

ToxUpdate

Regional Poison Control Center, Birmingham, AL

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1-800-222-1222

Paradoxical Seizures in Newer Anticonvulsant Medications

By Laura Read, RPh, CSPI, Regional Poison Control Center

Anticonvulsants are the fifth most common source of prescription drug overdose in the United States. Anticonvulsants act primarily through one, or a combination of five, mechanisms. These mechanisms and medications that act on these mechanisms include:

1. **Inhibition of sodium channels:** carbamazepine, lacosamide, lamotrigine, oxcarbazepine, phenytoin, valproic acid, topiramate, zonisamide
2. **Inhibition of calcium conductance:** ethosuximide, zonisamide, valproic acid, pregabalin, gabapentin
3. **Inhibition of excitatory neurotransmitters N-methyl-D-aspartate (NMDA):** perampanel, felbamate, lamotrigine, topiramate
4. **Stimulation of Inhibitory neurotransmitter gamma aminobutyric acid (GABA):** benzodiazepines, phenobarbital, tiagabine, vigabatrin
5. **Interaction with Synaptic Vesicle Protein (SV2A proteins):** levetiracetam

Many anticonvulsants are known to cause paradoxical seizures in an overdose scenario, with carbamazepine (Tegretol®) being the most commonly cited culprit of overdose seizures. Newer anticonvulsants, including topiramate (Topamax®), tiagabine (Gabitril®) and lamotrigine (Lamictal®) have also been found to cause seizures in overdoses. Clinicians have limited experience with assessment and treatment of overdose from newer anticonvulsant medications. A contradictory cause of seizures is the ability of anticonvulsants in overdose to induce convulsions. This is a well-recognized complication, although the mechanism is poorly understood. One theory is that high concentrations of the anticonvulsant may have a depressant effect on inhibitory interneurons. This may result in disinhibition of excitatory neurons and facilitation of epileptic discharges.

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Special Interest Articles

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Did you know?

The U.S. Food and Drug Administration has added a boxed warning to eszopiclone (Lunesta®), zaleplon (Sonata®) and zolpidem (Ambien). The agency cautioned that rare but serious injuries and even death have occurred as a result of patients taking these drugs and then engaging in complex sleep behaviors while not fully awake, including sleepwalking, sleep driving, and other activities.

Ultra-Rapid Metabolizers of CYP2D6 and Overdose Outcomes

By Leanna Barker, PharmD, PGY-1 Pharmacy Practice Resident, Children's of AL

“When an overdose of a medication is suspected, it is important to consider the metabolism of that drug.”



Cytochrome P450 (CYP) enzymes are found in most tissues throughout the body, most abundantly in the liver. Polymorphic differences in the function of these enzymes and the significance of those differences have been described in relation to drug action, metabolism, and toxicity. CYP2D6 has multiple gene variations that can result in either decreased or increased enzymatic activity, which may correlate to poor metabolizers and extensive metabolizers, respectively. A select group of extensive metabolizers can be described as ultra-rapid metabolizers. Many opioids, antidepressants, and antipsychotics are extensively metabolized by CYP2D6, further emphasizing the importance of these polymorphic variations and their effect on toxicity.

When an overdose of a medication is suspected, it is important to consider the metabolism of that drug. If the drug is converted to a less active or inactive metabolite, the effects of an ultra-rapid metabolizer are expected to be less than that of a poor metabolizer. In contrast, however, if a drug is enzymatically converted to a more active or more potent metabolite, an ultra-rapid metabolizer has an increased risk of toxicity. For example, codeine is an opioid analgesic that is converted to morphine by CYP2D6. Ultra-rapid metabolizers will have increased levels of morphine after ingesting a therapeutic amount of codeine due to enzymatic variation. This patient is now at risk for increased sedation and respiratory depression, which is heightened in an overdose scenario. Other pharmacological agents that are converted to active metabolites by CYP2D6 include tramadol, oxycodone, and dextromethorphan, which all carry an increased risk of toxicity in those patients who are ultra-rapid metabolizers.

In January 2018, the U.S. Food and Drug Administration (FDA) required labeling changes for any prescription cough and cold product containing codeine or hydrocodone. These labeling changes included limiting use to adults 18 years and older due to the increased risk of misuse, abuse, addiction, overdose, death, and slowed or difficult breathing in children. This was in addition to the boxed warning for life-threatening respiratory depression and death in which most cases were associated with ultra-rapid metabolism. The CYP2D6 gene has more than 100 alleles that have been described. The percent of individuals with varying enzymatic activity differs amongst different ethnic groups. Approximately 25% of prescription medications are affected by CYP2D6, therefore, it is important to understand the differing effects in an overdose situation.

