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Special Article

CLINICAL PRACTICE

Availability of dantrolene for the management of malignant hyperthermia crises: European Malignant Hyperthermia Group guidelines

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Summary

Faced with a malignant hyperthermia crisis, the immediate access to sufficient dantrolene is essential to achieve the best possible outcome for the patient. However, malignant hyperthermia crises are rare, and there may be administrative pressures to limit the amount of dantrolene stocked or, in some countries, not to stock dantrolene at all. There are no published guidelines to support anaesthetic departments in their effort to ensure availability of sufficient dantrolene for the management of malignant hyperthermia crises. After a literature review that confirmed a lack of clinical trials to inform this guideline, we undertook a formal consensus development process, in which 25 members of the European Malignant Hyperthermia Group participated. The consensus process used a modified web-based Delphi exercise, in which participants rated the appropriateness of statements that covered the dosing regimen for dantrolene in a malignant hyperthermia crisis, the types of facility that should stock dantrolene, and the amount of dantrolene that should be stocked. The resulting guidelines are based on available evidence and the opinions of international malignant hyperthermia experts representing a large group of malignant hyperthermia laboratories from around the world. Key recommendations include: the dosing regimen of dantrolene should be based on actual body weight, dantrolene should be available wherever volatile anaesthetics or succinylcholine are used, and 36 vials of dantrolene should be immediately available with a further 24 vials available within 1 h.

Keywords: dantrolene; European Malignant Hyperthermia Group; guidelines; malignant hyperthermia; safety; succinylcholine; volatile anaesthetics

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Editor's key points

- There are no guidelines regarding the availability of sufficient dantrolene for the management of malignant hyperthermia crises.
- The European Malignant Hyperthermia Group conducted a modified web-based Delphi exercise, in which 25 experts rated statements on the dosing regimen and stocking for dantrolene.
- Key recommendations include: the dosing regimen of dantrolene should be based on actual body weight, dantrolene should be available wherever volatile anaesthetics or succinylcholine are used, and 36 vials (720 mg) of dantrolene should be immediately available with a further 24 (480 mg) vials available within 1 h.

Malignant hyperthermia (MH) is a progressive, life-threatening reaction to general anaesthesia that occurs in genetically susceptible individuals. Early recognition of an MH reaction and prompt aggressive treatment are essential for the successful management of the reaction. A key component in the treatment of an MH reaction is an appropriate dose of i.v. dantrolene, administered as soon as possible after the diagnosis has been made. The introduction of the i.v. formulation of dantrolene in 1979 contributed to a dramatic reduction in the death rate from MH (from ~80% down to 6–10%).[1–4] It is well documented that an increased time interval between the first signs of MH and dantrolene administration is associated with increased complication rates.[5–7] The product data sheet describes an initial dose of 1 mg kg^{-1} and a maximum dose of 10 mg kg^{-1},[8] but most recent guidelines and reviews on the subject recommend a higher initial dose and no cumulative ceiling.[9–11]

Despite its efficacy and the demonstration that stocking dantrolene is cost-effective even at ambulatory surgery centres,[12] the pressures imposed by limited healthcare resources mean that advice concerning the minimum locations where dantrolene needs to be stocked and the minimum quantity to be stocked is frequently sought. The pharmaco-economic model for dantrolene is unusual as it is relatively expensive, is not often used, has a limited shelf life, and might expire unused because MH reactions are rare. There may be a reluctance to buy, store, and restock such a drug, and, in some countries, dantrolene is unavailable or only available in larger hospitals.

There is general agreement that dantrolene should be stocked wherever inhalational anaesthetics are used, but there is controversy especially over the necessity to stock dantrolene at the many locations where succinylcholine is used without inhalation anaesthetics[13–16] because of the suggestion that succinylcholine alone may not trigger MH.[17]

One of the key goals of the European Malignant Hyperthermia Group (EMHG) is to produce guidelines to inform practice and improve outcomes from MH reactions. Our aim in this paper was to develop a guideline that provides detailed recommendations concerning the administration of dantrolene and recommendations on where dantrolene should be stocked and the amounts to stock. We initially undertook a literature search, but as MH reactions are very rare, there is not sufficient high-quality evidence upon which to base recommendations. Our guidelines are therefore based on the available evidence combined with a Delphi consensus analysis amongst specialists in the field of MH from EMHG-affiliated MH centres.

