

# Drug-Induced Hyperthermic Syndromes

## Part I. Hyperthermia in Overdose

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### KEYWORDS

- Hyperthermia • Thermoregulatory system • Hypermetabolism • Sympathomimetics
- Cocaine • Methylenedioxymethamphetamine • Anticholinergics • Salicylates

### KEY POINTS

- Drugs and natural compounds that affect the thermoregulatory system can induce or contribute to hyperthermia when used in excess.
- Hyperthermia associated with drug overdose is dangerous and potentially lethal.
- Appropriate treatment strategies such as cooling and the administration of counteractive medications are discussed.

Emergency physicians frequently manage patients with drug overdoses. When the ingested drug induces reactions that cause hyperthermia, the diagnostic process and treatment become particularly challenging. Although the terms fever and hyperthermia are commonly used interchangeably, they are not equivalent. Fever is the normal physiologic response to an inflammatory pyrogen, and hyperthermia is an elevated core body temperature.

Drugs and toxins that affect the thermoregulatory system can cause or contribute to hyperthermia through one of two mechanisms: increased production of heat or impaired ability to dissipate heat. The body is sensitive to temperature changes. Severe or prolonged hyperthermia can result in disseminated intravascular coagulopathy (DIC), delirium, rhabdomyolysis, and death.<sup>1</sup> This article discusses sympathomimetics,

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anticholinergics, uncouplers of oxidative phosphorylation, hypermetabolism caused by levothyroxine, and overdoses that induce seizure.

## THE THERMOREGULATORY SYSTEM

Changes in thermoregulation are initiated in the brain and hypothalamus, and an expansive network of neurons feeds information back to the hypothalamus.<sup>2</sup> Heat-sensitive and cold-sensitive neurons are located in the hypothalamus, spinal cord, skin, vessels, and even viscera.<sup>3</sup> The human body's intrinsic core body temperature is typically maintained at 37°C (98.6°F), with a standard deviation of 0.4°C (0.8°F).<sup>4</sup> Core body temperature fluctuates in most people during a 24-hour period, and in women of child-bearing age depending on their point in the menstrual cycle.

The body's normal response to heat stress includes vasodilation in the skin in an attempt to dissipate heat. To increase blood flow to the skin, cardiac output must increase. Blood flow to the skin is increased by the diversion of cardiac output from the renal and splanchnic vessels.<sup>5</sup>

The anatomic physiology of thermoregulation is well understood, but the mechanism by which neurotransmitters assist with action potential propagation is not as clear. Neurotransmitters such as serotonin, acetylcholine, norepinephrine, dopamine, prostaglandins, and adrenocorticotropic hormone are all involved, but studies on the effects of individual neurotransmitters have not elucidated precise pathways. In the autonomic nervous system, for example, the postsynaptic neuron and the neurotransmitter that it secretes determine whether the neuron is part of the sympathetic or parasympathetic system. Norepinephrine is generally the sympathetic neurotransmitter and acetylcholine the parasympathetic neurotransmitter. One of the most notable exceptions to this rule is the sympathetic postganglionic neurons controlling the sweat glands that secrete acetylcholine,<sup>6</sup> which explains why a person perspires during a fight-or-flight (sympathetic or adrenergic) response. The perspiration dissipates the heat produced by increased motor movement and helps maintain temperature equilibrium.

Drugs and toxins that affect any part of this thermoregulatory system can cause or contribute to hyperthermia through one of two mechanisms: increased production of heat (eg, sympathomimetics) or impaired ability to dissipate heat (eg, anticholinergics). Heat can also be produced by uncouplers of oxidative phosphorylation, such as salicylates,<sup>7</sup> and drugs that induce a hypermetabolic state, such as levothyroxine.<sup>8</sup> A physical increase in musculoskeletal activity, as in psychomotor agitation<sup>9</sup> and seizures, can also increase heat production. Some of the most profound cases of hyperthermia are seen in syndromes and disease states that affect specific neuronal or metabolic pathways. For example, in malignant hyperthermia, a genetic disease, the defective ryanodine receptor<sup>10</sup> within the sarcoplasmic reticulum does not resequester intracellular calcium after the calcium-mediated actin-myosin filament contraction mechanism has been initiated.<sup>11</sup> This irregularity causes continued contractions of skeletal muscle, increased heat production, and severe hyperthermia, usually after the administration of succinylcholine and/or inhaled volatile anesthetics such as halothane or sevoflurane. Serotonin syndrome and neuroleptic malignant syndrome involve serotonergic and dopaminergic pathways, respectively, which lead to severe hyperthermia.<sup>12</sup>