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Anticonvulsants and Seizures (continued)

Topiramate is indicated as adjunct therapy for the treatment of partial seizures, Lennox–Gastaut syndrome, and generalized tonic-clonic seizures. It has also been used in the treatment of cluster headache, essential tremor, binge-eating disorder, acute mania, Tourette’s and Prader-Willie syndromes, neuropathic pain, bipolar disorder, drug and alcohol dependence, and to facilitate weight loss in obese patients. The exact mechanism remains unknown. It may be able to block voltage-dependent sodium channels, augment the activity of the neurotransmitter gamma-aminobutyrate as some subtypes of GABA-A receptor, antagonize the α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)/kainate subtype of the glutamate receptor, and inhibit the carbonic anhydrase enzyme, particularly isozymes II and IV. Studies have shown that patients with no prior treatment of topiramate are more likely to present with toxicity. Status epilepticus has developed during the first two to six hours following an overdose along with non-anion gap metabolic acidosis that can persist for days.

The mechanism of action for lamotrigine is similar to of carbamazepine and phenytoin, but it is used for a greater spectrum of seizure disorders. This suggests that lamotrigine may have additional actions. Lamotrigine is a phenyltriazine anticonvulsant and one proposed mechanism is that it inhibits sodium channels, resulting in membrane stabilization of neurons and control of excitatory neurotransmitter release. Lamotrigine reduces both simple and complex partial seizures and secondarily generalized tonic-clonic seizures. Generalized seizures, particularly absence seizures, atonic or drop seizures, and Lennox–Gastaut syndrome have a tendency to be more responsive to lamotrigine than partial seizures do. At therapeutic concentrations, lamotrigine activity is selective for high-frequency firing. At toxic concentrations, both spontaneous sodium channel activity and high-frequency firing are blocked. Lamotrigine is also effective in the treatment of mood disorders such as bipolar disorder through the inhibition of serotonin re-uptake.

Tiagabine is used as adjunctive therapy in adults and children 12 years of age and older to treat simple or complex partial seizures, with or without secondary generalization. Tiagabine blocks the neuronal and glial reuptake of gamma aminobutyric acid (GABA) after its release from postsynaptic GABA receptors, thereby enhancing GABA-mediated inhibition at central nervous system (CNS) sites. Tiagabine has no effect on sodium or calcium channels. Many theories by which tiagabine causes seizures have been proposed. One theory is, different brain regions may variably respond to GABA, and excessive GABA-mediated thalamic inhibition by tiagabine may result in seizures.

Anticonvulsants can cause severe toxicity and may be associated with seizure, coma and death. Treatment should include initial control of seizures with a benzodiazepine and if seizures persist or recur, administer phenobarbital or propofol. Symptomatic and supportive care is the mainstay of treatment after most anticonvulsant overdoses. Valproic acid may require, L-carnitine, while sodium bicarbonate may be required after a carbamazepine overdose. Consult with the Regional Poison Control Center at 1-800-222-1222 after any anticonvulsant overdose.

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The Truth About Elimination Half-life and How it Applies to Toxicology

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Pharmacokinetic and pharmacodynamic principles should be utilized in the assessment and management of a patient in the setting of a toxic ingestion.¹ Of the principle pharmacokinetic parameters, elimination half-life is perhaps the most easily understood. Elimination half-life expresses a change in concentration in units of time, specifically the time taken for the concentration of a drug to fall to half its original value.² Elimination half-life is often utilized to evaluate how long to monitor for signs and symptoms of adverse effects after an ingestion. However, there are multiple factors which contribute to the disruption of pharmacokinetic processes and parameters in a patient with acute poisoning.³

Elimination half-life is a dependent variable related directly to volume of distribution and inversely to clearance and has limited predictive value in single dose pharmacokinetics.⁴ When utilized in multiple dosage pharmacokinetics, elimination half-life has a much better predictive value for the rate and extent of drug accumulation. Additionally, during an acute toxic ingestion, pharmacokinetic parameters may be altered by saturation, alteration of gastrointestinal motility, increased volume of distribution, alterations of acid-base balance, or decreased organ perfusion.¹ Understanding the variability of pharmacokinetics for toxic ingestions is largely referred to as toxicokinetics.

A foundational understanding of pharmacokinetics and toxicokinetics is important for optimal patient care during toxic ingestions. Additionally, these principles are critical in proper utilization of antidotes, as many antidotes use variable doses and have an elimination half-life that is much shorter than the poison they are used to treat.¹ Elimination half-life can be severely altered in toxic ingestions depending on the offending agent. For example, the opioid oxycodone extended-release has a half-life in therapeutic ingestion of ~5 hours, however, gastrointestinal motility can significantly slowdown in the setting of toxic ingestion resulting in a much longer half-life. Aspirin in the setting of toxic ingestion converts from first order to zero order kinetics and has an alteration in protein binding going from 90% to 30%. These pharmacokinetic alterations significantly affect the predicted half-life thus rendering half-life alone as the parameter for monitoring a patient unreliable.⁵

While elimination half-life may be an important factor in the appropriate assessment and management of a patient in the setting of a toxic ingestion, it should not be utilized as the sole pharmacokinetic parameter employed.¹ Full utilization of pharmacokinetic and toxicokinetic parameters should be utilized for optimal clinical care.¹ Specifically, in single dose toxic ingestions, clinicians should consider volume of distribution and clearance in addition to elimination half-life.⁴ Elimination half-life is an important pharmacokinetics parameter, but care must be taken to employ it appropriately in the context of toxicology.

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