Methods

Our approach to developing this guideline was informed by the AGREE (Appraisal of Guidelines for Research & Evaluation) proposals.[18]

Guideline development and writing group

This guideline was conceived, developed, and written by the anaesthetist members of the Executive Committee of the EMHG (2015–9), whose names and affiliations are provided in the author details of this paper and who we will refer to henceforth as the Writing Group.

Literature search

Our primary search of PubMed and Embase databases combined the following search terms: (i) 'dantrolene' and 'malignant hyperthermia' (MeSH terms, keywords, and text words) with no time or other limits. Further searches combined the following search terms: (ii) 'succinylcholine' and 'malignant hyperthermia', and (iii) 'dantrolene' and 'pharmacokinetics'. Again, no limits were applied to these searches. The titles; abstracts; and, ultimately, the full text were screened for relevance based on whether they contained information on (i) access to dantrolene or amount of dantrolene stocked, (ii) succinylcholine triggering an MH reaction where potent inhalation anaesthetics were not used, and (iii) kinetics of dantrolene administered intravenously; all types of articles were considered.

Expert consensus panel

In addition to the eight members of the Writing Group, we invited 17 experts in MH from 16 MH centres affiliated to the EMHG to participate in the consensus development process. This invitation was made initially at the annual meeting of the EMHG in Ferrara, Italy in May 2018 and was followed-up by e-mail.

Modified Delphi process

We used a web-based adaptation[19] of the RAND/UCLA Appropriateness Method[20] for generating consensus. This uses a 9-point scale (1=completely inappropriate; 9=completely appropriate) by which panel members rate the appropriateness of a series of statements. The level of agreement amongst the panel is expressed as the disagreement index (DI). The DI is based on the inter-percentile range (difference between the 66th and 33rd centile appropriateness scores) with a correction factor for asymmetry. When the 66th and 33rd centiles have the same value, DI=0, which is interpreted as full agreement. Although Fitch and colleagues[20] described DI <1 to indicate consensus or agreement, we chose to aim for a stricter level of consensus, where DI <0.5. We planned a Delphi process of at least two rounds, thereafter using stopping criteria for each statement of DI <0.5, or if the DI failed to improve by more than 15% between rounds.

The statements for the first Delphi round were based on the literature review and expert opinion of the Writing Group. They were discussed at consecutive face-to-face meetings of the committee and finalised through e-mail correspondence.

The Delphi process was undertaken online using Google Forms. None of the statements was compulsory. In addition to rating each statement, the panel members had the opportunity to submit freehand comments on the statements. In Round 1 of the Delphi process, the panel members were also invited to propose additional statements. The panel members were given 3 weeks to respond to each round with an e-mail reminder after 2 weeks.

After each round, the panel members were sent their own scores along with the de-identified scores and comments of other panel members. They were also provided with the calculated median appropriateness score and DI for each statement along with freehand comments. For subsequent rounds, the wording of statements could be adjusted in response to freehand comments or a high DI. Subsequent rounds were conducted in a similar way to Round 1.

Guideline recommendations

We used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) network[21] classification for strength of recommendation (1=strong; 2=weak) and quality of evidence (a=high quality, b=moderate quality, and c=low quality). When applying the results of a consensus process, the quality of evidence is 'c', but we distinguish strong recommendations (median appropriateness score >7.9 and DI <0.5; GRADE 1c), where we use the term '*recommend*' from weak recommendations (median appropriateness score >6.9 and DI <0.5 or median appropriateness score >7.9 and DI >0.5, but <1.0; GRADE 2c), where we use '*suggest*'.[22]

Results

All 17 experts who were approached, along with the eight Writing Group members, agreed to participate in the modified Delphi process. Their names and affiliations can be found in the Appendix.

The primary literature search (dantrolene/malignant hyperthermia) produced 864 articles from PubMed and 1706 articles from Embase. The succinylcholine/malignant hyperthermia search generated 549 (PubMed) and 547 (Embase) articles, whereas the search for papers covering the pharmacokinetics of dantrolene found 93 (PubMed) and 348 (Embase) articles. However, only 41 articles cited in this article were considered informative in developing the guideline or Delphi statements.

