GABAPENTIN (Neurontin®)

Gabapentin is an antiepileptic drug that was approved by the United States Food and Drug Administration (FDA) in 1993 for the adjunctive treatment of partial seizures with and without secondarily generalized seizures in adults. More recently, though, the drug is being used therapeutically for diabetic peripheral neuropathy and other neuropathic pain syndromes. With this expansion in gabapentin prescribing practices, there arises the concern for increased intentional and unintentional use.

Clinical Pharmacology

Gabapentin, 1-aminomethyl cyclohexanecarboxylic acid, is a molecular analog of the brain's inhibitory neurotransmitter gamma-aminobutyric acid (GABA). Although it was originally described as a centrally active GABA agonist acting on the postsynaptic GABA receptors, it is now recognized that gabapentin does not react at the GABA receptors; furthermore, it does not alter GABA uptake nor does it interfere with GABA transaminase. Therefore, its exact mechanism of action remains to be identified. While gabapentin is water soluble, the structure's cyclohexane rings allows it to be transferred through the blood-brain barrier unchanged where it is thought to bind to the L-amino acid carrier protein. Here, it may act at a unique receptor.

Gabapentin is 60% bioavailable in tablet and capsule formulation. Its volume of distribution is 0.6-0.8 L/kg. The therapeutic maintenance dose for patients over 12 years of age is 900-1800 mg/day administered in three divided doses and 10-15 mg/kg/day in three divided doses for patients aged 3-12 years. Gabapentin is recognized in the gastrointestinal tract by the L-amino acid carrier protein, a protein which actively transports the drug across the gut membrane. When gabapentin binds to this system, it allows for saturation of the transport mechanism. Thus, bioavailability decreases with increasing dose. It is weakly protein bound (3%) and not metabolized by the liver, making it an unlikely candidate in drug-drug interactions. Instead, gabapentin is excreted unchanged by the kidneys with an elimination half life of 5-7 hours. The half-life has been found to be as long as 52 hours in patients with renal failure. Therefore, it is important to make dosage adjustments in those patients who have renal insufficiency.

Clinical Toxicology

There is a limited data available on the toxicity of gabapentin in humans; this information is based on case reports and from the known pharmacology of the drug. Since its bioavailability decreases with increasing doses, the potential for toxicity is not thought to be as severe as in other anticonvulsant ingestions. Case reports reveal that the most prominent symptoms are secondary to central nervous system effects. These may include somnolence, ataxia, dizziness, slurred speech, and diplopia. Gastrointestinal effects including diarrhea are reported also in overdose. The serious cardiovascular and neurological sequelae seen with ingestion of other anticonvulsants such as carbamazepine and phenytoin are not seen with gabapentin.

A case report of a gabapentin overdose describes a 16-year-old girl who presented to the emergency department 8 hours status post reportedly ingesting 48.9 grams (800 mg/kg) of gabapentin (163 capsules of the 300 mg gabapentin formulation). At 6 hours post ingestion, the girl complained of dizziness and also diarrhea that had occurred during sleep. In the emergency department, the girl was lethargic but arousable. The patient's vital signs, physical exam, and ECG were all normal. Treatment performed by the Emergency Department staff included gastric lavage without capsule return followed by 50 grams of activated charcoal with 70% sorbitol. In-hospital toxicology screening of the blood and urine was positive for cocaine but all other laboratory tests were within normal limits. 18 hours after the ingestion, the girl was alert and oriented without further sequelae.

An acute overdose of both gabapentin and lamotrigine is reported in a 17-year-old female adolescent. Approximately one hour post ingestion of 12 grams of gabapentin (40 capsules of the 300 mg gabapentin formulation) and 2 grams of lamotrigine tablets (20 tablets of the 100 mg lamotrigine formulation), she presented to an outpatient clinic with complaints of feeling drowsy; slurred speech was noted on her exam. Her pulse was 100bpm, temperature 36°C, and her blood pressure was 150/100 mmHg. The Emergency Department staff decontaminated her with syrup of ipecac followed by one liter of water. Twenty minutes later she was given another 10 ml of ipecac and she vomited about 1 liter of fluid that appeared similar to both medications' yellow-peach color. Next, she was given 50 grams of charcoal. She became very drowsy and lethargic with significant dystarthis and motor coordination problems. Two hours post ingestion, the girl's blood pressure returned to 120/80 mmHg. The rest of her vital signs remained within normal limits and she was stabilized by the next morning.

