

A 23 Year Old Woman who Presents with New Onset SE

Brandon Wills, DO, MS

A 23 year-old female presented to the emergency department following several generalized seizures. The patient was found at home by family members, initially in a somnolent state, followed by seizure activity. She arrived by EMS and was given diazepam en route. Upon arrival the patient was somnolent, could answer only simple questions, and proceeded to have another generalized seizure.

Initial history was absent while awaiting family members arrival.

Physical examination revealed a somnolent woman who responded only to simple questions with primarily unintelligible answers. Airway was open and intact. Pulse was 116, BP 90/50, respirations 24/minute, and oxygen saturation of 97% on non-rebreather mask. Temperature was 37.1. The patient moved all extremities and no facial asymmetry was seen. Pupils were equal, 5 mm, and reacted to light. The skin was warm, pink, and without rashes. Chest was clear, heart was tachycardic without murmur/ gallop/ or rub.

While in the emergency department the patient was treated with several doses of benzodiazepines and continued to have brief, intermittent seizures. She was subsequently intubated for airway protection and placed on a diprovan infusion for sedation.

Family members arrived and informed the emergency physician that the patient was recently started on INH prophylaxis and an empty bottle of 30 tablets were found at home.

Key Clinical Questions

What would be your initial management plan for a patient presenting with seizures?

How would you approach the patient with seizures refractory to “standard” therapy?

What is the role of laboratory testing in these patients?

What adjunctive therapy could be considered?

What is the pathophysiology of INH overdose?

How does the treatment of INH-induced seizures differ from other etiologies of seizure?

Key Learning Points

- The initial management of patients presenting with seizure should focus on the A,B,C's, termination of the seizure with benzodiazepines, and efforts to rapidly determine the etiology.
- When seizures are refractory to “standard” therapy, consider INH toxicity.
- The *Gyromitra* species of mushroom (false morel) share pathophysiology similar to INH toxicity
- When the diagnosis is established or at the time it is strongly suspected, pyridoxine (vitamin B6) should be administered.
- Recommended pyridoxine dose is 5 grams IV for an unknown ingestion, or, when the quantity of INH ingested is known, administer a gram IV B6 for every gram of INH ingested.

Isoniazid-Induced Seizures

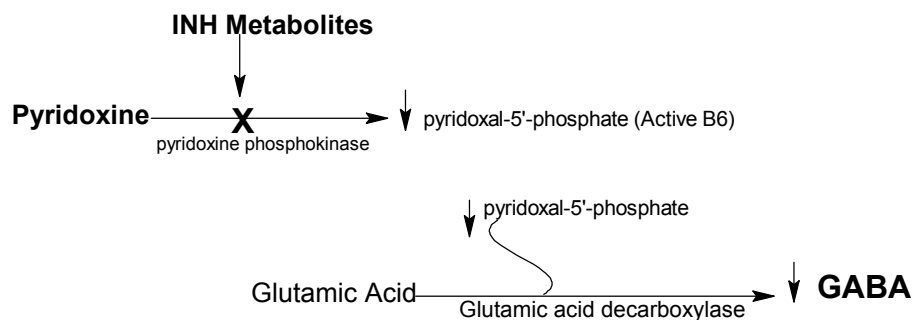
Background, Risk Factors and Epidemiology

According to 2001 data from the American Association of Poison Control Centers *Toxic Exposure Surveillance System* (TESS)¹, there were 426 reported cases of INH overdose. Of these, there were 70 moderate outcomes, 80 major outcomes, and one death.

A therapeutic INH dose is 5-15 mg/kg. Toxicity may be seen with doses >20 mg/kg, and is common above 40 mg/kg. Peak serum concentrations are reached in two hours.

Pathophysiology²

INH as well as toxins found in *Gyromitra* mushroom species, and even some types of rocket fuels are metabolized to hydrazines. In overdose, these cause a functional pyridoxine (vitamin B6) deficiency. This occurs by inhibition of pyridoxine phosphokinase, the enzyme that converts pyridoxine to active B6. Activated B6 is required by glutamic acid decarboxylase to convert glutamic acid to γ -amino butyric acid (GABA), an inhibitory neurotransmitter. Decreased levels of GABA are believed to lead to seizures (see diagram below).



Severe lactic acidosis develops as a result of seizure activity. INH also inactivates NAD and interferes with NAD synthesis. This decrease in functional NAD inhibits the conversion of lactate to pyruvate resulting in more profound lactic acidosis.

ED Presentation^{2,4,6}

Acute INH overdose is associated with a triad consisting of: seizures refractory to conventional therapy, severe metabolic acidosis, and coma.

Initial manifestations may include: nausea/ vomiting, ataxia, tachycardia, mydriasis, and CNS depression, which could mimic an anticholinergic toxidrome.