Based on this literature review and their many years of clinical experience of MH, the Writing Group agreed on 18 statements for the first Delphi round. Twenty-four of the 25 panel members (96%) responded. Only one statement, concerning the use of a dantrolene infusion after an acute episode, has been reversed and had a median appropriateness score <7 and DI >0.5. However, there were 14 freehand comments (some which related to more than one statement) suggesting improvements could be made to many of the statements. For the second Delphi Round 1, a new statement was added and the remaining 18 statements were all modified from the Round 1 version to some degree. Of the 25 panel members, 21 (84%) responded to Round 2. Analysis of the Round 2 scores revealed that stopping criteria had been reached for all statements. The median appropriateness score and DI for each statement from Round 2 are shown in Table 1.

Discussion

Considering the temporal association between the introduction of i.v. dantrolene and reduction in mortality from MH,[1–4] the relationship between delay in administration of dantrolene and increasing morbidity from MH[5–7] and complete consensus among our expert panel, we *recommend* that an early and appropriate dose of i.v. dantrolene is essential in the treatment of fulminant MH. This statement recognises that an MH reaction identified in its early stages may be completely reversed by discontinuation of volatile anaesthetics and hyperventilation of the patient's lungs before dantrolene is ready to be administered, but we emphasise that this should not be relied on and that preparation of dantrolene should not be delayed.

Dosing schedule for dantrolene

We *recommend* an initial dose of 2–2.5 mg kg^{-1} of dantrolene in the treatment of an MH reaction. Our consensus opinion is informed by the pharmacokinetics of i.v. dantrolene,[23,24] extrapolation of *in vitro* animal, and awake human pharmacodynamic studies,[23,25–27] the average dose of dantrolene used in MH case series,[7] and a pragmatic appreciation that a recommended dose within a range may be easier and less distracting to apply in a crisis situation. The use of a dose range also means that this focused guideline is compatible with other guidelines that cover all aspects of the management of an MH crisis.[9–11] We *recommend* that the initial dose of dantrolene should be repeated every 10 min (or as often as possible if administration takes >10 min) until the signs of MH regress. We further *recommend* that repeat dosing should continue even if this means exceeding 10 mg kg^{-1}, which is the maximum cumulative dose recommended in the dantrolene product monograph.[8]

The criteria we *recommend* for stopping administration of dantrolene are P_{ACO_2} <6 kPa with normal minute ventilation and a decreasing core body temperature. The use of P_{ACO_2} in assessing the response to treatment recognises that the balance between P_{ACO_2} and minute ventilation directly reflects the metabolic rate, such that synchronised normalisation of these variables indicates control of the cellular processes driving the MH reaction. The immediate management of an MH crisis involves applying an increased minute ventilation to mitigate the respiratory acidosis and enhance the elimination of volatile anaesthetic. It should also be noted that the end-tidal CO_2 may underestimate P_{ACO_2}. These factors mean that, once the increased end-tidal CO_2 has been corrected, it will take several minutes to see if this will be maintained during normal minute ventilation and for P_{ACO_2} <6 kPa to be confirmed by arterial blood gas analysis: if a further dose of dantrolene is due (10 min since previous dose) in this period, it should not be withheld. The other criterion for discontinuation of dantrolene is for the core body temperature to be decreasing: this assumes that active body cooling has been implemented as part of the MH treatment protocol.[9]

It should be noted that the hypermetabolic features of MH may recur within the first 24 h after initial resolution,[28] and will require further treatment with dantrolene. Such recrudescence was reported to occur in 20% of North American MH cases,[29] but 10–15% is perhaps a more realistic estimate.[30] The likelihood of recrudescence is increased in more severe cases,[29,30] suggesting that the higher the dose of dantrolene required to control the initial reaction, the more likely is the

Table 1 Statements included in the final round of the Delphi process, their median appropriateness score, level of assessment (DI), and strength of recommendation. DI, disagreement index; GRADE, Grading of Recommendations Assessment, Development and Evaluation; Median, median appropriateness score; MH, malignant hyperthermia.

