Drug-Associated Heat Stroke

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Abstract and Introduction

Abstract

During the June 1998 heat wave in New Orleans, 8 patients came to the emergency department of a large public hospital over a 14-day period. They were subsequently admitted to the intensive care unit with a diagnosis of heat stroke. On each of these days, the ambient temperature exceeded 33.3°C (91.9°F). Although the highest recorded temperature was only 35.6°C (96°F), the heat index reached a high of 44.5°C (112°F). Weather-related heat illnesses are well documented, but the reports rarely address contributing medications or drugs. In this series, 6 patients (75%) had been using medication or drugs known to induce or worsen hyperthermia. A seventh patient had been prescribed a phenothiazine, but actual use could not be established. An eighth patient had an unidentified agent detected on toxicologic screening. The most common drug identified was cocaine. Other drugs included diphenhydramine, tricyclic antidepressants, and phenothiazines. Six patients (75%) had rhabdomyolysis; 3 of them also had disseminated intravascular coagulation. There were 2 deaths, yielding a 25% mortality rate.

Introduction

Heat-related illnesses are syndromes of physiologic injury such as heat stroke that result from an environmentally induced elevated body temperature.[1] A rise in body temperature may also be the result of increased metabolic activity or a toxin that either directly or indirectly raises body temperature. Body heat is transported from the body to the skin surface by blood flow. Once there, direct radiation and evaporation of sweat eliminate most of the excess heat.[2] Other mechanisms that usually play a smaller role include conduction to cooler surfaces and convection. The movement of heat requires adequate cardiac output, blood volume, and cutaneous vascular capacitance.

As the ambient temperature rises above body temperature, heat elimination by radiation is eliminated. As the humidity increases, the amount of heat lost by evaporation is markedly reduced. The influence of humidity with ambient temperature on heat elimination is reported as the heat index. It is an adjustment to reflect the equivalent effect on the body at lower humidity.

The 8 patients described in this report represent all cases of heat stroke diagnosed at our facility during the 2-week period of June 1 to June 14, 1998 (Table). All 8 cases occurred during a period of hot weather, and 7 were associated with drugs known to induce or worsen heat illness. The heat index is included to account for the effects of humidity. Two cases are discussed to provide more detail and examples of classical and exertional heat stroke.

The first example (Case 2) is the 40-year-old man who was found unresponsive in a boarding home. His medications included thioridazine, lithium, imipramine, valproic acid, and carbamazepine. On arrival at the emergency department, his score on the Glasgow Coma Scale was 3. His respiratory rate was 40/min, and bibasilar crackles were heard on chest examination. Heart rate was 158/min, and pulse oximetry was 90%. Rectal temperature was 41.9°C (107.4°F). He was intubated, cooled with ice and water mist, and given fluid replacement. Electrocardiogram showed a prolonged QT segment. Gastric lavage was done, and activated charcoal was administered for possible overdose. A urine toxicology screen was positive for

imipramine, phenothiazines, and caffeine. Serum levels of his medications were normal. He was admitted to the intensive care unit. Rhabdomyolysis and disseminated intravascular coagulation (DIC) complicated his hospital course. Cultures of blood, urine, and cerebrospinal fluid had no growth. His mental status improved slowly, and he was extubated 1 week later. He was transferred to a psychiatric facility 11 days later for the treatment of bipolar disease and psychosis.

The patient in Case 7 was a 45-year-old man who had been outside mowing grass. Emergency medical personnel later found him unresponsive, and he arrived at the emergency department with a Glasgow score of 3. His skin was warm and dry. Rectal temperature was 42.2°C (107.9°F), and heart rate was 170/min. He was intubated and cooled with ice packs, a fan, and cold-water gastric lavage. Urine toxicology screen was positive for cocaine and marijuana. He had no contributory medical history. He was admitted to the intensive care unit, and rhabdomyolysis developed. He recovered with supportive care and was discharged 1 week later.

Heat Syndromes

Several heat-associated and hyperthermic illnesses are well known but are often confused with each other because they share the commonality of an elevated body temperature. Normal body temperature is maintained by hypothalamic regulation of blood flow. Neurologic responses to elevated temperature may manifest themselves as vasodilatation and tachycardia. Behavioral responses can include maintaining hydration and seeking shelter from hot environments. Impairment of these mechanisms can lead to heat-induced illness.

