Dantrolene delivery for the treatment of malignant hyperthermia

Adverse events should be reported.
Reporting forms and information can be found at www.mhra.gov.uk/yellowcard.
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AGILUS™
DANTROLENE SODIUM HEMIHEPTAHYDRATE

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In combination with adequate support measures, AGILUS® is indicated for the treatment of malignant hyperthermia in adults and children of all ages.[1]

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Malignant hyperthermia impacts patients and clinicians

In the UK there are approximately 20 cases of malignant hyperthermia (MH) every year.[2]

Whilst an MH reaction can occur at any age, most reactions occur in children or young adults.[3]

Previous uneventful anaesthetics do not eliminate the risk of MH

It is possible to have had multiple previous anaesthetics without developing an MH crisis, with one series of cases finding 77 of 152 patients who developed MH reported ≥2 prior unremarkable general anaesthetics.[4]

Patient outcomes have improved with changes to treatment

Advances in the management of MH, including the introduction of dantrolene therapy, early detection of an MH crisis using capnography, and the introduction of diagnostic testing, have contributed to a reduction in mortality from over 70-80% when MH was first recognised as a complication of anaesthesia to less than 5% by 2012.[5]

MH can present at any time during an anaesthetic, or in the postoperative period.[6]

The cardinal signs of an MH crisis can include:[3]

- A rise in end-tidal CO_2 ($ETCO_2$) (or tachypnoea in a spontaneously breathing patient)
- Unexplained increase in heart rate
- Rise in core body temperature
- Muscle rigidity

Signs that occur later in the course of MH may include:[6]

- Hyperkalaemia
- Body temperature rising by greater than 1°C every 5 minutes
- Increase in creatine kinase (CK) activity
- Increase in myoglobulin level
- Myoglobinuria
- Disseminated intravascular coagulation (DIC)

Dantrolene is at the centre of MH treatment

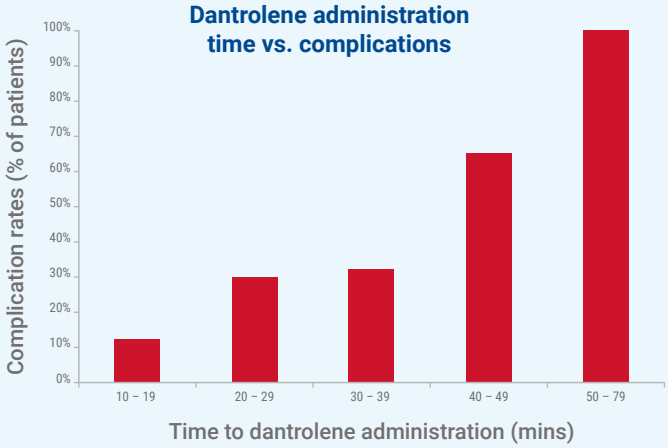
Early recognition and prompt treatment is essential to manage an MH crisis.[6,7]

Dantrolene is an important component of MH therapy

A central part of the treatment of an MH reaction is intravenous (IV) dantrolene, administered as soon as possible.[8]

Once MH is suspected, treatment must be started immediately

Delays in instigating therapy can have serious consequences, with an increased time between the first signs of MH and dantrolene administration associated with increased complication rates.[8]



Adapted from Riazi S, *et al.* 2014, from a series of 16 patients.[9]*

Poor solubility could impair the use of legacy dantrolene (DANTRIUM IV) during an MH crisis

The main disadvantage of legacy dantrolene formulation is its poor water solubility, which may have led to difficulties in rapidly preparing IV solutions in emergency situations.[10]

*Relationship between dantrolene administration time (interval between first clinical sign and first dose of dantrolene) measured in minutes and percentage of MH complications from a series of 16 patients.[9]

An evolution in malignant hyperthermia treatment

AGILUS® is indicated for the treatment of malignant hyperthermia in adults and children of all ages, in combination with adequate support measures.[1]

AGILUS® has been developed using different excipients to legacy dantrolene formulation, in order to enhance solubility and speed of preparation.[11]

With AGILUS®, the same dose of dantrolene can be reconstituted more rapidly and in smaller volumes than with previous dantrolene formulation.[11]*

*Performed under simulation conditions, using a single operator in a controlled environment.

The AGILUS® difference

Compared to the legacy dantrolene formulation, a laboratory non-clinical simulation study found:[11]*

1 vial of AGILUS® (containing 120 mg of dantrolene) takes **1 min 53 sec** to prepare and administer. DANTRIUM IV needs **6 vials** (each containing 20 mg of dantrolene) to achieve 120 mg dose and takes **18 mins** to prepare and administer.

Note: times come from a laboratory and pharmacy simulation with a single operator.

Preparation and administration time

More than **9.5x faster** to prepare an equivalent dose.

