Abstract
Exposure to pharmaceutical, occupational, or environmental toxins may cause or increase the risk of certain neurological emergencies. Early identification of the exposure and the toxin can be instrumental in the diagnosis and management of toxin-induced neurological emergencies. This chapter reviews the toxins associated with hyperthermic syndromes, ischemic and hemorrhagic stroke, seizures and status epilepticus, weakness, and acute encephalopathy.

Keywords
Amphetamine • Cocaine • Malignant hyperthermia • Neuroleptic malignant syndrome • Serotonin syndrome • Status epilepticus

Toxin-Induced Hyperthermic Syndromes

General Considerations
Regulation of body temperature is a balance between the production and dissipation of heat. Toxin-induced hyperthermia occurs when heat production is increased or the body’s ability to dissipate heat is impaired [1]. The complex process of thermoregulation is regulated by hypothalamic control of the sympathetic nervous system and by mitochondrial oxidative phosphorylation. Serotonin and sympathomimetic syndromes cause hyperthermia via heat generation from increased motor activity and uncoupling of oxidative phosphorylation as well as impaired dissipation from vasoconstriction of cutaneous blood vessels [1]. Anticholinergic syndrome causes hyperthermia by muscarinic inhibition, resulting in impaired sweating in the setting of severe agitation and hyperactivity. Severe salicylate toxicity results in hyperthermia via uncoupling of oxidative phosphorylation. Withdrawal of gamma-aminobutyric acid (GABA) agonists, including ethanol, benzodiazepines, barbiturates, baclofen, and gamma-hydroxybutyrate (GHB), can cause hyperthermia via autonomic overstimulation.
Serotonin Syndrome

Introduction

The serotonin syndrome was first defined by Sternbach in 1991 [2], although the clinical manifestations of the syndrome were described in patients taking monoamine oxidase inhibitors (MAOIs) and tryptophan in 1960 [3]. It is typically characterized by mental status changes, autonomic instability, and motor hyperactivity. The practitioner must have a high level of suspicion for this diagnosis, as the altered mental status often precludes a reliable history and many patients present without one or more of the cardinal findings [2]. In addition, symptoms of mild or early serotonin syndrome such as diarrhea, tremor, and irritability may be overlooked, and thus the causative medications may not be discontinued. The severe complications of serotonin syndrome include seizures, rhabdomyolysis, respiratory failure, and cardiac arrhythmia.

Epidemiology

Serotonin syndrome occurs most often when two or more proserotonergic medications are used in combination [2, 4]. It is difficult to determine the true incidence of this syndrome, as the majority of cases remain unrecognized [5]. Symptoms of moderate-to-severe toxicity occur in 17% of patients who overdose on selective serotonin reuptake inhibitors (SSRIs), and death occurs in 0.2% [6]. In a survey of consecutive admissions to an inpatient toxicology unit, serotonin syndrome occurred in 14% of patients with overdose of a single SSRI [7]. In patients taking nefazodone, the incidence of two or more symptoms of serotonin syndrome is 0.4 cases per 1,000 treatment-months [5]. A large number of pharmaceuticals have been reported in association with serotonin syndrome. The major drug categories implicated are SSRIs, MAOIs, tricyclic antidepressants (TCAs), antibiotics, opioid analgesics, antiemetics, migraine abortives, drugs of abuse, and herbal supplements (Table 18.1).

Pathophysiology

Serotonin, or 5-hydroxytryptamine (5-HT), is synthesized by hydroxylation and decarboxylation of L-tryptophan. After vesicular release from neurons, serotonin is removed from the synapse by the serotonin reuptake transporter. The first step in serotonin metabolism is deamination, preferentially performed by monoamine oxidase type A, to 5-hydroxyindoleacetic acid (5-HIAA). There are seven subgroups of serotonin receptors, and serotonin syndrome is likely a combination of effects at several of these individual receptor types. However, activity of 5-HT2A receptors appears to be integral to the development of serotonin syndrome [8–12].

Serotonin syndrome is characterized by hyperactivity of both central and peripheral serotonergic neurons. In the central nervous system, serotonergic neurons are located mainly in the midline raphe nuclei of the brainstem [13]. These structures are involved in thermoregulation, wakefulness, muscle tone, and chemoreceptor-mediated emesis. Serotonergic receptors are abundant in the peripheral nervous system, and are responsible for gastrointestinal motility and vascular smooth muscle tone [14]. The function of serotonergic neurons in the central and peripheral nervous systems correlates directly with the clinical features of serotonin syndrome: cognitive dysfunction, autonomic instability (hyperthermia, hypertension, diarrhea), and motor hyperactivity.

The possible mechanisms of increased serotonergic activity are (1) increased serotonin synthesis, (2) increased serotonin release, (3) direct serotonin receptor agonism, (4) inhibition of serotonin reuptake, and (5) decreased serotonin metabolism. There are xenobiotics that may cause serotonin syndrome by each of these mechanisms. Tryptophan supplementation results in increased serotonin synthesis. Amphetamines and cocaine cause increased serotonin release. Sumatriptan, buspirone, and lysergic acid diethylamide are all serotonin receptor agonists. The SSRIs and TCAs inhibit serotonin reuptake, and the MAOIs decrease serotonin metabolism. Serotonin syndrome is caused by an acute increase in intrasynaptic serotonin, and is a drug reaction for which all patients are at risk [15].

Clinical Features/Diagnosis

The original diagnostic criteria proposed by Sternbach [2] require the addition or titration of a serotonergic agent, without a recent addition or
titration of a neuroleptic, and three of the following clinical findings: altered mental status, agitation, myoclonus, hyperreflexia, diaphoresis, shivering, tremor, diarrhea, incoordination, and fever. Other possible etiologies, including infection and withdrawal, must be excluded.

In 2003, the Hunter Serotonin Toxicity Criteria were published in a comparison study to the Sternbach criteria in a retrospective analysis of prospectively collected data. The Hunter criteria allow the diagnosis of serotonin syndrome with the administration of a serotonergic agent within the past 5 weeks and any one of the following scenarios: (1) spontaneous clonus, (2) inducible clonus and agitation or diaphoresis, (3) ocular clonus and agitation or diaphoresis, (4) tremor and hyperreflexia, and (5) muscle rigidity and hyperthermia (>38°C) and either ocular or inducible clonus. The Hunter criteria were more sensitive (84% vs. 75%) and slightly more specific (97% vs. 96%) than the Sternbach criteria [16]. Symptoms of motor hyperactivity, manifested by spontaneous, inducible, or ocular clonus, are the hallmark of serotonin toxicity [2, 3, 15, 17, 18]. Mydriasis occurs in more than 30% and tachycardia in 40% of patients with serotonin syndrome [16].

