Diagnosis and treatment of drug-induced hyperthermia

MEGAN E. MUSSELMAN AND SUPRAT SAELY

Purpose. The etiology, pathophysiology, clinical presentation, and management of drug-induced hyperthermia (DIH) syndromes are reviewed.

Summary. DIH syndromes are a rare and often overlooked cause of body temperature elevation and can be fatal if not recognized promptly and managed appropriately. There are five major DIH syndromes: (1) neuroleptic malignant syndrome, (2) serotonin syndrome, (3) anticholinergic poisoning, (4) sympathomimetic poisoning, and (5) malignant hyperthermia. The differential diagnosis of DIH syndromes can be challenging because symptoms are generally nonspecific, ranging from blood pressure changes and excessive sweating to altered mental status, muscle rigidity, convulsions, and metabolic acidosis. Evidence from the professional literature (per a MEDLINE search for articles published through November 2011) indicates that few currently available treatment options can reduce the duration of hyperthermia; therefore, prompt identification of the provoking agent based on the patient's medication history, the clinical presentation, and the timing of symptom onset is essential to determine the appropriate treatment and mitigate potentially life-threatening sequelae. For all DIH syndromes, appropriate management includes the immediate discontinuation of the suspected offending agent(s) and supportive care (external cooling, volume resuscitation as needed); in some cases, pharmacologic therapy (e.g., a benzodiazepine, bromocriptine, dantrolene) may be appropriate, with the selection of a specific agent primarily determined by the medication history and suspected DIH syndrome.

Conclusion. DIH is a hypermetabolic state caused by medications and other agents that alter neurotransmitter levels. The treatment of DIH syndromes includes supportive care and pharmacotherapy as appropriate.

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Hyperthermia is generally defined as the elevation of the core body temperature to above 37 °C. In addition to exposure to extremely hot or humid environments, the causes of hyperthermia include the use of some medications, taken alone or in combination. A long duration of drug-induced hyperthermia (DIH) correlates with permanent neurologic sequelae such as cerebellar syndrome with long-term neurologic deficits, ataxia, dysarthric speech, ocular dysmetria, and generalized weakness.[1] Therefore, hyperthermia can be extremely harmful and potentially fatal if not recognized early and treated properly. This article provides an overview of basic concepts of thermoregulation and five well-described DIH syndromes: neuroleptic malignant syndrome (NMS), serotonin syndrome, anticholinergic syndrome, sympathomimetic syndrome, and malignant hyperthermia syndrome.

Physiology of thermal regulation

Temperature regulation. Core body temperature is tightly regulated by a negative feedback system to maintain a precise interthreshold range, or "set point," defined as a temperature range within which no thermal regulatory responses occur.[2,3] This set point is not precisely defined but generally fluctuates by approximately 0.5–1.0 °C around the normal core body temperature of 37 °C (Figure 1).[2,4]

The exact mechanism that determines the absolute threshold temperature is not known, but it appears to be mediated by norepinephrine,

