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EXPERT OPINION

Do we foresee new emerging drugs to treat malignant hyperthermia?

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Malignant hyperthermia (MH) is a life-threatening genetic sensitivity of skeletal muscles to volatile anesthetics and depolarizing neuromuscular blocking drugs occurring during or after anesthesia. Mortality of MH has been significantly reduced by using the skeletal muscle relaxant dantrolene. However, pharmacological disadvantages are known. By approval of a nanocrystalline dantrolene sodium suspension (DSS), a new product enters the market. DSS is a promising substance, but clinical data are lacking up to now. Especially with regard to newer knowledge on MH and its associated clinical presentations, there might be an increasing interest on DSS.

Keywords: anesthesia, dantrolene, dantrolene sodium suspension, malignant hyperthermia, nanocrystalline suspension

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1. Background

Malignant hyperthermia (MH) is an inherited pharmacogenetic disorder of the skeletal muscle triggered by exposure to halogenated volatile anesthetic gases and succinylcholine [1].

In Europe and North America, MH used to be the commonest cause of death directly attributable to general anesthesia. In the 1970s, mortality ranged between 70 and 80% even after initializing therapy [2]. Nowadays, an analysis of death rates in cases from Canada and the United States as reported to The North American Malignant Hyperthermia Registry exhibited mortality of 1.4% [3]. Dramatically, MH often appears in cases of emergency and/or urgency [4]. An analyzing study of five European MH centers showed fulminant MH crises where associated in 80% with the use of succinylcholine and volatile anesthetic [5], a combination commonly used in emergency cases.

The incidence of MH episodes during anesthesia ranges between 1:5000 and 1:50,000–100,000 anesthesias. However, the frequency was described to be increased in recent years [6] and prevalence might be higher than suggested [7].

2. Current pharmacologic treatment

There are several guidelines for the management of MH. As pointed out by the European Malignant Hyperthermia Group, an early recognition of a MH crisis and its immediate and consequent treatment are essential. If an MH crisis is suspected, diagnosis and treatment have to start immediately respecting the difficult diagnosis due to more or less unspecific symptoms. First steps that can easily and immediately be established are to stop administration of trigger agents, to remove the vaporizer from the anesthesia machine and hyperventilate the patient with high-flow oxygen in high concentrations. Anesthesia must be changed to nontriggering agents such as propofol and sufentanil, and relaxation can be established with nondepolarizing muscle relaxants [8,9].

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The hydantoin derivative dantrolene (hydrated 1-(((5-(4-nitrophenyl)-2-furanyl) methylene) amino)-2,4 imidazolidinedione sodium salt) was the first specific drug for treatment of MH. It was used initially as a muscle relaxant for long-term treatment of muscle spasticity. A multicenter study, performed from 1977 to 1979, showed a significant decrease in mortality in patients with a suspected MH reaction if dantrolene was administered [10]. As a consequence, dantrolene was introduced for clinical treatment of MH.

2.1 Dantrolene inhibits Ca^{2+} release from the skeletal muscle cell without influencing its reuptake

In healthy conscious volunteers, intravenous administration of dantrolene 2.4 mg/kg results in plasma concentrations of 4.2 µg/ml, which blocks up to 75% of skeletal muscle contraction. Plasma concentrations remain stable within the therapeutic range for ~ 5 h after administration. The plasma elimination half-life time is estimated to be 12 h [2]. Dantrolene is excreted via urine and bile after metabolism by liver microsomes to 5-hydroxydantrolene.

Dantrolene is highly lipophilic and therefore poorly soluble in water. It 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 at pH 9.5. The commercially available package contains 12 vials of dantrolene and 12 vials of distilled water. 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 [2].

Therefore, tissue necrosis in the event of accidental extravascular injection is one of the disadvantages. Furthermore, prompt administration might be delayed because of the time to prepare the vials due to its poor solubility in water. For example, for the recommended initial bolus dose of 2.5 mg/kg in an 80-kg patient, 10 vials of dantrolene sodium solution 20 mg need to be reconstituted in 600 ml of water. In addition, due to the large volume of solution required for administration, complete delivery of the dantrolene dose can take several minutes. In an *in vivo* study, administration of dantrolene required 860 s [11]. Consequently, reconstitution and administration times can cause a significant delay in treating the MH episode, adding to the stress of the anesthesia team. Therefore, in the last years, research on dantrolene focused on improving its solubility.

3. Future pharmacological agents

A promising new product for treatment of MH is a nanocrystalline dantrolene sodium suspension (DSS) [8]. Nanosuspensions of drugs are sub-micron colloidal dispersions of pure particles of drug, which are stabilized by surfactants and are predicated to offer novel solutions for innovative drugs of the future [12].

When prepared for intravenous administration, DSS is 150 times more concentrated (50 mg/ml) than standard dantrolene (0.33 mg/ml). Because of the greater solubility in water, 250 mg of DSS can be reconstituted and administered in only 5 ml of water. The same dose of dantrolene using the standard solution would require a volume of about 750 ml.