### Table 18.1 Serotonergic xenobiotics

<table>
<thead>
<tr>
<th>Category</th>
<th>Drugs</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Selective serotonin reuptake inhibitors</td>
<td>Citalopram, Fluoxetine, Fluvoxamine, Paroxetine, Sertraline</td>
<td>Serotonin reuptake inhibitors</td>
</tr>
<tr>
<td>Tricyclic antidepressants</td>
<td>Amitriptyline, Clomipramine, Desipramine, Doxepin, Imipramine, Nortriptyline</td>
<td>Serotonin reuptake inhibitors</td>
</tr>
<tr>
<td>Monoamine oxidase inhibitors</td>
<td>Isocarboxazid, Moclobemide, Phenelzine, Selegiline, Tranlylcypromine</td>
<td>Decreased serotonin metabolism</td>
</tr>
<tr>
<td>Other antidepressants/anxiolytics</td>
<td>Buspirone, Trazodone, Venlafaxine</td>
<td>Serotonin receptor agonist</td>
</tr>
<tr>
<td>Analgesics</td>
<td>Meperidine, Pentazocine, Tramadol</td>
<td>Serotonin reuptake inhibitors</td>
</tr>
<tr>
<td>Antimigraine medications</td>
<td>Sumatriptan, Other triptans</td>
<td>Serotonin receptor agonists</td>
</tr>
<tr>
<td>Antimicrobials</td>
<td>Linezolid, Ritonavir</td>
<td>MAO inhibitor</td>
</tr>
<tr>
<td>Supplements and over-the-counter drugs</td>
<td>Dextromethorphan, l-tryptophan, MDMA</td>
<td>Serotonin reuptake inhibitor, Increased serotonin synthesis</td>
</tr>
<tr>
<td>Drugs of abuse</td>
<td>Amphetamines, Cocaine, MDMA</td>
<td>Increased serotonin release</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>Fenfluramine, Reserpine, Bromocriptine, L-dopa, Lithium</td>
<td>Increased serotonin release, Nonspecific increase in serotonin activity</td>
</tr>
</tbody>
</table>

MDMA 3,4-methylenedioxymethamphetamine, LSD lysergic acid diethylamide.
Serotonin syndrome represents a spectrum of symptoms (Fig. 18.1) and usually develops and progresses over a few hours. Individual patients with serotonin toxicity might not meet the Hunter or Sternbach criteria for diagnosis. This is most likely to occur early in the course prior to the onset of more severe symptoms [19], or late in the course when muscle rigidity has become severe enough to prevent tremor or clonus [16]. Patients with life-threatening serotonin toxicity are more likely to have muscle rigidity and hyperthermia, and may require intubation if the rigidity causes respiratory compromise [16].

**Differential Diagnosis**

Neuroleptic malignant syndrome, malignant hyperthermia, sympathomimetic syndrome, anticholinergic syndrome, strychnine toxicity, tetanus, and salicylate toxicity are alternate toxicologic diagnoses to consider. Meningoencephalitis, stiff-person syndrome, nonconvulsive status epilepticus, hyperthyroidism, and sepsis also bear consideration in the differential diagnosis.

The symptom onset and progression of neuroleptic malignant syndrome is slower, occurring over days to weeks instead of hours. In addition, neuroleptic malignant syndrome is a hypokinetic syndrome characterized by bradykinesia and rigidity, whereas mild or moderate serotonin syndrome is a hyperkinetic syndrome. The rigidity of severe serotonin syndrome is usually much more prominent in the lower extremities than in the upper extremities [20].

Serotonin syndrome, neuroleptic malignant syndrome, and malignant hyperthermia are all hyperthermic syndromes, but the causative medications are vastly different. A comprehensive history regarding recent changes in medications will typically favor one diagnosis over another. Because of the medications involved in malignant hyperthermia, this syndrome is very unlikely to occur outside of the operating room. There is, unfortunately, no laboratory test that will accurately distinguish between serotonin syndrome and neuroleptic malignant syndrome. There may be differences in the levels of neurotransmitter metabolites in cerebrospinal fluid [21, 22]; however, the results of these specialty labs may not be available in time to be clinically helpful.

Anticholinergic and sympathomimetic syndromes are both associated with agitation, mydriasis, tachycardia, hypertension, and tremor. In contrast to serotonin syndrome, anticholinergic syndrome is characterized by absent bowel sounds, dry skin, and normal reflexes. Those with sympathomimetic syndrome will exhibit excessive neuromuscular activity that can be difficult
to differentiate from the tremor and clonus of serotonin syndrome. The key to the diagnosis rests in the history, although a reliable history is not always available. Fortunately, the mainstay of treatment for all of these syndromes is cooling, benzodiazepines for agitation and increased muscle activity, intravenous fluids, and supportive care.

**Treatment**
The first steps in management of serotonin syndrome are removal of the causative agents and provision of supportive care. Many cases of serotonin syndrome will resolve within 24 h of treatment initiation. In patients with mild symptoms (tremor and agitation without fever or autonomic instability), intravenous fluids and benzodiazepines may be adequate. However, any clinical deterioration should prompt a rapid, aggressive response [15, 16].

The etiology of hyperthermia in serotonin syndrome is severe, excessive muscle activity; thus, antipyretics may not be effective in its management. Benzodiazepines are useful in decreasing muscle activity and attenuating the hyperadrenergic response [15], but benzodiazepines and external cooling alone may not be effective in treating the rigidity and hyperthermia of severe serotonin syndrome. Paralysis with nondepolarizing agents, immediately followed by orotracheal intubation and mechanical ventilation, should be considered for patients with hyperthermia (temperature >38.5°C), severe truncal rigidity, or a rising pCO₂ [4, 15, 16].

Cyproheptadine, an antihistamine with nonselective antiserotonergic effects, may be considered in patients with moderate or severe symptoms. It has been shown to prevent serotonin syndrome in animal models [23, 24]. Human case series detail improvement in symptoms after administration of cyproheptadine [15, 25–27]. The recommended dosing of cyproheptadine is an initial dose of 12 mg, followed by 2 mg every 2 h until symptoms improve. Maintenance dosing is 8 mg every 6 h [4]. Cyproheptadine is available in pill form only, but it may be crushed and administered via a nasogastric tube. Resolution of mydriasis after cyproheptadine administration has been reported [26]. While this finding has not been validated as a diagnostic tool, it may support the diagnosis of serotonin toxicity.

Chlorpromazine is a phenothiazine antipsychotic that has antiserotonergic properties. It has also been reported as an effective symptomatic therapy for serotonin syndrome. This medication is not routinely recommended because serotonin syndrome is often difficult to distinguish from neuroleptic malignant syndrome, and chlorpromazine may worsen neuroleptic malignant syndrome. It may also cause hypotension, as well as increasing the risk of seizures and dystonic reactions [20]. However, if the diagnosis is certain and a parenteral treatment is desired, chlorpromazine 50–100 mg may be given intramuscularly [4].

Serotonin syndrome can be life-threatening and is underrecognized. A high level of clinical suspicion will lead to accurate diagnosis, and appropriate treatment can prevent significant morbidity and mortality.

**Neuroleptic Malignant Syndrome**

**Introduction**
Neuroleptic malignant syndrome is an idiosyncratic drug reaction to dopamine antagonists that was first reported in 1960 [28]. It is characterized by hyperthermia, diffuse rigidity, autonomic instability, and encephalopathy. Many patients who are prescribed neuroleptics are also prescribed antidepressants, so neuroleptic malignant syndrome and serotonin syndrome must be considered simultaneously. The severe, life-threatening complications of neuroleptic malignant syndrome include rhabdomyolysis, acute renal failure, and respiratory failure. Appropriate, prompt consideration of medication effect as a cause of encephalopathy and hyperthermia is critical to avoid these potential complications.

**Epidemiology**
The reported incidence of neuroleptic malignant syndrome with therapeutic use of neuroleptics ranges from 0.02 to 2.4% [29–34]. It is most
common with typical neuroleptics, but has been reported with the atypical neuroleptics and antiemetics as well [30, 35]. The mortality rate is around 10% [29, 31]. Risk factors for development of neuroleptic malignant syndrome with therapeutic doses of neuroleptics are young age [31], use of the depot formulation of fluphenazine [33], intramuscular administration [36], presence of mental retardation [37], higher dose of neuroleptic [37], psychomotor agitation [37–39], and dehydration [39]. In a retrospective review of the California Poison Center database, the incidence of neuroleptic malignant syndrome in acute overdose was 1.2% for typical neuroleptics and 0.3% for atypical neuroleptics [40].