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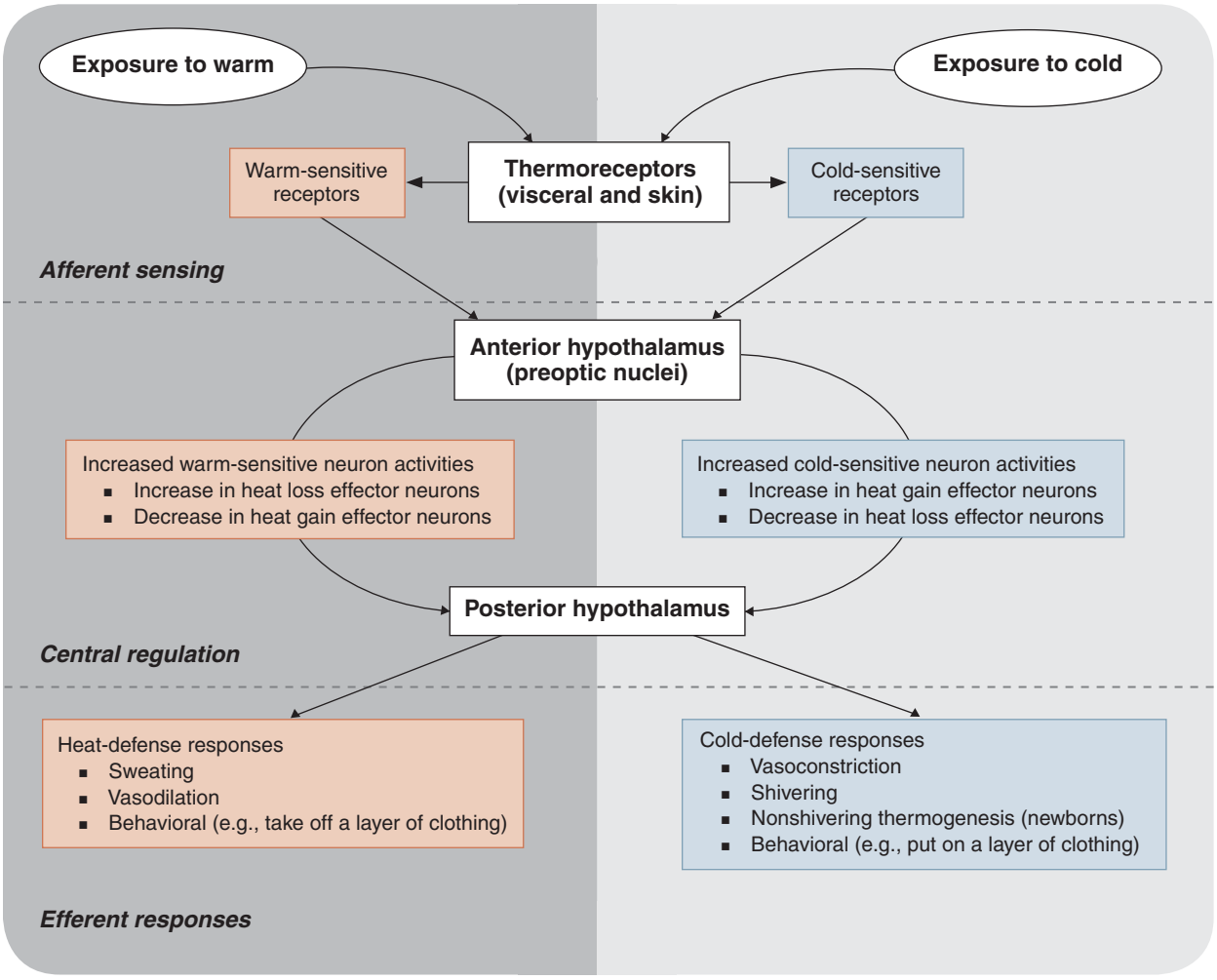
dopamine, serotonin, acetylcholine, prostaglandin, and neuropeptides.[2] The anterior hypothalamus integrates and processes afferent thermal information. The preoptic area of the hypothalamus contains both heat- and cold-sensitive neurons that exert increased activities by stimulating efferent mechanisms in response to temperature changes. The posterior hypothalamus integrates signals from peripheral and preoptic areas of the hypothalamus and initiates the effector responses.[3] Efferent responses include active arteriovenous shunt vasoconstriction, piloerection, and shivering in response to the cold threshold; active vasodilation and sweating occur in response to the warm threshold.[3] Despite the body's complex thermoregulatory responses, behavioral responses such as taking off or putting on additional layers of clothing are usually the most effective way to control body temperature.

Hyperthermia versus fever. Both hyperthermia and fever result in increased core body temperature; however, their underlying mechanisms and treatment are different. Fever, defined as a temperature of ≥38.3 °C, is a process in which the hypothalamus increases the core body temperature set point, or core temperature threshold, in response to infection or noninfectious causes such as adrenal insufficiency.[5] Antipyretics, the standard treatment

Figure 1. Thermoregulation consists of three phases: afferent thermal sensing, central regulation, and efferent responses.[2] Thermal-sensitive receptors are located in the skin and viscera throughout the body, and their function is to sense changes in temperature. When the core body temperature falls below or rises above the set-point range, thermoregulatory defense responses are triggered,[2] and the thermoreceptors send and relay afferent thermal information via the spinal cord to the hypothalamus (the central thermoregulatory control center).[4]



for fever, reduce the elevated set point within the hypothalamus. In contrast, in hyperthermia, the body develops a hypermetabolic state; the heat-loss mechanisms governed by the hypothalamus fail, which results in excessive heat production that exceeds the body's dissipative ability.[6] The term *hyperthermia* is not consistently defined but is generally used in reference to temperature elevation above 37 °C.[7] Although effective against fever, antipyretics are ineffective at reducing elevated core body temperature because the hypothalamus-governed temperature set point is not involved in the mechanism of hyperthermia.[5]

