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Drug- and Toxin-Associated Seizures Brandon Wills, DO, MS^{a,b,*}, Timothy Erickson, MD^a

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Generalized seizure activity may be a presenting symptom of poisoning or a preterminal manifestation of serious toxicity. Seizures may result from a large number of drugs and toxins, such as isoniazid (INH), carbon monoxide, theophylline, cyclic antidepressants, and salicylates. Additionally, withdrawal states, such as from ethanol and sedative hypnotic agents, may induce refractory seizure activity.

In this article the authors review the pathophysiology of drug- and toxinassociated seizures (DTS), discuss the differential diagnosis, and provide a logical approach to management of DTS. Their aim is to discuss those specific agents for which seizure activity is a primary sequela in therapeutic use, exposure, or overdose.

Epidemiology

It is difficult to estimate the true incidence of DTS, because the literature shows a paucity of epidemiologic data. The Toxic Exposure Surveillance System [1] is an annually updated database documenting outcomes for all poisonings reported to regional poison centers throughout the United States, but it does not record data for seizures in its own category. A prospective study of status epilepticus (SE) by Delorenzo and colleagues [2] reported that, of 204 SE events, ethanol-related seizures were responsible for 13%, whereas drug overdose was responsible for less than 5%, with case/fatality rates of approximately 20% and 25%, respectively. A retrospective review of California Poison Control System data from 1993 reported that the most common DTS were cyclic antidepressants (29%), stimulants (29%), antihistamines (7%), theophylline (5%), and isoniazid (5%) [3]. The same authors

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reviewed poison center data from 2003 and found that the leading causes for drug-induced seizures had evolved to the following agents: bupropion (23%), diphenhydramine (8.3%), cyclic antidepressants (7.7%), tramadol (7.5%), amphetamines (6.9%), INH (5.9%), and venlafaxine (5.9%) [4]. In this series, 68% had only one seizure, 27% had two or more seizures, and only 3.6% had SE. The definition of SE is in evolution; however, some believe that it should be defined as either continuous seizures for more than 5 minutes or two or more seizures without a lucid interval [5,6].

Pathophysiology

Nerve signals in the central nervous system (CNS) are generally transmitted by neurotransmitters. Neurotransmitter binding results in either nerve signal propagation or termination. Neurotransmitter receptors located at the postsynaptic nerve terminal mediate opening or closing of ion channels. Receptors may be directly linked to an ion channel or modulate ion channels by stimulation of a second messenger (ie, cyclic adenosine monophosphate or cAMP). Nerve signal propagation occurs when the resting membrane potential rises to the threshold potential that triggers an action potential. Generally, excitation occurs with influx of sodium ions or a decrease in either chloride conduction or potassium efflux. Inhibition results from a decrease in sodium influx or an increase in either chloride influx or potassium efflux.

All seizure activity is a result of chaotic electrical discharge in the CNS. With tremendous advances in neurobiochemistry, a variety of neurochemical linked pathways have been implicated in the genesis of seizures. Seizure and epilepsy research frequently uses a kindling model to study the effects of proconvulsant agents. *Kindling* is a paradigm in which CNS stimulation from a xenobiotic or electrical stimulus results in epileptiform activity. Kindling also refers to sensitization of neuronal tissue by the addition of a drug or electrical stimulus that renders it susceptible to subsequent seizure activity [7]. Certainly, not all pathways for the genesis of seizures have been elucidated. The following are descriptions of specific neurochemical pathways known to induce seizures.

Gamma-aminobutyric acid

Gamma-aminobutyric acid (GABA) is the main inhibitory neurotransmitter of the CNS. When stimulated, GABA receptors modulate chloride ion flux, inhibiting membrane depolarization [8]. Conversely, GABA antagonists or functional depletion of GABA increases membrane depolarization and may result in seizures [9]. GABA agonists (direct or indirect) therefore play a vital role in seizure termination [6]. Loss of GABA-mediated inhibition results in seizures, as occurs in withdrawal from ethanol, sedative hypnotics, gamma-hydroxybutyrate, and baclofen [10].

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DRUG- AND TOXIN-ASSOCIATED SEIZURES

Glutamate

The excitatory amino acid glutamate binds one of four glutamate receptors, allowing the influx of sodium, calcium, or both and causing neuron depolarization. Excessive neuronal excitation by glutamate by means of N-methyl-D-aspartate (NMDA), alpha-amino-3-hydroxy-5-methyl-4-isoxazo-lepropionic acid (AMPA), or kainate receptors may result in seizures [11,12].

Glycine

Glycine is another excitatory neurotransmitter that binds to NMDA receptors, causing sodium influx in the CNS. Postsynaptic glycine receptors modulate chloride influx. Postsynaptic glycine antagonists, such as strychnine, cause seizure-like myoclonic activity, but this occurs with an intact mental status that is not a true seizure [13].