## SYMPATHOMIMETICS

### *Mechanisms of Hyperthermia*

The adrenergic, or sympathetic, nervous system consists of neurons that secrete neurotransmitters that are agonists of  $\alpha$  and/or  $\beta$  receptors. The  $\alpha$  receptors are contained in the peripheral vasculature, typically inducing vasoconstriction when an agonist

binds with them. Presynaptic  $\alpha_2$  receptors mediate a negative feedback inhibition loop, but peripheral  $\alpha_2$  receptors still cause vasoconstriction.<sup>13</sup> The  $\beta$  receptors have subtypes  $\beta_1$ ,  $\beta_2$ , and  $\beta_3$ .<sup>14</sup> The  $\beta_1$  receptors are generally located within the myocardium along with some  $\beta_2$  receptors. The  $\beta_2$  receptors are contained mainly in peripheral vasculature as well as smooth muscle.  $\beta_3$  Receptors are contained within adipose.

Sympathomimetics are agonists at  $\alpha$  and/or  $\beta$  receptors, or mimic these effects on the adrenergic system. This discussion focuses primarily on drugs that are agonists, with peripheral mention of other drugs that mimic positive adrenergic stimulation. These agonist drugs can stimulate the receptor either directly or indirectly. Some sympathomimetics have a mix of direct and indirect effects (**Table 1**). The mechanism by which they cause hyperthermia is multifactorial and depends, at least in part, on the type of sympathomimetic as well as its behavioral/psychotropic effects. Direct-acting  $\alpha$ -receptor agents such as ergot alkaloids<sup>15</sup> cause hyperthermia through vasoconstriction and impaired cutaneous heat loss. Direct-acting  $\beta$ -specific agents such as albuterol typically do not cause hyperthermia, because they dilate the vessels. The indirect-acting and mixed agents have adrenergic effects and other effects related to behavioral response. Euphoria, psychomotor agitation, hallucinations, and blunted response to pain are seen with amphetamines,<sup>16</sup> cocaine,<sup>17</sup> phencyclidine,<sup>18</sup> methylenedioxymethamphetamine (MDMA),<sup>19</sup> and other amphetamine derivatives. The combination of adrenergic surge, response to external stimuli (hallucinations), and lack of pain perception can cause excessive psychomotor agitation, which leads to increased heat production and is often a contributing factor in the clinical presentation of these overdoses.

#### **Agents that Produce Sympathomimetic Toxicity**

Illicit sympathomimetic drugs can cause severe toxicity. Hyperthermia is one of the major effects that correlate with mortality. In a study from a medical examiner's office, Bohnert and colleagues<sup>20</sup> found that the number of deaths related to cocaine increased dramatically when the ambient temperature was higher than 24°C. The relationship between drug overdose and ambient temperature was most pronounced among cocaine users, suggesting a heightened deleterious effect of the sympathomimetic hyperthermic response when combined with elevated ambient temperature.

**Table 1**  
Sympathomimetics that cause hyperthermia

<b>Drug</b>	<b>Direct/Indirect/Mixed Sympathomimetic</b>
Amphetamines	Indirect
Caffeine	Mixed
Cocaine	Indirect
Ephedrine	Mixed
Ergot alkaloids	Direct $\alpha$
Midodrine	Direct $\alpha$
MDMA (Ecstasy)	Mixed
MDPV (bath salts)	Mixed
Phencyclidine	Indirect
Phenylephrine	Mixed
Phenylpropanolamine	Mixed
Pseudoephedrine	Mixed

*Abbreviations:* MDMA, methylenedioxymethamphetamine; MDPV, methylenedioxypyrovalerone.

