

TOXALERT

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Overdoses Of Newer Anticonvulsants

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Overdoses with anticonvulsants are frequently reported. In 2004, a total of 40,021 exposures to anticonvulsants were reported to the American Association of Poison Control Centers. A little more than half of these exposures were to “new” anticonvulsants: gabapentin, lamotrigine, topiramate, levetiracetam, tiagabine, oxcarbazepine, vigabatrin, zonisamide and pregabalin. We will review the toxicity of these new agents and discuss management of overdoses.

Gabapentin (Neurontin®)

Gabapentin is a cyclohexane derivative of GABA, approved as adjunctive therapy for the management of partial seizures in adults and children and post-herpetic neuralgia. In a case series of 20 gabapentin overdoses, lethargy, ataxia and gastrointestinal symptoms developed within 5 hours and resolved over 4-24 hours. In one case report of a chronic overdose in a patient with renal failure, tremulousness and cognitive deficits were noted. The symptoms resolved following a dose adjustment. Catatonia following abrupt withdrawal of gabapentin is described. The treatment of patients with gabapentin overdose starts with administration of activated charcoal to limit absorption. There is no specific antidote. Patients with persistent neurologic symptoms need to be admitted to the hospital. Hemodialysis and hemoperfusion are not generally required, except in severely symptomatic patients with significant renal impairment.

Lamotrigine (Lamictal®)

Lamotrigine is approved as an adjunctive medication for the treatment of partial seizures in adults and pediatric patients. It is also approved for maintenance treatment of bipolar mood disorder. Lamotrigine binds to sodium channels and prolongs their recovery from inactivation. At therapeutic concentrations, the sodium channel blockade is selective. At toxic levels, the selectivity is lost and all sodium channels are inhibited, and some GABA enhancement is detected.

Neurologic manifestations such as lethargy, ataxia, nystagmus and gastrointestinal symptoms are described following lamotrigine overdose. A previously healthy toddler developed two seizures after an acute unintentional lamotrigine overdose. The lamotrigine level two hours post-ingestion was 3.8 mg/L. Repeat levels were lower. Seizure activity did

New anticonvulsants are responsible for over 50% of anticonvulsant overdoses reported to poison centers.

All of these drugs produce some degree of CNS impairment with notable differences in other toxic effects.

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not recur and the ataxia and muscle weakness resolved over 48 hours. Coma and cardiac conduction disturbances may also occur following large overdoses of lamotrigine. Therefore, lamotrigine behaves much like other sodium channels blockers, such as cyclic antidepressants, in overdose situations.

Chronic overdoses of lamotrigine result in multiorgan involvement, including rashes, elevation in hepatic aminotransferases, rhabdomyolysis and elevation of serum creatinine phosphokinase. The treatment of lamotrigine overdose starts with the administration of activated charcoal to limit absorption. Observation and ECG monitoring are recommended. Prolongation of the QRS interval beyond 100 msec requires admission to telemetry and administration of sodium bicarbonate 1-2 mEq/kg intravenously, until serum pH is 7.45-7.55. Lamotrigine-induced seizures should be treated with benzodiazepines. There are no data on the value of hemodialysis and hemoperfusion.

Topiramate (Topamax®)

Topiramate is a sulfamate-substituted monosaccharide approved as adjunctive therapy for adults with partial-onset seizures. It is also used for migraine prophylaxis and for the treatment of infantile spasms and other refractory epilepsies in infants and children. Topiramate binds to the *kainate* glutamate receptor subtype and blocks the Na⁺ entry into the neuronal cell.

Lethargy, ataxia, nystagmus, myoclonus, coma, seizures and status epilepticus are reported following topiramate overdose. Interestingly, repetition of words (echolalia) and repetitive movements of the mouth (oral-buccal dyskinesia) are reported. Non anion gap metabolic acidosis due to inhibition of renal cortical carbonic anhydrase may be present, along with hyperchloremia and hypokalemia (2.0-3.2 mEq/L). The metabolic acidosis appears within hours of ingestion and can persist for days.

Activated charcoal is recommended. Monitoring of electrolytes and blood gases is important. Severe hyperchloremic metabolic acidosis should be treated with sodium bicarbonate 1-2 mEq/kg intravenously. Systemic administration of sodium bicarbonate may impair the anticonvulsive effect of topiramate, however. Therefore, admission to a higher level of care is recommended in the context of sodium bicarbonate administration. Hemodialysis is recommended in severe overdoses associated with neurologic impairment, electrolyte abnormalities that have failed to respond to conventional therapy and/ or renal insufficiency. Hemodialysis is especially useful to correct intractable metabolic acidosis.

Tiagabine (Gabatril®)

Tiagabine inhibits the reuptake of GABA and is approved as an adjunctive treatment for focal and secondarily generalized seizures. It is also being prescribed for a variety of psychiatric disorders. Tiagabine inhibits the GAT-1 GABA transporter and prevents the re-uptake of GABA into presynaptic neurons.

Lethargy, tachycardia, facial myoclonus (grimacing), nystagmus and posturing are described in overdoses. The Maryland Poison Center has been contacted about many unusual manifestations of tiagabine poisoning, including bizarre facial grimacing and bizarre myoclonic jerks. At very high plasma levels, seizures and status epilepticus are reported. A previously healthy toddler developed three seizures after an unintentional overdose of tiagabine. Serum level of tiagabine was 530 ng/mL. An adult patient presented in status epilepticus and was misdiagnosed until a very high tiagabine level was reported and an acute overdose was confirmed. Most symptoms last 12-24 hours and result in no permanent neurologic sequelae.

