Review

Clinical review: Treatment of heat stroke: should dantrolene be considered?

Eran Hadad[1], Yoav Cohen-Sivan[1], Yuval Heled[1] and Yoram Epstein[2]

[1]Heller Institute of Medical Research, Sheba Medical Center, Tel Hashomer, Israel
[2]Heller Institute of Medical Research, Sheba Medical Center, Tel Hashomer, and the Sackler Faculty of Medicine, Tel-Aviv University, Tel-Aviv, Israel

Corresponding author: Yoram Epstein, hlrinst@post.tau.ac.il

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Abstract

Rapid and efficient cooling is the most important therapeutic objective in patients with heat stroke (HS). This article reviews the mechanism of action and rationale for the use of dantrolene as a potential supportive cooling method in the treatment of HS. Relevant studies were included to support discussion of the role of dantrolene for the treatment of HS. In some studies dantrolene was shown to accelerate cooling rate when administered after the development of exertional HS. Dantrolene was also found to be effective in reducing the extent of HS signs when given as pretreatment in an animal model. Accumulated data do not support the routine use of dantrolene as an adjuvant cooling technique in HS, but administration of this drug in severe cases, or in which no improvement is observed, appears rational. Further trials are needed in order to assess the true effectiveness of dantrolene in HS.

Keywords cooling, dantrolene, exertional heat stroke, heat stroke, hyperthermia, temperature

Introduction

Hyperthermia is defined as any core temperature rise to above the hypothalamic set-point at which heat-dissipating mechanisms are impaired. Normal core temperature values are in the 36.5–37.5°C range at rest and can rise to 40°C during strenous exercise. Hyperthermia is usually caused by an imbalance between total heat (metabolic and environmental heat) accumulated and total heat lost from the body. Hyperthermia *per se* may be physiological and can be compensated for (as in the moderate elevation in core temperature that occurs in an exercising and otherwise asymptomatic individual), or it may be pathophysiological but generally well tolerated. It may also be associated with adverse pathophysiological consequences such as inability to continue physical exertion (heat exhaustion). At the extreme, hyperthermia represents a state in which the elevation in core temperature is either already accompanied by organ injury or is sufficient to produce such injury if left untreated.

Several syndromes have been reported to be associated with extreme hyperthermia, including malignant hyperthermia (MH), neuroleptic malignant syndrome (NMS) and heat stroke (HS). The mainstay of treatment of these syndromes includes the administration of basic resuscitative measures together with simultaneous cooling aimed at reducing body temperature [1,2]. Cooling may be achieved by several methods, such as immersion in cold water and evaporation of water over the skin [3–7]. Because heat is primarily produced by hyperactivity of muscles in the various syndromes, dantrolene sodium, a muscle relaxant, has also been suggested to accelerate cooling [8–10]. In MH, dantrolene administration resulted in a rapid reduction in mortality rate, and therefore it is now considered an essential part of treatment in this syndrome [11–13]. Dantrolene has also been recommended for the treatment of NMS [14]. To date, no drug has shown significant efficacy in improving the outcome of patients with HS.

CHS = classic heat stroke; CNS = central nervous system; EHS = exertional heat stroke; HS = heat stroke; MH = malignant hyperthermia; NMS = neuroleptic malignant syndrome.

Experience with dantrolene use in HS is in its initial phases (Tables 1–3). In some studies a possible benefit from dantrolene treatment was reported, whereas in others it was not found to be effective [15–22]. We reviewed relevant studies concerning dantrolene use in HS in order to establish its role in the treatment of this condition.

Studies included in this review were identified by means of a comprehensive Medline search, limited to the English language literature, using the following keywords: 'dantrolene' and 'hyperthermia' or 'heat'. Each article identified was further examined for relevancy.

Dantrolene

Dantrolene sodium is a hydantoin derivative. It acts directly on muscle contractile elements, attenuating the amount of calcium released from the sarcoplasmic reticulum of skeletal muscle to the cytosol [23–25]. As a result, calcium dependent excitation–contraction coupling and consequent muscle contraction are inhibited.