Although no study has extrapolated this association to other sympathomimetics, the biological mechanism of the other drugs is similar. Classified as a prototypical indirect sympathomimetic, cocaine works via noncompetitive reuptake inhibition of biogenic amines, and causes profound hypertension, tachycardia, diaphoresis, and psychomotor agitation.<sup>17</sup>

MDMA, an amphetamine derivative, has serotonergic effects that induce tactile hallucinations.<sup>19</sup> Abusers of MDMA also experience hypertension and tachycardia, but usually not to the extremes that cocaine can induce. Secondary to its serotonergic effect, MDMA can cause syndrome of inappropriate antidiuretic hormone secretion (SIADH), leading to confusion, headaches, and even death if hyponatremia and the resulting cerebral edema are severe.<sup>21</sup> Many amphetamines and other sympathomimetics have serotonergic effects and thus have the potential to cause SIADH, but MDMA has a larger propensity to cause this imbalance. Methamphetamine, or "Ice," is known for its sympathomimetic effects and prolonged psychotropic effects that lead to psychosis. Prolonged use over several days, known as "tweaking," can lead to a prolonged psychotic presentation.<sup>22</sup>

New designer drugs such as "bath salts" have been implicated in many visits to emergency departments. The producers of "bath salts" use this marketing term on labeling to avoid legal prosecution, and some packaging states that the product is "not for human consumption."<sup>23</sup> Most "bath salts" contain a cathinone-derived molecule, such as methylenedioxypyrovalerone (MDPV) or mephedrone, which acts like an amphetamine. The drug can be insufflated, taken orally, injected, or smoked. It is easily accessible through "head shops" and the Internet. Hyperthermia, psychomotor agitation, psychosis, and death have been reported after use of such agents.<sup>23</sup>

### ***Clinical Presentation***

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The clinical presentation of sympathomimetic overdose is the adrenergic response of hypertension, tachycardia, psychomotor agitation, and subsequent hyperthermia. The hyperthermia is a consequence of impaired heat dissipation through  $\alpha$ -mediated vasoconstriction and increased heat production resulting from psychomotor agitation and impaired pain response. The sympathomimetic toxidrome also includes dilated but reactive pupils (unlike anticholinergic effects, which cause nonreactive dilated pupils). The patient can deteriorate to tremors, psychosis, and seizures. Death is attributable to hyperthermia, seizure, or end-organ damage caused by the hyperadrenergic stimulation.<sup>20</sup>

### ***Treatment***

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The cornerstone of the treatment of hyperthermia and the sympathomimetic toxidrome is the control of psychomotor agitation and adrenergic stimulation. Gaining control of the psychomotor agitation usually begins to normalize the hypertension, hyperthermia, and tachycardia. Medications that increase the central nervous system inhibitory tone, such as benzodiazepines, will calm the psychomotor agitation; these drugs must be titrated to the desired effect. The normalization of vital signs should be attempted first with a benzodiazepine. No single benzodiazepine has been found to be clinically more effective than another for a patient who is sympathomimetic; however, midazolam or diazepam will provide the desired pharmacokinetics, rapid onset, and ability to titrate to the clinical end point of controlling psychomotor agitation and normalizing vital signs.<sup>23</sup> In the specific case of sympathomimetic-induced myocardial infarction, cessation of chest pain should be another clinical end point.<sup>24</sup> If benzodiazepines and nitroglycerin fail, reversal of the vasoconstriction through the use of an  $\alpha$ -receptor antagonist such as phentolamine might be necessary.<sup>24</sup> In severe cases,

paralysis with a nondepolarizing agent such as vecuronium may be required to prevent further heat production and to control the psychomotor agitation. Care must be taken, because paralysis can mask seizure activity. Benzodiazepines should be given concurrently, as the patient might still be sympathomimetic and require further treatment despite being paralyzed.

