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UNAVAILABILITY OF DANTROLENE IN PAKISTAN: A WAY FORWARD

Samia Latif Khan[1], Amna Nadeem[2*], Muhammad Rafiq[3], Rizwan Haider[4], Rana Sajawal Joiya[5], Muhammad Haris Javed[6]

[1]Pediatrician, Psychiatrist, Psychotherapist, Shaikh Zayed Hospital, Lahore. drsamiakhan17@gmail.com
[2]Assistant Professor, Department of Physiology, CMH Lahore Medical College and Institute of Dentistry.
[3]Associate Professor/HOD, Lahore School of Behavioural Sciences, The University of Lahore, Lahore-Pakistan. rafiqdar@hotmail.com.
[4]MBBS, CMH Lahore Medical College and Institute of Dentistry. riziharal@gmail.com
[5]MBBS, CMH Lahore Medical College and Institute of Dentistry. sajawaljoiyaa@gmail.com
[6]MBBS, CMH Lahore Medical College and Institute of Dentistry. javedharis81@gmail.com

[*]**Corresponding Author:** Amna Nadeem
dr.amnausman.kazi@gmail.com

Abstract

Background: In this rapidly advancing period of scientific knowledge and technology, Pakistan is facing enormous challenges in maintaining physiological health and psychological wellness. This is taking a toll on the basic standards of living of the people of Pakistan. More than 80% of the prevailing diseases in the country exhibit severe muscular spasticity and a high rate of mortality and morbidity. This state of affairs is primarily due to the unavailability of a vitally important muscle relaxant drug, Dantrolene, in Pakistan.

Purpose: The current study aimed to explore challenges associated with the unavailability of Dantrolene in Pakistan and propose an evidence-based recommendation to enhance its awareness and importance and encourage its import.

Methods: An extensive literature review was conducted using the PRISMA methodology to explore the challenges and issues linked with the unavailability of Dantrolene in Pakistan. The keywords used to review the literature were “malignant hyperthermia," "Dantrolene," "mortality," "morbidity," and "treatment." The articles were taken from Google Scholar, PubMed, and Sciences Direct. The relevant articles are taken from 1975 – 2022.

Results and Conclusion: The article discusses Dantrolene availability's past, present, and future aspects and its importance in Pakistan. The paper also reflected the status of the health sector in Pakistan as compared to that of other countries of the world. The hindrances related to Dantrolene's import, availability, and utility are discussed. Recommendations and future strategies for creating awareness regarding diseases exhibiting severe muscular spasticity, especially malignant hyperthermia, have been discussed. The areas that need amendment and development have also been suggested.

Keywords: Dantrolene, muscle relaxant, Dantrolene, MHAUS, pathophysiology, skeletal muscle contraction, Dantrolene therapy, supportive therapy, Modified Delphi Process, DRAP.