Total fluid volume administered

Lower total fluid volume. The volume of water for injections needed to reconstitute 120 mg of AGILUS® is only 20 mL compared to 360 mL needed to prepare 120 mg of DANTRIUM IV.[1,12]

AGILUS® contains 120 mg dantrolene per vial, with each vial reconstituted with 20 mL water for injections.[1] Dantrolene legacy formulation contains 20 mg dantrolene per vial, and each vial needs to be reconstituted with 60 mL water for injections.[12]

*Performed under simulation conditions, using a single operator in a controlled environment. This study prepared AGILUS® by shaking until reconstituted, which took an average of 32s.[11] AGILUS® Summary of Product Characteristics states that the product should be shaken for 1 minute before being examined.[1] Please see the Summary of Product Characteristics for full preparation information.

How to prepare and administer AGILUS®

Treatment with AGILUS® must be started as soon as an MH crisis is suspected.[1]

Summary of preparation and administration

How to prepare AGILUS®[1]

1. Each vial should be reconstituted by adding 20 mL water for injections and shaking for approximately 1 minute, before inspecting for particulates.
2. Further shaking may be necessary.
3. Reconstituted AGILUS® does not need to be filtered prior to administration.

How to administer AGILUS®[1]

1. A reconstituted vial of AGILUS® contains 120 mg of dantrolene, with a final volume of 22.6 mL.
2. Reconstituted AGILUS® must not be mixed with other solutions or given via the same venous access.
3. The therapy is given rapidly by intravenous injection at a dose of 2.5 mg/kg body weight for adult and paediatric patients. For all body weights ≥120 kg, the maximum amount given as a single bolus for each individual dose (whether an initial or repeat dose) should not exceed 300 mg.

Observations and actions after administering AGILUS®[1]

In the management of MH, along with the treatment of the patient with AGILUS®, other supportive measures must be continued.

Further bolus injection of 2.5 mg/kg should be repeated every 10 minutes when the main clinical symptoms of MH are still present.

Continued monitoring of the patient is necessary, as the hypermetabolic features of an MH may recur within the first 24 hours after initial resolution.

If this occurs, AGILUS® should be re-administered at a dose of 2.5 mg/kg every 10 minutes until the signs of an MH regress once more.

If a cumulative dose of 10 mg/kg or above is considered, the diagnosis of an MH should be re-examined.

Please refer to the Summary of Product Characteristics for full details on preparation and administration.

Special warnings and precautions[1]

This information is not comprehensive, please refer to the Summary of Product Characteristics for a complete list of all warnings and precautions.

Contraindications

Hypersensitivity to the active substance or to any of the excipients.

Ototoxicity

AGILUS® contains 3530 mg hydroxypropylbetadex (a cyclodextrin) in each vial, which is equivalent to 156.2 mg/mL in the reconstituted solution.

Hydroxypropylbetadex has been associated with ototoxicity in animal studies and cases of hearing impairment have been observed in studies in other clinical settings. Cases of hearing impairment have been observed at hydroxypropylbetadex exposure levels comparable to the higher range of recommended AGILUS® doses. In most cases the hearing impairment has been transient and of slight to mild severity.

The potential risk for hearing impairment may be of particular concern in patients with increased risk for hearing loss, e.g. recurring/chronic ear infections.

Exposure to hydroxypropylbetadex from AGILUS® is expected to be higher in patients with renal impairment. The potential risks associated with hydroxypropylbetadex may be higher in these patients.

Calcium channel blockers

Isolated case reports and animal studies indicate an interaction between dantrolene and calcium channel blockers, such as verapamil and diltiazem, in the form of heart failure. Concomitant use of AGILUS® and calcium channel blockers is not recommended.

Muscle relaxants

Concomitant administration of AGILUS® with non-depolarising muscle relaxants, such as vecuronium, can enhance their effect.

Special warnings and precautions[1]

Pregnancy

There are no or limited data for the use of dantrolene in pregnant women. Animal studies are insufficient with respect to reproductive toxicity. Postpartum uterine atony has been reported after intravenous dantrolene therapy. The risk of floppy child syndrome in neonates has also been described when intravenous dantrolene was administered to the mother during caesarean section. Dantrolene crosses the placenta and should only be used during pregnancy when the potential benefit outweighs the possible risk to mother and child.

Breast-feeding

No information is available on the use of dantrolene during breastfeeding. According to its safety profile, a risk to a breastfed infant cannot be excluded as dantrolene is excreted in breastmilk. Therefore, breastfeeding should be discontinued during administration of AGILUS®. Based on elimination half-life of dantrolene, breastfeeding can be restarted 60 hours after the last dose.

See the Summary of Product Characteristics for a complete list of all warnings and precautions.