Depending on the degree of hyperthermia and ability to control the agitation, if the initial treatment modalities are not effective, plans for passive and active cooling must be implemented. Hyperthermia can lead to permanent neuronal damage,<sup>25</sup> so the cooling process is time dependent. The placement of ice packs on the groin and axilla, and the use of cooling fans and misting are often attempted and are easy to perform, but are not typically effective. Because of more routine use of therapeutic induction of hypothermia following cardiac arrest,<sup>26</sup> many emergency departments now have access to other methods of actively cooling patients. Administration of cooled intravenous saline through a peripheral or central venous catheter is an easy and practical intervention. Cooling mattresses have become standard issue in the maintenance of therapeutic hypothermia.<sup>26</sup> A new device uses convection-immersion by rapidly circulating ice water from a perforated topsheet and an underblanket.<sup>27</sup> Complete submersion of the patient in a tub filled with chilled water and ice is highly effective though less practical. During the treatment of hyperthermia, clinical suspicion for occult trauma must be heightened because of its possible masking by agitation, behavioral changes, and impulsivity.

Nonsteroidal anti-inflammatory drugs (NSAIDs) and acetaminophen are not effective in managing toxin-induced hyperthermia, because sympathomimetic-induced hyperthermia is not prostaglandin mediated. Treatment options that should be avoided include medications that can further impair the thermoregulatory system. Agents used routinely to suppress agitation (eg, haloperidol and other antipsychotics) have anticholinergic effects, which can worsen hyperthermia.<sup>28</sup> In fact, haloperidol and many antipsychotics can independently induce another hyperthermic state known as neuroleptic malignant syndrome. Finally, the sympathomimetic effect is mediated through a mix of  $\alpha$ - and  $\beta$ -agonism. If a  $\beta$ -blocker is administered in an attempt to normalize hypertension and tachycardia, an unopposed  $\alpha$  effect could worsen vasoconstriction.<sup>29</sup> This response has been reported to worsen cardiac hemodynamic indices and to exacerbate the risk of myocardial infarction.<sup>30</sup>

In summary, the classic clinical presentation of a sympathomimetic overdose is the amplified sympathomimetic toxidrome. Hyperthermia and psychomotor agitation resulting from this type of overdose are treated with benzodiazepines, passive and active cooling, and paralysis if needed. Normalization of vital signs is the clinical end point. The combination of hyperthermia and a hyperadrenergic state can lead to end-organ damage, including intracerebral hemorrhage, myocardial infarction, rhabdomyolysis, DIC, and cerebrovascular ischemia. One must also be wary of occult trauma in these patients. A clinical challenge and toxicologic emergency, hyperthermia resulting from sympathomimetic overdose is a potentially lethal condition if not aggressively treated in the emergency department.

## ANTICHOLINERGICS

### *Mechanisms of Hyperthermia*

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Anticholinergic toxicity is commonly associated with hyperthermia. Anticholinergics cause hyperthermia primarily through impaired dissipation of heat from the body. Muscle activity can be increased, as seen during central muscarinic acetylcholine receptor blockade, and leads to restlessness, agitation, and seizures, all of which greatly

increase heat production. Peripheral blockade of acetylcholine-mediated muscarinic receptors in exocrine sweat glands produces anhidrosis and impaired heat dissipation. Antipyretic agents that function via prostaglandin suppression (eg, acetaminophen) are ineffective, because the hyperthermia is not a result of resetting the hypothalamic thermostat.

### ***Agents that Produce Anticholinergic Toxicity***

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Both pharmacologic and nonpharmacologic agents have anticholinergic properties (**Table 2**). Toxicity from naturally occurring anticholinergics has been reported since the advent of the written word. *Datura stramonium* was reportedly the drug that was consumed by Mark Anthony's troops in 38 AD as they were leaving Parthia. This ingestion caused the troops to become stuporous and confused, ultimately contributing to their defeat.<sup>31</sup> In more contemporary history, British soldiers attempting to suppress Bacon's Rebellion in 1676 in Jamestown, Virginia, inadvertently ate a salad containing *Datura* and "turned [into] natural fools" for 11 days.<sup>32</sup> "Jamestown weed," now referred to as jimson weed, remains a natural drug of abuse. Numerous other plants and mushrooms also have anticholinergic properties.

