Acta Anaesth. Bel., 2025, 76 (2): *83-85*

Editorial

Agilus®, a novel formulation of intravenous dantrolene as an alternative to Dantrium® for the treatment of a malignant hyperthermia crisis

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Promising outcomes have emerged from the European Medicines Agency's decision to approve the novel formulation of dantrolene as an effective treatment for perioperative malignant hyperthermia crises. This formulation has never been marketed in Europe.

Malignant hyperthermia (MH) is an inherited, multifactorial channelopathy marked by uncontrolled release of calcium ions (Ca^{2+}) from the sarcoplasmic reticulum of skeletal muscle that results in sustained muscle contraction following exposure to volatile anesthetics and succinylcholine[1].

The pathophysiology of MH is widely understood to entail the sustained activation of the ryanodine receptor (RyR1)[2]. The energy expenditure required to restore cellular calcium homeostasis generates a demand for adenosine triphosphate (ATP), subsequently resulting in heat production. The integrity of the muscle membrane becomes compromised, culminating in rhabdomyolysis and life-threatening ion disturbances. If not addressed swiftly through the cessation of anesthetic use and the administration of dantrolene, the mortality rate may exceed 70%.

Until the 1970's, no pathogenetic pharmacological intervention existed for this particular pathology, resulting in a notably high mortality rate. In 1975, Dr. Harrison and his colleagues suggested that dantrolene be used as an effective remedy for the swift management of MH crises[3]. Dantrolene operates by obstructing the release of Ca^{2+} from the sarcoplasmic reticulum. Its mechanism of action involves the antagonism of RyR1, thereby diminishing the excitation-contraction coupling in muscle cells. The advent of the intravenous formulation of dantrolene in 1979, in conjunction with other measures, led to a dramatic reduction in the mortality rate associated with MH crises, which plummeted from 84% to 9%[4].

Nowadays, dantrolene represents the most important component in the causal treatment of MH crises, serving as the sole agent capable of rapidly alleviating MH symptoms by diminishing the release of Ca^{2+} from the endoplasmic reticulum[5]. Dantrolene sodium is currently the only available medication for targeted and effective management of MH crises in humans. According to the current guidelines of the European Malignant Hyperthermia Group (www.emhg.org): "An early and appropriate dose of IV dantrolene is essential in the treatment of fulminant MH… An initial dose of dantrolene 2-2.5 mg kg^{-1} IV should be used in the treatment of an MH reaction"[6].

Any delay to the intravenous administration of dantrolene is associated with an increased rate of complications[6]. In Europe, the sole form of dantrolene for intravenous use has been Dantrium®, which is supplied in packs of 12 vials. Each vial contains 20 mg of dantrolene sodium powder, that requires reconstitution with 60 mLs of sterile water. In the USA a nanoparticle suspension formulation of dantrolene (RYANODEX®) is available and contains 250 mg per vial.

Notwithstanding the life-saving benefits of Dantrium® in Europe, its usage presents several challenges. A notable drawback is that the powder is prepared with mannitol and sodium hydroxide as excipients. This limits the water solubility of the formulation, thus limiting the swift preparation of intravenous solutions during emergency situations[7].

Due to the low quantity of Dantrium® per vial, preparation of multiple vials is required in order to administer an appropriate clinical dose. This consumes both time and resources during a critical period for the patient. According to the publication by Kugler et al, an 80 kg patient requires the preparation of 10 vials to achieve an initial dose of 2.5 mg kg^{-1}. At room temperature, the preparation of this dose, with the usual diluent, would require an average of 40.5 minutes[8]. In addition, the dilute concentration of the dissolved product implies substantial volumes of water must be used, which may lead to adverse effects, particularly in pediatric populations. Each 30-minute delay following the onset of initial symptoms nearly doubles the risk of complications, while every increment of 2ºC in core temperature almost triples that risk[8]. Therefore, the prompt preparation of Dantrium® remains imperative, as patients may rapidly deteriorate with the onset of severe acidosis, shock, and ventricular fibrillation within a mere 20 minutes[8].

On May 29, 2024, a novel intravenous formulation of Dantrolene, branded as Agilus® (Dantrolene Sodium, hemiheptahydrate, 120 mg powder per vial, for IV injection - Norgine B.V.), obtained marketing authorization within the European Union (EU). This formulation has never been marketed in Europe. Agilus® is indicated for the treatment of MH crisis in adults and children of all ages. According to the studies provided by the company, Agilus® has been demonstrated to be 'bioequivalent' to the reference medication, Dantrium® IV; however, it incorporates different excipients—specifically 2-hydroxypropyl-beta-cyclodextrin (HP-β-CD) and polyethylene glycol (PEG) —which facilitate swifter preparation and administration in a reduced volume of fluid[9]. Both formulations of dantrolene yield equivalent concentrations of the active ingredient within the body and are thus anticipated to exert a similar therapeutic effect.

Agilus® contains 120 mg of dantrolene per vial and requires only 20 mLs of sterile water for injection. Pharmaceutical and simulation data revealed that each step in the preparation and administration process was 26% to 69% more efficient for Agilus® than for Dantrium® IV. The preparation and administration of one vial of Agilus® takes 1 minute and 53 seconds, whereas Dantrium® necessitates six vials to achieve a 120 mg dose, extending the administration time to 18 minutes[9]. Furthermore, the volume of water required for reconstituting 120 mg of Agilus® is merely 20 mLs, compared to the 360 mLs needed for preparing the same dose of Dantrium®.

No new safety concerns emerged when comparing the clinical profiles of Agilus® and Dantrium® in healthy human volunteers; any of the adverse effects observed were of a comparable magnitude across treatments and were attributable to the pharmacological properties of dantrolene[9].

There exists some ambiguity regarding the potential adverse effects of one of the excipients, 2-hydroxypropyl-beta-cyclodextrin (HP-β-CD). This has been included to increase the aqueous solubility of dantrolene, thereby diminishing preparation time and the volume of fluid required. Nonetheless, the European Medicines Agency (EMA) has acknowledged that the scant instances of hearing loss documented in patients treated with HP-β-CD for an unrelated condition were predominantly mild and transitory. Instances of auditory impairment have been noted at exposure levels of HP-β-CD commensurate with the upper limits of the recommended Agilus® dosage. Consequently, the EMA has concluded that the benefits of Agilus® outweigh its associated risks, permitting its authorization for use within the EU.

It is important to note, however, that the reported advantages associated with Agilus®, in comparison with the traditional dantrolene formulation, are derived from laboratory-based simulation. Also, Ng Kwet Shing et al acknowledge the limitations of their study – namely the small sample size, paucity of data concerning female participants, and the lack of data from higher dosage levels and repeated dosing. The safety of Agilus®, as well as Dantrium® IV in pregnant women has not been established: dantrolene crosses the placenta, and should be given only when the potential benefits have been weighed against the possible risk for mother and child.

In summary: the recent publication by Ng Kwet Shing et al has shown similar efficacy for both Agilus® and Dantrium®, confirming their bioequivalence with respect to overall exposure. The safety profiles in healthy volunteers were comparable. The advantages for the preparation and administration of the new formulation of dantrolene compared to Dantrium® IV have been emphasized.

Acknowledgment: The Belgian Malignant Hyperthermia Research Unit has been awarded a research grant from Norgine N.V. Belgium. The contents of this publication are solely the responsibility of the author and do not necessarily reflect the official views of Norgine N.V.

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doi.org/10.56126/76.2.12