



The New York State Poison Centers

TOXICOLOGY

LETTER

COMPRISING THE NEW YORK CITY AND UPSTATE NEW YORK POISON CENTERS

CASE STUDIES IN TOXICOLOGY

Series Editor: Lewis S. Nelson, MD

Rats!

A Toxic Ingestion in an Unattended Toddler

Lewis S. Nelson, MD

Case

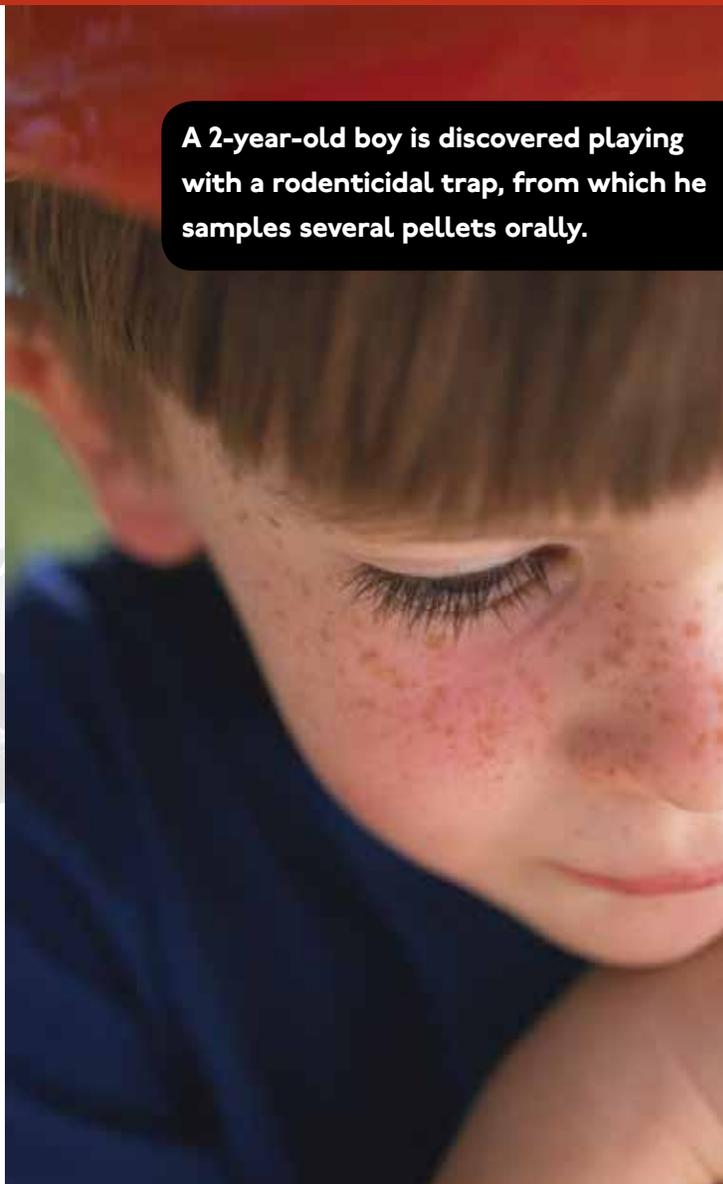
A 2-year-old child is found by his mother playing with a rodenticidal bait placed in the corner of the living room. The mother removes several pellets of the substance from the child's mouth and brings him to the ED within 30 minutes of exposure. The emergency physician finds him to be asymptomatic, with normal vital signs and a normal physical examination.

What rodenticides are available for home use?

The most likely exposure in this child is to a long-acting anticoagulant (LAA) rodenticide. LAAs, also known as super-warfarins, are widely available in retail outlets and are prized for their relative safety compared to previously available—and toxic—rodenticides, such as strychnine, zinc phosphide, and

Continued on page 2

A 2-year-old boy is discovered playing with a rodenticidal trap, from which he samples several pellets orally.



Program Announcements ♦♦

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Rats!

