

Hyperthermia Syndrome and Medications Used to Treat It

Sokhib Rashidov Zamon o'g'li ¹

Raufjon Usmonov Rajabboy o'g'li ²

Firdavs Boboqulov Khurshid o'g'li ³

Mukhtasarxon Nazirova Ibrokhim qizi ⁴

Abstract

Extreme increases in body temperature, or hyperthermia, can be fatal and can be brought on by illegal or prescribed medicines that act at several different levels of the nervous system. The characteristic clinical condition of hyperthermia, skeletal muscular hyper-metabolism, stiffness or rhabdomyolysis, autonomic dysfunction, and altered mental status ranging from catatonic stupor to coma has been linked to a number of psychotropic medication classes and combinations. In order to prevent significant morbidity and mortality, clinicians must be very suspicious of these relatively rare drug-induced side effects and educated about how to manage them. Despite their similar appearance, these illnesses are caused by quite distinct causes, and while careful medical care and the withdrawal or restoration of potentially triggering medications are necessary, specific therapies may differ. There may be a common "thermic stress syndrome" that is brought on in human and animal models by a range of pharmacological or environmental stressors, according to theoretical conjectures based on clinical similarities regarding common mechanisms and shared genetic predispositions underlying these syndromes. No improvement in clinical outcomes has been linked to the use of antipyretics. In a recent pilot study, therapeutic hyperthermia brought on by physical warmth was examined, and the group that experienced the hyperthermia fared better in terms of survival. In conclusion, the available research supports at least a temperature tolerance strategy for non-neurocritical patients, however there is currently insufficient evidence to justify the use of therapeutic hyperthermia outside of clinical trials.

Keywords: Serotonin syndrome, neuroleptic malignant syndrome, induced hyperthermia, malignant hyperthermia, antipsychotic medications, substance use disorders.

^{1, 2, 3, 4} Department of pharmacology of Tashkent medical academy

Introduction. Health depends on thermoregulation, or maintaining a normal body temperature. One of the most strictly controlled physiological functions is body temperature. Numerous layers of the nervous system, in addition to other body organs and systems, are involved in the intricate physiological process of thermoregulation. Drugs or toxins can thereby impact a number of processes, impairing thermoregulation and resulting in hyperthermia. All medications that disrupt thermoregulation should be known to doctors, but one class includes medications that, in the absence of a hot environment, increase the generation of heat internally, so contributing to hyperthermia [1-4]. These disorders, which are typified by skeletal muscular contraction and hypermetabolism, exhibit symptoms that are similar to malignant hyperthermia of anesthesia (MH), including increased temperatures, muscle rigidity, rhabdomyolysis, elevated vital signs, and alterations in mental status. There is a chance that this clinical picture could be a medical emergency with life-threatening consequences. These disorders may be seen and should be taken into consideration during consultations in psychiatric and medical hospital settings, even though they are often seen in emergency rooms. For instance, individuals undergoing neuropsychiatric treatment who experience hyperthermia frequently have been taking several potentially triggering medications due to the prevalence of polypharmacy, particularly in the elderly. Finally, the differential diagnosis is crucial since there may be differences in how these syndromes are managed in terms of avoiding major negative consequences [5-11]. A typical therapeutic intervention in medical practice is the modification of body temperature, primarily by the use of antipyretics. Hyperthermia, however, may be used as an adjuvant treatment for individuals with infections, according to new research. The use of therapeutic hyperthermia in the treatment of infection was investigated using a narrative review. Patients with neurosyphilis and gonococcal infections were enrolled in several studies conducted prior to the invention of antibiotics, with cure rates ranging from 60% to 80%. The probable immunological and molecular processes that could account for the potential advantages of therapeutic hyperthermia have been described. Higher temperatures directly reduce virulence in certain infections, but the most significant factor influencing microbial viability is thought to be temperature-driven immune system activation. Last but not least, we reviewed research from the present day that employed body temperature regulation as a therapeutic approach. In clinical trials including patients with infections, the hypothermia group has shown worse outcomes [12-16]. In addition to centrally disrupted regulatory abnormalities, a severe hypermetabolic reaction in the skeletal muscles frequently leads to hyperthermia. This can be lethal and mostly results in rapidly developing muscle rigidity, widespread rhabdomyolysis, electrolyte imbalances, and renal failure. Reducing body core temperature is the aim of treatment, which includes both targeted therapeutic options and symptomatic supportive care, such as active cooling [1,2,11,14,15,17].