Sodium channel blockade

Because depolarizations generated in the nerve body are propagated down the axon through the opening of sodium channels, local anesthetics slow neuronal transmission by virtue of sodium channel blockade. This phenomenon has led to the use of lidocaine as a possible treatment for SE [14]. Conversely, in overdose, it is known to produce seizures by an unknown mechanism. Other pharmaceuticals that block sodium channels, such as carbamazepine, may be anticonvulsant in therapeutic doses and yet produce seizures in overdose. It has been suggested that the local anesthetic effects of cocaine may potentiate seizures [15]. Concomitant administration of cocaine and lidocaine has additive effects on seizure incidence in an animal model [16].

Norepinephrine

Autonomic overstimulation may occur as a direct or indirect effect of drugs. Ethanol withdrawal, despite having multifactorial effects, results in marked sympathetic outflow. Ethanol withdrawal results in increased norepinephrine release and may lead to seizures [17].

Acetylcholine

Cholinergic overstimulation may result in seizures [8]. This effect may be seen with exposure to cholinesterase inhibitors, such as carbamates and organophosphate pesticides, or nerve agents [18].

Adenosine

Adenosine-1 (A_1) receptors are found in the CNS [19]. Experimentally, agonists of A_1 receptors inhibit glutamate release, causing an anticonvulsant

effect, whereas A_1 antagonists markedly increase spontaneous seizure activity [20]. This mechanism may be a contributing factor in theophylline toxicity.

Histamine

Histamine may have anticonvulsive properties mediated by the central H_1 receptor [21]. Administration of toxic doses of antihistamines in animal models results in generalized seizures and is attenuated by the addition of the histamine precursor—histidine [21,22].

Metabolic disturbances

Disturbances in electrolyte or glucose homeostasis may result in seizures; these may include hyponatremia, hypornatremia, hypomagnesemia, hypo-calcemia, hypoglycemia, and hyperglycemia [23].

Differential diagnosis and clinical presentation

Differentiation of DTS from epilepsy is challenging. Without any history of a predisposing cause or overdose, few "screening" tests will help to narrow the differential diagnosis. If a seizure patient is suspected of having a drug or toxin as the cause, the clinician must attempt to use all potential historians (family, paramedics, bystanders, coworkers, pharmacy, primary care physician) to provide clues to the possible causative agent. Box 1 contains a list of agents implicated in DTS. On a more lighthearted note, the mnemonic "Otis Campbell" (the town drunk from the Andy Griffith television show) has been used as a teaching tool to recall common causes of DTS (Box 2).

Specific clinical presentations may assist in narrowing the differential diagnosis. A sympathomimetic toxidrome preceding seizure activity may involve cocaine, amphetamines, or drug withdrawal. Patients with a history of foraging for wild plants or mushrooms may have inadvertently ingested water hemlock (ie, *Cicuta douglassi*) or false morel mushrooms (eg, *Gyromitra*). Patients with a psychiatric history may have overdosed from their own psychiatric medications, which could include such agents as antidepressants (ie, cyclic antidepressants, bupropion, and venlafaxine), lithium, or carbamazepine. A history of recent positive purified protein derivative (PPD) skin test or cavitary lesion on chest radiograph may be a clue to INH exposure. A presentation of seizures with an associated widened QRS interval on electrocardiogram may be a clue to cyclic antidepressants, propoxyphene, venlafaxine, diphenhydramine, or other agents (Box 3).

Patients may present with myoclonic activity with or without mental status alteration mimicking seizures. Possible seizure mimics include strychnine [13] and serotonin syndrome [24]. Opioid analgesic overdose traditionally presents with the toxidrome of mental status depression,

respiratory depression, and miosis. In addition to the classic toxidrome, the opioids meperidine, tramadol, and propoxyphene may precipitate seizures [25–28]. Additionally, these opioids may produce mydriasis rather than miosis. Severe hypokalemia may be a clue to methylxanthine toxicity.

Discussion of selected agents

Drugs of abuse

A past review of 49 cases of seizures related to recreational drug use between 1975 and 1987 found that 65% were related to cocaine, 22% to amphetamines, 14% to heroin, and 8% to 1-phenylcyclohexyl-piperidine (PCP) [29]. With the emergence of new d esigner drugs of abuse, seizures induced by different agents, such as 3,4-methylenedioxymethamphetamine (MDMA) and gamma hydroxybutyric acid (GHB) are being reported.