A case report describes a 32 year old, 89 kg man who presented one hour status post ingestion of 91 grams of gabapentin (1022 mg/kg), 54 grams of delayed-release valproic acid (607 mg/kg), beer, and whiskey. The patient reportedly complained of feeling dizzy, sleepy, and depressed with suicidal ideation. Physical exam was notable for nystagnus, slurred speech, and a drowsy appearance. His airway was intact with ethanol detected on his breath. Vital signs were stable except for a heart rate of 100 bpm. The Emergency Department staff decontaminated him with gastric lavage followed by 100 grams of activated charcoal in sorbitol; he also received intravenous fluids. Many gabapentin capsules were revealed while lavaging the patient; interestingly, two hours post lavage, the patient vomited twenty intact depakote® tablets as he was further decontaminated with activated charcoal. The patient was then given 10 mg of intravenous metoclopramide followed by 100 grams of activated charcoal in water without further vomiting episodes. His initial serum ethanol level was 136 mg/dl while his valproic acid level was 107.1 mg/L on arrival followed by a peak level of 193.9 mg/L 5 hours post ingestion. Gabapentin levels obtained by high pressure liquid chromatography were found to be...
44.5 mg/L one hour post ingestion, 22.8 mg/L 5 hours post ingestion, and 16.4 mg/L 10 hours post ingestion. The patient was admitted to a telemetry unit where he stayed without further symptoms. A 30 year-old female with renal insufficiency who had been prescribed gabapentin 600 mg three times daily and valproic acid 1250 mg/day in divided doses presented to her rheumatologist three weeks after starting these medications; the physician noted tremors and difficulties with cognition. Serum levels revealed a valproic acid level of 71 mcg/ml (therapeutic range 50-100 mcg/ml) and a gabapentin level of 85mcg/ml (presumed therapeutic level 2-15 mcg/ml, see "Monitoring" section below). Her dose of gabapentin was decreased to 600 mg after each dialysis treatment and her anticonvulsant therapy altered; her neurological symptoms then resolved and a three month repeat serum gabapentin level was 12 mcg/ml. This case reiterates the fact that gabapentin is excreted unchanged by the kidneys.

**Monitoring**

Although therapeutic and toxic ranges of plasma serum levels have not been definitively established, case studies suggest that levels of 2-15 mcg/ml (2-15 mg/L) to be therapeutic for gabapentin. Careful attention to the airway is important given the frequency of somnolence and risk of aspiration in gabapentin overdose. Monitoring parameters to consider include pulse oximetry, blood gases and a chest x-ray. Kidney function tests should be performed since gabapentin is primarily renally eliminated; the potential for gabapentin toxicity may be amplified in the setting of renal failure due to accumulation of the drug. Given the pharmacokinetic and toxicokinetic properties of the drug, an asymptomatic patient who is observed in the Emergency Department for 4 to 6 hours without a change in exam could be safely sent home if the ingestion was unintentional; a referral for psychiatric evaluation will be necessary if the ingestion was intentional. Symptomatic patients need monitoring until their physical exam findings resolve. In the case studies reviewed above, patients were admitted for a 24-hour observation period.

**Treatment**

Unlike other anticonvulsants, gabapentin has not been shown to be an extremely toxic drug in overdose. Therefore, gabapentin poisoning can be treated primarily with supportive care and decontamination measures. Induced emesis is not recommended given the risk of central nervous depression. Gastric lavage could be considered if the ingestion occurred within one hour of presentation to a health care facility; activated charcoal, however, is the mainstay of treatment from a decontamination standpoint. There is no specific antidote for the drug. While the pharmacological properties of gabapentin, namely its water solubility, low volume of distribution, and lack of protein binding, indicate that it would be amenable to hemodialysis, enhanced elimination is usually not needed. The exception to this recommendation is in the case of a patient with renal insufficiency or an elderly person with renal function that has decreased with age. As discussed, gabapentin is excreted unchanged by the kidneys and thus dosing adjustments must be made in those individuals exhibiting renal insufficiency.

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**REFERENCES:** (Lead Author Only)