The main aim. This review covers the causes, pathophysiology, clinical manifestations, and treatment of drug-induced hyperthermia (DIH) syndromes.

An overview. Drugs that can change the equilibrium between heat production and dissipation can significantly affect body temperature. These incidents could quickly turn lethal if they are not addressed with vigor. Via various underlying processes, a number of toxins can cause these non-infection-based temperature changes. Medications that can uncouple oxidative phosphorylation, inhalation anesthetics, antidopaminergic, anticholinergic, serotonergic, sympathomimetics, monoamine oxidase inhibitors, and unspecific agents that cause drug fever are among the medications that contribute to the emergence of these syndromes [2,4,11,17,18]. If not identified and treated swiftly, DIH syndromes, a rare and sometimes disregarded cause of elevated body temperature, can be lethal. Neuroleptic malignant syndrome, serotonin syndrome, anticholinergic poisoning, sympathomimetic poisoning, and malignant hyperthermia are the five main DIH disorders. Since the symptoms of DIH syndromes are typically nonspecific and range from blood pressure fluctuations and excessive perspiration to altered mental status, muscle rigidity, convulsions, and metabolic acidosis, it can be difficult to make a differential diagnosis [1-7]. Few currently available treatment options can shorten the duration of hyperthermia, according to evidence from the professional literature (a MEDLINE search for articles published through

November 2011). For this reason, it is crucial to identify the provoking agent as soon as possible based on the patient's medication history, clinical presentation, and the timing of symptom onset in order to determine the best course of action and prevent potentially fatal sequelae. The proper management of all DIH syndromes entails stopping the suspected offending agent or agents right away and providing supportive care (such as external cooling and volume resuscitation when necessary). Pharmacologic therapy, such as benzodiazepines, bromocriptines, or dantrolene, may be necessary in certain situations; the choice of an agent is mostly based on the patient's medication history and suspected DIH syndrome. Drugs and other substances that change neurotransmitter levels can induce DIH, a hypermetabolic condition. When necessary, supportive care and medication are used to treat DIH symptoms [8-12].

Treatment of temperature changes caused by toxins and associated pathology. Fever with an adrenaline rush. Adrenergic fever can be brought on by intoxication with phenethylamine-class drugs (such as amphetamine, methamphetamine, and 3,4-methylenedioxyamphetamine (MDMA), the most widely used sympathomimetic chemical at the moment), cocaine, and MAO inhibitors. By releasing too much serotonin and dopamine, MDMA and other serotonergic drugs may centrally de-regulate thermogenesis. A genetic susceptibility where the CYP2D6 enzyme is not functioning causes MDMA to be cleared more slowly and to remain in the blood for longer. Motor activity raises the toxicity of stimulants like amphetamine and MDMA, in addition to high ambient temperatures and dehydration. In addition to catecholamine-induced vasoconstriction that impairs heat dissipation, psychomotor agitation causes an increase in muscle activity and the generation of heat by the muscles [4-11]. Moreover, it has been proposed that serotonin, dopamine, and norepinephrine regulate thermoregulation in the hypothalamus. The hypothalamic-pituitary-thyroid-adrenal axis is activated by direct and indirect stimulation of the hypothalamus by substances including MDMA, methamphetamine, cocaine, and MAO inhibitors. The amount of thyroid and adrenal hormones in the blood determines the subsequent thermogenesis and toxicity. Both MDMA and cocaine use have been shown to cause a significant increase in norepinephrine. Norepinephrine causes vasoconstriction and poor heat dissipation by acting on vascular α 1-adrenoreceptors. Together with increased thyroid hormones, it also binds to and activates α 1- and β 3-adrenoreceptors, which through uncoupling phosphorylation control the activity of thermogenic tissues like brown fat. In conclusion, hypothalamic stimulation results in excessive heat generation through motor effort and uncoupling as well as poor heat dissipation through vasoconstriction. In this type of intoxication, hyperthermia (together with other occasionally fatal symptoms) is a sign of severe poisoning and portends a bad prognosis. Therefore, it is essential to treat hyperthermia with rigor [1,2,9,15,17].