Methodology

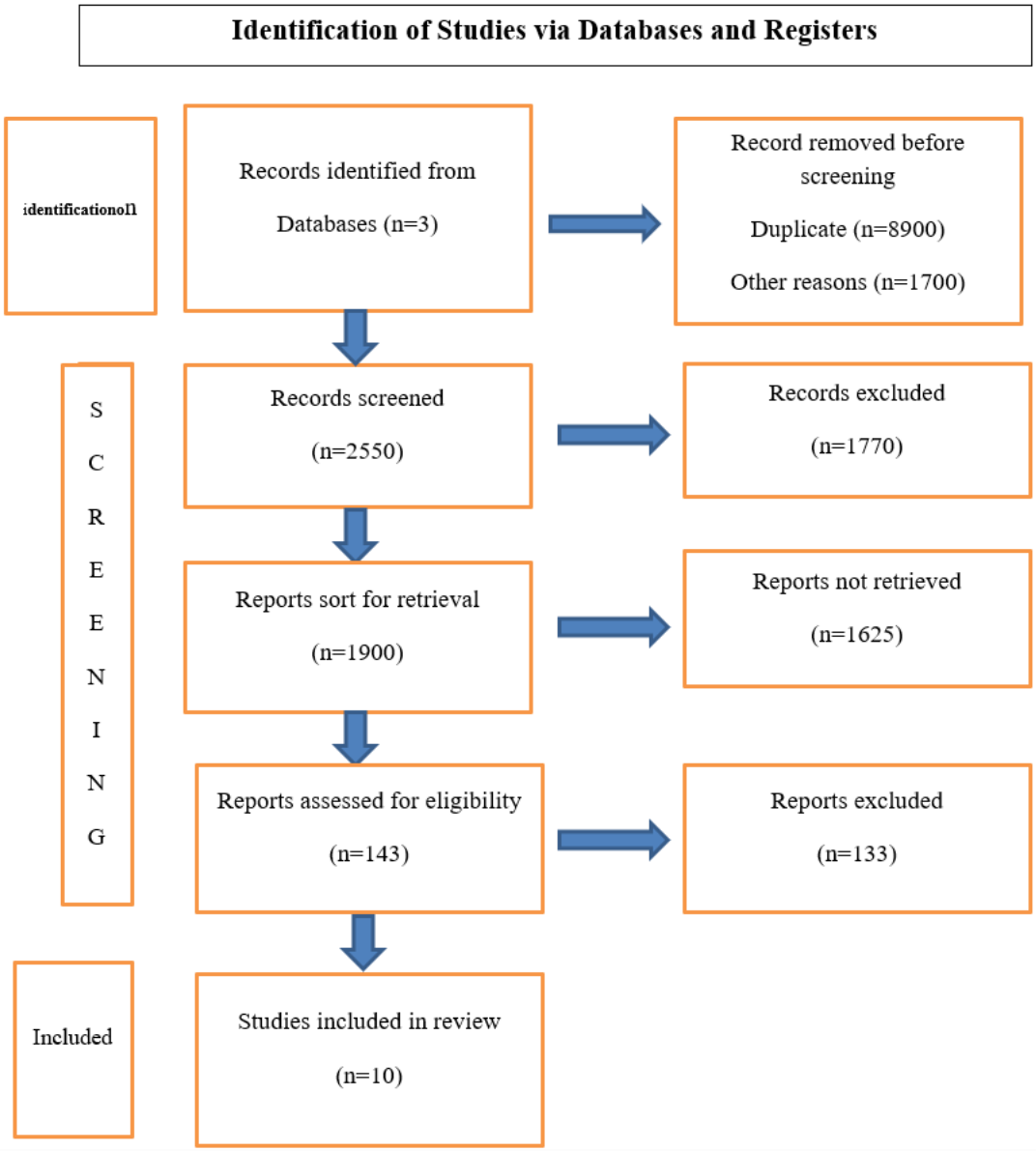

Fig.1.*The PRISMA flow diagram for systematic review*

The figure shows the systematic review process from 3 databases: Google Scholar, PubMed, and ScienceDirect. Initially, 8900 records were identified, with only 2550 qualified for screening. 1770 records were excluded, and 1625 records needed to be retrievable. One hundred thirty-three reports were excluded out of 143 based on relevance, with a final ten reports included for review. The keywords searched in the databases were as follows: Dantrolene, muscle relaxant, availability, import, malignant hyperthermia, treatment, morbidity, mortality, awareness seminars, researches on Dantrolene, health sector, MHAUS, skeletal muscle contraction physiology, pathophysiology of skeletal muscle contraction, Dantrolene therapy, supportive therapy, Modified Delphi Process, DRAP. The extensive review included articles from 1975 to 2022, covering all aspects of the Dantrolene availability and utility, locally and globally.

In 1961, a young man in Australia, Melbourne, visited the emergency ward of the hospital with a fractured tibia. More than the pain and distress of the cleavage, he was concerned about the general anesthesia that he was about to undergo for the reduction of the fracture. On inquiry, it was established that he had lost ten members of his family to high-grade temperature soon after receiving general anesthesia for surgery. Dr. Micheal Denborough was one of his physicians and observed that all those ten patients were given ether during general anesthesia. Hence, it was decided by the team of anesthesiologists that the patient would be given general anesthesia with halothane instead. Within 10

minutes of introduction to halothane anesthesia, the patient started to experience hypoxia, tachycardia, hyperthermia, and hypotension. Immediately, the surgery was discontinued, and the patient was given supportive therapy with ice packs; fortunately, he recovered without impairment.

Dr. Micheal Denborough noticed that all ten cases showed elevated serum creatine phosphokinase levels and discovered an autosomal dominant inheritance pattern. Dr. Denborough publicized that this inherited syndrome could be the reason for the grave hyperthermic emergency. More cases of hazardous high-grade temperature associated with severe muscle rigidity and rhabdomyolysis occurred within the same period. It had a high death rate that rolled up to 70% and more. Due to life-threatening high temperatures, the syndrome was coined "malignant hyperthermia" at Royal Melbourne Hospital.

In 1981, the Malignant Hyperthermia Association of the United States was established. The same year, MHAUS forwarded a request to WHO to enlist MH in the globally recognized diseases and disorders list. A hotline was made active in 1982, and since then, MHAUS has provided continuous access to board-certified anesthesiologists to assist teams in treatment. In 1983, the first MHAUS healthcare professional and patient teaching conference occurred. The North American Malignant Hyperthermia Registry (NAMHR) was formed in 1987. In 1992, the FDA ordered pharmaceutical companies that manufacture succinylcholine (a volatile anesthetic agent) to change the package. In 1995, the MH Hotline was formalized as a 24-hour service, and MHAUS merged with the North American MH Registry. In 1997, the MHAUS website and the Neuroleptic Malignant Information Service of MHAUS were formed. The MH ID Tag program was created the following year, with the MH Procedure Manual created in 2000 for ambulatory surgery centers, hospitals, and office-based surgery suites. In 2001, the MH Patient Liaison Committee was formed. In 2003, a new mutation in the ryanodine receptor gene was discovered and appears to be causal for malignant hyperthermia.