Stimulants

Cocaine and the amphetamines increase the release of norepinephrine [30] and serotonin [31]. Hallucinogenic amphetamines (eg, MDMA) may have greater serotonergic effects [31]. Seizures from MDMA may be a result of direct drug effect or may be secondary to hyponatremia. MDMA-induced hyponatremia may be due to a central effect or marked consumption of water at "rave" parties [32]. Cocaine and drugs within the amphetamine family all can produce a sympathomimetic toxidrome and have been associated with seizures [31–33]. Seizures from cocaine intoxication may be mediated by its effects on serotonin receptors [34]. Cocaine body stuffing and packing can result in delayed-onset toxicity and seizures [35]. Treatment should be focused on supportive measures, including intravenous fluids and evaporative cooling for hyperthermia [31]. Liberal doses of benzodiazepines should be considered first-line therapy for the treatment of both the autonomic signs and seizure activity [30,31].

Gamma hydroxybutyric acid

GHB and its precursors (gamma-butyrolactone and 1,4-butanediol) produce a variety of CNS effects, most commonly mental status depression and coma [36]. From its early use as an induction agent for anesthesia, GHB has been noted to cause myoclonic jerking in humans and has been associated with seizures in animal models [36–38].

Abrupt cessation of GHB following chronic abuse has been associated with a profound withdrawal syndrome that includes many features similar to ethanol and sedative withdrawal [39,40]. Despite similarities, including sympathomimetic syndrome, tremor, and visual hallucinations, seizures have not been reported [39,41] and were not observed in an animal model of GHB withdrawal [42].

Box 1. Pharmaceuticals and toxins associated with seizures

Analgesics Meperidine Propoxyphene Tramadol Salicylates Anticonvulsants Carbamazepine

Phenytoin

Cellular asphyxiants Carbon monoxide Cyanide Hydrogen sulfide Azides

Drugs of abuse Cocaine Amphetamines Phencyclidine Gamma-hydroxybutyric acid

Envenomations Scorpion Elapid

Heavy metals Arsenic Lead Thallium

Plants, herbs, and natural products Water hemlock *Gyromitra esculenta* mushroom Ephedra Nicotine

Psychiatric medications Bupropion Cyclic antidepressants Lithium Olanzapine Selective serotonin reuptake inhibitors Venlafaxine

| <i>Rodenticides</i> Bromethalin Zinc phosphide | |
|---|--|
| <i>Withdrawal</i> Ethanol Sedative-hypnotic Baclofen | |
| Miscellaneous Boric acid Camphor Diphenhydramine Fluoride Isoniazid Iron Lidocaine and local anesthetics Methylxanthines (theophylline, caffeine) Organochlorine pesticides (dichlorodiphenyltrichloroethane [DDT], Lindane) Organophosphates and carbamates Thujone Quinine | |

1-Phenylcyclohexyl-piperidine (phencyclidine, PCP)

PCP and its derivative ketamine are NMDA antagonists that produce a myriad of physical and behavioral effects [32]. Substantial alterations in behavior may include agitation, bizarre actions, hallucinations, and violence [43,44]. Other features of PCP intoxication include nystagmus, hypertension, hyperthermia, rhabdomyolysis, and seizures [44]. One review of 1000 cases of PCP intoxication reported generalized seizures in approximately 3% [44]. However, seizures were not reported in a poison center review of 28 cases of ketamine abuse [45]. Despite being structurally similar to PCP, ketamine may actually have antiepileptic properties and is used by some clinicians for intractable seizures. One animal model of SE using high-dose ketamine [46] and one pediatric case series of nonconvulsive SE [47] demonstrated effective seizure termination with ketamine.

Withdrawal

Ethanol

Ethanol withdrawal resembles the sympathomimetic toxidrome and is manifested by agitation, tachycardia, hypertension, hyperthermia, and

Box 2. Agents that cause seizures

OTIS CAMPBELL^a Organophosphates Tricyclic antidepressants Isoniazid, insulin Sympathomimetics Camphor, cocaine Amphetamines, anticholinergics Methylxanthines (theophylline, caffeine) Phencyclidine (PCP) Benzodiazepine withdrawal, botanicals (water hemlock) Ethanol withdrawal Lithium, lidocaine Lead, lindane

^a The "town drunk" on *The Andy Griffith Show*.

seizures [48]. In describing the temporal course of ethanol withdrawal, Victor and Adams [49] found that seizures often preceded autonomic overactivity.

Treatment for severe withdrawal and delirium tremens is generally targeted at the autonomic signs, which are often difficult to control.

Box 3. Drugs potentially causing both wide QRS interval and seizures

Amantadine Bupropion Carbamazepine Citalopram Cocaine Cyclic antidepressants Diphenhydramine Disopyramide Hydroxychloroquine Procainamide Propoxyphene Quinidine Quinine Thioridazine Venlafaxine Withdrawal seizures that typically precede autonomic signs and delirium tend not to be protracted. Benzodiazepines are first-line agents to control both withdrawal seizures and autonomic hyperactivity; high doses may be required. Cumulative doses of 2640 mg of diazepam and 2850 mg of midazolam were reported in severe withdrawal cases [50,51]. Intravenous phenobarbital and propofol have been used successfully to treat refractory ethanol withdrawal [52–54].