The mean biological half-life of dantrolene in healthy volunteers or patients was reported to range from 6 to 9 hours, with extremes of 3 and 22 hours [25–30]. It is primarily metabolized in the liver, with 15–25% of the dose administered being excreted by the kidneys [27,29,30]. Dantrolene is marketed as Dantrium (Norwich Eaton Pharmaceuticals, Norwich, NY, USA) and can be administered intravenously (in solution with mannitol and sodium hydroxide) or orally.

When dantrolene is used as an emergency therapy, such as in acute hyperthermic syndromes, it is unlikely to cause major adverse effects [25]. However, prolonged use may be associated with undesirable side effects that include weakness, drowsiness, diarrhea and malaise [25]. Hepatotoxicity, which can be irreversible, is also a major concern. The risk for hepatic injury appears to be about twofold greater in females, in patients receiving doses over 300 mg/day and in those treated for over 60 days [31]. In addition, dantrolene sodium solution is highly alkaline (pH 9.6), and intravenous injection may cause extravasation and tissue necrosis [25].

Heat stroke and 'thermic stress syndrome'

HS is a life-threatening illness characterized by an elevation in core body temperature to above 40°C with central nervous system (CNS) dysfunction that results in delirium, convulsions, or coma [32,33] in the absence of any other cause of CNS dysfunction, and skin dryness. The affected individual may suffer from a characteristic multiple organ clinical and pathological syndrome caused by temperature-induced tissue damage [1,34]. HS results from exposure to a high environmental temperature, in which case it is called 'classic' heat stroke (CHS; or 'nonexertional' HS), or from strenuous exercise, in which case it is called 'exertional' heat stroke (EHS) [34–36]. CHS is usually seen in the very young or elderly and in poor socioeconomic settings with limited access to air conditioning. EHS is seen more commonly in exercising individuals, for instance soldiers in army training. Further reviews on HS are available [32,33,34–36].

Epidemiological incidence data for HS are imprecise because of varying definitions of heat-related death and under-diagnosis [35]. One study conducted in urban USA found a variation from 17.6 to 26.5 cases per 100,000 capita. Data from Saudi Arabia show a seasonal incidence pattern, ranging from 22 to 250 cases per 100,000 capita. The crude mortality rate in Saudi Arabia has been estimated at 50%. Treatment consists of immediate cooling and support of organ system function.

Some authors believe that HS, as well as MH and other hyperthermic syndromes, are different manifestations of a broader underlying condition called 'thermic stress syndrome' [9,10,15,17,37]. This common malady, which is triggered by different mechanisms, is characterized by an extreme elevation in body temperature and CNS dysfunction, which may be complicated by bleeding diathesis, elevated serum enzyme levels and renal failure. Because dantrolene was found to be effective in the treatment of MH and NMS, its usage has also been recommended for the treatment of HS [8–10,15].

Dantrolene use in heat stroke

Two reports from the early 1980s demonstrated a beneficial effect from using dantrolene in HS. Lydiatt and Hill [15] reported on a patient with EHS who responded favourably to dantrolene (4 mg/kg intravenously) after symptomatic therapy had failed. In a case report, Denborough [8] reported that intravenous dantrolene (20 mg bolus) therapy produced rapid recovery in a young soldier suffering from EHS after a march.

In a controlled study, the adjuvant effects of dantrolene in comparison with passive cooling were investigated in a canine model of CHS [16]. Intravenous administration of dantrolene (5 mg/kg) did not significantly improve cooling rates, haemodynamic parameters, pathological changes, or clinical outcome when compared with passive cooling.

Channa and coworkers [17] conducted a study in which 20 EHS patients were randomly assigned to two groups with only one group receiving dantrolene (2.45 mg/kg intravenously). Patients in both groups were cooled either using the Makkah body cooling unit or by 'conventional methods', namely spraying of tap water over the patients while fanning. Cooling rates were found to be significantly higher in the dantrolene group. All patients survived and there was no difference in the incidence of neurological sequelae between the groups.