DIH syndromes. Hyperthermia induced by medication use is uncommon and therefore often overlooked as a cause of elevated temperature. The clinical symptoms associated with all of the DIH syndromes are similar; therefore, it is imperative to obtain a precise medication history to aid in differential diagnosis when a DIH syndrome is suspected. Other causes of hyperthermia such as thyrotoxicosis, infection, and substance use (including alcohol use) should be ruled out first. The general approach to the treatment of the five DIH syndromes discussed below is similar: As soon as a DIH syndrome is suspected, the suspected precipitating agent should be discontinued, and supportive treatment should be initiated.

Literature review

Articles on DIH syndromes were identified through a MEDLINE search (through November 2011) using the following key words: *anticholinergic syndrome, bromocriptine, cyproheptadine, dantrolene, drug-induced hyperthermia, malignant hyperthermia, neuroleptic malignant syndrome, serotonin syndrome,* and *sympathomimetic syndrome*. Additional articles were identified from the reference lists of search-identified publications and toxicology textbooks. Most of the published literature is in the form of case reports, case series, and review articles, as hyperthermia-associated syndromes are relatively rare. Articles included in this review highlighted information pertaining to drug-induced hyperthermia, as well as current areas of controversy. Four aspects of each DIH syndrome are reviewed here: (1) causes and, in some cases, incidence, (2) pathophysiology, (3) symptoms and diagnosis, and (4) treatment options.

NMS

Causes and incidence. NMS is a rare but serious complication of the use of medications that act on dopamine receptors. The medications most commonly implicated in NMS are antipsychotic drugs. Other drugs that act as dopamine antagonists also have been associated with NMS but to a lesser degree than the antipsychotics; these other drugs include prochlorperazine,[8-10] metoclopramide,[11-13] droperidol,[14,15] and promethazine.[16,17]

The risk of developing NMS appears to correlate with the dose, potency, and rate and route of administration of dopamine antagonists.[18] Widely varying estimates of the incidence of NMS have been reported, with estimates in retrospective studies ranging from 0.2% to 12.2%.[19] In one prospective study involving 2695 presumed neuroleptic-treated patients, the estimated frequency of NMS was 0.1–2.0%.[20] NMS is associated with a high fatality rate, variously estimated at 15.0–18.8%.[21,22]

Pathophysiology. The underlying pathophysiology of NMS is poorly understood but believed to involve dopamine depletion or blockade within the hypothalamus. This dopamine-mediated effect results in the derangement of central thermoregulation.[21] Hyperthermia is caused by antidopaminergic drugs blocking the heat-loss pathways in the anterior hypothalamus along with increased heat production secondary to extrapyramidal rigidity.[23]

Symptoms and diagnosis. NMS symptoms vary widely, but major characteristic features must be present in order to make the diagnosis. According to the *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision* criteria, the core features of severe muscle rigidity and elevated temperature associated with the use of neuroleptic medication should be present for the diagnosis of NMS, as well as two or more of the following symptoms: diaphoresis, dysphagia, tremor, incontinence, changes in level of consciousness, mutism, tachycardia, elevated or labile blood pressure, leukocytosis, and laboratory evidence of muscle injury (an elevated creatine kinase level).[24]

More sensitive criteria proposed by Levenson[21] require the presence of three major manifestations, or two major and four minor manifestations, to establish the diagnosis of NMS. The major manifestations are hyperthermia, rigidity, and an elevated creatine kinase level; the minor manifestations are tachycardia, abnormal blood pressure, tachypnea, altered consciousness, diaphoresis, and leukocytosis.[21]

NMS may be accompanied by abnormal laboratory findings such as impaired liver function, electrolyte disturbances, renal impairment, metabolic acidosis, rhabdomyolysis, and low serum iron concentrations.[25]

Of course, in addition to the signs and symptoms described above, a history of exposure to neuroleptic medication is essential to establish a diagnosis of NMS.