Sedative hypnotics/flumazenil

Withdrawal from sedative hypnotic medications resembles ethanol withdrawal. Key differences are that withdrawal from sedatives may be delayed or prolonged depending on the pharmacokinetics of the agent [55]. Similarly, the benzodiazepine antagonist flumazenil may induce seizures in selected patient populations. A paper analyzing 43 cases of seizures associated with flumazenil administration found that 47% were due to reversal of benzodiazepines given to control a drug-induced seizure (42% of this group coingested a cyclic antidepressant), 16% were due to reversal of a benzodiazepine suppressing non-drug-induced seizures, 7% were due to reversal of chronic benzodiazepine dependence, 5% were due to reversal of benzodiazepines given for procedural sedation, and 14% had no apparent relationship [56]. Based on these data, one author suggests narrowing the potential indications for flumazenil to iatrogenic overdose, pediatric ingestion, or paradoxical response to benzodiazepines [57].

Baclofen

Baclofen is a $GABA_B$ agonist and is used for muscle spasticity [58]. Withdrawal has been noted from both intrathecal pump failure and discontinuation of oral therapy [58–61]. The clinical presentation of baclofen withdrawal is similar to that of ethanol and sedative withdrawal, including autonomic sympathomimetic signs, hallucinations, and seizures. Treatment includes benzodiazepines and the readministration of oral baclofen. However, in those patients experiencing intrathecal pump failure, it is difficult to obtain adequate cerebrospinal fluid concentrations with oral baclofen [58,59]. Dantrolene is reported to reduce muscle spasticity and hyperthermia from refractory baclofen withdrawal due to pump removal [62].

Psychiatric medications

Cyclic antidepressants

Cyclic antidepressants (TCA) have a variety of pharmacologic effects that give rise to several features in overdose. The psychopharmacologic action of TCA is the inhibition of the reuptake of serotonin and norepinephrine [63].

In addition, TCA are antagonists of histamine (H₁), muscarinic, and alpha (α_1) receptors [63]. In overdose, TCA can produce anticholinergic toxidrome, hypotension, QRS interval prolongation, ventricular arrhythmias, and seizures (see Box 3) [63]. The presence of seizures increases mortality from TCA overdose [64].

Much investigation has been performed to identify surrogate markers for those patients who are at risk for seizures, arrhythmias, and death in TCA overdose. Some authors have suggested that level of consciousness predicts outcome [65,66], whereas others have predicted outcome by investigating TCA serum levels and electrocardiographic markers. In a recent meta-analysis, Bailey and colleagues [67] evaluated the performance of TCA levels and ECG for predicting seizures, arrhythmias, and death. They found the sensitivity and specificity for predicting seizures using QRS were 0.69 and 0.69, respectively, compared with 0.75 and 0.72 using TCA level [67]. Given that the pooled sensitivities and specificities had large confidence intervals and that it is difficult to obtain rapid quantitative TCA levels, the ECG remains a helpful tool to stratify patients at risk. Treatment of severe TCA overdose should include aggressive resuscitation and supportive care, benzodiazepines for seizures, and sodium bicarbonate loading for cardiac toxicity [63]. Beneficial effects of sodium bicarbonate may be due to both elevation of pH and increase in the sodium gradient [68]. Although some authors have suggested a role for phenytoin in cyclic overdoses, animal studies suggest it is helpful neither for seizures nor for ventricular arrythmias [63,69].

Antidepressants: other

The newer classes of antidepressants are thought to be generally safer than TCA in overdose. However, all selective serotonin reuptake inhibitors (SSRI) may be associated with seizures in overdose [70,71]. Among the SSRI, citalopram may have a higher occurrence of seizures in overdose, with a 6% prevalence in one series [72]. Data on other antidepressants that have substantial toxicity in large overdose are emerging.

Bupropion. Bupropion is a unique antidepressant and smoking cessation aid. Its mechanism is not fully understood, but it is thought to inhibit reuptake of dopamine, norepinephrine, and serotonin [73]. Despite being structurally dissimilar to TCA, bupropion has similarities to them in overdose. Of 2424 intentional bupropion exposures, seizures were noted in 15%, compared with less than 1% for unintentional exposures [74]. Conduction delay noted on ECG has been reported in bupropion overdose [74–77] but occurs in only 2% to 3% of symptomatic overdoses (see Box 3) [74,75]. The observed conduction delay does not appear to lead to ventricular arrythmias [75] or to respond to sodium bicarbonate therapy [77].