The effects of dantrolene were also evaluated in 53 patients suffering from CHS [21]. All patients were treated by using a

Table 1

Summary of studies of dantrolene treatment of heat stroke in humans

Reference	Study type	Setting	Numbers included		Dantrolene dose (mg/kg bw)	Improved parameters	Nonimproved parameters
			Dantrolene treatment arms	Control arms			
[21]	Randomized, double-blind, controlled	Patients with classic heat stroke	26	26	2	–	Cooling rate, mean number of hospital stays
[17]	Randomized controlled	Heat stroke patient	8	12	2–4	Cooling rate	Survival, neurological sequelae

bw, Body weight.

Table 2

Summary of studies of dantrolene treatment of heat stroke in animals

Reference	Study type	Model	Numbers included	Dantrolene dose (mg/kg bw)	Improved parameters	Nonimproved parameters
[18]	Randomized controlled	Exercising rats	7	140	Cooling rate	–
		Nonexercising rats	7	140	–	Cooling rate
[19]	Randomized controlled	Nonexercising piglets	4	3	Cooling rate[a]	Cardivascular parameters
[16]	Randomized controlled	Nonexercising dogs	5	5	–	Cooling rate, haemodynamic parameters, pathological changes, clinical outcome

[a]Improvement was reported with or without mannitol. bw, Body weight

Table 3

Summary of studies of dantrolene pretreatment of heat stroke in animals

Reference	Study type	Model	Numbers included		Dantrolene dose (mg/kg bw)	Improved parameters	Nonimproved parameters
			Dantrolene treatment arms	Control arms			
[20]	Randomized controlled	Exercising sheep	6	6	1.5–3	Body temperature, severity of heat stroke signs, changes in serum enzymes and hormones, survival[a]	–
[18]	Randomized controlled	Exercising rats	7	7	140	–	Physical capacity
		Nonexercising rats	7	7	140	Endurance in the heat	–

[a]Trend only. bw, Body weight.

body cooling unit in which atomized water was sprayed over the victim while they were fanned with hot air. In addition, treatment with either dantrolene (2 mg/kg) or placebo was given intravenously after blind, randomized selection. Dantrolene administration did not result in any enhancement of the cooling rate, and there was no significant difference in the number of hospital stays between the two groups. It should be noted that in this study both treatment groups achieved satisfactory cooling in under 1 hour. Therefore, a possible positive effect of dantrolene in extreme cases of HS, in which cooling times might be longer, cannot be ruled out. It should further be noted that in this study Bouchama and coworkers [21] treated their patients with dantrolene and mannitol simultaneously. Thus, it could not be concluded whether the reported positive effects were attributed to dantrolene or to mannitol.

Mannitol may be beneficial in the setting of HS because of its effect on expanding the intravascular volume and reducing tissue injury after ischemia by scavenging oxygen free radicals [38,39]. In order to address this question, Zuckerman and coworkers [19] designed a randomized controlled study in which heat stroked piglets were treated by one of the following four methods: passive cooling, 'conventional cooling' (intravenous fluid resuscitation, sponging with tap water, mechanical fanning and ice gastric lavage), conventional cooling along with dantrolene, and conventional cooling along with mannitol. Although dantrolene significantly shortened the cooling time when compared with conventional cooling, it did not shorten the cooling time when compared with mannitol. Moreover, it was shown that dantrolene did not improve cardiovascular parameters when administered in addition to conventional methods.

Tayeb and Marzouki [20] investigated whether dantrolene might be advantageous in prophylaxis against HS in exercising sheep. They found that pretreatment with dantrolene (3 mg/kg and 1.5 mg/kg intravenously) caused a significant reduction in body temperature, and decreased the extent of HS signs as well as some of the induced changes in enzymes and hormones. These effects were more significant in the group receiving dantrolene 3 mg/kg than in the group receiving 1.5 mg/kg. The dantrolene group also exhibited a trend toward reduced mortality from HS (0/12) in comparison with the group that did not receive dantrolene treatment (2/6).

Using a rat model of EHS and CHS, Moran and coworkers [18] studied the efficacy of dantrolene both as a prophylactic agent and as a therapeutic drug. Administration of high doses of dantrolene (140 mg/kg intravenously) before heat stress delayed the development of HS in the sedentary animals. Estimated temperatures were lower in the exercising rats that received Dantrolene pretreatment, but this was most reasonably attributed to the limited physical capacity induced by dantrolene. When dantrolene, at the same dose, was administered after the development of HS, it significantly improved the cooling rate in the exercising rats – an effect that was not seen in the sedentary group.

