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Treatment of drug-induced seizures

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Seizures are a common complication of drug intoxication, and up to 9% of status epilepticus cases are caused by a drug or poison. While the specific drugs associated with drug-induced seizures may vary by geography and change over time, common reported causes include antidepressants, stimulants and antihistamines. Seizures occur generally as a result of inadequate inhibitory influences (e.g., gamma aminobutyric acid, GABA) or excessive excitatory stimulation (e.g. glutamate) although many other neurotransmitters play a role. Most drug-induced seizures are self-limited. However, status epilepticus occurs in up to 10% of cases. Prolonged or recurrent seizures can lead to serious complications and require vigorous supportive care and anticonvulsant drugs. Benzodiazepines are generally accepted as the first line anticonvulsant therapy for drug-induced seizures. If benzodiazepines fail to halt seizures promptly, second line drugs include barbiturates and propofol. If isoniazid poisoning is a possibility, pyridoxine is given. Continuous infusion of one or more anticonvulsants may be required in refractory status epilepticus. There is no role for phenytoin in the treatment of drug-induced seizures. The potential role of ketamine and levetiracetam is promising but not established.

Introduction

Seizures are a common toxic complication of numerous drugs and poisons, as well as drug withdrawal syndromes. Studies have estimated that 6% of new-onset seizures and up to 9% of status epilepticus cases are due to drug toxicity [1, 2]. Several case series have identified a variety of drugs and other substances associated with seizures [3–8]. Antidepressants, diphenhydramine, stimulants (including cocaine and methamphetamine), tramadol and isoniazid account for the majority of cases. However, substances implicated in drug-induced seizures have evolved over time as new drugs enter the market. For example, a California case series analyzing calls to the regional poison control centre found that over a 10 year interval, newer antidepressants replaced tricyclics as the most common cause of seizures and the frequency of cocaine and theophylline cases fell dramatically (with reports of theophylline decreasing to zero) [7]. Causes of drug-induced seizures also vary by geographic region. In two recent US studies bupropion was the leading drug [5, 7], whereas a Swiss study found mefenamic acid and citalopram were the most commonly reported seizure-causing drugs [8]. In Iran [9] and Austrialia [10] tramadol overdose is a common cause of seizures. In developing countries and agricultural regions herbicides and insecticides are an important consideration [11–15].

Most drug-induced seizures are self-limited and do not cause permanent sequelae. However, repeated or prolonged seizure activity may lead to irreversible neurological injury [16] as well as other life-threatening complications such as hypoxia, hypotension, pulmonary aspiration, hyperthermia, rhabdomyolysis and metabolic acidosis. In retrospective studies of drug-induced seizures reported to a regional poison control centre, status epilepticus (defined as continuous seizure activity lasting more than 30 min or two or more seizures without full recovery of consciousness between seizures) occurred in 3.6 % to 10% of cases [7, 17]. Thus, prompt treatment including good supportive care and administration of effective anticonvulsant drugs are imperative. In this article, we review the mechanisms and treatment of drug-induced seizures.

Pathophysiology

Exposure to certain drugs and chemical substances can result in the abrupt onset of altered mental status with or without

localized or generalized motor activity (convulsions) combined with epileptic-like brain activity (seizures) seen on the electroencephalogram (EEG). This altered EEG electrical activity is the result of abnormal neuronal discharges that start in cortical or subcortical brain regions and may persist for an extended amount of time. This is not epilepsy, which is a disease state associated with recurrent spontaneous paroxysmal epileptic brain activity on EEG with or without associated motor activity. While the clinical condition of patients with epilepsy certainly can be made worse (with more severe or frequent seizures) by exposure to many drugs or chemicals, this is usually not considered a primary drug-induced seizure.