Multiple classes of pharmaceuticals possess anticholinergic properties. Antihistamines are a leading cause of anticholinergic toxicity. In 2010, the American Association of Poison Control Centers reported 69,291 single presentations attributable to antihistamines, with more than 28,000 being associated with diphenhydramine alone.<sup>33</sup> Other classes include antipsychotics, antiparkinsonian medications, anti-spasmodics, and ocular medications.

Cyclic antidepressants deserve special mention because of their intrinsic anticholinergic properties. Overdoses of these drugs can present with the classic anticholinergic syndrome. However, they also have fast sodium-channel-blocking properties that slow the propagation of depolarization across the myocardium, leading to widening of the QRS complex on the electrocardiogram. This effect has implications for the use of antidotal therapy for anticholinergic toxicity in these cases (see later discussion).

### ***Clinical Presentation***

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The clinical presentation of a patient with anticholinergic toxicity reflects the blockade of muscarinic and acetylcholine receptors both centrally and peripherally. Central blockade leads to agitation, confusion, hallucinations, delirium, and even seizures or coma. Peripheral manifestations include dilated pupils, dry, flushed skin, urinary retention, adynamic ileus, and dry mucous membranes. Vital-sign abnormalities may include tachycardia, mild hyperthermia, and hypertension. The hyperthermia is not typically of the magnitude of that induced by sympathomimetics. The mnemonic commonly used to remember the anticholinergic toxidrome is "mad as a hatter, hot as a hare, dry as a bone, red as a beet, blind as a bat, full as a flask."

The anticholinergic and sympathomimetic toxidromes have significant overlap, but important differences are found in the skin, gastrointestinal tract, and reactivity of the mydriatic pupils (typically unreactive in anticholinergic overdose but reactive in sympathomimetic overdose) (**Table 3**). Elderly patients and those with brain injury can present with more of the central manifestations and fewer of the peripheral manifestations, making the diagnosis more challenging in these groups, and emphasizing an enhanced index of suspicion.

### ***Treatment***

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The goals of treatment in anticholinergic toxicity are to restore hemodynamic stability, manage agitation, and prevent secondary injury such as rhabdomyolysis. Many

Table 2

Selected agents that can lead to anticholinergic toxicity

Antihistamines	Antiparkinsonian Agents	Antipsychotics	Ocular Agents	Antispasmodics	Plants	Mushrooms
Diphenhydramine	Benztropine	Phenothiazines	Homatropine	Oxybutynin	<i>Atropa belladonna</i> (deadly nightshade)	<i>Amanita muscaria</i>
Dimenhydrinate	Trihexyphenidyl	Butyrophenones	Cyclopentolate	Cyclobenzaprine	<i>Datura stramonium</i> (jimson weed)	<i>Amanita pantherina</i>
Hydroxyzine		Clozapine	Tropicamide	Dicyclomine	<i>Cestrum nocturnum</i> (angel's trumpet)	
Promethazine		Olanzapine			<i>Mandragora officinarum</i> (mandrake)	

<b>Organ System</b>	<b>Sympathomimetic</b>	<b>Anticholinergic</b>
Eyes	Dilated and reactive	Dilated and nonreactive
Oral mucosa	Moist	Dry
Lungs	Bronchodilator	Bronchodilator
Cardiovascular	Hypertension and tachycardia	Hypertension and tachycardia
Gastrointestinal	Bowel sounds unchanged	Decreased/absent bowel sounds
Genitourinary	Urination unchanged, occasional urinary retention	Urinary retention
Skin	Diaphoretic	Dry flushed skin
Neurologic	Euphoria, psychomotor agitation	Hallucinations