Statement	Median	DI	GRADE
1. An early and appropriate dose of i.v. dantrolene is essential in the treatment of fulminant MH.	9	0	1a
2. An initial dose of dantrolene 2–2.5 mg kg^{-1} should be used in the treatment of an MH reaction.	9	0	1c
3. The initial dose should be repeated every 10 min (or as often as possible if administration takes >10 min) until the signs of MH regress.	9	0.050	1c
4. The criteria for stopping the administration of dantrolene are P_{ETCO_2} <6 kPa (with normal minute ventilation) and a decreasing core body temperature.	8	0.132	1c
5. The recommended maximum dose of dantrolene (10 mg kg^{-1}) may need to be exceeded to treat a fulminant MH reaction.	9	0	1c
6. After reversing the MH episode with a loading dose of dantrolene, a continuous infusion of dantrolene should not be used routinely.	9	0.192	1c
7. If recrudescence does occur, further doses of dantrolene 2–2.5 mg kg^{-1} every 10 min should be given until the signs of MH regress once more.	9	0	1c
8. Dosing of dantrolene in the treatment of an acute MH reaction should be based on the patient's actual body weight (not their ideal body weight) up to a maximum initial dose of 300 mg.	8	0.192	1c
9. Every institution where MH trigger drugs are used should have a plan for an initial bolus dose of dantrolene (2–2.5 mg kg^{-1}) to be available within 5 min of diagnosis of an MH reaction and to mobilise sufficient dantrolene to administer 2–2.5 mg kg^{-1} every 10 min until the reaction is controlled.	9	0	1c
10. For locations where MH trigger drugs are used on a regular basis, a typical stock level would be 36 vials of dantrolene immediately available.	9	0.132	1c
11. For locations where MH trigger drugs are used on a regular basis, a typical stock level would be 48 vials of dantrolene immediately available if further dantrolene cannot be obtained within 30 min.	9	0.132	1c
12. For locations where MH trigger drugs are used on a regular basis, a typical stock level would be 60 vials of dantrolene immediately available if further dantrolene cannot be obtained within 1 h.	9	0.132	1c
13. If dantrolene stocks have been used, the elective use of MH triggering agents for new cases at that facility should be avoided until dantrolene has been replaced.	9	0.132	1c
14. Dantrolene should be available at all locations where volatile anaesthetic drugs are used.	9	0	1c
15. It is probable that succinylcholine used without volatile anaesthetics can trigger a fulminant MH reaction.	7	0.374	2c
16. It is possible that succinylcholine used without volatile anaesthetics can trigger a fulminant MH reaction.	7	0.269	2c
17. Dantrolene should be available at all locations where succinylcholine is used routinely.	8	0.257	1c
18. Dantrolene may not have a place in the pre-hospital emergency setting even though succinylcholine is used, because it is impractical to carry, recognition of an MH reaction is less likely, and there are not enough resources to carry out the administration.	9	0.132	1c
19. The requirement to stock dantrolene where suxamethonium is available should not be used as a reason not to stock succinylcholine for emergency airway rescue (treatment of laryngospasm).	9	0	1c

need for further dantrolene to be required. However, after reversing the MH episode with a loading dose of dantrolene, we *do not recommend* a continuous infusion (or intermittent boluses) of dantrolene to be used routinely. After a loading dose of i.v. dantrolene, therapeutic plasma concentrations are maintained for ~6 h,[24] and further dantrolene is not needed in the majority of cases; however, infusion of i.v. dantrolene is associated with a high incidence of thrombophlebitis,[31–33] and there is dose-dependent muscle weakness[32] that may compromise weaning from mechanical ventilation, especially in patients with coexisting disease. Although we did not include a statement about the routine use of 6 hourly bolus doses of dantrolene for the first 24 h after initial resolution of the reaction, the pros and cons are the same as for a dantrolene infusion. If recrudescence does occur, we *recommend* giving further doses of 2–2.5 mg kg^{-1} dantrolene every 10 min until the signs of MH regress once more.

Although there is evidence that the disposition of dantrolene is similar in children to adults,[34] our literature search did not retrieve information on the impact of obesity on the pharmacokinetics of dantrolene. As dantrolene is a hydrophobic compound and under-dosing is associated with increased morbidity and mortality, we *recommend* that the dosing of dantrolene is based on actual body weight rather than ideal body weight with the qualification that the initial dose should be capped at 300 mg. See Figure 1 for a summary of the dosing schedule.