Pathophysiology
The exact pathophysiology of neuroleptic malignant syndrome is not yet clear; however, dopamine blockade likely plays a central role in the generation of neuroleptic malignant syndrome. Of the drugs known to cause neuroleptic malignant syndrome, dopamine blockade is the common mechanism of action. The cerebrospinal fluid of patients with neuroleptic malignant syndrome has lower concentration of the dopamine metabolite homovanillic acid than controls [41]. In addition, withdrawal of dopaminergic medications can produce a syndrome similar to neuroleptic malignant syndrome [42, 43], and dopaminergic drugs are useful in the treatment of neuroleptic malignant syndrome. Elevation of catecholamines in the plasma and urine [44], as well as the cerebrospinal fluid [41], suggests that the autonomic dysfunction of neuroleptic malignant syndrome is related to sympathoadrenal hyperactivity [45].

Clinical Features/Diagnosis
The diagnosis of neuroleptic malignant syndrome should be entertained for hyperthermia or rigidity in the setting of neuroleptic therapy or recent withdrawal of dopaminergic medications. Levenson’s criteria allow for diagnosis of neuroleptic malignant syndrome in the presence of all three major criteria: fever, rigidity, and elevated serum creatine phosphokinase (CPK). If only two of the major criteria are present, the diagnosis may be made in the presence of four of the minor criteria: tachycardia, abnormal blood pressure, tachypnea, altered consciousness, diaphoresis, and leukocytosis [46].

The onset of neuroleptic malignant syndrome is usually insidious and occurs over days, although acute onset within hours of neuroleptic administration does occur [47]. Nearly all cases of neuroleptic malignant syndrome occur within 1 month of neuroleptic initiation. With supportive care and discontinuation of the offending agent, average recovery time is 7–10 days [47]. A rating scale has been proposed for following the clinical course of neuroleptic malignant syndrome [48]. It is based upon severity of hyperthermia, extrapyramidal symptoms, autonomic instability, altered consciousness, leukocytosis, and CPK elevation. This rating scale may be used to objectively determine severity over time.

Differential Diagnosis
Because neuroleptic malignant syndrome is an idiosyncratic adverse drug reaction, it remains a diagnosis of exclusion. Some laboratory findings (leukocytosis and elevation of CPK) can be supportive; however, no single laboratory abnormality can secure the diagnosis. Therefore, a complete diagnostic evaluation should be performed, including electrolyte panel with calcium and magnesium, renal and hepatic function tests, creatine kinase level, complete blood count, urinalysis, lumbar puncture, and neuroimaging of the brain [49].

The differential diagnosis for neuroleptic malignant syndrome is similar to that of serotonin syndrome and includes malignant hyperthermia, central nervous system infection, anticholinergic delirium, nonconvulsive status epilepticus, salicylate poisoning, baclofen withdrawal, thyrotoxicosis, and heat stroke [49, 50].

Treatment
Stabilization of vital signs and removal of the offending agent(s) are the primary steps in management of neuroleptic malignant syndrome. Severe hyperthermia has been associated with poorer outcome [51], so prompt institution of cooling measures is indicated. Aggressive volume resuscitation and repletion of electrolytes are important, as dehydration is a common presenting feature of neuroleptic malignant syndrome.
Complications of neuroleptic malignant syndrome include aspiration pneumonia, respiratory failure, rhabdomyolysis with subsequent renal failure, and coagulopathy [44, 50]. Patients should be carefully monitored for these complications in an intensive care setting.

Supportive care measures may be sufficient treatment in milder cases of neuroleptic malignant syndrome; however, in more severe cases, pharmacological treatment may be indicated. Although the efficacy of benzodiazepines is modest [52], they are indicated as first-line therapy for agitation and may be effective in treating mild neuroleptic malignant syndrome. A parenteral dose of lorazepam at 1–2 mg is a reasonable initial treatment [50].

Dantrolene is a peripheral muscle relaxant that attenuates calcium release at the sarcoplasmic reticulum of skeletal muscle via inhibition of the ryanodine receptor [53]. Neuroleptic malignant syndrome-related hyperthermia is partially due to the heat produced by muscular rigidity. This tonic, diffuse contraction may also cause rhabdomyolysis. Dantrolene should be considered in patients with severe rigidity and hyperthermia. An initial dose of intravenous dantrolene 1–2.5 mg/kg of body weight should be administered, followed by 1 mg/kg every 6 h. Tapering or transition to oral dantrolene may be made after 48–72 h, although symptoms may return if this change is made prematurely [50, 53]. Dantrolene has been associated with drug-induced hepatitis, so hepatic function should be monitored during treatment [49, 50]. Dopamine agonists and benzodiazepines may be given in combination with dantrolene, but dantrolene should not be given with calcium channel antagonists because of risk of cardiovascular collapse [50].

In addition to the heat produced by rigidity, the hyperthermia of neuroleptic malignant syndrome may also be related to dopamine blockade in the anterior hypothalamus, resulting in inhibition of heat-loss pathways [53]. Dopamine agonists have been associated with reduced time to recovery [54] and mortality rates [55]. First-line dopamine agonist therapy is bromocriptine 2.5 mg orally 2–3 times daily or oral amantadine 200–400 mg/day in divided doses [50]. Both of these medications may be given by nasogastric tube if necessary. Bromocriptine may worsen underlying psychosis and may cause hypotension. If a parenteral agent is necessary, l-dopa can be given intravenously at 50–100 mg/day in divided doses [56]. l-Dopa [57], bromocriptine [58], and amantadine [59] have all been reported to increase central serotonergic activity, so they should be avoided if serotonin syndrome remains in the differential diagnosis.

Severe neuroleptic malignant syndrome that is refractory to dantrolene and dopamine agonists may respond to electroconvulsive therapy (ECT) [60, 61]. ECT may also be effective for the underlying condition for which the neuroleptic was prescribed. It is a reasonable treatment choice for neuroleptic malignant syndrome if idopathic malignant catatonia is a possible alternative diagnosis [50].

Acute withdrawal of dopamine replacement therapy may cause a neuroleptic malignant-like syndrome. Symptom onset usually occurs 3–4 days after discontinuation of dopaminergic medications, and is usually characterized by worsening of baseline rigidity followed by hyperthermia and altered consciousness [42]. Treatment of neuroleptic malignant-like syndrome is discontinuation of any medications with dopamine blocking activity, and reinstitution of l-dopa therapy [42, 43].

**Malignant Hyperthermia**

**Introduction**

Malignant hyperthermia is a rare, autosomal dominant pharmacogenetic disorder of calcium regulation in striated muscle that was first described in the 1960s [62]. It manifests as a hypermetabolic response to inhaled volatile anesthetics and the depolarizing muscle relaxant succinylcholine. Increased carbon dioxide (CO₂) production, hyperthermia, tachycardia, tachypnea, muscle rigidity, and rhabdomyolysis are the classic characteristics of malignant hyperthermia. Complications of malignant hyperthermia include hyperkalemia-induced arrhythmias, compartment syndrome, congestive heart failure, bowel ischemia, disseminated intravascular coagulation, rhabdomyolysis-induced renal failure, and death. Prompt recognition of the early signs of malignant
hyperthermia, which are an increase in end-tidal carbon dioxide, tachycardia, and rigidity, is critical [63].

**Epidemiology**

Estimates of malignant hyperthermia susceptibility range from 1 in 200 to 1 in 250,000 [64, 65], depending upon geographical location and prevalence of malignant hyperthermia susceptibility genes. In the state of New York, the prevalence rate of malignant hyperthermia is 1 in 100,000 surgeries [66]. The risk for developing malignant hyperthermia is higher in males than in females [63, 66]. A successful anesthesia with agents known to trigger malignant hyperthermia does not exclude the possibility of malignant hyperthermia during future anesthetics [63].

**Pathophysiology**

The clinical effects of malignant hyperthermia are secondary to uncontrolled calcium release from the sarcoplasmic reticulum, resulting in sustained muscle contraction [67]. Anaerobic metabolism is increased, resulting in hypoxia and acidosis. This is followed by rhabdomyolysis, which may produce hyperkalemia and acute renal failure. Uncoupling of oxidative phosphorylation produces heat, manifested as hyperthermia.

