DOI: https://doi.org/10.5114/ait.2022.115348

Malignant hyperthermia in Mazovia Province – are we adequately prepared?

Agnieszka Cieniewicz, Janusz Trzebicki

1st Department of Anaesthesiology and Intensive Care, Medical University of Warsaw, Poland

Abstract

Background: Malignant hyperthermia (MH) is a life-threatening syndrome caused by sudden skeletal muscle hypermetabolism in response to inhalation anaesthetics and depolarising relaxants. The estimated incidence of MH is between 1 : 10,000 and 1 : 250,000 anaesthetic procedures. In Poland the incidence of MH is unknown. Dantrolene is imported as a life-saving drug and temporally authorised for sale. The aim of the study is to assess the incidence of MH and access to dantrolene in the Mazovia Province.

Methods: Anonymous questionnaires were sent to anaesthesia departments in the Mazovia Province after prior contact by phone and e-mail. The survey was approved by the local ethical review board.

Results: Completed surveys were received from 60 respondents which represents 72% of anaesthesiology departments in Mazovia. In the last 5 years there have been 4 episodes of MH in the Mazovia Province. Three patients survived the MH crisis. In a centre that did not have access to dantrolene, the patient died. Dantrolene is found only in 11 (18.3%) anaesthesiology departments in Mazovia. Only 6 (10%) hospitals are able to administer dantrolene within 5 minutes of suspecting MH crisis, while 5 centres may receive it after a few days. Only 38% of units have an algorithm for dealing with MH crisis in the operating theatres.

Conclusions: MH is rare, but if untreated, it can be fatal. Therefore prompt diagnosis and treatment are crucial to avoid fatal outcome. Every centre using inhalational anaesthetics and/or succinylcholine should have dantrolene. To ensure the safety of our patients, we must be better prepared.

Key words: perioperative care, malignant hyperthermia, dantrolene, safety of patient.

Anaesthesiol Intensive Ther 2022; 54, 2: 99–102

Received: 01.07.2021, **accepted:** 02.09.2021

CORRESPONDING AUTHOR:

Agnieszka Cieniewicz, 1st Department of Anaesthesiology and Intensive Care, Medical University of Warsaw, 4 Lindleya St., 02-005 Warsaw, Poland, e-mail: a.cieniewicz@gmail.com

Malignant hyperthermia (MH) is a pharmacogenetic disorder that manifests as a hypermetabolic response to halogenated anaesthetics and/or depolarizing muscle relaxants [1]. The estimated incidence of MH ranges from 1 : 10,000 to 1 : 250,000 anaesthetic procedures [2]. The essential element of causal treatment is the prompt administration of dantrolene. Thanks to the popularisation of the drug, the mortality rate associated with MH crisis significantly decreased [2–4]. According to the data presented by Mayzner-Zawadzka in 2004, 10 cases of MH were observed annually in Poland [5]. Considering that reporting of MH episodes is not mandatory, their current incidence in Poland is difficult to assess.

Mazovia Province is the largest and most populous province in Poland. According to the data of the Statistics Poland (Polish: GUS), it has almost 5.5 million inhabitants, which is about 15% of the country's population [6]. In 2019, about 450,000 surgical procedures were performed in Mazovia; over 250,000 of them were performed under general anaesthesia [7]. In Poland, dantrolene is imported as a life-saving drug (target import) and temporally authorized for sale with no approval required based on the Regulation of the Minister of Health of 2001 [8]. The drug is relatively expensive and not reimbursed, which could constitute a significant economic challenge for hospitals.

The study aimed to assess the incidence of MH in Mazovia Province and the availability of dantrolene in Mazovian hospitals.

METHODS

The study design was approved by the Bioethics Committee at the Medical University of Warsaw (AKBE/256/2019).

The questionnaire was conducted among the chiefs of Mazovian anaesthesia departments. After prior contact by phone, a link to the questionnaire was e-mailed to them. The questionnaire consisted of an introduction letter and 17 questions about the hospital's activities, the number of anaesthesia work-

TABLE 1. Availability of dantrolene in 60 Mazovian hospitals

Is dantrolene available in the hospital?	
Yes	11 (18%)
No	49 (82%)
If not, do you know where it is stocked?	
Yes	44 (90%)
No	5 (10%)
How fast is it possible to administer dantrolene in case of a malignant hyperthermia crisis?	
< 5 minutes	6 (10%)
5–60 minutes	21 (35%)
> 60 minutes	28 (47%)
I do not know	5 (8%)
Dantrolene is available in the healthcare facilities located in:	
Towns with < 100,000 inhabitants	3
Towns with 100,000–500,000 inhabitants	2
Towns with > 500,000 inhabitants*	6

*Warsaw is the only city in the Mazovia Province with > 500,000 inhabitants.

stations, the population treated (paediatric, adult), the number of MH episodes and their treatment. Moreover, the questions regarded the availability of dantrolene and of the algorithm for managing an MH crisis.