Discussion

The rationale for the use of dantrolene in HS emerged from the overlap in the systemic manifestations of HS and other hyperthermic syndromes, particularly MH. However, some researchers claimed that, although hyperthermia was characteristic of both MH and HS, these syndromes represent two clinical entities with different heat generating cellular mechanisms. Although MH is characterized by muscular rigidity, which causes active heat production, HS usually manifests in the form of flaccidity, and heat production does not continue uncontrolled [17,40]. Therefore, dantrolene, which uncouples the excitation–contraction sequence heat generating mechanism, may not be beneficial in the treatment of HS. Moreover, MH is a genetically transmitted disease, which is triggered by several depolarizing muscle relaxants or volatile anaesthetic agents [41,42]. In comparison, to the best of our knowledge, no genetic predisposition has been definitely incriminated in the typical HS patient.

However, several reports suggest a possible link between HS and MH. Tobin and coworkers [43] reported a case of fatal HS in a patient who experienced MH 8 years earlier and speculated whether other HS victims are MH susceptible. An abnormal caffeine–halothene contracture test, which is considered indicative for MH susceptibility, was found in more than 40% of individuals who survived EHS, whereas less than 1% of the general population exhibited this response [44]. It is important to note that adequate recovery time must be given before performing such tests after a bout of rhabdomyolysis. Muscle function takes considerable time to recover and, inferentially at least, so does muscle metabolism. Therefore, care must be taken before relying on post-HS muscle contracture tests. A possible underlying myopathy in EHS patients was demonstrated by Bendahan and coworkers [45], who found abnormal muscle energetics in such patients by using a ^{31}P magnetic resonance spectroscopy. Therefore, there is some evidence to suggest that a subset of individuals with HS may also be predisposed to MH. Theoretically, this subset of individuals might continue to have a relatively high level of heat production even after collapse. They may also be at increased risk for EHS because an attenuated muscular efficiency can increase muscular caloric production at the same absolute work intensity. The fact that some individuals with HS might have a contribution of MH-type pathophysiology might also explain why there has been anecdotal evidence suggesting a possible benefit from dantrolene in selected cases.

The above studies indicate that the cooling rate was the only parameter among those evaluated that improved when

dantrolene was administered after the development of HS [17–19]. However, this effect was not demonstrated in all studies. The diversity of results may be accounted for by the models investigated. When dantrolene was administered in an exercising model, it was found to be more effective than in a CHS model. This is not surprising because dantrolene inhibits muscle contraction, which does not play a role in the pathophysiology of CHS.

Collectively, most of the studies suggest that dantrolene is not beneficial in reducing mortality rate when it is given for the treatment of HS. However, survival rates in EHS currently approach 95%, and the studies were not large enough to exhibit a reduced mortality [1,46]. Moreover, some reports suggest that dantrolene may even prevent death in cases of severe HS [15,17]. For example, one patient in the study conducted by Channa and coworkers [17] who received dantrolene made a complete recovery in spite of an initial core temperature of 44°C. An EHS patient described by Lydiatt and Hill [15] had a rectal temperature of 42°C for more than 30 min and responded only to dantrolene. Noteworthy, the authors did not state the upper recording limit of their thermometer. If a clinical thermometer has an upper limit of 42°C, then it will record 42°C when the actual temperature is 46°C. Despite successful cooling for 30 min, the thermometer still shows 42°C even though the temperature has been reduced by 4°C. Taking dantrolene at this instant will lead to an impressive, albeit misinterpreted, result.

Some researchers indicated that the relative ineffectiveness of dantrolene in some of the studies may be related to an inadequate dose [21,47]. Dantrolene was administered in doses of 2–5 mg/kg, which were selected according to recommended protocols with regard to the use of this agent in MH. However, the optimal dose of dantrolene in MH is still questionable. Although Britt [48] reported a complete recovery from MH when dantrolene was used at a dose of 6 mg/kg, others [31] postulated that an increased dose of dantrolene may be associated with hepatotoxicity. The risk for hepatotoxicity is even more concrete in HS patients because the liver is commonly injured in HS and increasing the dose of dantrolene may worsen this hepatic damage. Nevertheless, hepatotoxicity has never been reported in HS victims who received dantrolene.