Drug-induced seizures can occur as a direct result of altering neural pathways and specific excitatory or inhibitory transmitters and receptors within those pathways. Figure 1 offers a simplified representation of these processes. In Figure 1A, the normal balance is represented between excitatory and inhibitory neural pathways, transmitters and receptors. Gamma aminobutyric acid (GABA) mediated receptors and pathways are inhibitory, while those involving glutamate are excitatory. Decreasing excitatory pathway activity, neurotransmitters or receptor function, or increasing inhibitory actions, leads to reduced neural activity that can manifest itself as clinical sedation (Figure 1B). Reducing inhibitory pathways, neurotransmitters or receptor function by drugs or chemicals, or increasing excitatory activity, can result in over activation and seizures (Figure 1C). If the effect of a drug is to reduce GABA activity (e.g. isoniazid or a cephalosporin), seizures can result. Drugs such as barbiturates or benzodiazepines can increase the functional effect of GABA-mediated inhibitory activity and as a result prevent or terminate drug-induced or drug-withdrawal seizures. Using this model, the sudden withdrawal of high doses of drugs applied chronically that have a strong inhibitory neuronal function (e.g. ethanol or barbiturates) can result in acute withdrawal seizures. This may be exacerbated by up-regulation of the excitatory N-methyl-D-aspartate (NMDA) subtype of the glutamate receptor/pathway [18, 19].

Neuronal pathways are much more complex than represented in Figure 1 [20]. Besides GABA and glutamate, central nervous system (CNS) neurotransmitter systems known to be involved in seizure generation in animal models of epilepsy include norepinephrine, dopamine, serotonin, acetylcholine, histamine [21, 22] and adenosine [23, 24]. Presynaptic and postsynaptic adenosine receptor stimulation generates an inhibitory effect on many excitatory pathways such as those that are glutamate mediated. Presynaptic adenosine receptor stimulation may reduce the release of the excitatory neurotransmitter glutamate and postsynaptic adenosine receptor stimulation may directly inhibit excitatory pathways. Adenosine type one (A_1) receptor antagonists like theophylline and caffeine can reduce seizure thresholds and prolong seizures by interfering with mechanisms of seizure termination.

Because CNS neuronal interactions are complex, with both direct and indirect drug and chemical effects, and variable pro- or anticonvulsant effects depending on concentration, no single mechanism exists for explaining all cases of drug-induced seizures. For example, in animal models both acetylcholine receptor antagonists [25] and acetylcholinesterase inhibitors [12, 26] can cause seizures. In animal models of nerve agent poisoning there is an early phase in which anticholinergic agents are effective in terminating seizures, followed by a phase in which these drugs are less effective and prolonged epileptiform activity appears to be mediated

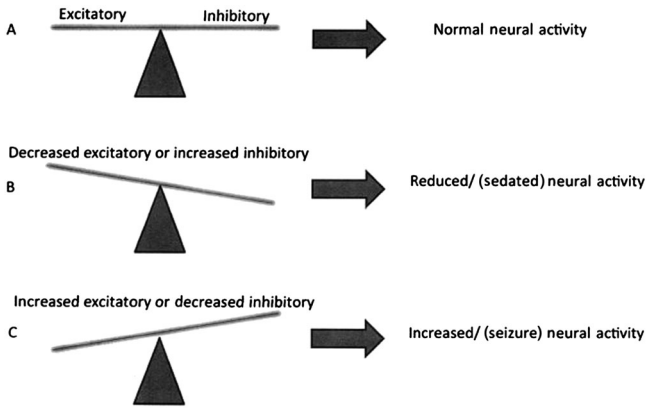

Figure 1

A model of drug- or chemical-induced effects on neural activity. (A) The normal balance between excitatory and inhibitory neuronal activity, receptor function, transmitters and pathways. (B) Decreasing excitatory or increasing inhibitory neuronal activity can result in sedation, and is likely involved in terminating seizure activity. (C) When increased excitatory or decreased inhibitory neuronal activity results from drug or chemical exposure, seizures may occur. Although greatly simplified in this model, in actuality feedback loops, transmitter depletion and up-and down-regulation of receptor numbers and sensitivities are but a few of the complexities of this physiological process

by stimulation of NMDA receptors by excitatory amino acids [26].