patients with anticholinergic toxicity can be managed with supportive care alone. Airway management may be needed, depending on the patient's mental status and sedation requirements. Gastric decontamination with activated charcoal can be considered, depending on the time since ingestion and the patient's mental status. As already noted, drug-induced hyperthermia does not respond to antipyretics, because it is caused by impaired heat dissipation rather than the resetting of the hypothalamic thermostat. Sedation should be accomplished with benzodiazepines. Aggressive management of agitation is recommended to prevent worsening hyperthermia and other sequelae such as trauma and rhabdomyolysis. Patients should be managed with cooling mists and ice packs over the major arteries after adequate sedation has been achieved. Although it may be tempting to administer an antipsychotic from the phenothiazine or butyrophenone class (eg, haloperidol) in combination with the benzodiazepine, these agents possess anticholinergic properties and can lower the seizure threshold.<sup>34</sup> In a patient with elevated body temperature and altered mental status, standard medical practice is to perform a lumbar puncture. If the patient has ingested an anticholinergic and the clinician can completely reverse the delirium, hallucination, and agitation, the lumbar puncture could reasonably be omitted, as confidence in a noninfectious cause has been bolstered.

Physostigmine is a reversible inhibitor of acetylcholinesterase, the enzyme that breaks down acetylcholine. The resultant increase in acetylcholine levels overcomes the effects of the anticholinergic drug at both nicotinic and muscarinic acetylcholine receptors. Physostigmine can be used as specific antidotal therapy in cases of anticholinergic toxicity. Routine use in all cases of anticholinergic toxicity is not recommended, because this drug has several potentially serious side effects. The use of physostigmine is typically reserved for treating severe agitation, tachycardia with hemodynamic instability, and severe hyperthermia with impaired sweating.<sup>35</sup>

The administration of physostigmine to a patient with an anticholinergic overdose can lead to bradycardia or heart block, especially in someone who is not anticholinergic; therefore cardiac monitoring is essential with the use of this drug. Atropine should be available at the bedside. An electrocardiogram should be obtained before administering physostigmine. Prolongation of the PR, QRS, or QTc interval precludes administration of this drug.<sup>36</sup> Physostigmine lowers the seizure threshold and may lead to status epilepticus. In addition, symptoms of cholinergic excess can occur with physostigmine treatment, especially in patients who are not anticholinergic or have ingested low doses of anticholinergic drugs. A cholinergic crisis is characterized



by increased secretions with possible airway compromise, nausea, vomiting, diarrhea, and bronchospasm. Seizures and bradycardia can occur when physostigmine is given rapidly or in excessive doses, although the link between rate of administration and seizures is mere speculation.<sup>36</sup>

The use of physostigmine in patients exhibiting anticholinergic toxicity from cyclic antidepressant overdose remains controversial. A well-publicized article from the 1980s described complications of physostigmine treatment in cyclic antidepressant overdose, which ultimately led to asystole and death.<sup>37</sup> These cases led to the virtual abandonment of the use of physostigmine in any patient suspected of cyclic antidepressant use. This blanket moratorium has come under some scrutiny in more recent studies. Burns and colleagues<sup>38</sup> studied patients who had ingested cyclic antidepressants and were treated with physostigmine unless changes on their electrocardiograms were evident (PR interval >200 milliseconds or QRS interval >100 milliseconds). No patients experienced significant cardiac side effects. The investigators concluded that physostigmine is safe in cyclic antidepressant overdose in patients with normal electrocardiograms. In a review article published in 2003, Suchard<sup>39</sup> hypothesized that patients without electrocardiographic changes may have less severe cyclic antidepressant toxicity, suggesting that Burns' findings might have been influenced by selection bias. Suchard proposed that in less severe cyclic antidepressant toxicity the anticholinergic effects predominate, so that physostigmine can be used safely, whereas in more severe poisonings the cardiotoxicity may be more pronounced than the anticholinergic toxicity, meaning physostigmine might be dangerous.<sup>39</sup>

Clinically, physostigmine is not the agent of choice for patients with cyclic antidepressant overdoses even if they have central anticholinergic symptoms. Management centers around treatment of the sodium-channel blockade and administration of sodium bicarbonate. The presentation of a patient with undifferentiated overdose and anticholinergic symptoms should prompt an immediate electrocardiogram to evaluate for sodium-channel-blocking effects of possible cyclic antidepressants. Classic electrocardiographic changes include a prominent R wave in lead AvR, an S wave in leads I and AvL, and a QRS interval duration of greater than 100 milliseconds. Physostigmine, when used, should be administered in doses of 0.5 to 2 mg intravenously, given slowly over 1 to 2 minutes while the patient is under continuous cardiac monitoring.