NMS is considered a diagnosis of exclusion; therefore, it is important to consider a wide range of other disorders that can be mistaken for NMS, including serotonin syndrome and malignant hyperthermia.[21] Due to similarity in the clinical presentation of NMS and malignant hyperthermia, establishing the timing

of the onset of symptoms is vital in differential diagnosis. The onset of symptoms in NMS occurs typically more than 24 hours (and may take up to 30 days) after the initiation or a change in the dosage of neuroleptic medications[26]; in contrast, symptom onset in malignant hyperthermia occurs within minutes to hours. As NMS progresses, complications such as pneumonia, acute renal failure secondary to rhabdomyolysis, seizures, sepsis, pulmonary embolism, pulmonary edema, cardiac arrest, and even death may occur.[27]

Treatment. As soon as NMS is suspected, dopamine-blocking agents should be discontinued. Supportive measures such as volume resuscitation and external cooling are the mainstays of treatment and should be initiated immediately. Benzodiazepines such as lorazepam and midazolam, administered at doses starting at 1–2 mg intramuscularly or intravenously every four to six hours, are considered appropriate supportive treatments and can be used to attenuate sympathetic activity such as agitation or restlessness.[25]

Bromocriptine and dantrolene have also been recommended; however, there are limited data to validate their use in patients with NMS. The use of bromocriptine, a centrally acting dopamine agonist, can increase dopamine activity in the hypothalamus, thereby reducing the rigidity and hyperthermia caused by dopamine blockade. When used in the management of NMS, bromocriptine is generally started at a dosage of 2.5 mg orally or via nasogastric tube every eight hours, with the dosage increased up to a total daily dose of 45 mg if necessary.[25] However, bromocriptine can worsen psychosis and hypotension and may also precipitate vomiting. Thus, it should be used carefully in patients at risk of aspiration.[25] Other centrally acting dopamine agonists such as levodopa[28] and amantadine[29] have been successfully used to treat NMS, but the supporting data are limited.

In severe cases of NMS, dantrolene, a ryanodine receptor type 1 (RYR-1) antagonist, can be used to relax skeletal muscle without causing total paralysis. Relaxation of skeletal muscle by dantrolene occurs through a dose-dependent inhibition of sarcoplasmic calcium release, primarily at skeletal-muscle RYR-1 receptors, thereby directly inhibiting excitation–contraction coupling.[30] Dantrolene can be used as a monotherapy or in conjunction with dopamine agonists. Dantrolene sodium is typically given initially as a bolus (1.0–2.5 mg/kg) and continued until signs of hypermetabolism subside or until a cumulative dose of 10 mg/kg is administered.[31,32] Dantrolene sodium is generally continued at a dosage of 1 mg/kg every 4–6 hours for at least 24 hours to prevent the recurrence of symptoms.[31]

Common adverse effects of i.v. or intramuscular dantrolene administration are muscle weakness and phlebitis caused by the highly alkaline solution. The most serious adverse effect associated with dantrolene therapy is liver toxicity; therefore, its use should be avoided in patients with liver disease. When patients are able to take oral medications, dantrolene sodium may be given orally at a dosage of 4–8 mg/kg/day (divided into four doses) and continued for 1–3 days to prevent the recurrence of symptoms.[31] Symptoms typically resolve within 6–10 days after treatment is initiated.

Serotonin syndrome

Causes and incidence. Serotonin syndrome is a potentially life-threatening iatrogenic disorder. It results from complications of therapeutic or inadvertent use of (or drug interactions involving) one or more medications with serotonergic activities.[33] Medications that have been implicated in serotonin syndrome include selective serotonin-reuptake inhibitors (SSRIs), serotonin–norepinephrine-reuptake inhibitors, monoamine oxidase inhibitors, tricyclic antidepressants (TCAs), tramadol, amphetamines, dextromethorphan, linezolid, sumatriptan, lithium, fentanyl, meperidine, and 3,4-methylenedioxymethamphetamine (MDMA). The use of dietary supplements with serotonin activities, such as St. John's wort[34] and tryptophan,[35] has also been reported to be associated with serotonin syndrome. The prevalence of serotonin syndrome is unknown, but it is reported to occur in as many as 14% of cases of SSRI overdose.[36]