Venlafaxine. Like bupropion, venlafaxine is a unique class: an inhibitor of norepinephrine and serotonin and, to a lesser extent, dopamine reuptake

[73]. Cardiotoxicity has been reported, including tachycardia, widened QRS, and arrythmias (see Box 3) [78,79]. Two reviews found that venlafaxine had only modest effect on the QRS compared with TCA [72,80]. Seizures, however, are common with venlafaxine, occurring between 8% and 14% in two case series [72,80].

Other psychiatric medications

Antipsychotic agents. The first-generation antipsychotic agents (eg, chlorpromazine) may lower the seizure threshold. Of the "novel" antipsychotic agents, clozapine and olanzapine have been associated with seizures [81,82]. In general, novel antipsychotic agents antagonize serotonin, dopamine, muscarinic, H₁, and α_1 receptors [73]. There is little experience with this class of antipsychotics in overdose. Two case reports of patients with history of seizure disorder and one of a patient without such a history have documented seizures temporally related to the addition of olanzapine [83–85].

Lithium. Lithium continues to be a challenging overdose to manage. Last year there were 5296 exposures and 13 deaths reported to United States poison centers [1]. Despite lithium's having been used for over a century [86], little is known about its pharmacologic mechanism, although it likely has effects on neuronal ion transport and inhibition of reuptake of norepinephrine and serotonin [73]. Features of intoxication include vomiting, tremor and myoclonus, ataxia, mental status changes, and seizures [86,87]. Toxicity may result in persistent neurologic sequelae and usually involves cerebellar dysfunction, including ataxia and dysarthria [88]. No antidotal therapy for lithium intoxication exists, and treatment has hence focused on supportive measures, intravenous hydration and anticonvulsants, gastrointestinal decontamination, and enhanced elimination by means of hemodialysis. Lithium does not significantly adsorb to activated charcoal [86]. Whole bowel irrigation using polyethylene glycol solution may be effective if instituted soon after overdose of a sustained-release preparation [89]. The use of the cation exchange resin polystyrene sulfonate (SPS) has been investigated as a potential modality of reducing lithium concentration. In both animal models [90,91] and humans [92,93], SPS treatment shortened elimination half life and area under the plasma concentration-time curve. However, the use of SPS in lithium intoxication is not universally recommended and carries a theoretic risk for hypokalemia [86]. Controversy exists regarding both the effectiveness of and indications for the use of hemodialysis, especially in chronic intoxication [94]. The decision to institute hemodialysis is complex and should be based on interpretation of serum levels in the context of timing of the overdose (usually 8 to 12 hours postingestion), acute versus chronic intoxication, renal function, and clinical symptomatology [86,94].

Opioids

Propoxyphene

Overdose of propoxyphene results in a clinical presentation similar to that of TCA, including mental status depression, cardiotoxicity, and seizures [95]. Cardiotoxicity may manifest as bradycardia, tachycardia, hypotension, and QRS interval prolongation (see Box 3) [28,95]. In one series of propoxyphene overdoses, seizures were observed in 10% of patients, whereas 48% developed hypotension and approximately 20% exhibited widened QRS [28]. Propoxyphene-induced cardiotoxicity, like that induced by TCA, may be due to myocardial fast sodium channel blockade and is responsive to sodium bicarbonate therapy [96,97].

Tramadol

Tramadol is an analgesic with weak mu-opioid receptor agonist and inhibits serotonin and norepinephrine reuptake [98]. Tramadol has been reported to cause seizures in therapeutic use [99] and overdose [100]. Seizure risk appears to be higher with chronic dosing [99]; however, one case control study cosponsored by McNeil Pharmaceuticals found no increased seizure risk compared with other analgesics [101]. One review of 87 tramadol-only overdoses found the incidence of seizures to be 8% [27]. Naloxone reversed sedation in four of eight patients, with one report of seizure following its use [27].

Meperidine

Meperidine is metabolized by N-demethylation to normeperidine or hydrolysis to meperidinic acid, both of which are renally excreted [26]. Accumulation of normeperidine, either following administration of large doses of meperidine or in persons with renal insufficiency, may lead to myoclonic activity and seizures [25,26].

Natural agents

Water hemlock

Water hemlock (*Cicuta douglasii*), commonly referred to as wild carrot, is profoundly toxic. This plant contains cicutoxin, a neurotoxin that causes seizures [102]. Intractable seizures and death have been reported from even a few bites of the root [102,103]. Other than traditional care, there is no specific antidotal therapy.

Mushrooms

The cytotoxic mushroom *Gyromitra esculenta*, or "false morel," is frequently mistaken for the edible true morel or *Morchella* sp. These mushrooms contain gyromitrins, a family of hydrazines that are metabolized to monomethylhydrazine, which is structurally related to INH and some types of rocket fuel [104]. The pathophysiology of hydrazines is discussed in the INH section. Ingestion may result in delayed gastrointestinal symptoms, seizures, and hepatic and renal toxicity [105]. Severe intoxications are rare in the United States and occur more frequently in Eastern Europe [1,104].