Continued from page 1

cholecalciferol. These substances, however, remain available for commercial use, and antiquated rodenticides, including barium, cyanide, and thallium, are occasionally found in attics by curious children.¹

In response to the recognized dangers of rodenticides and other pesticides, the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) and subsequent laws empower the Environmental Protection Agency to regulate these chemicals. Although legislation exists to remove LAAs from the consumer market due to lingering safety concerns among children and wildlife, it has not yet been implemented.

Rodenticides of particular and practical concern are those imported into the United States—by people who might not recognize the illegality or the dangers of these products. For example, Tres Pasitos, a product allegedly imported from the Dominican Republic, contains aldicarb, a potent carbamate cholinesterase inhibitor. This chemical has limited agricultural use in some states as an insecticide, but is not approved for use by unlicensed personnel and certainly not for home use. Clinical findings following exposure to Tres Pasitos and other carbamate cholinesterase inhibitors are those typical of exposure to the related organophosphorus insecticides, including increased glandular secretions, vomiting and diarrhea, lifethreatening bronchorrhea, and neuromuscular weakness (cholinergic toxidrome).² In addition to supportive care and attentive ventilatory management, the therapeutic approach to aldicarb toxicity includes the use of pralidoxime, a cholinesterase reactivator, along with progressive doses of atropine.

Another dangerous rodenticide, Dushuqiang, is illicitly imported from China. It contains tetramine (tetramethylene disulfotetramine), a potent convulsant that likely works by blocking inhibitory neuronal chloride channels. Ingestion may result in status epilepticus. Although only a single case has been identified in the United States, this rodenticide has produced epidemic poisoning and death in China.³ Various compounds, such as pyridoxine and sodium dimercaptopropane sulfonate, have purported beneficial effects in tetramine-poisoned patients, but none has been adequately studied.

Fortunately, the availability of most of these alarming toxins is limited, and most have a rapid onset of clinical effect. For the majority of asymptomatic patients with exposure to one of the older rodenticides, Tres Pasitos, or Dushuqiang, an observation period of several hours is generally sufficient to exclude poisoning. The corollary is that the failure to manifest overt signs of poisoning following a documented exposure to a rodenticide generally, though not always, implicates an anticoagulant agent.

What are anticoagulant rodenticides?

Humans and rodents share a similar physiology, and chemicals that are highly effective rodenticides, with a few exceptions, are also highly toxic to humans. The anticoagulant rodenticides are generally considered to be of low lethality to

humans, however. Theoretically, they should be equally toxic to both man and rodent, but they take advantage of the dramatically different living conditions of the two. Humans live a relatively atraumatic life in which being anticoagulated is compatible with longevity. Rodents, on the other hand, routinely are required to squeeze through holes, jump from heights, and undertake other potentially injurious actions. Thus, even humans who develop clinically relevant anticoagulation following a rodenticide exposure tend to have excellent outcomes, provided they do not develop spontaneous or provoked hemorrhage. The anticoagulant rodenticides have a mechanism analogous to warfarin: they prevent the activation of vitamin K, thereby inhibiting the activation of relevant clotting factors (II, VII, IX, X). Most are of the long-acting type, and even a single ingestion in rodent or human can produce anticoagulation lasting weeks or longer.

There were more than 9,500 exposures to LAA rodenticides reported to poison control centers in 2011, making these the second most frequently reported class of pesticide exposure after the pyrethroid/pyrethrin insecticides.⁴ As with many other poison exposures, the two common means by which exposures occur are intentional ingestion, usually in the setting of attempted suicide, and unintentional ingestion, generally as an exploratory finding in a child between the ages of 1 and 4 years old. Intentional ingestion routinely leads to numerical and clinical anticoagulation, while unintentional ingestion rarely results in either. Paradoxically, this complicates the management of the latter group of patients. Of the anticoagulant rodenticide exposures that were reported in 2011, approximately 2.5% were to warfarintype (short-acting) products and the remainder was to superwarfarin, or long-acting anticoagulant, products, such as brodifacoum.⁴

How should patients with anticoagulant rodenticide exposure be managed?

