given, the diagnosis must be questioned [69]. Continuous intravenous dantrolene infusion at 10 $mg.kg^{-1}.day^{-1}$ should be given for at least 24 h after initial successful therapy. Supportive therapy includes body cooling, administration of sodium bicarbonate to treat acidosis, beta-blockers or lidocaine in case of persisting cardiac arrhythmias, and furosemide and glucose-insulin infusions in case of hypercalcaemia, hyperkalaemia and myoglobinuria. After successful treatment, the patient should be taken to an intensive care unit for at least 24 h in case of recurrence of the syndrome. Early diagnosis and guideline-orientated treatment is successful in most patients. Therefore, it must be emphasised that a adequate dose of dantrolene to treat an adult patient (10 $mg.kg^{-1}$) should be available in any operating theatre suite, including ambulatory surgery units [68].

Is dantrolene prophylaxis indicated in MH-susceptible patients?

Prophylactic dantrolene administration before trigger-free general anaesthesia for MH-susceptible patients has been recommended. A variety of drugs have been suspected of having triggering potential over the past 30 years. Therefore, experts have recommended oral dantrolene prophylaxis [70]. This prophylactic regimen was started 1 or 2 days before surgery at doses of 4–8 $mg.kg^{-1}.day^{-1}$ [70]. Most of the patients underwent uneventful anaesthesia. However, oral therapy does not guarantee the required dantrolene plasma concentrations, and patients may suffer from adverse effects [14]. Therefore, oral prophylaxis is now thought to be obsolete. Moreover, even intravenous dantrolene prophylaxis is no longer recommended [71]. With appropriate anaesthetic management, the question of the need for prophylactic dantrolene administration was discussed as long ago as the 1980s [72]. In a retrospective study, 2214 anaesthetics performed for diagnostic muscle biopsies between 1971 and 1993 were analysed [73]. Ninety seven per cent of these anaesthetics were performed with trigger-free general anaesthesia without dantrolene prophylaxis, and 1082 patients were shown to be MH-positive. Five of the MH-positive patients showed increased body temperature, tachycardia and tachypnoea in the recovery room, and dantrolene was given intravenously to four of these five patients. The postoperative course of all five patients was uneventful. However, due to the retrospective design

of the study, it could not be determined whether the observed clinical signs were classifiable as specific for MH. Other studies including fewer patients showed no complications during general anaesthesia without dantrolene prophylaxis [74–76]. In the MH centre of the University Hospital Hamburg-Eppendorf, Germany, 706 anaesthetics for muscle biopsy were performed without dantrolene prophylaxis between 1991 and 2001 (unpublished data). Of these 706 patients, 303 were found to be MH-positive. Within this group, 67 trigger-free general anaesthetics and 236 regional anaesthetics were performed. None of the patients developed MH-like symptoms.

Malignant hyperpyrexia is unlikely to occur during or after trigger-free anaesthesia in MH-positive patients. Therefore, the adverse effects of dantrolene have to be balanced against the questionable benefits. The occurrence of muscle weakness for up to 48 h, hepatotoxicity, local phlebitis, dizziness, confusion and drowsiness is an argument against dantrolene prophylaxis [69]. The recommendation not to use dantrolene prophylactically is based on adequate peri-operative patient management and the immediate availability of dantrolene in case of an emergency [77].

Neuroleptic malignant syndrome

Neuroleptic malignant syndrome is a rare and potentially lethal disorder that follows the administration of neuroleptic drugs. It is characterised by three major symptoms: hyperthermia, generalised muscular rigidity and increased plasma creatine kinase levels. Catatonia and autonomic nervous system dysfunction are often observed. Hypotheses for the pathophysiology of the neuroleptic malignant syndrome include abnormalities of neuroregulatory mechanisms, abnormal skeletal muscle reactions to neuroleptic drugs and hyperactivity of the sympatho-adrenergic system. Dopamine decreases basal temperature via the anterior hypothalamus. Dopamine D2 receptor antagonism of neuroleptic drugs may cause hyperthermia by blocking heat loss pathways and/or producing heat secondary to extrapyramidal muscular rigidity [78]. Therefore, hyperthermia associated with the neuroleptic malignant syndrome could result from a blockade of dopaminergic receptors [79]. Additionally, the missing dopaminergic neurotransmission within the corpus striatum is thought to induce general muscular rigidity, another mechanism that contributes to heat production.