Despite the absence of outcome-based data, it might nevertheless be pathophysiologically rational to try dantrolene in selected cases. Dantrolene may be beneficial where there is evidence of ongoing excessive heat production, such as in cases of HS that are accompanied by muscular rigidity. In these cases, the apparent HS may be misdiagnosed, and the patient may actually be suffering from MH or NMS. Finally, dantrolene might also have a role to play in limiting muscle injury and its consequences in rhabdomyolysis by impairing calcium release from the sarcoplasmic reticulum [49,50]. Loss of calcium homeostasis in muscle cells may be associated with muscle injury resulting from impairment in mitochondrial respiration and ATP production, activation of phospholipase A_2 with production of leukotrienes and prostaglandins, increased production of free radicals, and activation of calcium-activated proteases [49]. Although there is no evidence that dantrolene reduces the extent of muscle injury in EHS, it was found to protect against muscle injury associated with exercise in several studies [51–54].

Dantrolene pretreatment reduced the severity of HS signs in an exercising animal model. This effect may be attributed to decreased muscular production of metabolic heat or to an unknown modulation of neurotransmitter release [20]. However, the effect of dantrolene on muscle contracture may result in limited physical capacity. Furthermore, the administration of dantrolene before HS is more theoretical than real because the incidence of EHS is negligible in comparison with the number of individuals who are engaged in physical activity and/or are exposed to heat strain.

Conclusion

Therapy with the accepted MH prophylactic dose of 2–5 mg/kg resulted in a possible benefit from dantrolene treatment in HS in some studies, whereas in others it was not found to be effective. The limited literature does not support the routine use of dantrolene as an adjuvant cooling technique in the setting of HS. Nevertheless, because dantrolene does appear to increase cooling rate, furthur studies are advised for dantrolene use in severe cases or cases in which no improvement is observed with other cooling methods. Wider trials are still needed to evaluate the efficacy of dantrolene in reducing mortality, thereby justifying its use in HS. Noteworthy, dantrolene should not be used as a single cooling method, and its administration should only be in addition to the well established 'conventional methods'.

Competing interests

The author(s) declare that they have no competing interests.

References

1. Epstein Y, Sohar E, Shapiro Y: **Exertional heat stroke: a preventable condition.** *Isr J Med Sci* 1995, **31:**454-462.
2. Chan TC, Evans SD, Clark RF: **Drug-induced hyperthermia.** *Crit Care Clin* 1997, **13:**785-808.
3. Wyndham CH, Strydom NB, Cooke HM: **Methods of cooling subjects with hyperpyrexia.** *J Appl Physiol* 1959, **14:**771-776.
4. Weiner JS, Khogali M: **A physiological body-cooling unit for treatment of heat stroke.** *Lancet* 1980, **1:**507-509.
5. Al-Aska AK, Abu-Aisha H, Yaqub B, Al-Harthy SS, Sallam A: **Simplified cooling bed for heatstroke [letter].** *Lancet* 1987, **1:**381.
6. Armstrong LE, Crago AE, Adams R, Roberts WO, Maresh CM: **Whole-body cooling of hyperthermic runners: comparison of two field therapies.** *Am J Emerg Med* 1996, **14:**355-358.
7. Costrini A: **Emergency treatment of exertional heatstroke and comparison of whole body cooling techniques.** *Med Sci Sports Exerc* 1990, **22:**15-18.
8. Denborough MA: **Heat stroke and malignant hyperpyrexia.** *Med J Aust* 1982, **1:**204-205.
9. Meyers EF, Meyers RW: **Thermic stress syndrome.** *JAMA* 1982, **247:**2098-2099.