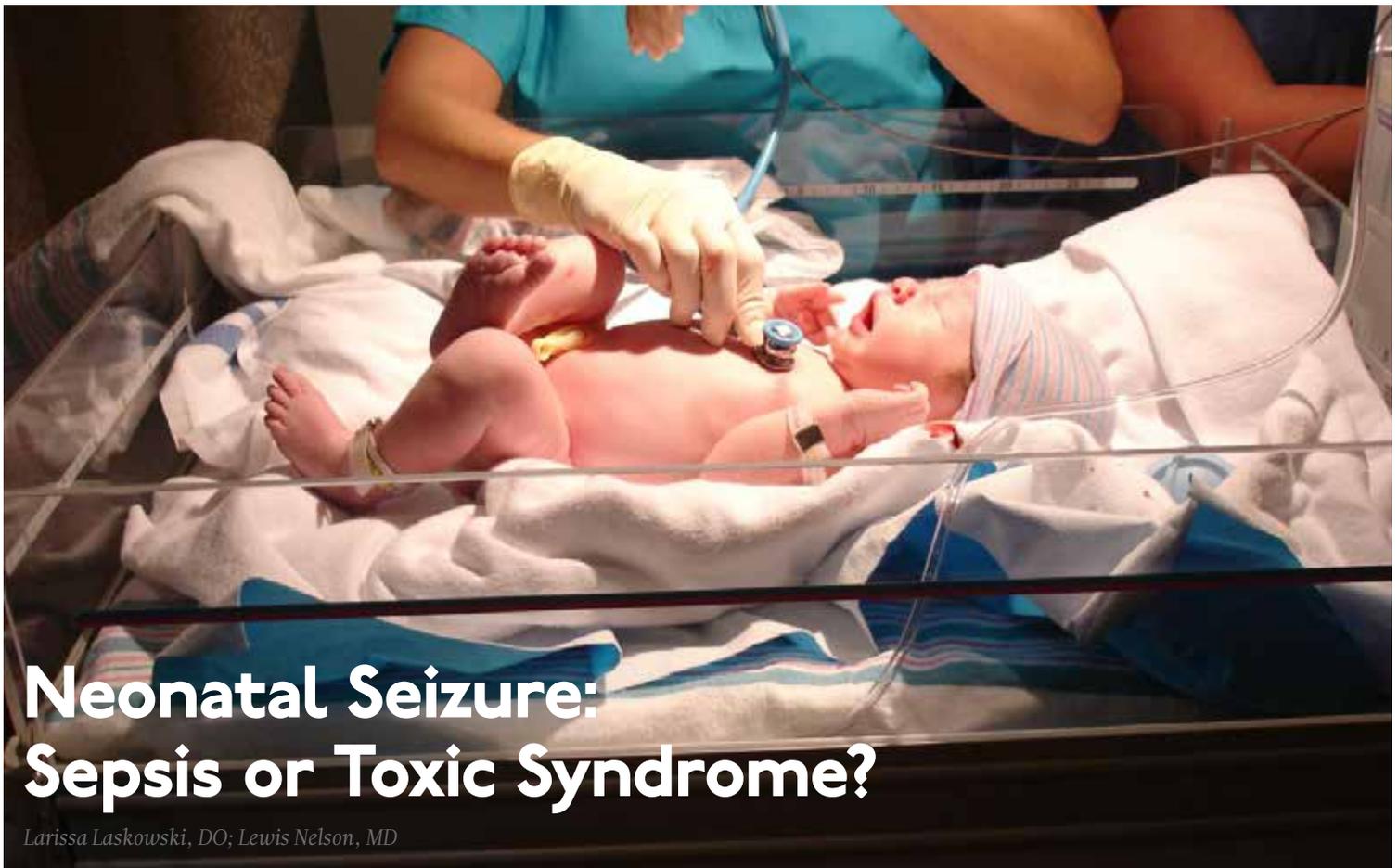
Hemorrhage is uncommon on presentation since the onset of anticoagulation generally occurs approximately 24 hours after exposure. If present, it must be controlled, and blood products such as prothrombin complex, which contains clotting factors II, VII, IX, and X, should be administered as needed. All patients should be assured of a safe environment pending the discovery of those who develop a coagulation disorder. Gastrointestinal decontamination is generally limited to oral activated charcoal, and the utility of even that measure is unproven.