Many drugs and toxins can also cause seizures as a result of indirect effects on brain perfusion, oxygenation or metabolic disturbances. Toxic exposures can reduce brain blood flow by depressing cardiac contractility, vasomotor tone, heart rate or inducing cardiac arrhythmias. Pneumonia due to pulmonary aspiration of gastric contents or direct chemical injury to lung parenchyma can cause hypoxaemia. Other poisons, such as carbon monoxide and cyanide, can interfere with oxygen delivery or cellular oxygen utilization, simulating cellular hypoxia. Electrolyte and metabolic disturbances such as hyponatraemia, hypomagnesaemia and hypoglycaemia can also be an indirect cause of drug-induced seizures [4].

Some poisons can induce convulsive activity that resembles seizures but does not originate in the cerebral cortex. Glycine is the major inhibiotry neurotransmitter of motor neurons in the spinal cord and brain stem and contributes to the suppression of reflex arcs [27]. Strychnine competitively inhibits the action of glycine on postsynaptic receptors [28]. Strychnine poisoning results in so-called 'spinal seizures' (involuntary muscle contraction, myoclonus, hyperreflexia and opisthotonus) without loss of consciousness until the victim becomes hypoxic due to impaired ventilation [29]. Inhibition of presynaptic glycine release by tetanus toxin produces an identical syndrome [30].

Management of drug-induced seizures

Initial stabilization and investigation

Most drug-induced seizures manifest as generalized tonic-clonic motor activity (grand mal). Convulsive muscle activity, especially if prolonged, can lead to hypoxia, hypercarbia, pulmonary aspiration of gastric contents, lactic acidosis, hyperthermia and rhabdomyolysis. Initial treatment should include airway management with adequate oxygenation and ventilation, stabilization of the blood pressure and heart rate and rapid bedside testing of serum glucose concentration and core body temperature. Hyperthermia is a critical complication of status epilepticus and needs to be treated promptly to prevent death or serious end-organ damage [17]. If initial anticonvulsant therapy does not stop excessive muscle activity and the temperature remains above 40°C, neuromuscular paralysis should be employed along with external cooling measures. Note that after neuromuscular paralysis, central neuronal seizure activity may persist without peripheral convulsions, and EEG monitoring is recommended to monitor response to additional anticonvulsants. It is critical to monitor and correct abnormalities in serum glucose and electrolytes. Gastric decontamination and enhanced elimination or antidote administration may be appropriate in some patients, and consultation with a medical toxicologist is recommended.

Computed tomography (CT) is usually not necessary in patients with self-limited and uncomplicated drug-induced seizures. A prospective observation study showed that patients presenting to the emergency department with altered mental status or headache caused by poisoning or drug overdose had a low likelihood of abnormal findings on head CT scan [31]. However, another study found that 6.2% of patients presenting to ED with their first alcohol withdrawal seizure had an intracranial lesion on CT scan [32]. It is reasonable to consider a CT scan in patients with evidence of head trauma, focal or repeated seizures, focal neurological deficits or prolonged alteration of consciousness.

Figure 2 provides a stepwise approach to treatment.

Initial anticonvulsant therapy

Benzodiazepines Benzodiazepines are commonly recommended as the first line anticonvulsant therapy in drug-induced seizures. Benzodiazepines enhance $GABA_A$ activity by increasing the frequency of chloride channel opening, leading to neuronal hyperpolarization [33, 34]. If available, intravenous lorazepam is the preferred initial benzodiazepine, although intravenous midazolam is also widely used. We were unable to find any randomized controlled trial or prospective study regarding the effectiveness of benzodiazepines specifically for drug-induced seizures. However, a Cochrane review and a large randomized controlled trial for status epilepticus of any cause found that intravenous lorazepam was better than intravenous diazepam or intravenous phenytoin alone for cessation of status epilepticus [35, 36]. If intravenous access is not readily available, the more water-soluble midazolam can be given intramuscularly as it is readily absorbed by this route and is at least as safe and effective as intravenous lorazepam for prehospital seizure cessation [37]. Benzodiazepines can also be given via the intra-osseous route. Detailed dosage information for commonly used anticonvulsants is shown in Table 1. Large doses of benzodiazepines can contribute to respiratory depression. In addition, some benzodiazepines are formulated with the diluent propylene glycol, which is metabolized to lactic acid and can cause hyperosmolality and acidosis in patients receiving prolonged high dose infusion [38].