The model of a primary muscular origin of the neuroleptic malignant syndrome is based on the clinical symptomatology, on the therapeutic efficacy of dantrolene and on results of *in vitro* contracture tests. However, with respect to the neuroleptic malignant syndrome, *in vitro* contracture test studies provide contradictory results [80]. A further hypothesis for the pathophysiology of the neuroleptic malignant syndrome was introduced by Gurrera in 1999 [78]. From his point of view, the clinical symptoms of the neuroleptic malignant syndrome might be explained by hyperactivity and dysregulation of the sympatho-adrenergic system. An adrenoceptor-mediated increase in intracellular calcium ion concentrations could contribute to an increase in muscle tone and metabolism that is followed by increased heat production. Recently, Gurrera hypothesised that inherent genetic mutations cause changes in calcium regulatory proteins. Thus, the neuroleptic malignant syndrome might be understood as a 'neurogenic form' of MH [41].

The treatment of neuroleptic malignant syndrome consists of immediate withdrawal of all neuroleptic drugs, extensive supportive therapy and intensive care. Specific pharmacological therapy should be considered [81]. Dantrolene and the dopamine agonists bromocriptine and amantadine may be beneficial, but this is based only on case reports, due to the lack of controlled clinical trials [82]. Tonic contractions of skeletal muscles during neuroleptic malignant syndrome can be successfully terminated by the intravenous administration of dantrolene at the same doses used for treatment of an MH crisis [83].

Spasticity

The first therapeutic use of oral dantrolene was for the treatment of spasticity [84]. The aims of therapy are functional improvement, prevention of expected functional disabilities, pain reduction and facilitation of nursing [85]. Dantrolene is still an effective antispastic drug, as are diazepam, baclofen and tizanidin [86]. Adults initially receive oral dantrolene 25 mg per day; the dose should be increased every 3–7 days. The maximum dose should be 100 mg four times a day. Children should begin with 0.5 $mg.kg^{-1}$ and should not be given more than 3.0 $mg.kg^{-1}$ up to four times a day [17].

Ecstasy intoxication

The signs of Ecstasy (3,4-methylenedioxymethamphetamine) intoxication include mental irritability, tachycardia, acidosis, hyperthermia and increased plasma creatine kinase. The origin of the hyperthermia seen after Ecstasy intoxication is presumably central serotonergic overstimulation. Intravenous dantrolene has been used successfully to treat hyperthermia and muscle rigidity [87, 88]. A general decrease in muscular heat production caused by dantrolene might serve as an explanation for its beneficial effects. Moreover, early administration of dantrolene may attenuate Ecstasy neurotoxicity [89]. However, controlled, randomised clinical studies are not available yet. A general recommendation for dantrolene therapy during Ecstasy intoxication does not exist but it could be a promising option.

Heat stroke

Heat stroke is usually diagnosed when core temperature exceeds 40.6 °C [90]. The underlying pathological mechanisms are still poorly understood, and mortality ranges from 10% to 50%. The symptoms of heat stroke are similar to those of MH, and therefore the possibility of an association between the two conditions has been raised. Moreover, several reports confirmed that patients suffering from heat stroke show a positive MH response in the *in vitro* contracture test [91–93]. Since a rapid decrease in body temperature is important in the management of heat stroke, dantrolene has been given in conjunction with a variety of physical cooling techniques [94, 95]. However, data from case reports have not definitively shown that dantrolene therapy is actually beneficial in the treatment of heat stroke, and randomised, controlled clinical studies have yet to be performed. Therefore, a general recommendation for dantrolene therapy during heat stroke cannot be made [90].

Conclusions

Despite more than 25 years of research, dantrolene is still the only currently available drug for the effective and specific treatment of MH crises in man. The principal disadvantages of dantrolene are its poor water solubility and difficulties in rapidly preparing a suitable solution for intravenous administration. In the emergency situation, dantrolene solutions should be warmed to improve water solubility, and should be administered through an intravenous line with a blood filter system. Recent therapeutic developments have been suggested but none of them have yet been introduced into the clinical treatment of human MH syndrome. Prophylactic dantrolene therapy in MH-susceptible patients undergoing general anaesthesia is no longer recommended, not least because of dantrolene's adverse effects. Dantrolene therapy should also be considered in cases of neuroleptic malignant syndrome, spasticity and Ecstasy intoxication.

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