Malignant hyperthermia is associated with abnormalities in both the ryanodine (RYR1) and dihydropyridine (DHP) calcium channels, and is inherited as an autosomal dominant disease [67, 68]. Most people with a genetic susceptibility to malignant hyperthermia do not exhibit signs of myopathy; however, there are a few genetic myopathies that are linked to malignant hyperthermia. These include central core and multiminicore myopathies, as well as King-Denborough syndrome and Brody myopathy [68, 69]. While not true malignant hyperthermia, inhalational anesthetics and succinylcholine may produce severe hyperkalemia and rhabdomyolysis in patients with Duchenne and Becker muscular dystrophies [68].

**Clinical Features/Diagnosis**

The initial sign of malignant hyperthermia is an unexplained rise in end-tidal \( \text{CO}_2 \) during a general anesthetic procedure that involves a triggering agent [67]. This is followed by tachycardia, hypertension, generalized muscle rigidity or masseter spasm, metabolic acidosis, and hyperthermia. Given the causative agents associated with malignant hyperthermia, the diagnosis will nearly always be made in the operating room or post-anesthesia recovery room. Those patients with symptoms consistent with malignant hyperthermia should be referred to specialized centers for consideration of genetic and in vitro contracture testing (IVCT) to confirm their malignant hyperthermia susceptibility [63].

**Differential Diagnosis**

Sepsis, thyrotoxicosis, and iatrogenic overheating may resemble malignant hyperthermia during anesthesia. The measurement of end-tidal \( \text{CO}_2 \) is helpful in distinguishing malignant hyperthermia from these disorders [63].

**Treatment**

Discontinuation of the etiologic agent should be followed immediately by hyperventilation with 100% oxygen, administration of dantrolene, external cooling measures, and treatment of hyperkalemia. Dantrolene sodium is an inhibitor of intracellular calcium release, and is an effective antidote for malignant hyperthermia [1, 53, 63, 67]. Dosing of the dantrolene is 2.5 mg/kg as a bolus intravenous dose, repeated at 5–15-min intervals as needed to a suggested maximum dose of 10 mg/kg. Maintenance dosing at 1 mg/kg intravenously every 4–6 h should be continued for 24–72 h postoperatively [1, 53, 63]. Potential side effects of dantrolene include weakness and respiratory failure, dizziness, gastrointestinal discomfort, and hepatic toxicity [53]. Electrolyte, creatinine, transaminase, and CK levels, as well as coagulation profiles, should be followed regularly. Arrhythmias and hypertension should be treated as indicated, with careful avoidance of calcium channel antagonists [63].

---

**Toxin-Induced Cerebrovascular Events**

**General Considerations**

Toxin-induced stroke is uncommon; however, abuse of recreational drugs has become a risk
factor for stroke in adolescents and young adults [70]. In addition, environmental toxins and pharmaceutical agents may contribute to cerebrovascular events. Toxic mechanisms of stroke include (1) sympathomimetic vasoconstriction (cocaine, amphetamines, lysergic acid diethylamide, phenocyline), (2) hypoxia (opioids and carbon monoxide), (3) cardioembolism (drug-induced cardiomyopathy and endocarditis), (4) vasculitis (amphetamines, cocaine, heroin), (5) enhancement of coagulation (cocaine), and (6) venous sinus thrombosis (asparaginase). In addition, there are an ever-increasing number of immunosuppressant and chemotherapeutic agents that can cause posterior reversible encephalopathy syndrome. Severe cases can result in cerebral infarction. Toxic mechanisms of hemorrhagic stroke include (1) hypertension-induced arterial rupture with or without underlying vascular malformation (cocaine, amphetamines, and phenocyline), (2) vasculitis (amphetamines, cocaine, heroin), (3) rupture of septic aneurysm (any intravenous drug use), and (4) coagulopathy (snake venom).

**Cocaine**

**Introduction**

Cocaine, or benzoylmethylecgonine, is a weak base that is extracted from the leaves of the *Erythroxylon coca* plant. It is treated with acid to form the water-soluble salt, cocaine hydrochloride. The cocaine is then ground into a fine powder, and may be mixed with diluents that contribute bulk (talc, sugar) or mimic the effect of cocaine (lidocaine, procaine, caffeine) [71]. The hydrochloride form of cocaine may be injected, insufflated, or applied directly to oral mucous membranes. The high melting point precludes smoking of cocaine hydrochloride. The alkaloid forms of cocaine (freebase and crack) are prepared from the hydrochloride form. Although extracted by different methods, freebase and crack cocaine are the same chemical compound. Because of a lower melting point, both can be smoked [71].

Cocaine has a half-life of 30–90 min. Peak concentrations occur at 30–60 min with nasal insufflation of cocaine hydrochloride [72], and at 2–5 min with smoking of crack cocaine [73]. The major metabolites of cocaine (ecgonine methyl ester and benzoylecgonine) are pharmacologically inactive. Norcocaine, a minor metabolite produced in the liver, has pharmacologic activity similar to cocaine [71, 74]. Cocaethylene is an active cocaine metabolite that is produced in the presence of ethanol. It prolongs the clinical effect of cocaine, and accounts for the frequent simultaneous ingestion of cocaine and alcohol [75].

**Epidemiology**

Stroke was first reported in association with cocaine use in 1977 [76]. As abuse of stimulants has increased, so has the awareness of cocaine-induced stroke. Cocaine abuse is associated with both hemorrhagic and ischemic stroke [77]. In young adults (aged 15–44 years) with ischemic stroke, 12.1% had a history of recent illicit drug use. In 4.7%, drug use was the probable cause of stroke [78]. In a case–control study of young adults (aged 15–44 years), those admitted for stroke were more likely to abuse drugs than those admitted for other reasons (34% vs. 8%). The risk of stroke in drug abusers was 6.5 times higher than controls. In 22% of stroke patients, drug use was the probable cause of stroke. The drug most frequently used by these patients was cocaine [70].

**Pathophysiology**

Cocaine is a potent sympathomimetic and causes vasoconstriction via inhibition of presynaptic reuptake of norepinephrine, serotonin, and dopamine. Vasoconstriction has been observed by magnetic resonance angiography after cocaine administration and appears to occur in a dose-dependent fashion [79]. Cocaine also promotes vasoconstriction by increasing intracellular calcium release in smooth muscle cells by direct action on calcium channels, an effect that appears to be independent of cocaine’s adrenergic effects [80, 81]. Blockade of fast sodium channels produces the local anesthetic effect of cocaine, and is the mechanism by which cocaine causes cardiac dysrythmias and seizures [82].

The proposed mechanisms by which cocaine produces ischemic stroke include vasospasm,
enhanced platelet aggregation, vasculitis, and cardioembolism. Other possible causes of stroke in patients who use cocaine are related to the adulterants of illicit cocaine. Direct toxic effects of contaminants, such as lidocaine, procainamide, and amphetamines, may contribute to clinical effects. Talc and sugar are sometimes added to cocaine to increase the volume, and when administered intravenously these substances can travel as an embolus to the cerebral vasculature. Bacterial endocarditis, as a complication of any intravenous drug use, may cause ischemic stroke via embolism or hemorrhagic stroke via rupture of septic aneurysm.

Vasospasm has been identified by angiography in patients with cocaine-associated ischemic stroke [83–87]. This appears to be related to a direct toxic effect of cocaine, both by adrenergic stimulation and effect on calcium channels, although acute severe hypertension may contribute to vasospasm as well [82]. Severe vasospasm may cause focal injury to the arterial endothelium [88]. In vitro, cocaine enhances platelet response to arachidonic acid, thus promoting platelet aggregation [89]. The combination of vasospasm-induced endothelial damage and the procoagulant effects of cocaine may result in cerebral arterial thrombosis.