Second line anticonvulsants

Barbiturates Barbiturates are recommended as the next treatment if benzodiazepines are ineffective [33, 34]. Barbiturates also bind to the $GABA_A$ complex, prolonging the duration of chloride channel opening and chloride ion influx. In addition, at high concentrations some barbiturates directly open the chloride channel [34].

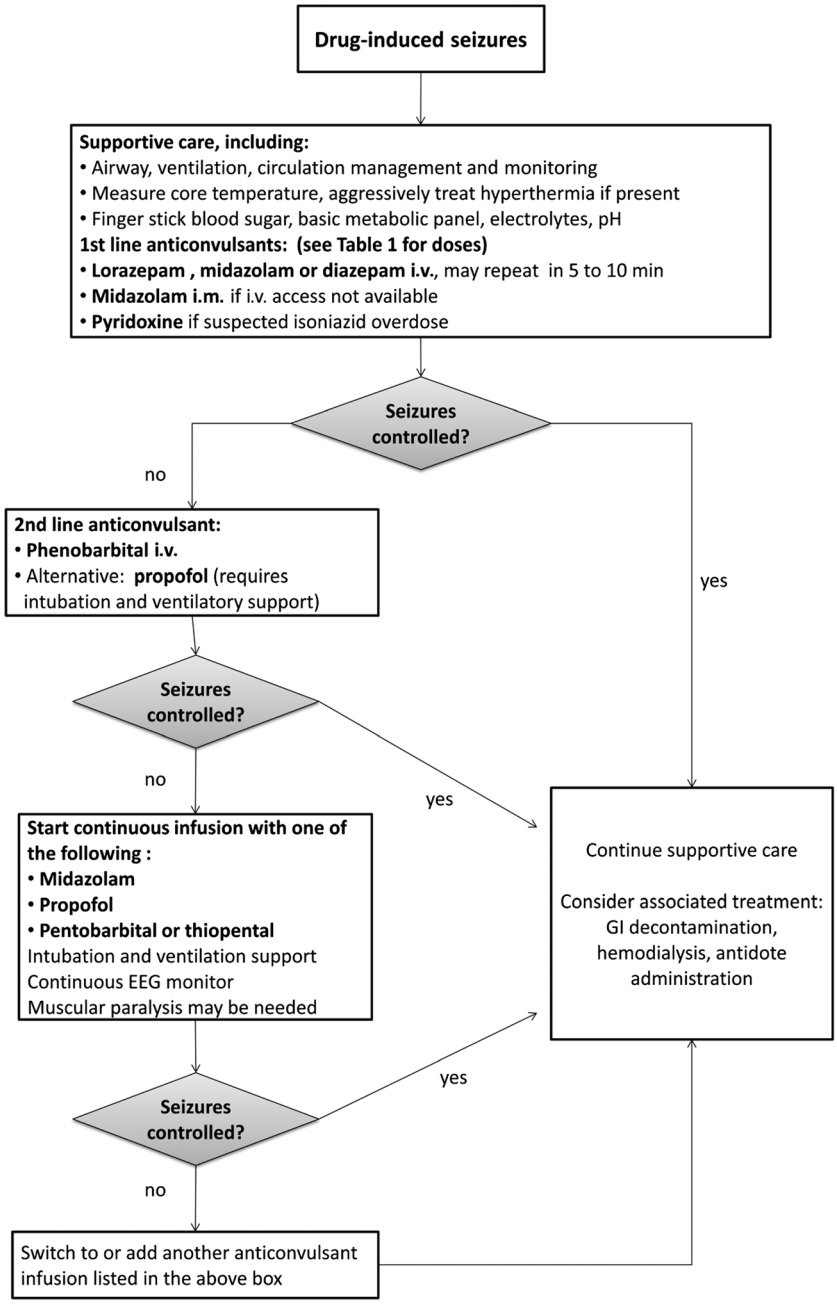

Figure 2

Recommended treatment approach for drug-induced seizures

Among various available barbiturates, phenobarbital is usually the drug of choice. Dosages for phenobarbital, pentobarbital and thiopental are shown in Table 1. Phenobarbital is as effective as lorazepam for patients with status epilepticus, although it requires a longer infusion time [36]. Barbiturates have been reported effective in treating citutoxin and fluvoxamine-induced seizures which were not responsive to benzodiazepines and phenytoin [39, 40]. Experimental evidence supports that phenobarbital is superior to phenytoin in prevention of theophylline-induced seizure and death [41, 42]. However, no prospective controlled studies have evaluated the effectiveness of barbiturates as a second line anticonvulsant for drug-induced seizures.

Propofol Propofol is an intravenous anaesthetic. Its anticonvulsant mechanism of action is not totally understood. It enhances GABA binding to its receptor on the chloride channel and it may also open the chloride channel directly at high concentrations [43, 44]. It may have an additive or synergistic effect when used with benzodiazepines or barbiturates [45, 46].

Table 1

Anticonvulsants for drug-induced seizures [48, 78, 79]

Drug	Initial/Loading dose	Continuous infusion
Diazepam	5–10 mg i.v. (children: 0.2–0.5 mg kg^{-1}) over 2–5 min (max 10 mg/dose); may repeat every 5–20 min.	Note: contains propylene glycol.
Lorazepam	2–4 mg i.v. (children: 0.05–0.1 mg kg^{-1}, max 4 mg/dose); may repeat every 5–10 min (max rate: 2 mg min^{-1}).	Note: contains propylene glycol.
