The Perils of Playing Catch-up

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While awaiting evaluation for gastric discomfort, a 16-year-old girl experienced a sudden onset of generalized seizure.

Case

A 16-year-old girl, who recently emigrated from Haiti, was brought to the pediatric ED by her mother for evaluation of a 2-hour history of gastric discomfort. Upon arrival at the ED waiting area, the patient experienced a sudden onset of generalized tonic-clonic movement with altered sensorium, though she did not fall to the ground and was not injured. Vital signs from triage were: blood pressure, 110/76 mm Hg; heart rate, 112 beats/min; respiratory rate, 22 breaths/min; and temperature, 97°F. Oxygen saturation was 98% on room air.

The patient was immediately attached to a cardiac monitor, given oxygen via a face mask, and received airway suctioning. Despite receiving a total of 4 mg of lorazepam, the seizure continued. Physical examination revealed no signs of external injury, but the ongoing generalized status epilepticus made the examination difficult.

What are the causes of refractory seizures in an adolescent patient?

The differential diagnosis for pediatric patients presenting with refractory seizure is the same as that for adult patients and

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should include treatment noncompliance, infection, vascular event (eg, stroke, hemorrhage), trauma (eg, cerebral contusions), metabolic and electrolyte disturbances, anticonvulsant toxicity, and exposure to a convulsant toxin.

While certain drugs (eg, cocaine) may cause status epilepticus through a secondary effect such as ischemia or a bleed, some drugs can directly cause refractory seizures. A few drugs and toxins are responsible for the majority of such seizures: bupropion; carbon monoxide; diphenhydramine; ethanol (withdrawal); hypoglycemics; lead; theophylline; tramadol; and certain antibiotics, including cephalosporins, penicillins, quinolones, and, in particular, isoniazid (INH).[1]

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Case Continuation

Upon further history-taking, the patient's mother informed the ED staff that during a recent visit to a local clinic, her daughter tested positive on routine screening for tuberculosis and was given "some medications." The patient's mother further noted that her daughter was scheduled for a follow-up appointment at the same clinic later this morning. She believed the patient had taken "a few" of the prescribed pills at once to "catch-up" on missed doses prior to that appointment, and provided the ED staff with an empty bottle of INH that she had found in her daughter's purse.

What are the signs and symptoms of acute isoniazid toxicity?

Isoniazid toxicity should be suspected in any patient who has access to INH—even if the drug was prescribed for someone other than the patient. Acute toxicity develops rapidly after the ingestion of supratherapeutic doses of INH and includes nausea, abdominal discomfort, vomiting, dizziness, and excessive fatigue or lethargy. Patients can present with tachycardia, stupor, agitation, mydriasis, increased anion gap metabolic acidosis, and encephalopathy.

Seizures occur due to an INH-induced functional pyridoxine deficiency. Isoniazid inhibits pyridoxine phosphokinase, the enzyme that converts pyridoxine (vitamin B_6) to its physiologically active form, pyridoxal 5'-phosphate (PLP). Because the conversion of glutamate (an excitatory neurotransmitter) to gamma-aminobutyric acid (GABA; the body's main inhibitory neurotransmitter) is dependent on PLP, an excess of glutamate and a deficiency of GABA occurs following INH overdose. The result is neuroexcitation, which manifests as generalized seizures in affected patients.

The most consequential effect of INH overdose, however, is the development of seizure refractory to conventional therapy, such as benzodiazepines. This occurs because benzodiazepines are indirect-acting GABA agonists, and require the presence of GABA to elicit their effect. Therefore, due to the impairment of GABA synthesis, benzodiazepines are limited or ineffective as anticonvulsants. Although INH doses in excess of 20 mg/kg may result in neuroexcitation, refractory seizures are uncommon with doses <70 mg/kg.

Complications of chronic INH use include hepatotoxicity, and patients will present with jaundice, hepatomegaly, and right upper quadrant pain and tenderness. Isoniazid must be discontinued rapidly in patients demonstrating hepatotoxicity, and the risk/benefit of treatment reconsidered. Patients can also develop peripheral neuropathy while using INH therapeutically, and prophylactic vitamin B_6 supplementation is recommended for certain at-risk patients, such as those who are pregnant or breastfeeding.[2] Supplementation, however, neither reduces the risk of hepatotoxicity

nor prevents onset of seizure following an INH overdose (the B_6 dose is not sufficient enough to exert this effect).

How is acute isoniazid-induced seizure managed?

Management of patients with refractory seizure should initially include an assessment and management of the patient's airway, breathing, and circulation. Although seizures induced by INH toxicity are often resistant to benzodiazepines, these agents remain the first-line therapy. For patients who fail to respond to a reasonable trial of benzodiazepines (eg, lorazepam 6 mg intravenously [IV]), pyridoxine should be administered.[3] The recommended dose is 1 g pyridoxine per every 1 g of INH ingested—if the initial dose ingested is known—with a maximum dose of 5 g pyridoxine. If the initial dose of INH is not known, 70 mg/kg of pyridoxine, up to 5 g, is recommended. Repeated doses of pyridoxine can be administered if the seizure continues, up to a total dose of 10 g in an adult. At extremely high doses, pyridoxine itself can be neurotoxic, limiting the maximal antidotal dose.

Rapid initiation of pyridoxine is a challenge since typical stocks in most EDs are not in an adequate supply required for treatment. Additionally, a typical vial of pyridoxine contains 100 mg, highlighting the rare need to open dozens of vials for a single patient. Drawing up adequate doses of the IV formulation can be a challenge and time-consuming.

Regardless, the most reliable and rapid route of administration for pyridoxine is IV, at a rate of 0.5 to 1 g/min. Even if the seizure resolves prior to completion of the initial dose, the remaining doses should still be administered over a 4- to 6-hour period. Oral or (more likely) nasogastric administration of pyridoxine can be administered if the IV formulation is not available, but neither are optimal routes of delivery. Every effort should be made to stock pyridoxine in the antidote supply in the ED to avoid time delays involving finding, preparing, and administering the drug in these scenarios. Previous studies have found that most EDs are not prepared to handle pyridoxine replacement.[4,5]

Since benzodiazepines and barbiturates are GABA agonists with complementary mechanisms of actions to pyridoxine, they should be administered to potentiate the antiseizure effect of pyridoxine. If the seizure does not terminate, the use of propofol or general anesthesia may be required. Once the seizure is terminated, oral activated charcoal can be administered if the ingestion occurred within several hours of presentation. Given the rapid onset of effect of a large dose of INH, most patients will develop seizure shortly after exposure, limiting the benefits of both aggressive gastrointestinal decontamination and delayed activated charcoal. Charcoal also can be used for patients who overdose on INH but do not develop seizures.

Although the utility of a head computed tomography (CT) scan or laboratory studies is limited given the context of the exposure, these are generally obtained for patients with new-onset seizure. Since many patients with INH toxicity do not

seize, such a patient may have a lower seizure threshold due to the existence of a subclinical cerebral lesion or metabolic abnormality.

Case Conclusion

The patient's INH-induced refractory seizure was treated with pyridoxine. Her history suggested that she had ingested an unknown number of INH tablets within an hour. On this initial basis, an IV dose of 5,000 mg of pyridoxine was administered. The patient's seizures terminated within 2 minutes of the infusion, and no additional doses of pyridoxine were required. Given the lack of concern for self-harm, an acetaminophen concentration was not obtained. A urine toxicology screen was negative for cocaine and amphetamines, and a CT scan of the head was negative for any abnormality. The patient was admitted to the pediatric intensive care unit for status epileptics and was discharged home on hospital day 2 after an uneventful stay.

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