Historically, patients presenting with intentional or unintentional exposure to superwarfarin rodenticides had INR measured daily for 2 or 3 days. Although this is not a point of contention for the few patients with intentional (and generally large) exposure, there is controversy over the need to monitor INR for the thousands of children with unintentional exposure. This controversy stems from the fact that few children

Continued on page 6

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Neonatal Seizure: Sepsis or Toxic Syndrome?

Larissa Laskowski, DO; Lewis Nelson, MD

A 4-day-old girl with abnormal jerking movements in her upper extremities is brought to the ED for evaluation.

Case:

A mother presents to the ED with her 4-day-old daughter after noting abnormal jerking movements of the neonate's upper extremities. She states the baby has had watery stools for the past day, but has been tolerating bottle formula feeds without vomiting and having appropriate urinary output. The patient was born full-term via normal spontaneous vaginal delivery, with Apgar scores of 8 at 1 minute and 9 at 5 minutes. The postdelivery course was uncomplicated, and both mother and baby were discharged home 2 days after delivery.

Initial vital signs are: heart rate, 135 beats/min; respiratory rate (RR), 48 breaths/min; and temperature, 98.7°F; blood glucose was normal. On physical examination, the baby is awake and well-appearing, with a nonbulging anterior fontanelle, soft, supple neck, and flexed and symmetrically mobile extremities. Moro, suck, rooting, and grasp reflexes are all intact. No abnormal movements are noted. The remainder of the examination is unremarkable.

Do the jerking movements indicate a focal seizure? What could cause these movements in a neonate?

As the length of the postpartum hospital stay has decreased over the past 20 years, EDs have experienced an increase in

neonatal visits for conditions that traditionally manifested in newborn nurseries. While most presentations are for benign reasons (eg, issues related to feeding, irritability), patients with concerning conditions, including central nervous system (CNS) abnormalities, may also initially present to the ED. Causes of such clinical findings may be structural (eg, cerebral malformations, subdural hematomas, herpes encephalitis) and/or metabolic (eg, hypoglycemia, hypocalcemia, inborn errors). Many early-onset neonatal seizures are benign and resolve by several months of age, but it is essential to identify those that are consequential and treatable.

Case Continuation

In the evaluation of the neonatal patient with suspected seizure, it is important to take a detailed maternal and labor history, and to consider a broad differential in the face of non-specific findings. In this case, the patient's mother disclosed a personal history of chronic pain, for which she took buprenorphine 2 mg orally in the morning and 4 mg orally at bedtime (total daily dose of 6mg/day) throughout her pregnancy.

Continued on page 4

Neonatal Seizure

Continued from page 3

How does drug withdrawal present in the neonate?

Neonatal abstinence syndrome (NAS) is the clinical syndrome of withdrawal in a newborn exposed in utero to drugs capable of inducing dependence. Agents associated with NAS include opioids, benzodiazepines, ethanol, selective serotonin reuptake inhibitors (SSRIs), mood stabilizers, and nicotine.^{1,2}

Over the past decade, there has been a 330% rise in the diagnosis of opioid-related NAS alone.³ In response to this increase, the US Food and Drug Administration recently added a black-box warning to all extended-release/long-acting opioid preparations detailing this risk.⁴ Presenting symptoms of NAS are protean, differ from patient to patient, and are a function of drug type, duration, and amount of drug exposure. NAS may mimic other severe life-threatening conditions such as those previously noted, and the inability to obtain an adequate symptom-based medical history from a neonate further complicates the diagnosis. Before making a diagnosis of NAS, other conditions should be carefully considered in the differential.