Antidopaminergic fever: neuroleptic malignant syndrome. The typical temperature disturbance disorder following the mechanism of antidopaminergic fever is NMS. It is a rare idiosyncratic reaction typically occurring in people taking neuroleptics or after the sudden withdrawal of dopamine agonists, with a reported prevalence between 0.02% and 0.4% [20]. Men are affected twice as often as women. Typical clinical presentation of NMS is a syndrome of hyperthermia with temperatures $>38^{\circ}\text{C}$ as a key finding, altered mental status, such as delirium, somnolence, coma and mutism, 'lead pipe' skeletal muscle rigidity, and autonomic dysfunction. Tachycardia, hypertension or hypotension, and diaphoresis are the most common symptoms of autonomic dysfunction [3-7]. Leukocytosis, increased liver transaminases and creatine kinase, and low serum iron are examples of laboratory abnormalities. But NMS can sometimes happen when some or all of the traditional clinical signs are absent, which could make diagnosis difficult. It could be challenging to distinguish between serotonin syndrome and NMS. Hyperreflexia, clonus, and the speed at which symptoms appear are said to be the major distinctive characteristics between these two syndromes. While NMS can occur at any point throughout a neuroleptic's treatment course, with peak symptoms not appearing for days, serotonin syndrome usually manifests intensely within 24 hours of beginning therapy with clonus, hyperreflexia, and myoclonus [4,7,18,19,21].

Treatment or Management. Administering dantrolene right away is essential for treating malignant

hyperthermia. All triggering substances must be stopped as soon as a malignant hyperthermia episode is suspected. The patient must also be hyperventilated with 100% oxygen while receiving non-triggering anesthetics for patient care, and surgery should be stopped as soon as possible. As soon as feasible, a dose of 2.5 mg/kg of dantrolene must be injected; this dose can be increased to a maximum of 10 mg/kg until the reaction stops. Along with giving dantrolene, care must be taken to prevent arrhythmias, hypoxemia, acidosis, hyperthermia, and to maintain renal function. Antiarrhythmics can be used to treat arrhythmias, and furosemide can be used to maintain a urine flow of at least 2 ml/kg/hr, protecting renal function against potential acute tubular necrosis [17-22].

The following are included in the management algorithm: Put an end to the triggering agent. Make an assistance call.

Up to 10 mg/kg of dantrolene should be administered until the reaction stops.

To reduce end-tidal CO₂, increase ventilation.

Cooling techniques (applying ice packs to exposed surfaces and cold intravenous fluids).

Treat arrhythmias with amiodarone, for example, and stay away from calcium channel blockers.

Laboratory tests include coagulation profile, serum and urine myoglobin, arterial blood gas, and electrolytes, particularly potassium.

For 24 to 48 hours, keep taking 1 mg/kg of dantrolene every 4 hours.

Make sure you produce 2 milliliters per kilogram every hour (each dantrolene vial has 3 grams of mannitol).

Rapid diagnosis, prompt dantrolene treatment, and the use of cooling techniques to stop the rapid rise in core temperature are all linked to better patient outcomes. The patient needs to be kept in the critical care unit for at least 24 hours after stabilization in order to be monitored and to look for indications of recrudescence. Patients who have a lot of muscle mass or who have been exposed to anesthesia for at least 150 minutes prior to triggering are most at risk for recrudescence. Although it has been done often in the past, pretreating patients who are prone to malignant hyperthermia with dantrolene is not necessary for their care and should not be done. These patients ought to be given a non-triggering anesthetic instead [15-24].