Which facilities should stock dantrolene?

It follows from our aforementioned recommendations that dantrolene should be immediately available wherever MH triggering drugs are used. However, there is some debate as to whether succinylcholine can trigger an MH reaction without co-administration with a volatile anaesthetic.[17,35]

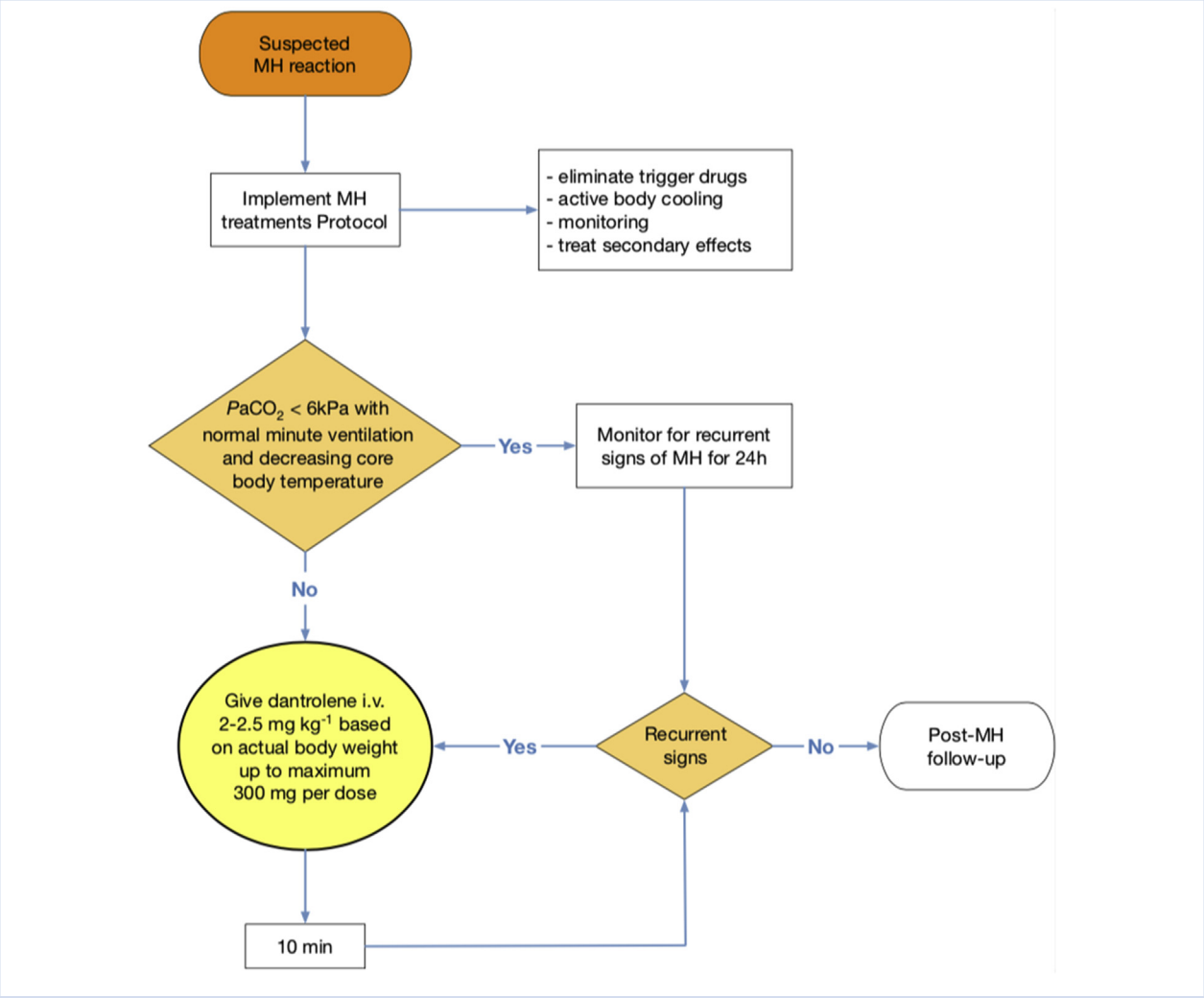

Fig 1. Summary flow chart of the dantrolene dosing schedule to be used in the treatment of a suspected malignant hyperthermia (MH) reaction.

