Drug-induced heat stroke

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Heat stroke, the most severe form of heat illness, has a high mortality rate in spite of aggressive therapy. A recognized phenomenon is iatrogenic heat stroke, usually reported in psychiatric patients who are taking medications that contribute to the development of hyperpyrexia.[1-15] We present a patient and review the pathophysiologic features, management and prognosis of heat stroke.

Case report

A 32-year-old man was admitted to hospital after he collapsed at an airshow where he was exposed to ambient temperatures reaching approximately 35°C and a relative humidity of approximately 38%. No other cases of heat stroke were reported in the area that day. He suffered from chronic schizophrenia and was taking maintenance doses of chlorpromazine, 400 mg daily, and benztropine mesylate, 2 mg daily. When admitted the patient was comatose and anhidrotic. His breathing was shallow and stridulous, blood pressure 100/80 mm Hg, pulse rate 160 beats/min and rectal temperature 42.9°C. There was no response to noxious stimuli. Tendon, plantar, pupillary, corneal and oculocephalic reflexes were absent.

An electrocardiogram showed sinus tachycardia, the rate being 160 beats/min. Chest and abdominal roentgenograms were normal. The hemoglobin concentration was 13.8 g/dl, but the other aspects of the hemogram were normal. The only blood abnormality was a serum creatinine level of 2.1 mg/dl (186 μmol/l) (normally 0.4 to 1.5 mg/dl [35 to 133 μmol/l]). Blood cultures subsequently showed no growth in aerobic or anaerobic media. Assays of the serum for lithium, barbiturates and ethanol had negative results. The urine contained phenothiazines but not myoglobin.

An endotracheal tube was inserted and mechanical ventilation begun. The patient aspirated the gastric contents during intubation and was immediately given 1 g of methylprednisolone intravenously. Cold soaks, fanning and icewater enemas were started, and the patient was placed on a cooling blanket. Physostigmine salicylate was given, 2 mg intravenously, and the patient was transferred to the intensive care unit, where peritoneal lavage with dialysate chilled to 26°C was carried out. The rectal temperature was 41.2°C before lavage and 38.5°C after lavage. The patient remained oliguric in spite of adequate fluid replacement. Two hours after admission, petechiae were seen on the face and in the axillae, and blood began to ooze from venipuncture sites. The platelet count was only 30 × 10^9/l. The prothrombin time was 28 (normally 10 to 12.5) seconds, and the partial thromboplastin time exceeded 150 (normally 25 to 35) seconds. After packed red blood cells, fresh frozen plasma, platelet concentrate and vitamin K were given intravenously the hemoglobin concentration was 10.3 g/dl, the platelet count 35 × 10^9/l and the plasma fibrinogen level less than 10 mg/dl (normally 150 to 400 mg/dl). The prothrombin time and the partial thromboplastin time both exceeded 150 seconds. The venous plasma lactate level was 19.9 (normally 0.5 to 2.2) mmol/l.

The patient became hypotensive, and the blood pressure did not respond to infusions of dopamine and dobutamine. The patient died 16 hours after admission.

Autopsy revealed uncal and cerebellar herniation, with pyknosis of small neurons in the cerebral cortex. The pericardial sac held 150 ml of serosanguineous fluid, and the heart showed numerous petechiae and ecchymoses. Both lungs were edematous, and there was about 400 ml of bloody fluid in each pleural cavity. The kidneys were pale and swollen, but sections showed no fibrin deposits.

Discussion

This patient fulfilled the three criteria required to diagnose heat stroke: hyperpyrexia (temperature greater than 41.1°C), hot, dry skin and severe central nervous system disturbance.[4,5,15-18] The medications he was taking likely precipitated this fatal illness. A therapeutic trial of the cholinergic agent physostigmine was given since it is recognized that anticholinergic poisoning can produce hyperpyrexia, respiratory failure, circulatory collapse and coma.[19,20]

The body normally loses heat by radiation, convection and conduction, mechanisms controlled by the anterior hypothalamus, which responds to increasing blood temperature by causing cutaneous vasodilation. However, when the temperature of the ambient air is more than 33°C body heat is lost mainly by sweating, which is also controlled by the hypothalamus and mediated through the cholinergic system. High humidity can interfere with this means of heat dissipation because it reduces the evaporation of sweat.[3] In an already stressful setting of hot, humid weather, disruption of thermoregulation by drugs can have devastating consequences.

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There are three major mechanisms by which drugs affect the control of body temperature (Table I). The first is disruption of hypothalamic thermoregulation, probably through interference with or depletion of dopamine (by chlorpromazine, for example); this would lead to poikilothermy. The second is blocking of sweat gland excretion through anticholinergic activity; a large group of medications, including chlorpromazine and benztropine mesylate, have this potential. The third is cutaneous vasoconstriction, as caused by sympathomimetic drugs. Although diuretics and β-blockers do not interfere with thermoregulation, they hamper the cardiovascular response to heat stress. Many cases of drug-induced heat stroke have been reported in the literature.[1-3,6-14] The true incidence of the condition is unknown but is likely higher than generally thought because of the large number of patients taking these medications.