Midazolam*	i.v.: 0.05–0.2 mg kg^{-1} (children: 0.1–0.3 mg kg^{-1}) over 20–30 s (max 10 mg). i.m.*: 0.1–0.2 mg kg^{-1} (max 10 mg).	0.05–2 mg kg^{-1} h^{-1} titrated to EEG.
Pentobarbital†	5–15 mg kg^{-1} i.v. (children: 3–15 mg kg^{-1}) no faster than 1 mg kg^{-1} min^{-1}.	0.5–5 mg kg^{-1} h^{-1}, titrated to EEG.
Phenobarbital†	15–20 mg kg^{-1} i.v. no faster than 1 mg kg^{-1} min^{-1}. An additional 5–10 mg kg^{-1} dose may be given 10 min after initial dose.	Note: contains propylene glycol.
Propofol†‡	1–2 mg kg^{-1} i.v.	1.5–10 mg kg^{-1} h^{-1} titrated to EEG. Note: doses >5 mg kg^{-1} h^{-1} over prolonged periods may increase risk of propofol infusion syndrome.
Thiopental†	2–7 mg kg^{-1} i.v. no faster than 1 mg kg^{-1} min^{-1}.	0.5–5 mg kg^{-1} h^{-1} titrated to EEG.

*Consider intramuscular route when there is no i.v. access. †May cause deep sedation requiring endotracheal intubation. ‡Propofol is not recommended for infants and young children. [78]

Propofol also antagonizes the NMDA receptor, theoretically an advantage where seizures may be secondary to increased NMDA activity [47].

Propofol is usually reserved for patients with refractory status epilepticus [48]. It was as effective as thiopental in treatment of refractory status seizures (unselected causes) [49, 50]. Refractory convulsive activity caused by amoxapine [51] and star fruit (*Averrhoa carambola*) [52] was successfully suppressed by propofol infusion (although EEG confirmation was not reported). The dose required for status epilepticus is generally greater than that for sedation and may approach the dose required for induction of general anaesthesia (2–5 mg kg^{-1}) [53]. Patients will nearly always require endotracheal intubation and ventilatory support. Propofol has been suggested as a second line anticonvulsant for drug-induced seizures [53, 54]. However, it should be noted that there are no randomized controlled trials or large case series regarding the use of propofol for drug-induced seizures.