Neonatal opioid withdrawal manifests primarily with CNS and gastrointestinal (GI) effects since there are high concentrations of opioid receptors in these areas. Although clinical findings are generally similar among opioid agents, the onset and duration following abstinence varies—largely based on individual drug half-life; this helps to differentiate between opioid agents. For example, while babies exposed to heroin in utero present with signs of NAS within 24 hours of birth, those exposed to buprenorphine or methadone tend to present 2 to 6 days after delivery.¹ Between 55% to 94% of neonates with in-utero opioid exposure develop NAS.⁵

Select Serotonin Reuptake Inhibitors

SSRIs have also been associated with a neonatal syndrome, and largely involve similar signs and symptoms as NAS. Although the specific etiology is not clear, it has been suggested that this syndrome is the result of serotonin toxicity rather than withdrawal; as such, it is often referred to as “serotonin discontinuation syndrome.” Clinical findings occur from several hours to several days after birth and usually resolve within 1 to 2 weeks.⁶

Cocaine Exposure

In-utero cocaine exposure is also associated with neurobehavioral abnormalities in neonates although a withdrawal syndrome is less clearly defined. Findings, however, are consistent with NAS and include increased irritability, tremors, and high-pitched cry—most frequently occurring between 24 and 48 hours postdelivery.⁶

Take Home Points

- Neonatal abstinence syndrome (NAS) should be considered in any symptomatic neonate with a history of in-utero exposure to opioids, benzodiazepines, selective serotonin reuptake inhibitors, mood stabilizers, and nicotine.
- The Finnegan Abstinence Scoring System is the most well-known and validated tool to guide both screening and management of NAS.
- Nonpharmacologic efforts to minimize excess external stimuli, such as swaddling, gentle handling, and minimizing light and sound, should be initiated.
- If pharmacotherapy is indicated, oral opioid replacement with morphine is the most well-studied and preferred agent.

Neonatal Alcohol Withdrawal Syndrome

Neonatal alcohol withdrawal syndrome, particularly in fetuses exposed to alcohol during the last trimester, is distinct from fetal alcohol syndrome (FAS). The latter is associated with typical dysmorphic features, growth deficiencies, and CNS findings reflective of permanent neurologic sequelae. Neonatal alcohol withdrawal presents with CNS findings similar to those listed for other in utero exposures—eg, increased irritability, tremors, nystagmus hyperactive reflexes.⁷

Screening for NAS: The Finnegan Scale

The Finnegan Neonatal Abstinence Scoring System is one of the most commonly employed and validated tools used to screen for NAS. It comprises a 31-item scale, listing the clinical signs and symptoms of NAS, which are scored by severity and organized by system to include neurologic, metabolic, vasomotor, respiratory, and GI disturbances (*Figure*). Point allocation is based on mild, moderate, or severe symptoms as follows:

- Mild findings (eg, sweating, fever <101°F mottling, nasal stuffiness) each score 1 point.
- Moderate findings (eg, high-pitched cry, hyperactive moro reflex, increased muscle tone, fever >101°F, increased RR >60 with retractions, poor feeding, loose stools) each score 2 points.
- Severe findings (eg, myoclonic jerks, generalized convulsions, projectile vomiting, watery stools) each score 3 points.

While each of the above are independently nonspecific, the constellation of findings, together with the appropriate history, provide for a clinical diagnosis. The Finnegan Scale is therefore designed not only to aid in diagnosis, but also to quantify the severity of NAS and guide management.

Continued on page 5

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Neonatal Seizure

Continued from page 4

System	Symptoms	Points	Score		
Central Nervous System	Excessive high-pitched (or other) cry (< 5 min)	2			
	Continuous high-pitched (or other) cry (> 5 min)	3			
	Sleep < 1 hour after feeding	3			
	Sleep < 2 hours after feeding	2			
	Sleep < 3 hours after feeding	1			
	Hyperactive Moro reflex	2			
	Moderately hyperactive Moro reflex	3			
	Mild tremors when disturbed	1			
	Moderate-severe tremors when disturbed	2			
	Mild tremors when undisturbed	3			
Moderate-severe tremors when undisturbed	4				
Increased muscle tone	1				
Excoriation (eg, chin, knees, elbows, toes, nose)	1				
Myoclonic jerks (twitching/jerking of limbs)	3				
Generalized convulsion	5				
Metabolism Vasomotor Respiratory	Sweating	1			
	Hyperthermia (37.2 – 38.2°C)	1			
	Hyperthermia (≥ 38.4°C)	2			
	Frequent yawning (>3-4/interval)	1			
	Molting	1			
	Nasal stuffiness	1			
	Frequent sneezing (> 3-4/interval)	1			
	Nasal flaring	2			
Respiratory rate > 60/min	1				
Respiratory rate > 60/min with retractions	2				
Gastrointestinal	Excessive sucking	1			
	Poor feeding (infrequent/uncoordinated suck)	2			
	Regurgitation (≥2 times during/past feed)	2			
	Projectile vomiting	3			
	Loose stool Watery stool	2 3			
TOTAL SCORE					