Activated charcoal and supportive care are recommended for the management of tiagabine overdose. Seizures respond to administration of benzodiazepines and refractory status epilepticus should be treated with barbiturates.

**For poisoning or overdose questions and consultations,
call the Maryland Poison Center at
800-222-1222**

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Levetiracetam (Keppra®)

Levetiracetam is approved as an adjunct medication for the management of intractable epilepsy. Its mechanism of action is poorly understood, although it inhibits pre-synaptic N-type calcium channels. Recent research has illustrated that levetiracetam has both a neuroprotective and an anti-inflammatory effect. In one case report of levetiracetam overdose, lethargy, coma and respiratory depression were reported. Nystagmus was absent. Symptoms persisted for 24 hours. The management of levetiracetam overdoses starts with the administration of activated charcoal to limit absorption. Monitoring for CNS depression and supportive care are recommended.

Oxcarbazepine (Trileptal®)

Oxcarbazepine is a keto-analog of carbamazepine which functions as a prodrug. It is rapidly converted to the pharmacologically active 10-monohydroxy-10-oxocarbazepine metabolite. Its mechanism of action is similar to carbamazepine (Tegretol®), except it is a less potent inducer of CYP3A4. Oxcarbazepine overdoses present with nystagmus, ataxia, and dysarthria, much like carbamazepine overdoses. Oxcarbazepine will be detected by the carbamazepine assay and levels will be in the order of 1-3 mg/L. Treatment of oxcarbazepine overdoses closely resembles that of carbamazepine and starts with the administration of activated charcoal. Occasionally, and especially when faced with very large overdoses, multiple doses of activated charcoal are recommended.

Zonisamide (Zonegran®)

Zonisamide inhibits the flow of calcium through low voltage T-type calcium channels, thus reducing the "pacemaker" current. It also inhibits sodium channels and possibly carbonic anhydrase. Somnolence is a commonly reported adverse effect. Although experience with overdoses of zonisamide is limited, one paper reported status epilepticus, coma and death following an acute zonisamide overdose. Management of zonisamide overdose includes administration of activated charcoal and monitoring for CNS effects.

Pregabalin (Lyrica®)

Pregabalin is a new gabapentinoid. Chemically related to gabapentin, it is more potent, achieving efficacy at lower doses. Like gabapentin, pregabalin modulates gabaminergic neurotransmission and calcium channel activity. It is approved as an adjunct for the treatment of partial seizures and for the management of diabetic neuropathic pain and post-herpetic neuralgia. Overdoses of pregabalin have not been reported. Thus far, however, limited unpublished experience with pregabalin shows that it is fairly well-tolerated in acute overdoses. The management of pregabalin overdoses includes administration of activated charcoal and monitoring for CNS depression.

In conclusion, new anticonvulsants are now responsible for over 50% of anticonvulsant overdoses. All overdoses to new anticonvulsant agents will present with some degree of CNS impairment but there are quite a few notable differences. Although serum electrolytes are important to obtain in all instances, they are especially important in topiramate and zonisamide overdoses because of their capacity to inhibit carbonic anhydrase activity. Specific serum levels of anticonvulsants are not usually recommended in the acute setting, except when the patient develops seizures or status epilepticus.

Treatment of these overdoses begins with administration of single-dose activated charcoal. Correction of electrolyte abnormalities is recommended, especially in cases of topiramate and zonisamide overdoses. There are no effective antidotes. Anticonvulsant-induced seizures usually respond to benzodiazepines and barbiturates. QRS prolongation should be treated with sodium bicarbonate. Hemodialysis can be considered in cases of life-threatening overdoses of gabapentin and topiramate, but is not generally required; supportive care is sufficient in most instances. It is unclear whether hemodialysis affects the outcome of pregabalin or zonisamide overdoses.

References for this article are available on request.



TOXNOTES

A 2 year old child was seen in my ED one hour after the ingestion of 1 or 2 pellets of a rat poison containing a long-acting anticoagulant. I called the poison center and was told that the ingestion was sub-toxic, but her INR was elevated. Is the abnormal INR related to the ingestion?

It could possibly be related to the ingestion if the history is not accurate and an extremely large amount was ingested at least 12 hours ago, or if the ingestion was chronic. A more likely explanation for the increased INR is that when taking the sample, the tube was not filled adequately. Studies show that when small (2.7 mL) pediatric tube fill volume is less than 90%, INR values are often falsely elevated. In one study, mean INR's in healthy volunteers were as high as 4.0 with 60% fill volume. In patients receiving warfarin, INR's of 4.9-10.35 were reported at 60% fill volume with actual INR's of 2.0-3.6 at 100%. Inaccurate results also may occur when using 5 mL tubes that are <60-80% full. The evacuated tubes contain a fixed amount of citrate (an anticoagulant). When tubes are not completely filled, the concentration of citrate is increased, leading to inaccurate INR results. When a falsely elevated INR is suspected, repeat the test making sure that the tube is completely filled.

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How Are We Doing?

The Maryland Poison Center would like to ensure that it is providing health professionals in MD with quality service. Please help us by completing an online survey. The survey will only take 3-5 minutes of your time. You'll find it on our website at www.mdpoison.com. We thank you for your time and input!

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This is the last issue of ToxAlert that will be printed and mailed to individuals. Emails with a link to new issues posted on our website will continue to be sent to those who have signed up for our email list. If you aren't already on our email list, go to our website, www.mdpoison.com, and click on *Sign-up*. If you do not have email, call 410-563-5583 to continue receiving ToxAlert.