Cocaine use has been associated with cerebral vasculitis by angiographic findings of characteristic narrowing and dilation of arteries [90, 91]. Two cases of biopsy-proven vasculitis have been reported in associated with crack cocaine use, although one of the patients had a history of intravenous cocaine use. Angiography was normal in one case and showed multiple large vessel occlusions without characteristic vasculitic findings in the other [92]. Cocaine-associated cerebral vasculitis occurs rarely, and its diagnosis is complicated by the difficulty in differentiating vasculitis from vasospasm on angiography. Vasculitis has been reported more commonly with amphetamine use, and cocaine may cause vasculitis by a similar mechanism. However, it is important to note that cocaine products are frequently adulterated with amphetamines, so determination of etiology can be difficult.

Both acute cocaine toxicity and chronic recurrent cocaine use increase the risk of cardioembolic stroke. Acute cocaine toxicity can induce dysrhythmia or myocardial infarction [93]. Chronic cocaine use predisposes to ischemic cardiomyopathy [94]. Either of these may result in embolic ischemic stroke in the event of left ventricular thrombus formation and subsequent embolism to the cerebral vasculature.

While cocaine-induced ischemic stroke is most likely attributable to vasoconstriction, the principal mechanism of cocaine-induced intracerebral and subarachnoid hemorrhage is acute blood pressure elevation. Cocaine-induced hemorrhagic stroke may occur with or without an underlying vascular abnormality. In the presence of an aneurysm or vascular anomaly, acute hypertension causes rupture of the weak, abnormal vessel wall. In the absence of a predisposing lesion, the effect of cocaine on cerebral autoregulation likely contributes to arterial rupture. Normal cerebral autoregulation allows maintenance of constant blood flow over a range of mean arterial pressure. Above the upper limit of autoregulation, vasodilation occurs, and cerebral blood flow increases [95]. Cocaine disrupts autoregulation by lowering the upper limit of this range [96]. Thus, cocaine not only causes systemic hypertension, but also shifts the autoregulation curve such that cerebral blood flow increases at a lower mean arterial pressure. This combination increases risk for arterial rupture and intracerebral hemorrhage. This mechanism may also contribute to reperfusion injury and hemorrhagic transformation of cocaine-induced ischemic stroke.

**Clinical Features/Diagnosis**

The onset of stroke symptoms usually occurs within 3 hours of cocaine use [97]. The type of stroke seems to differ based upon the form of cocaine used. In a comparative study of cerebrovascular events associated with the two different forms of cocaine use, the hydrochloride form was associated predominantly with hemorrhagic stroke (intracerebral or subarachnoid). The alkaloidal form (crack cocaine) was associated with...
equal numbers of hemorrhagic and ischemic strokes [86]. Cocaine has been associated with ischemic stroke in all vascular territories, as well as the retina and spinal cord. Cerebral hemorrhage may be intraparenchymal, intraventricular, or subarachnoid in location [97]. About half of patients with hemorrhagic stroke associated with cocaine have an underlying vascular abnormality [82, 83]. Therefore, it may be necessary to obtain additional neuroimaging after the acute hemorrhage has resolved.

**Differential Diagnosis**

As discussed above, the differential diagnosis of toxin-induced stroke includes amphetamines, PCP, LSD, opioids, and carbon monoxide. The etiologic evaluation of stroke is beyond the scope of this discussion. However, consideration should be given to obtaining urine cocaine, PCP, and amphetamine screens in addition to the usual laboratory evaluation of stroke in young adults. There are many substances that can produce false-positive results on urine PCP and amphetamine screens, and the presence of a drug or its metabolite does not prove causality. Thus, careful interpretation of urine drug screening is necessary.

**Treatment**

Management of acute ischemic or hemorrhagic stroke should be performed to the usual standard of care, independent of cocaine use. A retrospective review of cocaine-associated ischemic stroke patients demonstrated similar outcomes in patients who received tissue plasminogen activator (tPA) and those who did not. There were no complications related to tPA in the patients with cocaine-associated stroke [98]. Based upon this small retrospective study, it appears that tPA may be safe for patients with cocaine-associated ischemic stroke.

One exception to the usual care rule pertains to treatment of hypertension in patients with cocaine toxicity. During acute cocaine intoxication, use of beta-blocking antihypertensive agents may produce unopposed alpha stimulation, resulting in paradoxical hypertension [99]. Therefore, it is best to avoid beta-blockers in the acute setting. Benzodiazepines are often used as symptomatic management of agitation, and the subsequent decrease in sympathetic outflow results in improvement of hypertension and tachycardia [100]. If the sedating effects are acceptable, benzodiazepines are a reasonable first choice in acute cocaine intoxication.

**Amphetamines**

**Introduction**

Amphetamine is the generic term for the racemic α(alpha)-methylphenylethylamine of the phenylethylamine family. Substitutions on the phenylethylamine structure produce a variety of compounds with similar effects, including dextroamphetamine, ephedrine, methamphetamine, and 3,4-methylenedioxymethamphetamine (MDMA or ecstasy) [101].

**Epidemiology**

The true incidence of amphetamine-related cerebrovascular events is not known. Both ischemic and hemorrhage stroke have been reported in association with amphetamines, most often in case series of young stroke patients.

**Pathophysiology**

The mechanism of stroke in the setting of amphetamine use is similar to that of cocaine. Cerebral ischemia is most likely secondary to focal arterial vasoconstriction related to accelerated atherosclerosis or acute vasospasm [102]. Cerebral vasculitis has also been proposed as a mechanism of ischemic and hemorrhagic stroke, and may be a response to the amphetamine or to contaminants or diluents admixed with the amphetamine [103]. However, it is not clear if the findings in each of the reported cases represent true inflammatory arteritis, as the angiography results could also be consistent with vasospasm or multifocal stenosis. Hemorrhagic stroke induced by amphetamines is likely related to acute severe hypertension. Those with preexisting vascular malformations may be at increased risk of this complication [101].
Clinical Features/Diagnosis
Both hemorrhagic and ischemic stroke have been reported in association with amphetamines [70, 77, 104, 105], methamphetamines [102, 106], and MDMA [107–110]. Over-the-counter ephedra-like compounds (phenylpropanolamine, ephedrine, pseudoephedrine) have all been linked to stroke as well [111–115]. Hemorrhagic stroke may occur as subarachnoid or intraparenchymal hemorrhage with or without an underlying aneurysm or arteriovenous malformation. In ischemic stroke, angiography can demonstrate arterial occlusion, dissection, or vasospasm.

Treatment
The history of amphetamine use is often unavailable at the time of acute stroke care. This may be due to stroke-related deficits as well as lack of voluntary reporting of drug use. In addition, there are no clinical studies aimed at the specific treatment of amphetamine-related strokes. Therefore, the usual standard of stroke care, based upon the mechanism and location of infarct or hemorrhage, should be applied. The preferred treatment of amphetamine-related agitation, or any other sympathomimetic symptoms, is benzodiazepines.

Toxin-Induced Seizures

Introduction
Seizures are a common, serious manifestation of drug and toxin effects. Xenobiotics may contribute to seizures by (1) direct effect on electrocerebral activity, (2) induction of metabolic derangements, (3) decreased threshold in epilepsy patients, (4) withdrawal of drugs or alcohol, or (5) idiosyncratic drug reaction [116, 117]. The majority of toxin-related seizures are generalized tonic-clonic. The presence of focal or lateralizing features should prompt evaluation for an underlying lesion. The standard treatment algorithm for status epilepticus requires modification in this setting because toxin-related seizures may not respond to phenytoin [116]. Some toxins that cause seizures are associated with distinct clinical features that may guide diagnosis and treatment.