Heat Exhaustion

The least dangerous of the heat-related illnesses is heat exhaustion. Heat exhaustion usually results from exertion in hot weather. Excessive loss of water and sodium by sweating is the primary mechanism of this syndrome.[3] Body temperature is usually raised, but heat exhaustion without elevated body temperature may be seen. The hallmarks of the syndrome include fatigue, malaise, nausea. vertigo, and headache after prolonged heat exposure. Mental status is usually normal, but syncope may occur. Tachycardia and hypotension are common findings. Muscle cramping, also called heat cramps, may result from rehydration with free water without replacing electrolytes.[4] In general, the treatment of heat exhaustion includes removal from the hot environment and the replacement of lost fluid and electrolytes, either intravenously or orally.[5] The use of over-the-counter preparations, as well as prescription medications, may contribute to the development of heat exhaustion.

Heat Stroke: Classical vs Exertional

Unlike heat exhaustion, heat stroke is a true emergency. Heat stroke is caused by exposure to excessive heat and the inability to dissipate it. It is often preceded by symptoms of heat exhaustion, which progress to mental status changes such as confusion or coma.[6] The core temperature usually exceeds 40°C.[7] Furthermore, diffuse muscle, liver, and tissue injury lead to the release of cellular enzymes that is seen as elevations in creatine kinase, serum transaminases, and lactate dehydrogenase. Hypotension and tachycardia are common.[8] Miotic pupils have been observed and may be a predictor of severity.[9]

Heat stroke is often categorized as either "classical" and "exertional" on the basis of the demographic groups who are at risk. Classical heat stroke usually occurs during periods of excessively hot weather, as seen with the number of deaths from heat stroke in Philadelphia in 1993.[10] Typically, those at risk for classical heat stroke include the elderly and the very young, alcoholics, persons with psychiatric illness, the physically impaired, and those with dehydration.[11,12] The syndrome affects these patients without need of physical exertion. The elderly have been at particular risk, as seen with the large number of cases in Chicago during 1995.[13] The use of medications, especially those with anticholinergic or diuretic effects, accentuates the risk of heat stroke in these patients.

Exertional heat stroke is often seen in those considered healthy, such as athletes and military recruits. In this form of heat stroke, exercise in hot, often humid weather results in heat production that cannot be dissipated effectively by sweating.[11,12] Hot humid conditions thwart radiation of heat and the evaporation of sweat, which are the main mechanisms of heat loss.[14]

The rapid diagnosis and treatment of heat stroke is crucial. Treatment consists of rapid cooling, rehydration, and correction of electrolyte abnormalities. Patients with a temperature >42°C or those in whom cooling therapy is delayed for more than 70 minutes have the poorest outcomes.[15] Myocardial ischemia, shock, arrhythmia, renal failure, adult respiratory distress syndrome, DIC, hepatic failure, and neurologic impairment lead to a mortality rate of 10% of all patients with heat stroke.[16] With timely and appropriate treatment, complications are rare.[17,18]

Effects of Certain Drugs on Heat Exposure

Anticholinergics and Sympathomimetics

Anticholinergic drugs or drugs with anticholinergic effects are frequently associated with hyperpyrexia and heat illness. These drugs inhibit sweating, thereby reducing heat elimination.[3] Other anticholinergic effects include tachycardia, dry flushed skin, dilated pupils, decreased gastrointestinal motility, and urinary retention. In anticholinergic overdose, mental status changes with delirium may be present. Seizures, myoclonus, and dysrhythmias can also occur. Medications with anticholinergic properties include antihistamines, parkinsonism medication, atropine/scopolamine and the other belladonna alkaloids, neuroleptics, antispasmodics, and many species of plants. Tricyclic antidepressants have known quinidine-like sodium channel blockade, but they exert anticholinergic effects as well.

The clinical effects of sympathomimetics are similar to those of the anticholinergics, but the mechanisms are different. While anticholinergics block acetylcholine at the postsynaptic receptor, the sympathomimetics stimulate the a and b sympathetic receptors by releasing or preventing the reuptake of neurotransmitters. The effects include the tachycardia, hypertension, midriasis, and mental status changes in overdose. Drugs with sympathomimetic properties include cocaine, amphetamines, and ephedrine/pseudoephedrine, which are present in over-the-counter decongestants and popular dietary agents (ma huang). Methylxanthines, such as caffeine and theophylline, are indirect sympathomimetics. While not directly stimulating receptors, they potentiate sympathomimetic effects by inhibiting phosphodiesterase. Theophylline is also believed to be an inhibitor of adenosine, but effects on heat regulation have not been studied.