Ephedra

In December 2003, the US Food and Drug Administration banned an herbal supplement for the first time. Sale of the supplement ephedra (Ma Huang) was banned because of large numbers of reported adverse effects [106]. Haller and Benowitz [107] reviewed adverse events that were either possibly or probably related to the consumption of ephedra and found that seizures occurred in 7% of the events. Other herbal supplements reported to cause seizures include black cohosh, bearberry, kava kava, yohimbe, monkshood, pennyroyal, and guarana [108].

Anticonvulsant overdose

"Paradoxical seizures" from anticonvulsant overdose are uncommon; however, among the anticonvulsants, carbamazepine and phenytoin toxicity appear to induce this clinical phenomenon [109,110]. Valproic acid toxicity produces significant mental status depression and coma, cerebral edema, and hypotension, but seizures are generally not observed [109,111,112].

Heavy metals

Acute exposure to lead, arsenic, and thallium may result in severe toxicity and neurologic manifestations. Each of these metals may be found in a wide array of industries, but lead exposure from the environment is still common [113]. Thallium and arsenic share the distinction of being used for homicidal poisoning [113]. In acute overdose these metals share many similarities in clinical presentation. Symptoms may include severe gastrointestinal symptoms and neurologic manifestations, including confusion, delirium, encephalopathy, and seizures [113,114]. In addition to supportive measures, decontamination with whole bowel irrigation may be helpful when radiopaque material is seen in the gastrointestinal tract [89]. For severe acute toxicity, chelation therapy with dimercaprol (British Anti Lewisite, BAL) for arsenic, BAL/ethylenediaminetetraacetic acid (EDTA) for lead, or Prussian blue for thallium should be instituted [113,115].

Miscellaneous agents

Isoniazid

Like the *Gyromitra* mushroom species discussed above, INH is metabolized to hydrazines. In overdose, these cause a functional pyridoxine (vitamin B6) deficiency by inhibition of pyridoxine phosphokinase, the enzyme that converts pyridoxine to active B6 [116,117]. Activated B6 is required by glutamic acid decarboxylase to convert glutamic acid to GABA.

Decreased levels of GABA are believed to lead to seizures. Severe lactic acidosis may develop as a result of seizure activity. INH also inactivates nicotinamide adenine dinucleotide (NAD) and interferes with NAD synthesis. Decrease in functional NAD inhibits the conversion of lactate to pyruvate, resulting in more profound lactic acidosis [117]. Acute INH overdose is associated with a triad consisting of seizures refractory to conventional therapy, severe metabolic acidosis, and coma [117]. Initial manifestations may include nausea, vomiting, ataxia, tachycardia, mydriasis, and CNS depression, which could mimic an anticholinergic toxidrome [116]. One retrospective chart review evaluated 52 cases of INH overdose and reported associated complications [118]. Seizures were found in 100% of patients, CNS depression in 53%, vomiting in 45%, leukocytosis in 75%, metabolic acidosis in 29%, elevated hepatic enzymes in 21%, and elevated creatine phosphokinase (CPK) in 60% [118].

Activated charcoal readily absorbs INH. When given concomitantly with INH, activated charcoal will diminish toxicity [119]; however, patients often present several hours after ingestion. One study of healthy volunteers found that administration of activated charcoal 1 hour after INH dose resulted in a 20% decrease in area under the plasma concentration-time curve, which was not statistically significant [120]. Benzodiazepines should be first-line agents for seizures [116]. Seizures may be refractory to benzodiazepines, however, because these require the presence of GABA for their anticonvulsant activity. If benzodiazepines are unsuccessful, barbiturates should be used. As soon as INH overdose is suspected or confirmed by history, intravenous (IV) pyridoxine should be administered [116]. Pyridoxine will terminate seizures, possibly reverse coma [121], and improve lactic acidosis. The dose for an unknown ingestion is 5 g IV. When the amount of INH ingested is known, pyridoxine should be given in a dose of 1 g IV for each gram of INH ingested [116,117]. A hospital's supply of IV pyridoxine may be insufficient to treat a significant INH overdose. One study found that approximately 50% of pediatric institutions had less than 5 g of IV pyridoxine available [122].

Methylxanthines

Methylxanthines antagonize adenosine receptors and increase cAMP through inhibition of phosphodiesterase and beta-adrenergic activity [123,124]. Seizures are a frequent sequela of theophylline toxicity and do not appear to be solely due to its effects at the adenosine receptor [123]. Other causes may include depletion of pyridoxine [125] and inhibition of GABA [126]. A large retrospective review of 399 cases of theophylline toxicity (122 cases from overdose) found that the most common clinical effects of theophylline toxicity included nausea and vomiting (79%), tachycardia (75%), hypokalemia (28%), and seizures (27%) [124]. Seizures are less likely to occur with serum levels of less than 60 mg/dL [124], but they have been reported with therapeutic or mildly elevated levels [127].