Epidemiology
The exact incidence of drug- and toxin-induced seizures is not known. A retrospective review of the California Poison Control Center database revealed 386 drug-induced seizures in 2003. The leading cause of drug-induced seizures was bupropion (23%), whereas in 1993 the leading cause was tricyclic antidepressants. Other drugs commonly associated with seizures include stimulants (cocaine and amphetamines), diphenhydramine, tramadol, antidepressants, antipsychotics, isoniazid, and withdrawal from sedatives. In this population, 68.6% had a single seizure, 27.7% had multiple seizures, and 3.6% had status epilepticus [118].

Pathophysiology
The rate of tonic firing in the cerebral cortex is a balance of excitatory and inhibitory stimuli. Excitation occurs by (1) increased sodium influx, (2) decreased chloride influx, or (3) decreased potassium efflux. Inhibition occurs by (1) decreased sodium influx, (2) increased chloride influx, or (3) increased potassium efflux [116]. A general increase in excitatory or decrease in inhibitory stimuli increases the chance of seizure occurrence.

Glutamate and glycine are excitatory neurotransmitters that cause sodium influx, resulting in neuronal depolarization. Gamma-aminobutyric acid (GABA) is the chief inhibitory neurotransmitter in the central nervous system. Its effect on the neuron is to allow chloride influx, resulting in membrane hyperpolarization. Thus, an increase in glutamate activity (e.g., ibotenic acid), a decrease in GABA activity (e.g., cicutoxin), or withdrawal of GABA agonists (e.g., ethanol, benzodiazepines) increases the incidence of seizures [117].
Histamine and adenosine increase GABA and decrease glutamate in the brain; thus, antihistamines (e.g., diphenhydramine) and adenosine antagonists (e.g., theophylline) can cause seizures [116]. Pyridoxine is a cofactor required for synthesis of GABA from glutamate by glutamic acid decarboxylase (GAD). Pyridoxine is converted to its active form by pyridoxal kinase. Inhibitors of this enzyme (isoniazid, gyromitrins, hydrazines) result in decreased GABA synthesis and refractory seizures. Toxins may also produce seizures secondary to severe metabolic derangements, including hyponatremia (MDMA), hypoxia (carbon monoxide, cyanide, hydrogen sulfide), and hypoglycemia (insulin, sulfonylureas). Table 18.2 summarizes the categories of xenobiotics that are known to cause seizures.

### Clinical Features/Diagnosis

The associated signs and symptoms at presentation are often helpful in identifying the drug or toxin responsible for the seizure occurrence. If the seizure occurs prior to clinical assessment, it can be difficult to differentiate the effect of the seizure itself (the postictal state) with drug-induced delirium. If available, history regarding signs and symptoms prior to the onset of seizure can provide the key to the diagnosis.

Findings consistent with the sympathomimetic toxidrome, including mydriasis, tachycardia, hypertension, diaphoresis and agitated delirium, would suggest the involvement of cocaine, amphetamines, PCP, or MDMA. While the majority of toxin-induced seizures are generalized in onset, these sympathomimetics can cause intracerebral hemorrhage or ischemic stroke (as discussed above). These structural brain lesions may produce focal-onset seizures. Therefore, urgent head imaging is indicated if focal-onset seizure is suggested by the history.

Tricyclic antidepressants have multiple mechanisms of action, including inhibition of serotonin reuptake as well as blockade of fast sodium channels and muscarinic receptors. Mild tricyclic antidepressant toxicity may present with predominant anticholinergic symptoms. More severe toxicity is associated with seizures and QRS interval prolongation [119]. In fact, QRS duration longer than 100 ms is associated

<table>
<thead>
<tr>
<th>Table 18.2 Xenobiotics associated with seizures</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Category</strong></td>
</tr>
<tr>
<td>Antidepressants/antipsychotics</td>
</tr>
<tr>
<td>Anesthetics/analgesics</td>
</tr>
<tr>
<td>Anticonvulsants</td>
</tr>
<tr>
<td>Stimulants</td>
</tr>
<tr>
<td>Antimicrobials</td>
</tr>
<tr>
<td>Gases</td>
</tr>
<tr>
<td>Fungi/plants</td>
</tr>
<tr>
<td>Pesticides</td>
</tr>
<tr>
<td>Methylxanthines</td>
</tr>
<tr>
<td>Withdrawal</td>
</tr>
<tr>
<td>Miscellaneous</td>
</tr>
</tbody>
</table>
with increased risk of seizures [120, 121]. Serotonin syndrome may develop, especially if tricyclic antidepressants are taken with other serotonergic medications.

The combination of coma, respiratory depression, and miosis is characteristic of the opioid toxidrome. Propoxyphene causes seizures, and because of sodium channel blockade, can result in QRS prolongation. Normeperidine, a metabolite of meperidine, and tramadol also lower the seizure threshold.

The presence of agitated delirium prior to the seizure should also suggest the possibility of drug or alcohol withdrawal. Abrupt discontinuation of GABA agonists, including ethanol, barbiturates, benzodiazepines, and bacofoil, can cause a life-threatening withdrawal syndrome characterized by agitation, tremor, tachycardia, hallucinations, autonomic instability, and seizures. Ethanol withdrawal seizures are usually brief in duration; however, benzodiazepine or bacofoil withdrawal is more likely to cause status epilepticus [122, 123].

Isoniazid frequently causes refractory seizures by producing a functional pyridoxine deficiency. The neurotoxin in Gyromitra esculenta mushrooms (false morels) is structurally similar to isoniazid, and is also associated with status epilepticus. Severe theophylline toxicity also results in refractory seizures. Seizure activity that does not respond to benzodiazepines should prompt consideration of these toxins.

**Differential Diagnosis**

The consideration of toxin-induced seizures should not preclude an evaluation for structural, infectious, or metabolic causes of seizure. Detailed history should be obtained to determine the circumstances and characteristics of the reported seizure in order to differentiate a generalized (from onset) seizure that may be toxin-induced from a focal-onset seizure, nonepileptic myoclonus, psychogenic nonepileptic event, or acute movement disorder (chorea, tremor, dystonia). Some toxins can cause severe muscle spasms that can mimic seizure, including strychnine, tetanus, and black widow spider envenomation. Electroencephalogram, head imaging, lumbar puncture, and laboratory studies may be necessary to confirm the diagnosis.

**Treatment**

A single, self-limited toxin-induced seizure may be managed with careful clinical observation without the need for long-term anticonvulsant therapy. The first step in management of prolonged or recurrent seizures is benzodiazepines. Some toxins so reliably cause seizures that prophylaxis with benzodiazepines or phenobarbital should be considered. A single dose of lorazepam has been shown to decrease the risk of seizure recurrence in ethanol withdrawal [124], whereas phenytoin does not [125]. Bupropion overdose is associated with seizures in about 30% of patients, and seizure onset may be delayed, especially with the extended-release formulation. In one study, tachycardia, agitation, and tremor were more common in patients who developed seizures than those who did not [126]. Use of benzodiazepines to treat these symptoms may prevent the delayed seizure as well. Theophylline toxicity can result in refractory seizures that are associated with increased morbidity [127, 128]. Prophylaxis with a loading dose of phenobarbital (20 mg/kg intravenously) is recommended for altered mental status, agitation, or theophylline levels of greater than 100 μg/mL [117].

A comprehensive treatment algorithm for status epilepticus is discussed in Chap. 10: “Seizures and Status Epilepticus.” For drug- and toxin-induced seizures, the first-line therapy is benzodiazepines (lorazepam), followed by barbiturates (phenobarbital) if necessary. While phenytoin is the standard second-line therapy in management of status epilepticus, it is usually not effective and may actually worsen toxin-induced seizures [129]. In general, anticonvulsants with GABA agonist properties (benzodiazepines, barbiturates, propofol) are preferred.