Adverse effects after administration

The most commonly reported adverse event of intravenous dantrolene administration is skeletal muscle weakness, which is related to the mode of action.[1]

Reported adverse reactions observed linked to dantrolene are related to the formulations for acute, intravenous use and for chronic, oral use.[1] Some of the adverse reactions may also be observed as a result of the underlying malignant hyperthermia crisis.[1]

Adverse reactions by system[1]

System organ class	Frequency	Adverse drug reactions
Immune system disorders	Not known	Hypersensitivity, Anaphylactic reaction
Metabolism and nutrition disorders*	Not known	Hyperkalaemia
Nervous system disorders	Not known	Dizziness, Somnolence, Seizure, Dysarthria, Headache
Eye disorders	Not known	Visual impairment
Cardiac disorders*	Not known	Cardiac failure, Bradycardia, Tachycardia
Vascular disorders	Not known	Thrombophlebitis
Respiratory, thoracic and mediastinal disorders	Not known	Respiratory failure, Respiratory depression
Gastrointestinal disorders	Not known	Abdominal pain, Nausea, Vomiting, Gastrointestinal haemorrhage, Diarrhoea, Dysphagia
Hepatobiliary disorders	Not known	Jaundice,† Hepatitis,† Hepatic function abnormal, Hepatic failure including fatal outcome,† Idiosyncratic or hypersensitive liver diseases
Skin and subcutaneous tissue disorders	Not known	Urticaria, Erythema, Hyperhidrosis
Musculoskeletal and connective tissue disorders	Not known	Muscle weakness, Muscle fatigue
Renal and urinary disorders*	Not known	Crystalluria
Reproductive sytem and breast disorders	Not known	Uterine hypotonus
General disorders and administration site conditions	Not known	Fatigue, Administration site reaction, Asthenia

Adapted from AGILUS® Summary of product characteristics.[1]

Not known: frequency could not be estimated from the available data.
* These adverse reactions were observed in nonclinical studies
† These adverse reactions have been observed with chronic, oral treatment.

The frequency, type and severity of adverse reactions in children are expected to be the same as in adults.[1]

Dosing for AGILUS® (dantrolene sodium hemiheptahydrate) treatment for malignant hyperthermia

AGILUS® is indicated for the treatment of malignant hyperthermia in adults and children of all ages, in combination with adequate support measures.[1]

Initial dose

AGILUS® should be administered rapidly by IV injection at a dose of 2.5 mg/kg body weight for adult and paediatric patients.[1]

Further doses

If the main clinical symptoms persist, a bolus injection of 2.5 mg/kg should be repeated every 10 minutes until physiological and metabolic abnormalities improve.[1]

A cumulative dose of 10 mg/kg or above should prompt a re-examination of the diagnosis of MH.[1]

Dosing examples by body weight to achieve a dose of 2.5 mg/kg for both adults and children[1]

For all body weights ≥120 kg, the maximum amount given as a single bolus for each individual dose (whether an initial or repeat dose) should not exceed 300 mg.

Number of vials to be prepared	Body weight range	Example dosing recommendation	
		Body weight	Dose to be administered
1	Up to 48 kg	3 kg	7.5 mg
		6 kg	15 mg
		12 kg	30 mg
		24 kg	60 mg
		48 kg	120 mg
2	From 49 kg to 96 kg	72 kg	180 mg
		96 kg	240 mg
3	From 97 kg	120 kg	300 mg
		144 kg	300 mg

Please refer to the Summary of Product Characteristics for full dosing details.

Prescribing Information

Click or scan to view
DANTRIUM IV (dantrolene sodium)
Prescribing Information

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Prescribing Information

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Please refer to the Summary of Product Characteristics for full details on preparation and administration.

REFERENCES: 1. AGILUS®. Summary of Product Characteristics. **2.** Hopkins PM, *et al. Anaesthesia.* 2021;76:655–664. **3.** Gupta PK, Hopkins PM. *BJA Education.* 2017;17(7):249–254. **4.** Larach MG, *et al. Anesth Analg.* 2010;110:498–507. **5.** Kim D-C. *Korean J Anesthesiol.* 2012;63(5):391–401. **6.** Cieniewicz A, *et al. Anaesthesiol Intensive Ther.* 2019;51(3):169–177. **7.** Glahn KPE, *et al. Br J Anaesth.* 2010;105(4):417–420. **8.** Glahn KPE, *et al. Br J Anaesth.* 2020;125(2):133–140. **9.** Riazi S, *et al. Anesth Analg.* 2014;118:381–387. **10.** Krause T, *et al. Anaesthesia.* 2004;59:364–373. **11.** Ng Kwet Shing RH, *et al. Eur J Anaesthesiol.* 2024;41:1–10. **12.** DANTRIUM IV 20 mg powder for solution for injection. Summary of Product Characteristics.

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