First-line therapy for seizures should include benzodiazepines or barbiturates. Additionally, because theophylline may affect pyridoxine levels, a rationale may exist for the use of pyridoxine as adjunctive therapy [125]. Phenytoin is not recommended for theophylline-induced seizures. In animal models, phenytoin was not effective treatment [128] and actually lowered seizure threshold in one study [129]. Short-acting beta blockers may also be helpful for the hemodynamic effects of theophylline, even in the face of hypotension [124]. Additional treatment of severe theophylline toxicity should include enhancing its elimination with multidose activated charcoal and hemodialysis [124,130].

Diphenhydramine

Diphenhydramine is an antihistamine (H_1) with anticholinergic and sedating properties [73]. Overdose may produce significant anticholinergic symptoms, QRS prolongation, and seizures [131,132]. One series of 136 diphenhydramine overdoses reported seizures in less than 5% of cases [132].

Local anesthetics

The local anesthetics are associated with cardiotoxicity and neurologic symptoms in overdose. Ropivacaine and bupivacaine probably possess greater cardiotoxicity than lidocaine [133]. Overdose and seizures have been reported from oral administration of viscous lidocaine [134], from large subcutaneous infiltration [135], from IV overdose [136], and in association with the use of bupivacaine for Bier blocks [137,138]. Treatment of local anesthetic toxicity is supportive and includes benzo-diazepines for seizures. Phenytoin lowered seizure threshold and increased mortality in an animal model [139]. Another animal study found that propofol was as effective as midazolam for lidocaine-induced seizures [140]. Propofol is an attractive agent for additional study, given that lipid emulsion is a promising experimental treatment for lidocaine-induced cardiotoxicity [141,142].

Organochlorine pesticides

Organochlorine pesticides encompass a diverse group of compounds with various effects on the CNS. Acute toxicities of dichlorodiphenyltrichloroethane (DDT) and hexachlorocyclohexane (Lindane) include seizures [143,144]. Lindane is a commonly used scabicide and pediculicide. It is thought to antagonize GABA_A receptors at the picrotoxin binding site [114]. Neurotoxicity, including uncontrolled psychomotor activity and seizures, has been reported from both topical application [145] and oral ingestion [144]. As a result, Lindane is no longer recommended in children or as a first-line scabicide in adults. Cholestyramine may be an effective agent for gastrointestinal decontamination of Lindane [146]. Treatment of seizures should employ benzodiazepines or barbiturates [144].

Terpenes

Toxicity from terpene hydrocarbons, namely camphor and thujone, may result in seizures [147,148]. Thujone is a constituent of the essential oil of wormwood and is contained in the illicit beverage absinthe [149]. Camphor was previously found in mothballs and is currently used in many over-thecounter rubefacient products [150]. Last year more than 10,000 camphor exposures were reported to United States poison centers, with only 10 major outcomes reported [151]. Mental status depression and seizures are frequently seen even with small ingestions [148,152]. Treatment should focus on airway protection and termination of seizures with benzodiazepines or barbiturates. A rationale may exist for nasogastric aspiration of liquid ingestions for patients presenting early after exposure, but there is no published experience with this approach. Enhanced elimination of camphor with lipid dialysis has been reported but is unlikely to be available [153].

Treatment of drug- and toxin-associated seizures

A rational approach to consider for every patient presenting with a potential toxicologic condition includes attention to airway, breathing, and circulation, focused history and physical examination, rapid glucose determination and ancillary diagnostic testing, gastrointestinal decontamination, enhanced elimination, and specific or antidotal therapy.

When the clinician is faced with a patient seizing from an uncertain cause, the history is of paramount importance, because few drugs or toxins will be easily diagnosed by laboratory testing. When indicated, specific laboratory testing based on history and clinical presentation may be helpful to narrow the differential diagnosis. Distinguishing characteristics of many drug- and toxin-associated seizures are discussed in the earlier section on differential diagnosis and clinical presentation. When managing suspected toxininduced seizures, it is imperative not to overlook coexisting head injuries, spinal injuries, rhabdomyolysis, infection, or hyperthermia.

By virtue of administering large doses of sedative agents or the presence of refractory seizures, endotracheal intubation may be required for airway protection and ventilation. Neuromuscular blockade will likely be necessary to facilitate intubation. Succinylcholine, despite having favorable kinetics, has drawbacks in regard to increasing potassium and possibly intracranial pressure. Shorter-acting, nondepolarizing agents, such as rocuronium, are preferred [6]. Long-acting neuromuscular blocking agents should be avoided; if they are used, electroencephalographic monitoring should be performed [154].