Patients often have improvement in mental status between seizures, or may be comatose. Metabolic acidosis can be severe, with pH ranging from 6.8-7.3 with elevated serum lactate levels.

One retrospective chart review⁴ evaluated 52 cases of INH overdose and reported associated complications. Seizures were found in 100% of patients, CNS depression (53%), vomiting (45%), leukocytosis (75%), metabolic acidosis (29%), elevated hepatic enzymes (21%), and elevated CPK (60%).

Chronic effects of INH include hepatotoxicity and peripheral neuropathy, however these are usually not clinically significant entities with an acute overdose.

Lab Studies

A reasonable laboratory evaluation would include initial bedside glucose determination, and serum electrolytes. If a toxic overdose is suspected, additional studies to evaluate the poisoned patient could include: electrocardiogram, serum salicylate and acetaminophen levels, arterial blood gas, hepatic enzymes, CPK, and +/- drugs of abuse screen. The differential diagnosis for patients presenting with seizures is broad and includes both toxin-induced and non-toxin-induced etiologies. Patient history will guide much of the diagnostic evaluation. For example, if an underlying seizure disorder was suspected, serum anticonvulsant levels (valproate, carbamazepine, and phenytoin) may be sought. Please refer to the section on general approach to toxin-induced seizures for more details.

INH levels are usually not available quickly enough to impact initial care but may be sought in an unknown ingestion consistent with INH intoxication.

Emergency Department Care

The initial management of any patients presenting to the emergency department with seizures is attention to airway, breathing, and circulation. Patients should be placed in a monitored bed, IV established, placed on high-flow oxygen, and have cardiac monitoring. Rapid bedside glucose determination should be performed. Often it will take time to determine the etiology of the seizing patient, however history from EMS and family members should be vigorously pursued.

Benzodiazepines should be first-line agents used for seizures. If benzodiazepines are unsuccessful, barbiturates may also be used. Phenytoin is not recommended for toxin-induced seizures. When INH overdose is suspected or confirmed by history, IV pyridoxine should be administered. Pyridoxine will terminate seizures, and may reverse coma⁵ and lactic acidosis. The dose for an unknown ingestion is 5 grams IV, at a rate of one gram given per two to three minutes. If the amount of INH ingested is known, pyridoxine should be given one gram IV for each gram of INH ingested.

It is important to note that a hospital's supply of IV pyridoxine may be insufficient to treat a significant INH overdose. One study³ found that approximately 50% of pediatric institutions had less than 5 grams of IV pyridoxine available. It is important to contact your hospital pharmacy

to find out the availability of pyridoxine. If IV pyridoxine is unavailable, contacting the regional poison center may reveal an institution in close proximity that could courier the antidote. It is not unreasonable that, while awaiting either transfer or arrival of IV pyridoxine that oral B6 tablets could be crushed and infused through a nasogastric tube.

Decontamination

Activated charcoal readily absorbs INH. When given concomitantly with INH, activated charcoal will prevent toxicity⁷; however, patients often present several hours after ingestion. One study of healthy volunteers found that administration of activated charcoal one hour after INH dose resulted in a 20% decrease in area under the plasma concentration-time curve, which was not statistically significant⁸. Additionally, INH toxicity is associated with both seizures and CNS depression, which can increase the risk for aspiration. For these reasons activated charcoal should be used cautiously when the airway is not protected.

Gastric lavage is another modality that has been recommended in previous reviews⁹, however there are many reasons that gastric lavage should be reserved for a highly select group of patients. Gastric lavage carries an aspiration risk, consumes valuable time, may promote tablet passage past the pylorus, and is often ineffective at removing tablets².

Consultations and Admission

Patients presenting with significant toxicity from INH overdose should be admitted to an intensive care setting. Consultation with a medical toxicologist through a regional poison center may be helpful to guide therapy.

References

1. Data taken from the American Association of Poison Control Centers, Toxic Exposure Surveillance System, 2001. www.aapcc.org/.
2. Goldfrank, Lewis, et al. 2002. Goldfrank's Toxicologic Emergencies, 7th ed. McGraw-Hill, New York. 44-54 (Gastric lavage), 656-660 (INH).
3. Santucci, K.A., et al. Acute isoniazid exposures and antidote availability. *Pediatric Emergency Care*. 1999; 15(2): 99101.
4. Panganiban, L.R., et al. Rhabdomyolysis in isoniazid poisoning. *Clinical Toxicology*. 2001; 39(2): 143-151.
5. Brent, Jeffrey, et al. Reversal of prolonged isoniazid-induced coma by pyridoxine. *Arch Intern Med*. 1990; 150:1751-1753.
6. Olson, Kent, et al. 1999. Poisoning & Drug Overdose, 3rd Ed. Appleton & Lange, Stamford. 195-196.
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8. Scolding, N., et al. Charcoal and isoniazid pharmacokinetics. *Human Toxicol*. 1986; 5:285-286.
9. Alvarez, F.G., Guntupalli, K.K. Isoniazid overdose: four case reports and review of the literature. *Intensive Care Med*. 1995; 21:641-644.