Succinylcholine is used without volatile anaesthetics in several situations, for instance to facilitate intubation in emergency settings (including pre-hospital), or to provide muscle relaxation during electroconvulsive therapy in psychiatric institutions. We therefore sought to assess our panel's opinion separately for availability of dantrolene with respect to use of volatile anaesthetics and use of succinylcholine.

There are large numbers of case reports, case series, and animal studies that enable us to *recommend* that dantrolene should be immediately available wherever volatile anaesthetic agents are used. Whether it is a large operating theatre complex, maternity unit,[36,37] ICU,[38,39] interventional radiology suite, or a small mobile anaesthetic apparatus used in private practice, dantrolene should *always* be readily available where volatile anaesthetic agents are used. We cannot condone the reliance on other institutions or off-site companies to provide dantrolene if needed. The exception to this is in the pre-hospital setting for trauma analgesia, as it is not practical for emergency vehicles, especially helicopters, to carry a supply of dantrolene 20 mg $(60\ ml)^{-1}$.

There are very few (close to 1% of total) reported cases of fulminant MH triggered by succinylcholine alone compared with its widespread use.[6,40–43] It has been argued that these cases do not prove MH triggering by succinylcholine alone because the reports do not provide sufficient information to confirm that MH (a progressive life-threatening hypermetabolic reaction) occurred or that volatile anaesthetics were also administered.[15,17,41–44] We therefore used our Delphi process to initially seek a consensus evaluation of the published and unpublished case reports of succinylcholine-triggered MH. Slightly better agreement was achieved for the possibility (rather than probability) that succinylcholine used without volatile anaesthetics can trigger a fulminant MH reaction, but a median appropriateness score of 7 indicates that this is a GRADE 2c finding (Table 1). However, even 'just' the possibility that succinylcholine alone can trigger a fulminant MH reaction led us to *recommend* that dantrolene should be available at all locations where succinylcholine is used routinely. An exception is, again, the pre-hospital emergency setting, where we *recommend* that dantrolene may not have a place even though

succinylcholine is used, because it is impractical to carry dantrolene, recognition of an MH reaction is less likely, and there may be insufficient personnel to prepare and administer dantrolene 20 mg (60 ml)$^{-1}$.

It has been argued that the requirement to store dantrolene wherever succinylcholine is used may stop some institutions from having succinylcholine available for emergency airway rescue.[13,45] Succinylcholine is widely accepted as an effective treatment for laryngospasm refractory to conservative management.[13] Laryngospasm is an anaesthetic emergency that, if not promptly and effectively managed, can lead to significant morbidity and mortality. We *recommend* that the requirement to stock dantrolene where succinylcholine is available should not be used as a reason not to stock succinylcholine for emergency airway rescue.

How much dantrolene should be stocked?

Although a more soluble formulation of dantrolene (Ryanodex®, in 250 mg vials to be reconstituted with 5 ml sterile water) is licenced in the USA for i.v. administration, we will describe our recommendations for the stocking of dantrolene based on the more generally available traditional formulation (Dantrium®), which is supplied in packs of 12 vials, each containing dantrolene sodium 20 mg to be mixed with sterile water, 60 ml per vial.

As no two institutions where MH triggering drugs are administered are the same with respect to the number and location of places within the institution where trigger drugs are used, nor in terms of their geographical co-location with other institutions that may stock dantrolene, it is impossible to make prescriptive generalisable recommendations of precisely how much dantrolene should be stocked. Most importantly, therefore, we *recommend* that every institution where MH trigger drugs are used should have a plan for an initial bolus dose of dantrolene (2–2.5 mg kg^{-1}) to be available within 5 min of diagnosis of an MH reaction, and to mobilise sufficient dantrolene to administer 2–2.5 mg kg^{-1} every 10 min until the reaction is controlled. Developing such a plan is best coordinated by the hospital pharmacy in liaison with the anaesthetic department, but it will also benefit from coordinated planning with the pharmacy departments of neighbouring institutions and the local supplier of dantrolene.