A large body of literature deals with the treatment of SE. It is difficult to determine whether these treatment strategies will be equally efficacious for DTS. No trials have investigated an optimal anticonvulsant or treatment algorithm for DTS. In general, benzodiazepines followed by barbiturates are the first- and second-line therapies for DTS unless a specific antidote is

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available. Lorazepam appears to be the preferred agent for SE [6,155]; however, diazepam and midazolam are also appropriate.

Although phenytoin is the second-line agent indicated in the treatment of most causes of seizures, it is usually not efficacious in the management of drug-induced seizures. Phenytoin is not effective for TCA or ethanol withdrawal seizures [63,156,157] and may worsen seizures from theophylline, local anesthetics, and Lindane [128,129,139,144]. IV phenytoin has also been associated with arrhythmias and hypotension, probably owing to the rate of infusion [158].

IV administration of valproic acid is a new strategy for SE [159,160], but its role in DTS remains to be evaluated. Reports of hemodynamic compromise in pediatric patients exist [161,162], but other studies have reported no hemodynamic effects even with large doses [160]; valproic acid did not alter blood pressure in a group already on vasopressors for hypotension [163]. IV dosing for various anticonvulsants is listed in Table 1.

Much controversy exists in the area of gastrointestinal decontamination; no one modality is universally recommended. Patients presenting with seizures or with the anticipation of seizures introduce additional potential for morbidity, especially in regard to airway protection and aspiration. Patients being considered for gastrointestinal decontamination procedures should either be alert with intact protective airway reflexes or have their airway secured by cuffed endotracheal intubation if obtunded. In general, it is not recommended to intubate patients solely for the purpose of performing gastrointestinal decontamination procedures; the decision should be based on the clinical status of the patient.

| Ta | bl | e | 1 |
|----|----|---|---|
| | | | |

| Anticonvulsant | Loading dose (mg/kg) | Comments |
|------------------------|--------------------------|--|
| Benzodiazepines | | |
| Diazepam | Titrate up to 0.15 mg/kg | Onset: 1–5 min |
| Lorazepam | Titrate up to 0.1 mg/kg | Onset: 5 min |
| Midazolam | Titrate up to 0.2 mg/kg | Onset: 1–5 min |
| Other agents | | |
| Phenobarbital | 15–20 mg/kg | Loading infusion rate: 50-75 mg/min |
| Phenytoin ^a | 15–20 mg/kg | Loading infusion rate: 50 mg/min |
| Propofol | 3–5 mg/kg | Maintenance infusion: 30-100 mcg/kg/min |
| Valproic acid | 15–25 mg/kg | Loading infusion rate: 20–50 mg/min (up to 6 mg/kg/min) |
| Pyridoxine | | Pyridoxine dose should equal estimated INH dose |
| | | If amount is unknown, 5 g should be administered |

Intravenous anticonvulsant dosing

With all sedatives, larger doses may be needed to control-status seizures, and endotracheal intubation may be required for airway protection and ventilation.

^a Phenytoin is generally not expected to be helpful for drug and toxin-induced seizures and may cause harm (see text for details) [129].

| Therapy | Agent |
|----------------------|---|
| Atropine/pralidoxime | Organophosphate insecticides and nerve agents |
| BAL/EDTA | Lead and arsenic |
| Prussian blue | Thallium |
| Dextrose | Insulin, sulfonylurea, or other hypoglycemic agent |
| Hemodialysis | Lithium, theophylline, salicylates |
| Hyperbaric oxygen | Carbon monoxide |
| Octreotide | Sulfonylurea |
| Pyridoxine | INH, Gyrometria mushrooms, hydrazines, theophylline |

 Table 2

 Agents that may require specific therapy in addition to common therapy

Activated charcoal may be considered at a dose of 1 g/kg for agents that are known to adsorb to it. The airway must be intact to reduce the likelihood of aspiration. Whole bowel irrigation may be considered for body stuffers, body packers, heavy metals, or large ingestions of sustained-release preparations. It cannot be recommended for patients who are actively seizing, who have hemodynamic instability, or who have an ileus. Multidose activated charcoal may be useful for enhancing the elimination of methylxanthines or carbamazepine [130]. Hemodialysis is useful for enhancing the elimination of lithium, methylxanthines, and salicylates. Directed or antidotal therapy is discussed in individual drug or toxin headings and is summarized in Table 2.

Summary

Drug- and toxin-associated seizures may result from exposure to a wide variety of agents. Obtaining a comprehensive history behind the exposure is generally more helpful than diagnostic testing. Most DTS may be managed with supportive care, including benzodiazepines, except in the case of agents that require a specific intervention or antidote.

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