Therefore, it has been established that malignant hyperthermia is a genetically dominant disorder occurring due to mutation in the coding of a gene at the site of the ryanodine receptor on chromosome nine. It is triggered as a result of volatile anesthesia during surgery. Patients show unusually high levels of calcium in skeletal muscle cells, with a body temperature rising to 107 degrees, muscle rigidity, and multi-organ failure, often leading to death. Some patients have also developed malignant hyperthermia due to exposure to hot climates and also to exercise. Dantrolene sodium is the only treatment of choice available so far, without which the mortality rate is very high. Some conditions other than malignant hyperthermia in which Dantrolene therapy should be brought into consideration are neuroleptic malignant syndrome, heat stroke, shivering, serotonin syndrome, spasticity, and ecstasy intoxication.

Dantrolene, as a drug of choice for malignant hyperthermia, was initially synthesized by Snyder and his co-workers in 1967. It was described as an effective drug to combat malignant hyperthermia in 1975 by South African anesthesiologist Gaisford Harrison and published in the British Journal of Anesthesia. Dantrolene sodium is a water-insoluble, fat-emulsifiable, small molecule weight drug with a pKa of 7.7, suggesting poor blood-brain barrier permeability. However, it is also suggested that the blood-brain barrier is already damaged in case of ischemic injury to the brain, thus making way for dantrolene absorption. It is time-consuming and challenging to prepare for immediate intravenous use. Dantrolene requires warming to infuse it as I/V in an emergency state. Initially, it was also available as an oral formulation and was administered as a prophylactic measure. Lately, this protocol has yet to be followed due to its hazardous side effects. When Dantrolene is ingested orally, around 70% is absorbed. After 6 hours of ingestion, peak concentration is reached in plasma while half-life for elimination is 12 hours. It is metabolized in the liver and excreted via bile and urine.

Physiology of Muscle Contraction

Muscle contraction occurs when an action potential (AP) is generated, and excitation–contraction coupling occurs within the muscle fiber. Excitation-contraction coupling is a series of events that starts with generating the action potential in the skeletal muscle fibers until the initiation of muscle tension. Changes in voltage within the t-tubule membrane of the muscle fiber result in the efflux of calcium ions via the calcium-releasing channel, known as ryanodine one receptors (RYR1) of the

sarcoplasmic reticulum (a membrane-bound structure found within muscle cells that is similar to the smooth endoplasmic reticulum in other cells) into the myoplasm (the contractile portion of the muscle tissue). Once the contraction has occurred, it is followed by relaxation. Relaxation of the muscle fiber is achieved by the consumption of the adenosine triphosphate (ATP) molecule, thus transferring calcium back into the sarcoplasmic reticulum. Relaxation is completed when the concentration of calcium ions is less in the myoplasm than in the sarcoplasmic reticulum. Ryanodine receptors are expressed primarily in skeletal muscle (RYR1), heart muscle (RYR2), and brain tissue (RYR3). Mutation of these receptors is associated with pathologies of the specific channel. Dantrolene has less affinity for RYR2 despite having the same amino acid sequence (601 – 619) and also has less affinity for RYR3, which has a nearly identical sequence (577 – 597) – a phenomenon that has not yet been explained. It has been hypothesized that the recently identified amino acid area 590 – 609 of the RYR1 might be the molecular target of Dantrolene.

Pathophysiology of Muscle Contraction

Subjects who are susceptible are at risk of excessive release of calcium ions during muscle contraction. In MH-susceptible individuals, the RYR1 receptor shows a lengthy open state and a higher affinity to radio-ligands. This results in an enhanced calcium efflux from the sarcoplasmic reticulum into the myoplasm, followed by a prolonged and intensified interaction between actin and myosin**.** This leads to increased muscle aerobic metabolism and excessive production of heat. Massive lactic acid formation with an excessive collection of calcium ions in the mitochondria results in cytolysis. Diagnosis is based on the appearance of anticipated symptoms. Family members are tested to see if they are susceptible by muscle biopsy or genetic testing.