Whilst it is not possible to provide detailed location-by-location recommendations for stocking dantrolene, our Delphi process has produced recommendations that can be used to inform local institutional plans. We do not distinguish between paediatric and adult institutions because the obesity epidemic affects children and adults; the stocks of dantrolene should provide for MH developing in the heaviest patient that an institution might manage.[46] According to our aforementioned recommendations, any patient of 120 kg or more could be given 90 vials of dantrolene over 60 min.

For locations where MH trigger drugs are used on a regular basis, we *recommend* that 36 vials of dantrolene are immediately available. The 36 vials will be enough to treat an MH crisis for 20–30 min in all adult patients. Further dantrolene (to a total of 60 vials within 1 h) will need to be obtained from other sources, and each institution should carefully consider what other sources are available locally and the time taken to obtain them. If additional supplies cannot be obtained within 30 min, we *recommend* that the initial stock supply should be increased to 48 vials. We further *recommend* that remote institutions, where more dantrolene cannot be obtained within 1 h, should store 60 vials (Fig 2). In large hospitals with more than one operating theatre complex, the stocked dose of dantrolene may be split between the complexes, ensuring that it is readily at hand whenever needed.

Any plan should ensure that dantrolene is easy to locate; it is highly recommended that the dantrolene vials are stored together with the required amounts of sterile water to avoid any confusion about the type of fluid to mix it with. Operating theatre staff should know where in the operating complex dantrolene is stored. It is important that up-to-date telephone numbers to relevant nearby stores of dantrolene are easily accessible. Contact details and simple communication lines, according to pre-existing agreements, should be in place to ensure an urgent, smooth, and swift transfer of further dantrolene from one hospital site to another at all times.

Finally, if dantrolene stocks have been used, we *recommend* that use of inhalational anaesthetics and succinylcholine for elective cases at that facility should be avoided until dantrolene has been replaced.

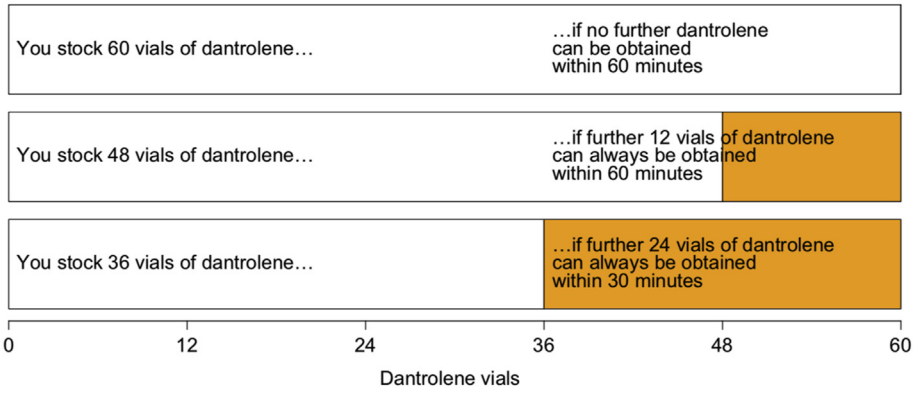

Fig 2. Recommended stock levels for locations where malignant hyperthermia triggering drugs are used (each vial contains 20 mg of dantrolene).

Conclusions

We provide detailed recommendations for the dosing regimen of i.v. dantrolene to be used in the event of a suspected MH reaction and the implications of this regimen for the stocking of dantrolene. In the absence of high-quality evidence, our recommendations are predominantly based on a validated consensus development process involving 25 international experts in MH. These dosing recommendations must be used in conjunction with guidelines that describe the entire management process for suspected MH; administration of dantrolene without implementation of other measures is not sufficient to resolve a fulminant-MH reaction.

Disclaimer

These guidelines represent the views of the EMHG. They are based on careful consideration and interpretation of the available evidence at the time that they were agreed. They are intended principally for clinicians and hospital pharmacists involved in the management of MH who are encouraged to take them fully into account when exercising their professional judgement. The guidelines do not over-ride the individual responsibility for clinicians to make appropriate decisions and take actions according to the circumstances of individual patients.

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Authors' contributions

Study conception/planning: all authors.
Drafting of article: all authors.
Approval of article: all authors.

Declarations of interest

PMH is an Editorial Board Member of the *British Journal of Anaesthesia*. All other authors confirm that they have no interests to declare.

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Appendix

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