Sympathomimetics elevate body temperature by two main mechanisms. First, cutaneous blood flow is decreased by vasoconstriction, reducing heat loss. Second, heat production is increased by expanded muscular activity from agitation and seizure activity.[19]

Neuroleptics

The neuroleptics are a broad category of drugs with antipsychotic effects. Most of their psychiatric effects are attributed to dopamine blockade. Many of the neuroleptics have been associated with heat illness, including heat stroke and neuroleptic malignant syndrome. The same mechanism that treats psychosis may create heat illness.

In heat illness, phenothiazines are the best-studied class of antipsychotic medication. Commonly used phenothiazines include thioridazine, chlorpromazine, promethazine, and prochlorperazine. They gained widespread use in the early 1950s for the treatment of psychiatric illness because they were believed to be safe. In 1954, Berti and Cima[20] published their report of lethal temperature deregulation in mice given chlorpromazine. This was followed in 1956 by a case report by Ayd,[21] who described a patient who died as a result of hyperthermia while using chlorpromazine. Since that time, several other reports have described heat stroke in patients using phenothiazine medication.[22-24]

Phenothiazines have combined anticholinergic and central thermoregulatory effects. They inhibit afferent neuronal input to the hypothalamus.[25,26] This inhibition decreases the hypothalamus's normal compensatory effect of increasing cutaneous blood flow to aid in heat dissipation. Heat elimination is therefore reduced, leading to systemic heat alteration.

Thioxanthenes are physiologically and structurally similar to the phenothiazines. Their effects on heat illnesses have not been studied well, but they may have similar effects due to their structural and physiologic similarities. Commonly used thioxanthenes include chlorprothixene and thiothixene.

Butyrophenones include haloperidol in the class. This class of antipsychotic medication blocks dopamine receptors and may mimic γ-aminobutyric acid and oppose the action of glutamic acid in areas of the extrapyramidal system. Some of the known side effects are dystonias and the development of parkinsonian type symptoms. Regarding heat illness, they have not been shown to induce heat stroke, but temperature dysregulation in animal models has been shown.[27]

Conclusion

Heat stroke may result from prolonged heat exposure without any compounding factors. However, certain classes of medication such as neuroleptics, sympathomimetics, and drugs with anticholinergic properties, may cause or worsen hyperthermia as a consequence of their pharmacologic effects. Heat exposure, in association with the use of many of these drugs, potentiates the risk of heat stroke. Physicians need to remain vigilant and aware of the side effects of the medications they prescribe. Proper patient education and prescription or dosing changes, especially during hot weather, may minimize the occurrence of heat stroke.

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Tables

Table. Data on Patients With Heat Stroke

Patient	Age and Sex	Body Temperature (C)	Peak Heat Index	Implicated Agents	Complication	Length of Stay (days)	Outcome
1	77 F	41.7	43.5	Thioridazine	Rhabdomyolysis, DIC	21	Died
2	40 M	41.9	43.5	Imipramine, thioridazine	Rhabdomyolysis, DIC	11	Discharged
3	49 M	42.3	41.1	Cocaine, diphenhydramine, caffeine, pseudoephedrine	Coma, pulmonary edema	6	Discharged
4	22 M	42.3	41.1	Cocaine	Rhabdomyolysis, renal failure	14	Discharged, dialysis
5	45 F	42.4	44.5	Cocaine, imipramine	Coma	3	Discharged
6	29 M	42.5	40.7	Unidentified	Rhabdomyolysis, DIC	1	Died
7	45 M	42.2	39.6	Cocaine	Rhabdomyolysis	7	Discharged
8	51 M	42.3	40.3	Haloperidol, diphenhydramine	Rhabdomyolysis	21	Discharged

DIC = Disseminated intravascular coagulation.

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Sidebar: Key Points

- The most common drug found was cocaine, followed by neuroleptics and diphenhydramine.
- The mean age of these victims was 45 years.
- Rhabdomyolysis developed in most patients (75%).
- Ambient humidity made effects worse than expected for the same temperature.