Pathophysiology. In serotonin syndrome, serotonergic agents can enhance synaptic serotonin (5-HT) concentrations, thereby inhibiting the metabolism or reuptake of 5-HT, potentiating 5-HT activity, or increasing substrate supply.[33] Excessive serotonin levels increase the stimulation of both central and peripheral serotonergic receptors. Of importance, the stimulation of central nervous system serotonergic neurons (found in the midline raphe nuclei) responsible for assisting in the thermoregulation process contributes to the signs and symptoms of serotonin syndrome.[37] Specifically, the agonism of the 5-HT_{1A}- and 5-HT_{2A}-receptor subtypes is most frequently implicated as the cause of serotonin syndrome.[37] Other neurotransmitters, such as norepinephrine, *N*-methyl-D-aspartate receptor antagonists, and γ-aminobutyric acid, have also been associated with serotonin syndrome.[37-39]

Symptoms and diagnosis. Serotonin syndrome has been described as a spectrum of toxicity characterized by a classic triad of clinical features: autonomic hyperactivity (hypertension or hypotension, tachycardia, hyperthermia), neuromuscular abnormalities (clonus, muscular rigidity, and hyperreflexia, usually more prominent in the lower versus the upper extremities), and

altered mental status (ranging from agitation and confusion to delirium, seizures, and coma).[36] In its most severe form, serotonin syndrome rapidly progresses to coma, seizures, multiple-organ failure with disseminated intravascular coagulation (DIC), and cardiac arrest.[40]

The clinical findings associated with the diagnosis of serotonin toxicity in a study of 2222 consecutive cases of serotonergic drug overdose were the following: autonomic derangements (including hypertension, tachycardia, body temperature of >38 °C, mydriasis, diaphoresis, and diarrhea), neuromuscular abnormalities (including hyperreflexia, inducible and spontaneous clonus, myoclonus, ocular clonus, nystagmus, tremor, shivering, and peripheral hypertonicity), and mental status abnormalities (including agitation, ataxia, delirium, and seizure).[41]

Serotonin syndrome is a clinical diagnosis based on signs and symptoms and medication history. Serum concentrations of 5-HT have no correlation with the clinical presentation; however, urinary 5-HT concentrations can possibly be used as a biomarker in serotonin syndrome.[42] To assist with the diagnosis of serotonin syndrome, the use of formal measures such as Sternbach's[43] criteria and the Hunter Serotonin Toxicity Criteria[41] has been proposed. According to Sternbach's[43] criteria, three of the following symptoms (combined with suspected serotonergic agent exposure) are required for a diagnosis of serotonin syndrome: mental status changes, agitation, myoclonus, hyperreflexia, diaphoresis, shivering, tremor, diarrhea, incoordination, and fever. Diagnostic criteria proposed by Dunkley and colleagues,[41] which are based on the Hunter criteria, include spontaneous, inducible ocular clonus; agitation; diaphoresis; tremor; hyperreflexia; hypertonicity; and body temperature of >38 °C.

There are many similarities in the symptoms of serotonin syndrome and NMS. In order to distinguish between the two syndromes, the timing of symptom onset may be useful. In serotonin syndrome, symptom onset is rapid, usually within minutes to hours after a change in neuroleptic medication or self-poisoning.[37] In contrast, NMS may take 24 hours to days to develop and up to two weeks to resolve once the offending agent is discontinued. It is important to recognize the distinction between NMS and serotonin syndrome because the pharmacologic treatments differ. For instance, bromocriptine is commonly used as a treatment option for NMS, but its use can exacerbate the symptoms of serotonin toxicity.[37]

Treatment. The mainstay of treatment for serotonin syndrome is discontinuation of the suspected offending serotonergic agent. Hyperthermia in serotonin syndrome is secondary to muscle rigidity; thus, antipyretic therapy to reset the hypothalamic temperature set point is not useful.[37] Supportive measures such as external cooling and benzodiazepine therapy are recommended to reduce muscle rigidity and hyperthermia. If those symptoms are left untreated, they can lead to further complications such as rhabdomyolysis and death. Many cases of serotonin syndrome resolve within 24 hours of the discontinuation of the precipitating drug(s) or the initiation of treatment. However, symptom resolution can take longer, depending on the half-life of the offending agent.[44]