Dantrolene Mode of Action

Dantrolene is a calcium-blocking, skeletal muscle relaxant that stops the release of calcium ions stored intracellularly in the sarcoplasmic reticulum. Muscle contraction is decreased with almost no effect on action potential patterns at the neuromuscular junction. Dantrolene inhibits the movement of a natural calcium ionophore (lipid-soluble molecules that transport ions across lipid cell membranes). It is seen that Dantrolene does not significantly change the charge when the excitation-contraction coupling starts during the process of muscle contraction. Instead, it shortens the duration of efflux, leading to a reduced collection of calcium ions in the muscle fiber. A graph exhibiting the mode of action of Dantrolene shows a steep strength-duration curve. Its unique mechanism of blocking the release of intracellular calcium ions might make it an essential medication in preventing or treating any neuronal injuries. The mortality rate significantly decreases with the introduction of Dantrolene. Chances of survival are almost as high as 70% with dantrolene administration and as low as merely 5% without it.

Side effects of Dantrolene include muscle weakness, phlebitis, respiratory failure, drowsiness, dizziness, confusion, nausea and vomiting. It can cause 'floppy child syndrome' and postpartum uterine atony during cesarean section. Chronic oral therapy has been associated with liver dysfunction. It can cause drug interaction when used in combination with verapamil, leading to decreased cardiac function. A new drug competing with Dantrolene, namely Azumolene, has been developed, an approximately 30-fold more water-soluble analog of Dantrolene.

Development of Dantrolene Globally

Many countries have participated in drafting guidelines and providing suggestions regarding the recommended dosage, formula preparation, and usage of Dantrolene. The countries that have joined to set up the European Malignant Hyperthermia Group include Switzerland, the UK, South Africa, Spain, Australia, Israel, Belgium, Sweden, Austria, France, New Zealand, Germany, Brazil, the Czech Republic, and Italy. However, the number of patients given this drug and their responses has not been documented. India has worked to make Dantrolene available in two corporate hospitals in New Delhi, Bangalore, and Chennai, two major government hospitals in Mumbai and Kolkata, and a major teaching hospital in Vellore. Technically, it is difficult to borrow this drug from hospitals that have

stocked it due to billing and license issues. China so far has not made the drug available but is working on it.

Unavailability of Dantrolene in Pakistan

Pakistan is one country where the use of Dantrolene has not been documented so far. Not much has been reported regarding its requirement in the medical sector. So far, just one case of malignant hyperthermia has been documented, which was managed without the use of Dantrolene. However, it has been seen through studies that 1 in every 25,000 patients who undergo general anesthesia is suspected to have suffered from MH within 10 minutes of induction. There are other conditions, including cerebral palsy, tetanus, multiple sclerosis, head injury, brain injury, spinal cord injury, stroke, and specific genetic syndromes that manifest with severe muscular spasticity. Individuals suffering from these agonizing conditions need relief from pain. Dantrolene has shown remarkable results as a muscle relaxant in harrowing conditions. When Dantrolene breaks down into its metabolites, these metabolites, too, have muscle relaxant properties. This makes the drug more efficient and efficacious by prolonging its effect.

Limitation

Dantrolene is still in the exploratory phase, and several research centers in numerous European countries are unearthing it. Unfortunately, Pakistan lacks equipped research centers and qualified professionals who could participate in this paramount cause and prove their competencies in the health sector. It is an expensive drug, and its number of applications in a single patient is high. Unfortunately, our government has a small budget for the health sector, which compromises many vital areas of wellness. Few local traders have purchased raw materials for Dantrolene from countries like Malaysia and are experimenting with making crude salts similar to Dantrolene. However, producing these unlicensed products is unethical and hazardous for human consumption since the ideal environment is unavailable for its making. There is no establishment to conduct the Modified Delphi Process to have a complete consensus among expert panels to recommend the introduction of Dantrolene in intravenous form for the reduction in the death rate from malignant hyperthermia. There is no proper evaluation committee to study the relationship between the rate of morbidity due to malignant hyperthermia and delay in the admission of Dantrolene.

Recommendations

Pakistan, as a nation, still needs to be made aware of its barriers to access to health privileges. Hence, organizing seminars and workshops to introduce new drugs being launched into the market and advertise their benefits is vitally important. Trade for life-saving medication like Dantrolene should be encouraged, and the economy should be stabilized to provide financial support. Experts should be stimulated, facilitated, and inspired to research Dantrolene and write review articles on it. The Drug Regulatory Authority of Pakistan should play its part with responsibility and enthusiasm to ensure the quality, safety, and efficacy of drugs along with the provision of appropriateness and accuracy of information to the public. Efforts should be made to start the import of Dantrolene, considering the importance of its requirement and usability. Dantrolene is one of the most needed drugs, considering the prevalence of a wide variety of disorders and diseases manifesting severe muscular spasticity in Pakistan. Studies have shown that the prevalence of cerebral palsy in Pakistan is 1.22/per 1000 live births. In the age group of 9 – 10 (39.6%) years, half of the affected children (39.2% cases) have spastic quadriplegia and severe deformities. This figure points to the urgency of meeting the needs of importing Dantrolene and making it accessible to the public at large.

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