The questionnaire was sent to 83 general hospitals where MH triggering agents are used. Three attempts were made to contact each of the hospitals. We reached 74% of the 112 hospitals reported in Mazovia by the Statistics Poland in 2019 [7].

We received most of the responses in the first trimester of 2020, but the survey was finally completed in the second half of 2020.

RESULTS

Questionnaires were returned from 60 hospitals, which constitutes a response rate of 72%. The centres involved were equipped with 406 anaesthesia workstations, constituting 73% of the 557 workstations reported in Mazovia Province [7].

Among the 60 hospitals surveyed, 41 (68%) anaesthetise only adults, 3 (5%) only children, and 16 (27%) adults and children. Of the responding departments, only 4 hospitals do not use volatile anaesthetics, while succinylcholine is available in all of them.

According to the data obtained, 4 MH reactions were observed in Mazovia Province in the last 5 years (2014–2019), including 2 in 2019. Assuming that 250,000 general anaesthetic procedures were performed in Mazovia Province in 2019, the incidence of MH was 2 : 250,000. In three out of the four reported MH cases, effective treatment with dantrolene was introduced. In the hospital where dantrolene was not stocked, the patient died.

Dantrolene is available in 11 (18%) of the 60 anaesthesia departments surveyed, i.e. in two paediatric hospitals, 5 hospitals treating adult patients and 4/16 hospitals treating both groups of patients. Six out of 11 hospitals stocking dantrolene are located in Warsaw. Most chiefs of the departments where dantrolene is not stocked (n = 44, 90%) know where they can get dantorolene in case of a MH crisis. Among 11 hospitals where dantrolene is stocked (n = 11), in six it can be administered within 5 minutes and in five within 60 minutes of diagnosis MH reaction. Sixteen hospitals declare they can receive dantrolene from outside the hospital within an hour. On the other hand, in less than half of the responding departments (n = 28, 47%), the time to receive dantrolene is longer than 60 minutes; in 5 of them, this time is several days. The above data were presented in Table 1.

In less than half of the surveyed hospitals, the operating theatres have an algorithm for the management of MH episode (n = 23, 38%).

DISCUSSION

This is the first questionnaire study conducted in Poland, evaluating the incidence of MH and the availability of dantrolene. In other countries, similar data can be obtained from the national MH registries, which are mandatory for all healthcare facilities. It is therefore difficult to compare our findings with the results reported by other authors who analysed the registries covering the entire populations. Considering the above, a reliable MH picture is still unobtainable in Poland.

The aim of our study was to gather information regarding MH, a severe general anaesthesia-associated complication, in the largest and most populous province in Poland – Mazovia over the past five-year period.

According to the data obtained, the number of MH episodes per the number of general anaesthesias in Mazovia Province in 2019 was 2 : 250,000, i.e. 1 : 125,000 (0.8 : 100,000), which is similar to the data from other countries (1 : 10,000 to 1 : 250,000). However, the differences in the quality of data received from our questionnaire and those obtained from official registries should be considered [4, 9].

Previously published studies proves that the risk of this serious anaesthesia-related complication is real. Therefore physicians should have knowledge about its managemnent and access to dantrolene should be provided.

In our study, one death was reported in Mazovia Province over 5 years. According to the Statistics Poland data, the annual number of general anaesthetic procedures each year, approximately 250,000 procedures under gerenal anaesthesia are

performed, what gives about 1,250,000 over the period of 5 years [7]. It can therefore be calculated that the MH-associated mortality rate is below 1 per million procedures. However, based on the number of MH events reported in our study, the mortality rate was as high as 25%. The patient who did not survive MH crisis did not receive dantrolene. The findings reported in other studies have demonstrated the MH mortality rate below 5% (from 1.5 to 5% depending on the population studied) when dantrolene was available [3, 4].

The results of our study revealed that only less than 20% of the hospitals stocked dantrolene, which is most likely associated with its high price and lack of reimbursement. Another issue may be incomplete knowledge and insufficient training of physicians regarding dantrolene.

According to the recommendations of the European Malignant Hyperthermia Group (EMHG), dantrolene should be available at all locations where volatile anaesthetics and succinylcholine are used. In Poland, dantrolene (tradenames Dantrolene or Dantrium) is available in 20 mg vials supplied in packs containing 12 vials.The shelf life is 36 months from the date of manufacture. When MH reaction is suspected, the administration of dantrolene is the only effective causal treatment that can save the patient's life. The initial dose of 2–2.5 mg kg^{-1} should be administered within 5 minutes of the diagnosis of MH crisis and followed by subsequent doses every 10 minutes until the symptoms have subsided [10, 11]. This recommendation can be implemented only by a small percentage (10%) of healthcare facilities in Mazovia Province. To treat an adult patient with MH reaction, up to 35–50 vials of dantrolene may be required.