As discussed above, many toxins have multiple mechanisms of action and thereby cause a constellation of symptoms that may include seizures. Therefore, it may be necessary to consider
additional treatments or antidotes. For example, enhanced elimination by hemodialysis may be indicated for theophylline, salicylate, or lithium toxicity. Sodium bicarbonate is indicated for QRS widening in tricyclic antidepressant and cocaine toxicity, and for serum and urinary alkalinization in salicylate toxicity. Magnesium supplementation and potassium repletion are indicated for QTc prolongation in olanzapine toxicity. Intravenous dextrose should be administered to correct hypoglycemia secondary to insulin or sulfonylurea toxicity. In sulfonylurea toxicity, octreotide may be indicated for refractory hypoglycemia. Prolonged seizures secondary to isoniazid or gyromitrin toxicity may respond to intravenous pyridoxine supplementation (1 g for every gram of isoniazid ingested or empiric dose of 5 g). Baclofen should be restarted, in addition to benzodiazepines, for seizures related to baclofen withdrawal. Multiple-dose activated charcoal may be useful in severe carbamazepine or theophylline toxicity because of the enterohepatic recirculation of these drugs. Atropine or pralidoxime may be necessary for management of organophosphate poisoning. For assistance with management of the poisoned patient, a clinical toxicologist is available for consultation by calling the National Poison Control Center at (800) 222–1222 [116].

**Toxin-Induced Acute Weakness**

While toxin-induced weakness is rare, it is important to consider toxins in the differential diagnosis of both spastic and flaccid weakness, especially when the history suggests a possible exposure. Removing the source of exposure (e.g., tick paralysis) and administration of specific antitoxin may be instrumental in management. Cholinergic symptoms with or without seizures should prompt consideration of organophosphate, carbamate, or nicotine toxicity. Descending paralysis is characteristic of botulism, while ascending paralysis is the hallmark of the demyelinating polyneuropathy of diphtheria. Botulism, diphtheria, tick paralysis, and anthracenone toxicity (*Karwinskia humboldtiana*, Fig. 18.2) cause flaccid paralysis. Tetanospsamin, strychnine, and latrotoxin (black widow spider) cause severe muscle spasms. Botulism, scorpion, and Elapidae snake venom are associated with cranial nerve palsies. Table 18.3 reviews the pathophysiology, clinical features, and treatment of toxins that can produce acute weakness. Many of the antitoxins used in the treatment of arthropod and snake envenomations are associated with anaphylactoid reactions. Pretreatment with antihistamines with or without epinephrine may be considered, and immediate availability of these medications during the initial infusion is wise [130–132].
Table 18.3  Toxin-induced acute weakness

<table>
<thead>
<tr>
<th>Category</th>
<th>Toxin</th>
<th>Mechanism of action</th>
<th>Source</th>
<th>Clinical presentation</th>
<th>Treatment (in addition to symptomatic and supportive care)</th>
</tr>
</thead>
</table>
| Synthetic compounds          | Organophosphates       | Inhibit AChE                                             | Pesticides                  | Cholinergic crisis (diarrhea, vomiting, bronchospasm) with fasciculations and paralysis | Atropine for muscarinic symptoms
                                                                                          |                                                                                      | Pralidoxime for nicotinic symptoms
                                                                                          |                                                                                      | Benzodiazepines for seizures
                                                                                          |                                                                                      | Atropine for muscarinic symptoms
                                                                                          |                                                                                      | Consider avoiding pralidoxime due to rapid reactivation of carbamylated AChE
                                                                                          |                                                                                      | Benzodiazepines for seizures                                                      |
| Synthetic compounds          | Carbamates             | Inhibit AChE                                             | Pesticides                  | Atropine for muscarinic symptoms
                                                                                          | Consider avoiding pralidoxime due to rapid reactivation of carbamylated AChE
                                                                                          | Benzodiazepines for seizures                                                      |
| Bacteria                     | Botulinum toxin        | Inhibits fusion of presynaptic ACh vesicles, prevents release of ACh | Clostridium botulinum       | Cranial nerve palsies, followed by descending flaccid paralysis                        | Botulinum antitoxin
                                                                                          | – Home-canned foods                                                                 | Notify the health department                                                        |
| Bacteria                     | Diphtheria toxin       | Inhibits protein synthesis, resulting in demyelination of motor and sensory nerves | Corynebacterium diphtheriae | Tonsillar pseudomembrane, followed within weeks by rapidly ascending flaccid paralysis | Diphtheria antitoxin
                                                                                          | – Respiratory droplets                                                             | Intravenous benzylpenicillin or oral penicillin V for bacterial eradication        |
| Bacteria                     | Tetanospasmin          | Prevents the release of GABA and glycine from spinal interneurons by cleaving synaptobrevin | Clostridium tetani          | Hypertonia, painful generalized muscle contractions, trismus, and increased sympathetic activity | Tetanus immunoglobulin
                                                                                          | – Soil contamination of skin wound                                                | Benzodiazepines
                                                                                          |                                                                                      | Paralytics with ventilatory support for severe muscle spasm                        |
| Plants                       | Anthracenones          | Decrease ATP production, resulting in Schwann cell injury | Karwinskia species, including K. humboldtiana (coyotillo) | Vomiting and diarrhea followed within weeks by ascending flaccid paralysis             | Atropine may be useful for bradycardia or hypersalivation                           |
| Plants                       | Aconitine              | Increases sodium influx via opening of sodium channels    | Aconitum species, including monkshood and wolfsbane | Paresthesias, followed by nausea, diarrhea, progressive weakness with bradycardia and/or dysrhythmia | Benzodiazepines or Phenobarbital
                                                                                          |                                                                                      | Paralytics with ventilatory support for severe muscle spasm                          |
| Plants                       | Strychnine             | Antagonizes glycine                                      | Strychnos species           | Muscle spasms followed by severe generalized convulsions with intact consciousness    | Atropine for muscarinic symptoms
<pre><code>                                                                                      |                                                                                      | Benzodiazepines for seizures                                                      |
</code></pre>
<p>| Plants                       | Nicotine               | Activates nicotinic ACh receptors                         | Nicotiana species, including multiple types of tobacco plant | Cholinergic crisis (diarrhea, vomiting, bronchospasm) with fasciculations and paralysis | Benzodiazepines for seizures                                                      |</p>
<table>
<thead>
<tr>
<th>Source</th>
<th>Neurotoxin</th>
<th>Mechanism</th>
<th>Symptoms</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shellfish</td>
<td>Saxitoxins</td>
<td>Inhibits sodium, calcium, and potassium channels, resulting in conduction block</td>
<td>Perioral then generalized paresthesias followed by pain and paralysis with nausea and headache</td>
<td>Notify the health department</td>
</tr>
<tr>
<td>Tetrodotoxin</td>
<td>Inhibits voltage-gated sodium channels</td>
<td>Vibriovaceae family of marine bacteria</td>
<td>Perioral then generalized paresthesias, followed by nausea, diarrhea, and paralysis</td>
<td></td>
</tr>
<tr>
<td>Arthropods</td>
<td>Latrotoxin</td>
<td>Stimulates neurotransmitter release (including ACh), resulting in vesicle depletion</td>
<td>Diffuse muscle spasms and rigidity with hypertension, nausea, and diaphoresis</td>
<td>Benzodiazepines for muscle spasm Black widow antivenom for severe cases</td>
</tr>
<tr>
<td>Scorpion venom</td>
<td>Ixovotoxin</td>
<td>Inhibits ACh release at neuromuscular junction</td>
<td>Ascending, flaccid paralysis</td>
<td>Tick removal Antitoxin used only in severe illness secondary to high risk of anaphylaxis and serum sickness</td>
</tr>
<tr>
<td>Scorpion venom</td>
<td>Scorpion venom (multiple components, species specific)</td>
<td>Opening of sodium channels, activation of sympathetic and parasympathetic nerves, causing ACh and catecholamine release</td>
<td>Pain and paresthesias, followed by neuromuscular excitability, cranial nerve palsies, and weakness</td>
<td>Antivenom currently not available in the United States</td>
</tr>
<tr>
<td>Snakes</td>
<td>α-Bungarotoxin</td>
<td>Inhibits binding of ACh at nicotinic receptors</td>
<td>Local swelling and nausea followed by cranial nerve palsies and paralysis</td>
<td>Monovalent antivenom if species is known, polyvalent antivenom if species is unknown Pressure immobilization of wound</td>
</tr>
<tr>
<td>Snakes</td>
<td>β-Bungarotoxin</td>
<td>Inhibits ACh release</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Snakes</td>
<td>Cobrotoxin</td>
<td>Inhibits binding of ACh at nicotinic receptors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Snakes</td>
<td>Dendrotoxin</td>
<td>Inhibits potassium channels, facilitating ACh release</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Snakes</td>
<td>Fasciculin</td>
<td>Inhibits AChE</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*AChE* acetylcholinesterase, *ACh* acetylcholine, *GABA* gamma-aminobutyric acid, *ATP* adenosine triphosphate.
Toxin-Induced Acute Encephalopathy