10. Meyers EF: **Thermic stress syndrome.** *Prev Med* 1979, **8:**520-522.
11. Kozack JK, MacIntyre DL: **Malignant hyperthermia.** *Phys Ther* 2001, **81:**945-951.
12. Wedel DJ, Quinlan JG, Iaizzo PA: **Clinical effects of intravenously administered dantrolene.** *Mayo Clin Proc* 1995, **70:** 241-246.
13. Strazis KP, Fox AW: **Malignant hyperthermia: a review of published cases.** *Anesth Analg* 1993, **77:**297-304.
14. Persing JS: **Neuroleptic malignant syndrome: an overview.** *S D J Med* 1994, **47:**51-55.
15. Lydiatt JS, Hill GE: **Treatment of heat stroke with dantrolene.** *JAMA* 1981, **246:**41-42.
16. Amsterdam JT, Syverud SA, Barker WJ, Bills GR, Goltra DD, Armao JC, Hedges JR: **Dantrolene sodium for treatment of heatstroke victims: lack of efficacy in a canine model.** *Am J Emerg Med* 1986, **4:**399-405.
17. Channa AB, Seraj MA, Saddique AA, Kadiwal GH, Shaikh MH, Samarkandi AH: **Is dantrolene effective in heat stroke patients?** *Crit Care Med* 1990, **18:**290-292.
18. Moran D, Epstein Y, Wiener M, Horowitz M: **Dantrolene and recovery from heat stroke.** *Aviat Space Environ Med* 1999, **70:** 987-989.
19. Zuckerman GB, Singer LP, Rubin DH, Conway EE Jr: **Effects of dantrolene on cooling times and cardiovascular parameters in an immature porcine model of heatstroke.** *Crit Care Med* 1997, **25:**135-139.
20. Tayeb OS, Marzouki ZM: **Effect of dantrolene pretreatment on heat stroke in sheep.** *Pharmacol Res* 1990, **22:**565-572.
21. Bouchama A, Cafege A, Devol EB, Labdi O, El-Assil K, Seraj M: **Ineffectiveness of dantrolene sodium in the treatment of heatstroke.** *Crit Care Med* 1991, **19:**176-180.
22. Watson JD, Ferguson C, Hinds CJ, Skinner HR, Coakley JH: **Exertional heat stroke induced by amphetamine analogues. Does dantrolene have a place?** *Anaesthesia* 1993, **48:**1057-1060.
23. Morgan KG, Bryant SH: **The mechanism of action of dantrolene sodium.** *J Pharmacol Exp Ther* 1977, **201:**138-147.
24. Oha T: **Influence of temperature and external Ca^{2+} concentration upon dantrolene action on exitation contraction coupling in frog skeletal muscle.** *Can J Physiol Pharmacol* 1981, **59:**358-363.
25. Ward A, Chaffman MO, Sorkin EM: **Dantrolene. A review of its pharmacodynamic and pharmacokinetic properties and therapeutic use in malignant hyperthermia, the neuroleptic malignant syndrome and an update of its use in muscle spasticity.** *Drugs* 1986, **32:**130-168.
26. Dykes MH: **Evaluation of a muscle relaxant: dantrolene sodium (Dantrium).** *JAMA* 1975, **231:**862-864.
27. Lietman PS, Haslam RH, Walcher JR: **Pharmacology of dantrolene sodium in children.** *Arch Phys Med Rehabil* 1974, **55:**388-392.
28. Meyler WJ, Mols-Thurkow HW, Wesseling H: **Relationship between plasma concentration and effect of dantrolene sodium in man.** *Eur J Clin Pharmacol* 1979, **16:**203-209.
29. Krause T, Gerbershagen MU, Fiege M, Weishorn R, Wappler F: **Dantrolene – A review of its pharmacology, therapeutic use and new developments.** *Anesthesia* 2004, **59:**364-373.
30. Dykes MH: **Evaluation of a muscle relaxant: dantrolene sodium (Dantrium).** *JAMA* 1975, **231:**862-864.
31. Utili R, Boitnott JK, Zimmerman HJ: **Dantrolene-associated hepatic injury. Incidence and character.** *Gastroenterology* 1977, **72:**610-616.
32. Bouchama A, Knochel JP: **Heat stroke.** *N Engl J Med* 2002, **346:** 1978-1988.
33. Epstein Y: **Exertional heatstroke: lessons we tend to forget.** *Am J Med Sports* 2000, **2:**143-152.