Early administration of dantrolene reduces the risk of MH complications. They occur in about 20–30% of patients; most often renal or myocardial dysfunction and consciousness disorders are observed. Furthermore, patients can develop pulmonary oedema, disseminated intravascular coagulation (DIC), impaired hepatic function and compartment syndrome. Any delay in administering dantrolene increases the risk of complications. Every 10 minutes of delay significantly increases this risk, and after 30 minutes the risk almost doubles. Its administration after 50 minutes is tantamount to the occurrence of complications [2, 12].

In almost half of Mazovian hospitals participating in the study (47%), dantrolene cannot be administered within one hour from the diagnosis of MH reaction. It can therefore be assumed that every patient who develops MH reaction and is treated in one of the these hospitals will have complications. This is one of the most important information that we obtained from the questionnaire, allowing us to show how serious the consequences of limited availability of dantrolene can be. Since reliable nationwide data are not available in Poland, comprehensive assessment of this matter is not possible. This may be the reason why systemic solutions have not been yet developed.

Considering the above, the current EMHG recommendations of 2020 are of particular importance [10]. According to them, each healthcare facility which uses MH triggering drugs should have an adequate stock of dantrolene, allowing the initial dose to be administered within 5 minutes, followed by subsequent doses administered every 10 minutes.

The EMHG recommends that the following should be available in the hospital:

- 36 vials – if another 24 vials can be available within 30 minutes;
- 48 vials – if another 12 vials can be available within 60 minutes;
- 60 vials – if the time needed to obtain further vials is longer than 60 minutes [10].

In the light of the above recommendations, it is essential to strive for better preparation of Mazovian hospitals to avoid this serious complication, the cause of which is known, and which is directly associated with the anaesthesia. The problem obviously does not concern only Mazovia Province. It seems necessary to create an efficient distribution network of dantrolene in each province, considering the time of transport of subsequent doses of dantrolene between hospitals. However, as already mentioned, any hospital using drugs that can trigger MH should stock adequate dose of dantrolene.

This will undoubtedly be a challenge not only for those responsible for the healthcare organization, but also for anaesthesiologists, who should take appropriate measures to ensure greater safety of patients during anaesthesia. In Poland, there are no national guidelines regulating this issue. In this situation, it seems that the European guidelines may show the direction of action to ensure patients' safety [10]. Moreover, the economic aspect of securing individual hospital units with appropriate doses of dantrolene should be considered. The drug is expensive (approx. PLN 4,433 for 12 vials, i.e. 240 mg) and it is necessary to strictly determine the manner of its distribution and the storage place of subsequent doses in the hospital. The incidence of MH is low, which can lead to expiration of dantrolene. Therefore, keeping large stocks is uneconomical and some systemic solutions should be sought. In our opinion, individual hospitals should not be charged with the initial dose of this drug. It should be reimbursed every three years (expiration date) from the budget of the Ministry of Health or the National Health Fund (NHF).

The study by Aderibigbe *et al*. conducted in the United States in outpatient facilities performing general anesthesias for one-day surgery has even demonstrated potential financial benefits associated with the possession of dantrolene [13]. According to the authors, if each surgical clinic had a stock of 36 vials of dantrolene, 33 deaths could be avoided annually; the incremental cost-effectiveness ratio (ICER) has been calculated at about $200,000 for each patient saved. The ICER stands for an additional cost of a medical intervention (surgery, laboratory testing, specialist consultation, etc.) per unit of the health effect gained compared to an alternative intervention (or no intervention). Due to the limited funding in the healthcare system, the ICER is helpful in deciding whether to fund a particular health technology, such as screening or a drug [14].

This confirms the legitimacy and necessity to consider the implementation of EMHG recommendations in Poland.

The European guidelines are very restrictive, as they recommend that if dantrolene stock have been used, the elective use of volatile anaesthetisc and succinylcholine should be avoided until the supply of dantolene is replenished. Further EMHG recommendations can generate even higher cost; according to them, dantrolene should be dosed per current patient weight up to a bolus dose of 300 mg. A patient weighing 120 kg or more may require even 90 vials of dantrolene within 60 minutes. It follows that each centre should have access to such a dose of dantrolene to ensure proper management to a patient with the highest body weight that can be treated in a particular healthcare facility. Undoubtedly, this can be an additional challenge for bariatric centres [10].

There is no doubt that the above information has its own financial burden, which has to be borne by hospitals. This is a fixed cost, which is difficult to justify from the economist's point of view. Therefore, it seems that the optimal solution ensuring safety of patients that can be acceptable for hospitals is to create a systemic solution in Poland, reimbursed by the National Health Fund, but also demanded by this institution.