## **OTHER XENOBIOTICS AS A CAUSE OF HYPERTHERMIA**

### ***Uncouplers of Oxidative Phosphorylation***

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The electron-transport chain is located in the inner membrane of the mitochondria. This chain of cytochrome and enzyme complexes is vital for energy production during aerobic metabolism. Oxidative phosphorylation is accomplished by the electron-transport chain in a multistep process. The 2 central steps in this chain are the transfer of electrons from reduced coenzymes to oxygen (oxidation/reduction) and the formation of energy-rich adenosine triphosphate (ATP) from its precursor adenosine diphosphate (phosphorylation). These 2 components are coupled together to maximize energy production and efficiency.<sup>40</sup>

If a xenobiotic uncouples oxidative phosphorylation, cells quickly exhaust their accessible energy supplies because ATP is not being produced. During this time other metabolic processes continue. The uninhibited pumps still push protons into the intermembrane space while electrons continue their path down the electron-transport chain in an attempt to reduce oxygen. Uncoupling of oxidative phosphorylation significantly compromises the established proton gradient that is necessary for mitochondrial

function. When the electron-transport energy is uncoupled from ATP production it is released as heat, causing potentially harmful increases in body temperature.<sup>41</sup>

The most commonly used salicylate, aspirin (acetylsalicylic acid), has been in existence since the late 1800s. A myriad of available products containing salicylates are available in oral and topical formulations. Choosing (and using) a product is complicated by the various names and strengths available, and the similarity to acetaminophen with respect to dosing. Hyperthermia is just one of the many signs and symptoms associated with acute or chronic salicylate poisoning. Salicylate toxicity is characterized by hyperthermia, respiratory alkalosis, metabolic acidosis, tachypnea, altered mental status, and abdominal complaints. Mild hyperthermia is common,<sup>42-47</sup> and severe hyperthermia, with temperatures higher than 40°C (104°F), has been reported.<sup>48-50</sup> This particularly deadly toxidrome should be considered when hyperthermia is present. A review of the treatment of salicylate overdose is beyond the scope of this article.

Dinitrophenol was introduced in the 1930s as an agent for weight loss.<sup>51</sup> Its mechanism of action is to increase energy expenditure via uncoupling oxidative phosphorylation. Dieters reported weight loss of up to 2 lb (0.9 kg) per week.<sup>52</sup> The chemical is now used in herbicides, dyes, wood preservatives, and explosives, but people still experiment with its weight-loss properties.<sup>53-55</sup> The hyperthermia associated with this drug can be severe, with core body temperatures as high as 42°C (108°F).<sup>56-59</sup> The treatment of patients with salicylate or dinitrophenol poisoning should include aggressive cooling measures. Acetaminophen and other centrally acting antipyretics will not be effective, because the hyperthermia is a peripherally induced problem. Adjunctive therapy should include the administration of a benzodiazepine.

### **Thyroid Replacement Therapy**

Overt hypothyroidism is prevalent, occurring in up to 2% of the general population.<sup>60</sup> Subclinical hypothyroidism may be even more common. Consequently, thyroid replacement therapy is common. To appreciate the clinical course of a thyroid replacement therapy overdose, it is important to have a basic understanding of the prescribed hormones. Thyroid hormone exists in 2 active forms: T<sub>3</sub> and T<sub>4</sub>. Although the majority of circulating thyroid hormone is T<sub>4</sub> (~95%), T<sub>3</sub> is more biologically active. Once in the nucleus of the cell, most T<sub>4</sub> is deiodinated to T<sub>3</sub> by deiodinase enzymes.<sup>61</sup>

In the past, thyroid supplementation products were derived from porcine thyroid (Armour), which contained both T<sub>3</sub> and T<sub>4</sub>. These products lacked stability and posed an increased risk of allergic reaction. The predominant form prescribed today, levothyroxine (T<sub>4</sub>), is synthetically derived and much safer. Liothyronine (T<sub>3</sub>) and liotrix (T<sub>3</sub>/T<sub>4</sub>) are also available but are rarely used. Levothyroxine's half-life is about 6 to 7 days and that of liothyronine is more on the order of 1 or 2 days.