In moderate-to-severe cases, pharmacologic therapies such as cyproheptadine, an antihistamine with 5-HT_{1A}- and 5-HT_{2A}-antagonist activities, can be considered. Cyproheptadine hydrochloride has been administered at an initial dose of 12 mg orally, followed by 2-mg doses every 2 hours until symptoms have ceased, followed by maintenance doses of 8 mg every 6 hours.[37] A cumulative dose of 12–32 mg of cyproheptadine hydrochloride in a 24-hour period binds 85–95% of the serotonin receptors.[45] Cyproheptadine may cause excessive sedation, especially in high doses. Chlorpromazine hydrochloride, a phenothiazine with antagonistic activities at 5-HT_{2A} receptors, has been used successfully as an alternative to cyproheptadine; it is given intramuscularly at doses of 50–100 mg, repeated as necessary every 6 hours.[46]

Therapies such as propranolol, bromocriptine, and dantrolene are not recommended in serotonin syndrome. Hypotension and shock may result from the use of propranolol, a long-acting β-blocker with 5-HT_{1A}-antagonist activities. The use of bromocriptine has been implicated in the development and exacerbation of serotonin syndrome. Dantrolene was reported to have no effect on survival in research involving animal models of serotonin syndrome and seems unlikely to be useful in patients.[37]

Anticholinergic syndrome

Causes and incidence. Anticholinergic agents are a common cause of hyperthermia at both therapeutic and toxic doses. Medications with anticholinergic activities, such as antispasmodics, antihistamines, TCAs, anti-Parkinsonian drugs, neuroleptics, atropine, and belladonna alkaloids can cause anticholinergic syndrome.[44,47]

The incidence of anticholinergic syndrome is unknown. According to the 2009 annual report from the National Poison Data System, that year there was a total of 99,366 exposures to anticholinergic agents and antihistamines in the form of cough and cold preparations; antihistamines alone or in combination with other agents were responsible for 61 fatalities.[48] Children are more prone than adults to develop anticholinergic-related hyperthermia, because children have a lower sweating rate, which reduces their ability to dissipate heat.[49]

Pathophysiology. Hyperthermia is caused by the blockade of both central and peripheral muscarinic

acetylcholine receptors. Therefore, anticholinergic poisoning is oftentimes referred to as antimuscarinic poisoning syndrome.[47] Central muscarinic blockade effects depend on the offending agent's ability to permeate the blood-brain barrier. For example, atropine and scopolamine possess a tertiary amine group that allows these compounds to cross the blood-brain barrier and cause central nervous system activity. Conversely, other agents, such as glycopyrrolate, contain a quaternary amine group that impairs the ability of the compound to cross the blood-brain barrier, and only peripheral adverse effects are seen.[47] Peripheral muscarinic blockade by anticholinergic agents interferes with cutaneous heat loss by impairing sweat-gland function. In such cases, hyperthermia results from the combination of heat production from increased muscle activity and the inability to dissipate heat through sweating.[6,44]

Symptoms and diagnosis. Symptoms produced by central muscarinic blockade include altered mental status, confusion, mumbling or muteness, tremor, myoclonus, hallucinations, agitation, and restlessness.[47] Peripheral symptoms of muscarinic blockade include dry mouth and axillae, mydriasis, blurred vision, sinus tachycardia, flushing, urinary retention, and decreased bowel sounds.[6,47] Severe cases of anticholinergic syndrome may progress to coma, convulsions, and respiratory depression.[47] The distinct peripheral signs and symptoms, in addition to the absence of muscle rigidity, distinguish anticholinergic toxicity from the other DIH syndromes.[50]