Pathophysiologic features

Heat stroke is a life-threatening emergency that affects most organ systems. Characteristics of heat stroke are acute disturbances of the central nervous system, producing coma, delirium, convulsions, weakness, areflexia, ataxia and dysarthria. The cerebrospinal fluid is usually normal.[2,4,16,21-23] Although damage to the central nervous system is a universal finding in fatal cases of heat stroke, permanent sequelae are rare in survivors.[1,5,18,22,24]

Survival depends on an adequate cardiovascular response, which may be jeopardized by transient myocardial failure or infarction from increased metabolic demands or intramyocardial hemorrhage.[22,25] Hypotension is common.[1,5,10,21-23,26-31] Most patients have a hyperdynamic circulation, with low total peripheral vascular resistance and increased circulatory demand, possibly due to vasodilation following tissue damage.[25] High-output cardiac failure and hypodynamic cardiac states are uncommon.[5,15,25] Extensive endothelial cell damage may account for fulminant vascular collapse.[26]

Coagulation disturbances, with widespread petechiae and hemorrhage, are common.[1,5,10,16-18,21-23,31-34] Abnormal coagulograms are seen in 60% of patients.[17] Low platelet counts and diminished fibrinogen levels are typical.[1,18,21,32,33] These findings are best explained on the basis of a disseminated intravascular coagulopathy resulting from thermal damage to endothelial cells.[5,23,26,27,33,34]

Renal failure may result from hypotension, direct thermal injury or disseminated intravascular coagulopathy. Relative kidney hypoxia can occur from decreased cardiac output, shunting and increased metabolic demands. Renal failure can follow pigmenturia or hyperuricemia, especially in heat stroke induced by exertion.[5,30,35]

Severe dehydration and electrolyte disturbances are uncommon because of anhidrosis.[16] However, hypovolemia, hemoconcentration and a severe hyperoncotic state have been reported, and determination of the plasma oncotic pressure may aid in fluid replacement.[36] Metabolic acidosis is rare, but hyperuricemia may occur following catabolic states.[35]

The estimated mortality of heat stroke is 5% when diagnosis and treatment are optimal, but it may exceed 80%.[5,8,16,17,37] Studies in the United States suggest that there are at least 4000 heat-related deaths yearly.[16] Extremes of the Canadian climate may not allow acclimatization to heat to take place, thereby increasing the risk of hyperpyrexia.[38]

Management

The treatment of heat stroke consists of rapid cooling while supporting cardiovascular function. Immersion in an icebath is recommended, but this may be impractical, may cause hemolysis and can be dangerous in the elderly. It may slow heat dissipation by causing peripheral vasoconstriction.[2,3,5,15-17,25,27,35] A reasonable alternative, which can be started at the scene of collapse and continued during transport to hospital, is to cover the patient's body with towels that are packed with ice and are then repeatedly soaked with ice water. Once the patient is admitted to hospital cooling fans and a cooling blanket may be helpful. Ice water lavage of stomach and rectum can be done. We found that in our patient rapid cooling followed peritoneal lavage with chilled dialysate. Temperature monitoring must be accurate and free from local effects of the cooling solution.[3] Paradoxically, chlorpromazine has been given to prevent shivering during cooling.[14,15,23,39,40]

Patients must be admitted to the intensive care unit for constant observation and monitoring of temperature and cardiac activity. Intubation and ventilation may be required.[3] Arterial blood gas values should be corrected for temperature. Hypotension usually responds to cooling, as this decreases peripheral perfusion. Unresponsive hypotension is ominous.

Sympathomimetic drugs such as nonepinephrine should be avoided, as they impair heat dissipation by inducing peripheral vasoconstriction.[5,22,25] Dopamine use has not been reported in heat stroke. Lack of response in our case may have been due to overwhelming endothelial cell damage. Average fluid requirements are 1200 ml in the first 4 hours, so fluid replacement must be cautious.[3,5,15,17,25,27] Swan–Ganz hemodynamic monitoring may be useful. A coagulogram and a platelet count should be done at the time of admission to hospital, and coagulation derangements should be treated with infusion of fresh frozen plasma, platelets and factor concentrates.[39]

Table I—Drugs that interfere with thermoregulation

Centrally acting drugs (disrupt hypothalamic thermoregulation)
Phenothiazines
Butyrophenones
Drugs with anticholinergic activity (block sweat gland excretion)
Anticholinergics
Belladonna and synthetic alkaloids
Antiparkinsonian agents
Antipsychotics
Phenothiazines
Butyrophenones
Thioxanthines
Tricyclic antidepressants
Antihistamines
Sympathomimetics (cause cutaneous vasoconstriction)
Epinephrine
Ephedrine
Levarterenol

Prognosis

The prognosis for survival is poor if cooling is delayed. An initial temperature exceeding 41.1°C, deep

coma, acute renal failure, hypotension unresponsive to cooling and the presence of pre-existing disease also diminish chances of survival.[5,17,22,30] Severe elevations of serum levels of glutamic oxaloacetic transaminase, glutamic pyruvic transaminase and lactic dehydrogenase are associated with an unfavourable outcome.[5,41] A plasma level of venous lactate above 3.3 mmol/l signifies a poor outcome in nonexertional heat stroke.[42]

Conclusion

It is important for physicians to be aware of the potentially lethal combination of hot, humid weather and drugs that interfere with protective mechanisms of body heat loss. Persons taking psychotropic medications represent a large group of patients at risk, especially because some patients with chronic schizophrenia have a diminished perception of unusually hot weather.[8] All of these patients must be warned to avoid high ambient temperatures, especially those exceeding 30°C, although fatal drug-related heat stroke has been reported with lower temperatures.[1] If these patients have to go outdoors they should be discouraged from physical exertion. Light clothing and frequent cold drinks are recommended. Their families should be given this information and also taught to recognize the early signs of heat stroke, such as a sudden behavioural change accompanied by anhidrosis during hot weather. Medical attention should be sought immediately. Medic-Alert bracelets may be helpful should the patients be transported alone to hospital when comatose.

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