Identifying a thyroid replacement therapy overdose can be challenging because the presentation can mimic other clinical entities, such as sympathomimetic poisoning or sepsis, and develops generally over 7 to 10 days (but has been reported as early as 2 or 3 days) as free T<sub>4</sub> is converted to T<sub>3</sub>. Thyroid function tests, including measurement of the levels of thyroid-stimulating hormone (TSH), free T<sub>4</sub>, and T<sub>3</sub>, can facilitate the diagnosis. However, observed symptoms following ingestion of thyroid hormone do not correlate well with either the measured concentrations or the amount of levothyroxine ingested.<sup>62</sup>

Thyroid medications cause hyperthermia via the hormone's thermogenic effect, in addition to adrenergic stimulation and psychomotor agitation.<sup>8,63-68</sup> Hyperthermia can be extreme (>41°C or 106°F), but in an overdose setting will not emerge for more than 24 hours.<sup>69</sup> Treatment should involve the external cooling measures

previously described as well as the intravenous administration of  $\beta$ -blockers such as propranolol to blunt the adrenergic response. Sodium ipodate, where available, is another option that inhibits peripheral conversion of  $T_4$  to  $T_3$ , but its onset of action is 6 hours.<sup>67</sup> Seizures should be treated with benzodiazepines, which are also synergistic for reducing adrenergic stimulation and motor activity.

### **HYPERTHERMIA AS A RESULT OF TOXIN-INDUCED SEIZURES**

Through alterations in inhibitory and excitatory neurotransmission or direct neurotoxic mechanisms, many xenobiotic overdoses manifest as seizures. The increased muscle activity associated with generalized convulsive seizures can predispose patients to hyperthermia. Most of the drugs previously discussed (sympathomimetics, anticholinergics, salicylates, and thyroid replacement preparations) have the potential to induce seizures. It is beyond the scope of this article to list every drug that carries the potential to cause seizures, but it is important to discuss a few commonly used xenobiotics that lower the seizure threshold in overdose and have been associated with hyperthermia.

Caffeine and theophylline, both in the methylxanthine class, have the potential to induce severe seizures that are refractory to treatment.<sup>70–72</sup> Temperatures of 39.5°C (103°F) have resulted from caffeine ingestion.<sup>73</sup> Isoniazid, an antituberculosis agent, causes a functional deficiency of pyridoxine, a cofactor in the synthesis of  $\gamma$ -aminobutyric acid (GABA).<sup>74,75</sup> Strychnine, used as a pesticide, causes loss of glycine inhibition in the central nervous system and spinal cord.<sup>76–79</sup> Temperatures as high as 43°C (109°F) have been reported.<sup>80</sup> Not surprisingly, these medications all have a propensity to cause true convulsive status epilepticus and, thus, severe hyperthermia.

In general, benzodiazepines should be considered first-line therapy, followed by barbiturates, propofol, or other sedative hypnotics. Rapid and timely treatment is necessary to prevent further seizure and the subsequent hyperthermia. Medications with GABA-agonist activity help control seizure activity and thereby reduce heat production generated by muscle contraction. Phenytoin rarely has a role in the management of toxin-induced seizures. Specifically for isoniazid, pyridoxine should be administered immediately with a benzodiazepine. An empiric intravenous pyridoxine dose of 5 g is recommended if the quantity of isoniazid ingested is unknown.

### **SUMMARY**

Hyperthermia from drug overdose results from several mechanisms, including increased motor activity, decreased heat dissipation, and uncoupling of oxidative phosphorylation. Because sustained core body temperatures above 42°C (108°F) quickly lead to brain dysfunction, disseminated coagulopathy, rhabdomyolysis, and death, aggressive external and internal cooling measures are paramount. Although some xenobiotics have specific antidotes directed to halt the harmful processes, sedative agents with GABA-agonist activity serve as important adjuncts to promote cooling. Benzodiazepines are effective in almost all cases of toxin-induced hyperthermia, and should be used liberally.

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