Introduction

Alteration of mental status is a nonspecific finding with a very broad differential diagnosis, including many drugs and toxins. Attention to the characteristic features of the change in mentation, as well as the associated symptoms, is the key to defining possible etiologies. Alteration of cognitive function is a common side effect of many medications, even at therapeutic doses. This discussion is limited to severe poisoning resulting in agitated delirium and stupor or coma.

Pathophysiology

Because of the complex neurophysiology of the central nervous system, drugs and toxins can cause encephalopathy by a variety of mechanisms. Agents with anticholinergic, sympathomimetic, serotonergic, GABA agonist, opioid agonist, adenosine antagonist, and antihistamine effects cause varying degrees of encephalopathy. Withdrawal of GABA agonists can also produce severe encephalopathy. Environmental toxins that cause hypoxia and drugs that cause hypoglycemia result in central nervous system depression.

Clinical Features/Diagnosis

Recognition of the syndromic presentation of specific drugs and toxins can reveal the diagnosis even in the absence of exposure history. Opioid and sedative-hypnotic toxidromes cause depression of the central nervous system, resulting in stupor and coma. Sympathomimetic, anticholinergic, and withdrawal toxidromes produce agitated delirium. Cholinergic syndrome, characterized by miosis, increased secretions, diarrhea, bradycardia, and weakness, is not commonly associated with encephalopathy except when seizures occur.

Opioid poisoning causes miosis, respiratory depression, and coma. Associated prolongation of the QRS or QTc interval is suggestive of propoxyphene or methadone intoxication, respectively. Seizures in the setting of the opioid toxidrome suggest propoxyphene, tramadol, or meperidine toxicity. Reversal of symptoms with naloxone supports the diagnosis of opioid toxicity.

Sedative-hypnotic toxicity from benzodiazepines or ethanol results in sedation, and is usually associated with normal vital signs. Respiratory depression can occur when sedatives are ingested with alcohol, opioids, or other sedating medications. Methanol and ethylene glycol ingestion result in central nervous system depression, similar to ethanol toxicity, but are also associated with an anion gap metabolic acidosis. Acidosis in this setting should prompt further laboratory evaluation (serum osmolality, methanol and ethylene glycol levels), treatment with fomepizole, and nephrology consultation. Evaluation for other causes of anion gap metabolic acidosis, including salicylate toxicity, diabetic or alcoholic ketoacidosis, and lactic acidosis, should also be performed.

Sympathomimetic toxicity is characterized by mydriasis, agitated delirium, tachycardia, hypertension, diaphoresis, and hyperthermia. The most common causes of this toxidrome are amphetamines and cocaine. When hallucinations are a prominent feature, especially in the presence of nystagmus, phencyclidine intoxication should be considered. Anticholinergic syndrome also causes an agitated delirium that is similar in presentation to sympathomimetic syndrome. The distinguishing features of anticholinergic toxicity are anhidrosis, decreased bowel sounds, and garbled speech. Patients may also exhibit the picking behaviors that are characteristic of this toxidrome. Tricyclic antidepressants, diphenhydramine, scopolamine, and cyclobenzaprine are common causes of anticholinergic symptoms. Withdrawal of ethanol and benzodiazepines results in mydriasis, tachycardia, tremor, and agitated delirium. Serotonin syndrome causes an agitated delirium with autonomic instability and motor hyperactivity in the setting of serotonergic medications. This is discussed in the hyperthermic syndromes section of this chapter.
Differential Diagnosis

Metabolic derangements, central nervous system or systemic infection, cerebral structural lesions or hemorrhage, and nonconvulsive status epilepticus may all cause a general alteration of mental status. Head imaging, lumbar puncture, laboratory testing, and electroencephalography are often necessary for diagnosis. Basic chemistry profile, serum acetaminophen and salicylate levels, and electrocardiogram (ECG) can assist in determining which drugs are most likely to be involved, especially when intentional overdose is suspected and historical information is unavailable. Urine drug screening should not be routinely performed because of the high rate of false-positive and false-negative results. Care should be taken when interpreting data from these screening tests. A positive result does not prove intoxication, and a negative result does not always exclude exposure.

Treatment

Identification and discontinuation of the toxic agent, in addition to supportive care, is the mainstay of therapy for toxin-induced encephalopathy. Benzodiazepines are the recommended treatment for toxin-induced agitated delirium, including sympathomimetic, anticholinergic, withdrawal, and serotonin syndromes. Antidotes exist for opioid, benzodiazepine, and anticholinergic poisoning. The potential side effects of these antidotes should be carefully considered prior to administration.

Naloxone is an opioid antagonist that is used therapeutically and diagnostically in the setting of presumed opiate or opioid toxicity. The initial dose of naloxone is usually 0.4 mg given intravenously; however, because naloxone can precipitate severe withdrawal symptoms, a smaller test dose should be considered when opioid dependence is suspected. Additional doses may be given at 5-min intervals until neurologic and respiratory status has improved [133]. Higher doses of naloxone may be required for reversal of the synthetic opioids. The clinical effect of naloxone may be as short as 45 min [134]. Resedation may occur after naloxone reversal, especially in the setting of toxicity from methadone or sustained release opioid preparations. Patients should be observed closely for 4–6 h after naloxone administration. If resedation does occur, a naloxone infusion can be initiated at an hourly rate of two-thirds of the effective bolus dose [135]. Admission to a monitored setting is required to monitor for withdrawal symptoms or resedation.

In general, benzodiazepine withdrawal is more likely to cause complications than benzodiazepine toxicity. Benzodiazepines are not potent respiratory depressants, so reversal is not likely to prevent the need for mechanical ventilation in patients who have ingested multiple sedating medications. In polysubstance overdose or benzodiazepine-dependent patients, reversal of benzodiazepines can precipitate refractory seizures [117]. For this reason, use of the benzodiazepine antagonist, flumazenil, should be limited to pediatric poisonings or iatrogenic toxicity.

Physostigmine is an inhibitor of acetylcholinesterase that may be used for severe anticholinergic poisoning. The diagnosis of isolated anticholinergic toxicity must be clinically certain prior to administration of this antidote. Potential complications of physostigmine administration include seizures, bronchorrhea, and arrhythmias. ECG evidence of prolongation of the PR, QRS, or QTc intervals contraindicates use of physostigmine [133]. As polysubstance ingestion is common, and many anticholinergic drugs have other mechanisms of action that may predispose to seizures, the routine use of physostigmine is discouraged. Benzodiazepines are the preferred treatment for the agitated delirium of anticholinergic toxicity.

Conclusion

Toxin-induced neurologic emergencies are common. Acute encephalopathy with or without hyperthermia, stroke in young patients, unexplained seizures, and acute weakness should prompt consideration of toxicologic etiologies. Early identification of the causative toxin allows for appropriate diagnostic testing and initiation of definitive treatment.
References