Disadvantages of propofol are its relatively high cost, the potential to cause hypertriglyceridaemia, propofol infusion syndrome and neuroexcitatory events such as opisthotonos, muscle rigidity and choreoathetoid movements [45]. Propofol infusion syndrome is a rare but fatal complication, mostly reported in children and adolescents after prolonged high dose propofol infusion. Features include bradycardia, hypotension, rhabdomyolysis and metabolic acidosis. A dose of more than 5 mg kg^{-1} h^{-1} over a prolonged period should be avoided in paediatric patients. [55]

Pyridoxine (vitamin B6) Pyridoxine is the drug of choice for seizures due to suspected isoniazid (INH) toxicity, and may also be useful in poisoning by certain hydrazine-containing *Gyromitra* mushrooms [56]. These toxins interfere with the enzyme that converts glutamate into GABA, reducing GABA levels. Pyridoxine is an essential cofactor in GABA synthesis [57], and it effectively restores GABA synthesis and suppresses seizures within minutes of administration [58]. Empiric dosing (5 g i.v. in an adult and 70 mg kg^{-1} i.v. in a child) should be administered if the INH dose is not known. If the amount ingested is known, then a pyridoxine dose equivalent to the amount of INH ingested (gram for gram) should be given. Synergistic effects between diazepam and pyridoxine have been reported in dogs and rats [59, 60].

Not recommended: phenytoin Phenytoin binds to and inhibits voltage-dependent sodium channels, increasing the membrane threshold for depolarization, which inhibits the propagation of seizure activity [61]. Although it may be effective in preventing the spread of abnormal electrical activity from an epileptic focus, its role in drug-induced seizures is questionable. It would not be expected to suppress the characteristically diffuse lowering of seizure threshold or oppose the increase of neuronal excitability induced by drugs or toxins [34]. Numerous experimental studies and human case reports have shown that phenytoin does not effectively terminate seizures produced by a variety of substances [62]. Moreover, based on animal studies, phenytoin may be harmful when used to treat seizures induced by lidocaine, theophylline or tricyclic antidepressants [41, 63, 64]. Phenytoin was also ineffective in preventing recurrent alcohol withdrawal seizures in several prospective, randomized, double-blind studies [65–67]. We do not recommend its use for drug-induced seizures.

Other drugs There are only a few reports of other possible anticonvulsants for drug-induced seizures. Valproic acid was reported to increase the threshold for theophylline-induced seizures in an animal study [68] and it has been recommended for the prophylaxis of clozapine-induced seizures [69]. Further studies are needed to verify these findings. During status epilepticus, $GABA_A$ receptors become less responsive while NMDA receptors become more responsive [20, 70] and there may be a role for NMDA/glutamate antagonists [71]. Ketamine proved useful in at least one case report of refractory status epilepticus [72] and in two cases of tetramine poisoning in which seizures were refractory to benzodiazepines and thiopental [14]. Levetiracetam is a novel anticonvulsant with several potential mechanisms of activity. It has been reported effective in patients with status epilepticus [73] and in animal models of nerve agent and pilocarpine neurotoxicity [74, 75]. Other potentially effective therapies still in development include adenosine analogues [76] and cannabinoid receptor agonists [77].

Conclusion

While many drug-induced seizures are brief and uncomplicated, prolonged or recurrent seizure activity may cause serious complications. Benzodiazepines are the first-line treatment for drug-induced seizures, with addition of pyridoxine if isoniazid or other hydrazine toxicity is suspected. If benzodiazepines fail to terminate seizures, second-line agents include barbiturates and propofol. There is no role for phenytoin in the management of drug-induced seizures. The role of valproic acid, levetiracetam, ketamine, adenosine agonists and other drugs is not established.

Competing Interests

All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare no support from any organization for the submitted work, no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years and no other relationships or activities that could appear to have influenced the submitted work.

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