Adequate availability of dantrolene should coexist with physicians' knowledge of the diagnosis and treatment of MH reaction. It is therefore essential that MH management algorithms are available in operating theatres. Their use reduces the number of errors and helps to properly manage the MH crisis [15]. It seems that such actions should be taken nationwide, which can bring measurable benefits as far as the safety of anaesthetised patients is concerned.

CONCLUSIONS

In the light of the questionnaire responses gathered, Mazovia Province is not yet optimally prepared for managing malignant hyperthermia episodes.

ACKNOWLEDGEMENTS

1. We would like to thank Prof. Radosław Owczuk – National Consultant in the field of Anesthesiology and Intensive Care for the substantive support of our idea of conducting the study.
2. Presentation: Preliminary data from this study were presented at the 39th European Malignant Hyperthermia Group (EMHG) Annual Meeting, online meeting, 13–15 May 2021.
3. Financial support and sponsorship: none.
4. Conflict of interest: none.

REFERENCES

1. Cieniewicz A, Trzebicki J, Mayzner-Zawadzka E, Kostera-Pruszczyk A, Owczuk R. Malignant hyperthermia – what do we know in 2019? Anaesthesiol Intensive Ther 2019; 51: 169-177. doi: 10.5114/ait.2019.87646.
2. Rosenberg H, Pollock N, Schiemann A, Bulger T, Stowell K. Malignant hyperthermia: a review. Orphanet J Rare Dis 2015; 10: 93. doi: 10.1186/s13023-015-0310-1.
3. Larach MG, Brandom BW, Allen GC, Gronert GA, Lehman EB. Cardiac arrests and deaths associated with malignant hyperthermia in North America from 1987 to 2006: a report from The North American Malignant Hyperthermia Registry of the Malignant Hyperthermia Association of the United States. Anesthesiology 2008; 108: 603-611. doi: 10.1097/ALN.0b013e318167aee2.
4. Sumitani M, Uchida K, Yasunaga H, et al. Prevalence of malignant hyperthermia and relationship with anesthetics in Japan: data from the diagnosis procedure combination database. Anesthesiology 2011; 114: 84-90. doi: 10.1097/ALN.0b013e318200197d.
5. Mayzner-Zawadzka E. Current status of malignant hyperthermia in Poland. 23th Annual Meeting of the European Malignant Hyperthermia Group in Leipzig 2004.
6. Biuletyn statystyczny 03/2021. Available at: www.stat.gov.pl.
7. Zdrowie i Ochrona Zdrowia w 2019 roku. Available at: https://stat.gov.pl/obszary-tematyczne/zdrowie/zdrowie/zdrowie-i-ochrona-zdrowia-w-2019-roku,1,10.html#.
8. Ustawa z dnia 6 września 2001 r. Prawo farmaceutyczne. Available at: http://isap.sejm.gov.pl/isap.nsf/download.xsp/WDU20011261381/U/D20011381Lj.pdf (Accessed: 25.06.2021).
9. Brady JE, Sun LS, Rosenberg H, Li G. Prevalence of malignant hyperthermia due to anesthesia in New York State, 2001-2005. Anesth Analg 2009; 109: 1162-1166. doi: 10.1213/ane.0b013e3181ac1548.
10. Glahn KP, Bendixen D, Girard T, et al.; European Malignant Hyperthermia Group. Availability of dantrolene for the management of malignant hyperthermia crises: European Malignant Hyperthermia Group guidelines. Br J Anaesth 2020; 125: 133-140. doi: https://doi.org/10.1016/j.bja.2020.04.089.
11. Glahn KP, Ellis FR, Halsall PJ, et al. Recognizing and managing a malignant hyperthermia crisis: guidelines from the European Malignant Hyperthermia Group. Br J Anaesth 2010; 105: 417-420. doi: 10.1093/bja/aeq243.
12. Riazi S, Larach MG, Hu C, Wijeysundera D, Massey C, Kraeva N. Malignant hyperthermia in Canada: characteristics of index anesthetics in 129 malignant hyperthermia susceptible probands. Anesth Analg 2014; 118: 381-387. doi: 10.2147/TCRM.S47632.
13. Aderibigbe T, Lang BH, Rosenberg H, Chen Q, Li G. Costeffectiveness analysis of stocking dantrolene in ambulatory surgery centers for the treatment of malignant hyperthermia. Anesthesiology 2014; 120: 1333-1338. doi: 10.1097/ALN.0000000000000257.
14. Orlewska M, Czech M. Słownik farmakoekonomiczny. Oficyna Wydawnicza UNIMED, Jaworzno 2002; p. 33.
15. Goldhaber-Fiebert SN, Howard SK. Implementing emergency manuals: can cognitive aids help translate best practices for patient care during acute events? Anesth Analg 2013; 117: 1149-1161. doi: 10.1213/ANE.0b013e318298867a.