Patient Outcome

Diagnosis: INH Overdose

Toxicology consultation was obtained. Recommended IV pyridoxine 5 grams IV. Only 50 mg of IV pyridoxine was available at this institution. The Rush Medical Center antidote depot was contacted and 10 grams of IV pyridoxine was sent, via police to the medical center.

Pt. was given an initial dose of 5 grams IV pyridoxine. Seizure activity terminated. Repeat ABG: 7.31/34/503/17. There was no subsequent seizure activity. Pt. was extubated the following day. On hospital day three, the patient was transferred to a psychiatric facility.

Annotated Bibliography

1. Data taken from the American Association of Poison Control Centers, Toxic Exposure Surveillance System, 2001. www.aapcc.org/.

An valuable resource for tracking outcomes for various toxic exposures. Data only reflects what is reported to regional poison centers and therefore, for many toxins may be underreported.

2. Goldfrank, Lewis, et al. 2002. Goldfrank's Toxicologic Emergencies, 7th ed. McGraw-Hill, New York. 656-660.

A comprehensive textbook and excellent reference for acute care toxicology

3. Santucci, K.A., et al. Acute isoniazid exposures and antidote availability. *Pediatric Emergency Care*. 1999; 15(2): 99101.

Prospective, survey of pediatric institutions. 50% of respondents report having less than 5 g IV pyridoxine available.

4. Panganiban, L.R., et al. Rhabdomyolysis in isoniazid poisoning. *Clinical Toxicology*. 2001; 39(2): 143-151.

Retrospective chart review of INH overdoses. Categorized both clinical findings and laboratory abnormalities.

5. Brent, Jeffrey, et al. Reversal of prolonged isoniazid-induced coma by pyridoxine. *Arch Intern Med*. 1990; 150:1751-1753.

Case series of three patients. Reported reversal of coma/ lethargy with administration of IV pyridoxine.

6. Olson, Kent, et al. 1999. Poisoning & Drug Overdose, 3rd Ed. Appleton & Lange, Stamford. 195-196.

An excellent reference for acute care toxicology. A compact reference to keep in your Workbag.

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8. Micromedex/ Poisondex

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Questions

- 1. Initial management of patients presenting with seizures should include?**
 - a. Attention to airway, breathing, and circulation
 - b. Bedside glucose determination
 - c. Establishing IV/O₂/Cardiac monitoring
 - d. Administration of benzodiazepines
 - e. All the above

- 2. A seizure from INH overdose is due to?**
 - a. Hypoglycemia
 - b. Pyridoxine deficiency
 - c. Metabolic acidosis
 - d. Decrease in GABA formation
 - e. B and D

- 3. All of the following compounds can be metabolized to hydrazines except?**
 - a. INH
 - b. *Gyromitra* mushroom species
 - c. Rocket fuel
 - d. Theophylline

- 4. Initial dose of IV pyridoxine for INH overdose should be?**
 - a. 500mg PO
 - b. 5 grams IV for unknown overdose
 - c. Gram for gram of the ingested dose
 - d. Should be based on the gram stain
 - e. B & C

- 5. Metabolic acidosis found in INH overdose is due to?**
 - a. Seizure activity
 - b. Production of ketoacids
 - c. Decreased clearance of lactate
 - d. Severe diarrhea
 - e. A & C

Answers

1. Answer e.

Remember to “treat the patient, not the poison.” A rational approach to all seizing patients is attention to airway, breathing, circulation, checking a bedside glucose, establishing intravenous access and appropriate monitoring equipment, and using benzodiazepines as a first-line agent.

2. Answer e.

INH overdose causes a functional B6 deficiency resulting in decreased GABA production resulting in seizure activity, which is often refractory to “conventional” anti-seizure medications.

3. Answer d.

Isoniazid, the toxin found in *Gyromitra* (“false morel”) mushrooms and certain types of rocket fuel are hydrazine derivatives.

4. Answer e.

Pyridoxine is dosed gram per gram of estimated INH dose ingested. Pyridoxine should be administered IV, however if pharmacy supply is limited/absent, a oral dose could be crushed and given via nasogastric tube until an adequate IV supply is obtained.

5. Answer e.

Profound lactic acidosis occurs as a result of lactate production during seizures as well as decreased conversion of lactate to pyruvate.