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Toxicologic Hyperthermia

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A man who was severely agitated a short time ago is now unresponsive in the ED. He has a temperature of 107°F and a history of cocaine abuse. What is the differential diagnosis for his condition, and which management steps take priority?

Case

A 38-year-old man with a history of cocaine abuse presents unresponsive to the ED. His family reports that after he went into a bathroom, he came out looking "loaded" and stated that he had been stabbed in his head. He became increasingly agitated in the street, and it took several police officers to subdue him and place him in an ambulance. En route to the hospital, he became unresponsive.

In the ED, his vital signs are as follows: blood pressure, 118/50 mm Hg; heart rate, 176 beats/min; respiratory rate, 20 breaths/min; and temperature, 107°F. On physical examination, the patient is unconscious with no response to noxious stimuli. His pupils are normal, and he is diaphoretic. There is a 3-cm laceration to his occiput. His cardiac exam reveals tachycardia with regular rhythm. His lungs are clear to auscultation, and his abdomen is soft with normal bowel sounds. His muscle tone is normal and there is no clonus.

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FIGURE. On ED arrival, severely hyperthermic patients should be rapidly cooled. One effective method is to cover the patient with ice and wet sheets.

After initial evaluation, he is intubated for airway protection and covered in ice (Figure). He is rapidly transported to the CT scanner.

How does thermoregulation go awry and produce hyperthermia?

Hyperthermia may be due to increased endogenous heat production, reduced heat loss, or a combination of both processes. One of the most common etiologies for hyperthermia in the ED is fever, a result of systemic inflammation in response to a pyrogen. A pyrogen raises

the hypothalamic set point and the body generates heat (eg, shivers) to warm itself. Few toxins are pyrogens, and toxicologic hyperthermia is most commonly due to excessive heat generation.

Thermoregulation is a complex symphony conducted by the hypothalamus via voluntary and involuntary responses. Despite alterations in environmental conditions, many systems, including the spinal cord, abdominal viscera, and skin, contribute to thermoregulatory functions, some of which are local feedback loops.[1] Other regulatory pathways communicate with the hypothalamus, which in turn orchestrates rapid regulation of the periphery before central systems are affected.[2] Normal responses to hyperthermia include vasodilation and perspiration. Peripheral vasodilation is regulated by inhibition of hypothalamic adrenergic outflow, while sweating is controlled via local cholinergic sympathetic stimulation.

FAST TRACK

Early recognition of elevated core body temperature is the most important step. Rapid cooling is required since patients who remain hyperthermic have worse outcomes.

What is the differential diagnosis for toxicologic hyperthermia?

Sympathomimetic drugs, such as cocaine or amphetamines, directly stimulate adrenergic receptors, causing psychomotor agitation, tachycardia, and hypertension. In severe cases, hyperthermia, seizures, and tachydysrhythmias can occur. Hyperthermia is generally due to excessive purposeful motor activity. Similar effects may be noted with thyroid hormone (endogenous or exogenous) and methylxanthines (to mention a few), as well as in patients with alcohol withdrawal.[3] Sympathomimetics also cause α-adrenergic–mediated peripheral vasoconstriction, disrupting an important thermoregulatory response to hyperthermia. Because heat dissipation mechanisms may be easily overwhelmed following cocaine use, particularly in warm and humid environments, there is an increase in cocaine-related fatalities under these conditions.[4]

Malignant hyperthermia occurs in genetically susceptible individuals after administration of a general anesthetic or succinylcholine, most commonly during surgery. In these patients, ryanodine receptor dysfunction causes uncontrolled calcium release from the sarcoplasmic reticulum, and the resulting excessive muscle activity generates an insurmountable amount of heat. Affected individuals become hyperthermic and typically have markedly increased muscle tone.

The mitochondrial electron transport chain creates high-energy phosphate bonds (ie, ATP) associated with the oxidation of various energy sources, such as glucose. Agents that uncouple oxidative phosphorylation, such as aspirin or dinitrophenol, impair ATP formation and result in the dissipation of this potential chemical reaction in the form of heat.

Neuroleptic malignant syndrome (NMS) is most commonly the result of central dopaminergic antagonism from antipsychotic medications. Clinical findings include increased muscle tone, altered mental status, hyperthermia, and autonomic instability. The tonic muscle activity leads to hyperthermia. Interestingly, NMS may also occur after withdrawal of dopaminergic agents (antiparkinsonian medications) due to a net reduction in dopaminergic stimulation.

Serotonin syndrome, or serotonin toxicity, occurs when proserotonergic drugs cause an excessive rise in serotonin levels. This results in altered mentation, autonomic instability, and enhanced neuromuscular activity, including tremor, hyperreflexia, and clonus. As with NMS, the excessive muscle activity leads to heat generation. The distinguishing factors between these two adverse drug reactions is their time course, with serotonin syndrome occurring rapidly after exposure and having a short duration.

Hyperthermia also occurs as a result of reduced heat dissipation. Patients using antimuscarinic (anticholinergic) agents may develop hyperthermia due to blockade of muscarinic cholinergic receptors. These patients may become confused and tachycardic and have dry skin and mucous membranes. Hyperthermia is rarely the only clinical finding in anticholinergic poisoning,

and heat generation may be worsened by the accompanying psychomotor agitation. Diuretics and antihypertensives can contribute to hyperthermia, since volume depletion can impair vasodilation.