Treatment. As with the other DIH syndromes, the offending agent must be discontinued immediately. The primary treatment options for anticholinergic poisoning are supportive care with external cooling measures and benzodiazepine administration. In addition, physostigmine, an acetylcholinesterase inhibitor, can be used to accelerate the resolution of anticholinergic symptoms. The tertiary structure of physostigmine allows it to cross the blood-brain barrier and act on both central and peripheral muscarinic and nicotinic receptors. The inhibition of acetylcholinesterases prevents the metabolism of acetylcholine, allowing acetylcholine to accumulate and antagonize anticholinergic effects such as disorientation, agitation, combativeness, and anhydrosis.[47,51] In adults, physostigmine salicylate is given at doses of 1–2 mg; in children, a dose of 0.02 mg/kg (to a maximum of 0.5 mg) is given intravenously over at least 5 minutes. The onset of action of physostigmine usually occurs within minutes, and its duration of action is short (often less than one hour but not more than four hours). If an adequate response is not achieved and muscarinic effects are not noted, the dose can be repeated after 10–15 minutes, with a cumulative total dose of 4 mg being sufficient in most cases.[51] However, because physostigmine can induce bradycardia or seizures, it is rarely used in managing anticholinergic syndrome[44] and is perhaps best reserved for cases in which all other treatment options have been exhausted.

In asthmatic patients, excessive cholinergic activity can precipitate bronchospasms and bronchorrhea; therefore, atropine should be available to reverse potential excessive cholinergic effects.

In severe cases of anticholinergic syndrome involving uncontrolled hyperthermia, the use of paralytics (with sedation) may be necessary.[6] As hyperthermia can persist for days, the patient's core body temperature should be monitored regularly until normal thermoregulation returns.

Sympathomimetic syndrome

Causes. Sympathomimetics are a class of medications and agents that can cause life-threatening hyperthermia. The most common agents responsible for hyperthermia are amphetamine, methamphetamine, MDMA ("ecstasy"), cocaine, and monoamine oxidase inhibitors.[44] Of these, ecstasy has become a major problem because of its recent increased use as a recreational drug by young adults.

Pathophysiology. The exact mechanism by which sympathomimetic agents induce hyperthermia is unknown but is believed to be related to central and peripheral thermoregulation disturbances. These agents cause hyperthermia by altering the levels of norepinephrine, dopamine, or 5-HT in the central nervous system. MDMA causes excessive dopamine and 5-HT release from the nerve endings, whereas cocaine stimulates the release and blocks the reuptake of endogenous catecholamines.[50] Amphetamines enhance the release of norepinephrine, dopamine, and 5-HT from presynaptic nerve terminals and inhibit their reuptake from the synapses.[47] Peripheral effects of catecholamines include increased metabolism and impaired heat dissipation through vasoconstriction. Furthermore, sympathomimetics can cause psychomotor agitation, motor excitability, and seizures leading to increased muscle activity. These actions along with ambient temperature contribute to the rise of core body temperature.[6,47]

Symptoms and diagnosis. Common symptoms in sympathomimetic syndrome are mental status changes such as agitation, confusion, panic, and hallucinations.[47] Ecstasy-related hyperthermia can be also associated with hyperkalemia, acidosis, hypocalcemia or hypercalcemia, hyponatremia, hypoglycemia, and coagulopathy. Oftentimes, these effects lead to complications such as rhabdomyolysis, hypoxia, myocardial dysfunction, renal failure, DIC, and even death.[47,50] The syndrome may progress quickly to status epilepticus and coma, both of which can con-

tribute to a poor neurologic outcome if not treated promptly. Electrolytes, creatine phosphokinase, and urinalysis results should be monitored to avoid these complications.

Treatment. Treatment of hyperthermia caused by sympathomimetics predominately involves supportive care and rapid, aggressive external cooling. Benzodiazepines, in addition to offering anticonvulsant properties, can be used to blunt increased sympathomimetic activity such as motor excitability. In cases where benzodiapines are insufficient to control severe agitation, shivering, or seizures, consideration should be given to the use of barbiturates, nondepolarizing paralytics, and mechanical ventilation so that aggressive cooling measures can be accomplished.[47] Core body temperature should be closely monitored. Dantrolene has been used in the treatment of ecstasy-related hyperthermia; however, the safety and efficacy of its use have yet to be established.[52] In patients with cocaine toxicity, drugs with β-blocking activity, such as propranolol, should be avoided because they may cause coronary artery vasospasm via unopposed alpha stimulation.[53]