34. Shibolet S, Coll R, Gilat T, Sohar E: **Heatstroke: its clinical picture and mechanism in 36 cases.** *Q J Med* 1967, **36:**525-547.
35. Semenza JC, Rubin CH, Falter KH, Selanikio JD, Flanders WD, Howe HL, Wilhelm JL: **Heat-related deaths during the July 1995 heat wave in Chicago.** *N Engl J Med* 1996, **335:**84-90.
36. Epstein Y, Moran DS, Shapiro Y, Sohar E, Shemer J: **Exertional heat stroke: a case series.** *Med Sci Sports Exerc* 1999, **31:**224-228.
37. Jardon OM: **Physiologic stress, heat stroke, malignant hyperthermia: a perspective.** *Mil Med* 1982, **147:**8-14.
38. Bratell S, Folmerz P, Hansson R, Jonsson O, Lundstam S, Pettersson S, Rippe B, Schersten T: **Effects of oxygen free radical scavengers, xanthine oxidase inhibition and calcium entry-blockers on leakage of albumin after ischaemia. An experimental study in rabbit kidneys.** *Acta Physiol Scand* 1988, **134:** 35-41.
39. Del Maestro R, Thaw HH, Bjork J, Planker M, Arfors KE: **Free radicals as mediators of tissue injury.** *Acta Physiol Scand Suppl* 1980, **492:**43-57.
40. Knochel JP: **Treatment of heat stroke.** *JAMA* 1983, **249:**1006-1007.
41. Leong P, MacLennan DH: **The cytoplasmic loops between domains II and III and domains III and IV in the skeletal muscle dihydropyridine receptor bind to a contiguous site in the skeletal muscle ryanodine receptor.** *J Biol Chem* 1998, **273:**29958-29964.
42. Denborough M: **Malignant hyperthermia.** *Lancet* 1998, **352:** 1131-1136.
43. Tobin JR, Jason DR, Challa VR, Nelson TE, Sambuughin N: **Malignant hyperthermia and apparent heat stroke.** *JAMA* 2001, **286:** 168-169.
44. Bourdon L, Canini F: **On the nature of the link between malignant hyperthermia and exertional heatstroke.** *Med Hypotheses* 1995, **45:**268-270.
45. Bendahan D, Kozak-Ribbens G, Rodet L, Confort-Gouny S, Cozzone PJ: **31Phosphorus magnetic resonance spectroscopy characterization of muscular metabolic anomalies in patients with malignant hyperthermia: application to diagnosis.** *Anesthesiology* 1998, **88:**96-107.
46. Shapiro Y, Seidman DS: **Field and clinical observations of exertional heat stroke patients.** *Med Sci Sports Exerc* 1990, **22:**6-14.
47. Orser B: **Dantrolene sodium and heatstroke.** *Crit Care Med* 1992, **20:**1192-1193.
48. Britt BA: **Dantrolene.** *Can Anaesth Soc J* 1984, **31:**61-75.
49. Odeh M: **The role of reperfusion-induced injury in the pathogenesis of the crush syndrome.** *N Engl J Med* 1991, **324:**1417-1422.
50. Parr MJ, Willatts SM: **Fatal theophylline poisoning with rhabdomyolysis. A potential role for dantrolene treatment.** *Anaesthesia* 1991, **46:**557-559.
51. Lopez JR, Rojas B, Gonzalez MA, Terzic A: **Myoplasmic Ca^{2+} concentration during exertional rhabdomyolysis.** *Lancet* 1995, **345:**424-425.
52. Amelink GJ, Van der Kallen CJ, Wokke JH, van Asberk BS, Bar PR: **Dantrolene sodium diminishes exercise-induced muscle damage in the rat.** *Eur J Pharmacol* 1990, **179:**187-192.
53. Bigard AX, Merino D, Lienhard F, Serrurier B, Guezennec CY: **Muscle damage induced by running training during recovery from hindlimb suspension: the effect of dantrolene sodium.** *Eur J Appl Physiol Occup Physiol* 1997, **76:**421-427.
54. Pagala M, Amaladevi B, Bernstein A, Herzlich B, Namba T, Grob T: **Dantrolene sodium reduces the enhanced leakage of creatine kinase caused by ethanol, cocaine, and electrical stimulation in isolated fast and slow muscles of rat.** *Alcohol Clin Exp Res* 1997, **21:**63-67.