A portion of compensatory heat loss is guided by behavioral changes that promote heat loss. Certain populations, such as the developmentally delayed, the extremely elderly, or those with psychiatric illnesses, not only may be taking medications that interfere with heat dissipation but also may be unable to modify their behavior or environment to prevent heat stroke. In addition, compensatory heat loss mechanisms are diminished in patients with dysfunctional autonomic systems as a result of underlying medical diseases.

What are the most important initial steps in caring for a hyperthermic patient?

Early recognition of elevated core body temperature is the most important step in management. Rapid cooling is required since patients who remain hyperthermic have worse outcomes than those who are quickly cooled. Prolonged hyperthermia causes the body to mount a more potent systemic inflammatory response and propagates more intense end-organ damage. Therefore, minimizing the duration of hyperthermia is the key to optimal treatment.[5]

The goal is to cool the patient to 102°F within 20 minutes of ED arrival. Ice bath immersion is the fastest way to cool severely hyperthermic patients.[2] Evaporative cooling with fans and water is effective, but often slow. Cooling with cooling blankets is generally inadequate.

To assist in cooling, other measures may be employed to optimize heat generation and dissipation. Sedation is critical; an agitated patient will not cool due to ongoing heat production. Clothes should be removed as soon as possible and evaporative cooling should begin immediately, using water, wet sheets, and fans until the patient can be covered in ice. Physical restraints such as body jackets and bags should be removed, as they can trap heat as the patient struggles.

What are the effects of heat stroke on various organ systems?

Heat stroke is a life-threatening medical emergency defined by a core body temperature greater than 105°F with concomitant neurologic dysfunction, such as altered mental status. Heat stroke results in multisystem organ failure due to the systemic inflammatory response and the related disseminated coagulation abnormalities.[6] Heat injury directly causes hemorrhage, edema, and necrosis in nearly every organ, including the heart, bowel, kidneys, and brain.

By definition, heat stroke implies a change in mental status. The duration of mental status change correlates with morbidity, and studies evaluating long-term outcomes in patients treated emergently for heat stroke have shown decreased functioning and impediments in activities of daily living. Following the Chicago heat wave of 1995, patients who survived to discharge from the hospital were surveyed 1 year later.[5] Only one of the 58 patients in this study population had been cooled within 30 minutes of arrival to the ED. Twenty-eight percent of initial survivors had died 1 year after discharge, with most of these deaths occurring within the first 12 weeks.[5] Similarly, following the 2003 heat wave in France, 22% of previously independent-living patients who survived to discharge required placement into institutions.[7] At 1 year after hospital discharge, 41% of patients were bedbound, compared to 4% prior to hospitalization.[7] During heat stroke, in addition to cerebral and cerebellar hemorrhage, damage to cortical and cerebellar neurons may occur, which can lead to long-term sequelae such as abnormal nerve conduction, cerebellar dysfunction, muscle wasting, extrapyramidal syndrome, or paresis.

Multiple factors increase bleeding propensity in the setting of heat stroke. In addition to the depletion of clotting factors, disseminated intravascular coagulation (DIC) and thrombocytopenia also have a role. DIC is thought be a result of capillary basement membrane injury, and thrombocytopenia is likely due to decreased survival of platelets and platelet precursors. Bleeding is a predictor of poor outcomes in heat stroke patients.

Should this patient be given an antipyretic?

Effective cooling of a heat stroke patient requires the transfer of heat from the patient to a neighboring cold environment via radiation, convection, conduction, and evaporation. In a febrile illness, in which endogenous pyrogens raise the hypothalamic set point, pa-

tients may receive antipyretics, such as acetaminophen or ibuprofen, to lower the set point. In heat stroke, these medications do not help since heat stroke does not involve a change in the hypothalamic set point but rather an imbalance between heat generation and dissipation.

Should this patient be treated with dantrolene?

Dantrolene is a skeletal muscle relaxant that has been suggested as a useful therapy in patients with severe hyperthermia. Dantrolene works within skeletal muscle at the ryanodine receptors, where it inhibits calcium release from the sarcoplasmic reticulum. Dantrolene is the treatment of choice in patients with malignant hyperthermia, in whom the ryanodine receptor is dysfunctional. Since heat stroke is not related to ryanodine receptor malfunction, dantrolene has no defined role in treatment for this patient. Given the delay involved in obtaining and administering this drug, a focus on aggressive external cooling measures and sedation with benzodiazepines is probably more beneficial.

Case Conclusion

The patient was cooled within 25 minutes in an ice bath and admitted to the ICU. He was found to have laboratory and clinical markers of myocardial injury, rhabdomyolysis, acute renal insufficiency, hepatic dysfunction, and DIC. His CT scan showed no injury to the brain. He was treated with supportive care and extubated on hospital day 3 and returned to a normal mental status. His end-organ injuries slowly resolved, and he was discharged from the hospital 2 weeks later. **EM**

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