Malignant hyperthermia syndrome

Etiology. Malignant hyperthermia is a rare autosomal dominant disorder of the skeletal muscle that results in an extreme form of hypermetabolic crisis. Exposure to potent inhalation agents (e.g., halothane, sevoflurane, desflurane), the depolarizing neuromuscular blocking agent succinylcholine, and, in rare cases, stresses (e.g., vigorous exercise, heat) can cause a hypermetabolic response in patients susceptible to malignant hyperthermia.[54] A survey of anesthesia departments in Denmark found that the overall incidence of fulminant malignant hyperthermia during anesthetic procedures is low (1 per 250,000 patients), with a mortality rate of 10%; however, when a combination of potent inhaled anesthetic agents and succinylcholine is used, the incidence is higher (1 per 62,000 patients).[55] Malignant hyperthermia is most common in the first three decades of life, with half of all cases occurring in patients younger than 15 years of age, and is more common in males than females.[6,18]

Pathophysiology. The manifestations of malignant hyperthermia syndrome are primarily due to a gene mutation affecting the RYR-1 channel, which facilitates calcium release in skeletal muscle during periods of excitation and contraction.[56] The receptor also is a binding site for adenosine triphospate, magnesium, inhaled anesthetics, and dantrolene.[33,54,57] Mutations of the RYR-1 gene cause an elevation of sarcoplasmic calcium within myocytes, inducing muscle contraction, which causes accelerated cell metabolism, excessive heat and lactate production, and rhabdomyolysis.[54]

Symptoms and diagnosis. Symptoms of malignant hyperthermia typically emerge within minutes to hours after administration of the offending agent.[18] Early signs of malignant hyperthermia include tachycardia, tachypnea, muscle rigidity, ventricular dysrhythmias, and hypercarbia; muscle rigidity is usually first noticed in the masseter muscles.[54] The late clinical findings associated with malignant hyperthermia are muscle rigidity, hyperthermia, and metabolic acidosis, all related to a hypermetabolic response.[54] These findings—the "classic clinical triad" of malignant hyperthermia—can lead to end-organ damage, including myoglobinuria, renal failure, hyperkalemia, liver failure, DIC, arrhythmias, congestive heart failure, pulmonary edema, bowel ischemia, neurologic injury, and death.[6]

Treatment. The management of malignant hyperthermia has been studied extensively and is well established. All suspected triggering agents should be discontinued immediately. Hyperventilation with 100% oxygen should begin immediately, and anesthesia should be maintained with opioids and hypnotic drugs.[58] If muscle relaxation is required, only nondepolarizing neuromuscular blocking agents should be used. Supportive therapy including external cooling measures (e.g., use of cooling blankets, cool water mist, and fans) should be instituted immediately. However, shivering can increase the metabolic rate and further contribute to the increased body temperature. Therefore, careful monitoring of core body temperature for undesirable effects of cooling (e.g., signs of end-organ damage, shivering) should be performed, with the treatment strategy modified as necessary.[54]

The pharmacologic treatment of choice is dantrolene. Dantrolene binds to the RYR-1 receptor located in the skeletal muscle, reducing the release of calcium from the sarcoplasmic reticulum, which leads to inhibition of the excitation–contraction coupling of skeletal muscle and muscle relaxation.[58] Dantrolene sodium is generally administered by rapid i.v. push initiated at a minimum dose of 1 mg/kg[31]; however, a mean starting dose of 2.5 mg/kg was successfully used in one study of patients who survived malignant hyperthermia.[32] Dantrolene sodium should be continued until symptoms subside or the maximum cumulative dose of 10 mg/kg has been reached.[31] Signs and symptoms of hypermetabolism generally begin to resolve within 30 minutes after the effective dose of dantrolene has been given. To prevent the recurrence of malignant hyperthermia, infusions of dantrolene sodium (1 mg/kg every 4–6 hours) can be continued for at least 24 hours, followed by administration of oral dantrolene sodium (4–8 mg/kg/day divided into four doses) daily for one to three days.[31,54]

In patients with known susceptibility to malignant hyperthermia, there are many potential alternative

agents that can be used to provide anesthesia or therapeutic paralysis, such as nitrous oxide, propofol, nondepolarizing neuromuscular blockers, and benzodiazepines.[54]

Conclusion

DIH is a hypermetabolic state caused by medications and other agents that alter neurotransmitter levels. The treatment of DIH syndromes includes supportive care and pharmacotherapy as appropriate.

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