Discussion. In medical practice, regulating body temperature—mostly with antipyretics—is a frequently used therapeutic technique. Nevertheless, new research indicates that hyperthermia may be used as an adjuvant treatment for infected patients. To investigate the use of therapeutic hyperthermia in the management of infection, we conducted a narrative review. In the pre-antibiotic era, several investigations were conducted with individuals who had gonococcal infections and neurosyphilis, with claimed cure rates ranging from 60% to 80%. We have described the various immunological and molecular processes that could account for the potential advantages of therapeutic hyperthermia. Temperature-induced immune system activation is thought to be the most significant factor influencing microbial viability, however for some infections, elevated temperatures directly reduce pathogenicity. Finally, we reviewed recent research that has employed body temperature regulation as a therapeutic approach. When therapeutic hypothermia is administered to infected patients, the hypothermia group has shown worse results [1,2,3,7,9]. While hyperthermia has a wide range of differential diagnoses, a number of medications can cause a malignant hyperthermia-like condition. In order to reduce morbidity and mortality, it is critical that clinicians identify these illnesses and initiate treatment promptly. Despite their similar appearance, these illnesses are caused by quite distinct mechanisms, and different treatments may be required in addition to providing acute care and withdrawing or restoring potentially triggering medications. Knowing how hazardous these medications are is crucial, particularly if you use them in combination or exert yourself in a hot climate. Sadly, the use of illicit and natural substances bought online is becoming more and more popular, and clinicians should be aware of the risks involved. Clinical

results have not been shown to improve with the use of antipyretics. One pilot study in the modern era examined therapeutic hyperthermia brought on by physical warmth, and the group that experienced the hyperthermia fared better in terms of survival [11-17]. In summary, there is currently insufficient evidence to justify the use of therapeutic hyperthermia outside of clinical trials; nevertheless, the studies that are available support the use of at least a temperature tolerance strategy for patients who are not neurocritical. Antimicrobials will remain the mainstay of non-surgical infection therapy in the future, but the rise in viral epidemics and the occurrence of multi-resistant bacteria make non-pharmacological therapeutic strategies necessary. In the past, TH has been used for infection management. Preventing fever in non-neurocritical patients with infection has not been linked to improved survival or a more favorable course of intensive care unit treatment, according to multiple studies. Even artificial rewarming may be appropriate for the highest-risk sepsis patients (those who do not experience a fever reaction), as there is evidence that lowering body temperature can be harmful [18-22].

Conclusions. A number of medications can cause a malignant hyperthermia-like illness, despite the fact that hyperthermia has a wide differential diagnosis. To reduce morbidity and mortality, doctors must identify these illnesses and begin therapy as soon as possible. Although these illnesses frequently share similarities in appearance, they are caused by quite diverse causes, and specific therapies may differ aside from the necessity of providing acute care and withdrawing or restoring potentially triggering medications. Understanding the toxicity of these medications is crucial, particularly when taking them together or while exerting oneself in hot conditions. Clinicians should also be aware of the risks involved in the use of illegal and herbal substances that are sadly becoming more and more popular online.

The development of viral epidemics and the growing incidence of multi-resistant bacteria call for the investigation of non-pharmacological therapeutic modalities, even though antimicrobials will remain the mainstay of non-surgical infection management in the future. The treatment of infections has previously made use of TH. According to a number of studies, preventing fever in non-neurocritical patients with infections is not linked to improved survival or a more advantageous course of intensive care unit care. Lowering body temperature may be harmful, according to data, and even artificial rewarming may be appropriate for the highest-risk sepsis patients. In the general population of intensive care unit patients, it is probably reasonable to employ a temperature tolerance strategy if fever occurs as a physiological reaction to infection.

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