It is important to note that the actual solubility of dantrolene in DSS is not changed and remains as 0.33 mg/ml, with the balance of the dantrolene being present in a nanosuspension. Therefore, in a volume of 1 ml of the DSS product, about 1.65 mg of dantrolene is in solution and about 48.35 mg is present as a nanoparticle suspension. The nanoparticles dissolve in a matter of seconds following intravenous administration, thereby providing much more rapid delivery of dantrolene to the body. Laboratory testing of DSS has demonstrated that the particles dissolve quickly in plasma at 37°C [11].

It was shown that DSS is as potent and effective as standard dantrolene in treating MH crisis in susceptible swine. In contrast, preparation, as well as administration, of DSS was significantly faster (preparation 860 – 51 s, dantrolene to DSS; administration 470 – 4 s, dantrolene to DSS). Furthermore, no relevant side effects were observed [11].

In healthy conscious volunteers, intravenous administration of DSS 1 – 2.5 mg/kg results in dose-proportional increase in plasma exposure of dantrolene and its metabolite, 5-hydroxydantrolene to 9 µg/ml. The plasma elimination half-life time for DSS was independent of the dose administered and ranged from 8.5 to 11.4 h over the 1 to 2.5 mg/kg dose range [13].

Recently, the U.S. FDA has approved DSS under the name Ryanodex® (Eagle Pharmaceuticals, Inc., Woodcliff Lake, New Jersey, USA) for the treatment of MH [14]. This is indeed, as according to the manufacturer, the first major development in > 30 years. The drug will be available in 250 mg vials containing the active lyophilized powder that can be dissolved in 5 ml of water [13].

As MH is a rare occurring crisis, DSS (Ryanodex®) was designated an orphan drug by the U.S. FDA in August 2013 [14]. This usually decreases the statistical burden on clinical trial development for approval, even if orphan drugs use to follow the same regulatory path as any other pharmaceutical product. However, clinical trials are still lacking. Because trials on healthy volunteers conducted by the manufacturer reported increased adverse events like flushing, dystonia and dysphagia [13], further research might concentrate on those observations and the underlying mechanisms. Adverse events were seen to increase in frequency with increasing doses of DSS. As clinical trials were conducted under widely ranging variation of conditions, adverse events cannot be directly compared to those of other drugs.

The Malignant Hyperthermia Association of the United States (MHAUS) appreciated the option to bring the crisis under control more rapidly and prevent severe

complications from MH by using DSS [15]. Furthermore, 'Now that FDA approval for the treatment of MH by Ryanodex has been granted, MHAUS recommends that The North American Malignant Hyperthermia Registry AMRA Report be utilized to report Ryanodex use. This will permit independent evaluation of its safety and efficacy in the treatment of human MH' [16].

4. Expert opinion

Since dantrolene was primarily synthesized, a specific drug for treatment of MH crisis exists. A main disadvantage is its poor solubility. With approval of DSS by the U.S. FDA, a promising substance has been introduced for MH crisis treatment.

However, dantrolene is known to present with common side effects like muscle weakness, phlebitis, gastrointestinal upset and respiratory failure. Those side effects are even more present when fluid administration is part of the treatment [17]. Because the administration of DSS requires dramatically lesser fluid load, those side effects may be attenuated.

Interestingly, the reference substance in MH treatment, dantrolene, was primarily used to treat spasticity as a muscle relaxant. Furthermore, its perception in the field of neurology and neurocritical care is increasing because dantrolene can treat the metabolic effects of fever in the presence of neurologic injury, cerebral vasospasm and neuroleptic malignant syndrome [2]. Whether DSS might be an interesting substance in the field of neurology is a question to answer. In addition, dantrolene is used in case of 3,4-methylenedioxymethamphetamine (MDMA, 'ecstasy') overdose too [18]. Notably, there is already one published trial on successful DSS use in MDMA overdose in swine [19]. Further trials would be eligible.

MH susceptible people are at risk for stress-induced hyperpyrexic death without contact to anesthesia [1]. Exertional heat illness, exertional rhabdomyolysis and MH are known as syndrome complexes with similar pathophysiology. To date, there is no clear evidence for the use of dantrolene in treatment of exertional heat illness. However, in severe cases, its use is worth a try. Further trials were already demanded and DSS might be a substance to analyze in treatment of heat stroke too.

After successful treatment of MH with dantrolene in some patients, recurrence of symptoms can be observed in ~ 20% of the patients. On multivariate analysis, muscular body type, a temperature increase and a longer time from induction to initial MH reaction were associated with recrudescence [20]. Whether there is a different amount of recrudescence after treatment with DSS might be a promising approach. Defining the risk factors may help especially critical care physicians to identify patients at higher risk for recrudescence. In the trial mentioned, mean time from initial reaction and recrudescence was 13 h. Therefore, the time for monitored care on intermediate care or intensive care unit should be extended in order to provide an adequate level of patient safety.

Declaration of interest

MU Gerbershagen received a consulting honorary in context of an animal study design from Eagle Pharmaceuticals. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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