Adapted from: Finnegan LP. Neonatal abstinence syndrome: assessment and pharmacotherapy. In: Rubatelli FF, Granati B, eds. Neonatal Therapy: An Update. New York, NY: Excerpta Medica; 1986:122-146

Figure. Finnegan Neonatal Abstinence Scoring System

Screening for NAS begins at birth in neonates with known in-utero exposure (ie, when risk of NAS is high) or at the time of initial presentation in other circumstances. Scoring is performed every 4 hours; the first two or three scores will determine the need for pharmacotherapy (see Table).

How is NAS treated?

The two main goals of management in the treatment of opioid-related NAS are to relieve the signs and symptoms of withdrawal and to prevent complications (eg, fever, weight loss, seizures). Therapy should begin with nonpharmacologic measures that minimize excess external stimuli, such as swaddling, gentle handling, and minimizing noise and light. To prevent weight loss, small hypercaloric feeds may be helpful. If pharmacologic treatment is indicated, oral opioid replacement

with morphine is considered by many to be the drug of choice. Oral morphine dosing may be guided by NAS severity based on the Finnegan score; alternatively, initial dosing at 0.1 mg/kg orally every 4 hours has also been recommended.¹

Other agents, such as methadone 0.1 mg/kg orally every 12 hours and buprenorphine 15.9 mcg/kg divided in three doses orally, may also be used. In patients whose symptoms persist despite opioid treatment, use of adjuncts such as phenobarbital and clonidine may be indicated.

Case Conclusion

The patient was admitted to the neonatal intensive care unit where she appropriately underwent a sepsis workup.

Continued on page 6

Neonatal Seizure

Continued from page 5

Table.

Pharmacotherapy is indicated in the following Finnegan scoring scenarios:

- a score ≥ 8 on three consecutive ratings
- the average of two scores ≥ 12
- two consecutive ratings ≥ 12

Laboratory evaluation, including blood and urine cultures, was obtained. A brain ultrasound was unremarkable, and since lumbar puncture was unsuccessful, the patient was started empirically on meningitis doses of the cefotaxime, vancomycin, and acyclovir.

An initial Finnegan score was calculated. With the exception of soft stools, there were no other persistent symptoms, and patient did not achieve a score indicating a need for pharmacologic management. After 48 hours, she remained afebrile and soft stools resolved. All laboratory values, including cultures, were unremarkable. The patient was discharged on hospital day 3, with a scheduled well-baby follow-up appointment.

Rats!

Continued from page 2

with unintentional exposure develop an elevated INR, and the sequelae in those who do are typically minor. However, in many of these cases, rodenticide may not have even been ingested, promoting a false sense of benignity in those with actual consumption.

Some poison control centers recommend management of these patients as essentially nontoxic exposures, with home observation and parental education, and indicating that an ED visit or immediate evaluation is not needed. Decision-making should be tempered by the fact that a poor outcome in even a single child with this type of readily evaluable toxic exposure is unacceptable. Although the vast majority of children with a superwarfarin rodenticide exposure will have an excellent outcome, it seems reasonable for a child to have an INR measured at 48 to 72 hours postexposure to exclude clinically significant exposure by documenting normal coagulation parameters.

Patients who develop an elevated INR after a superwarfarin overdose should be given prolonged oral vitamin K1 therapy. Pharmacologic doses (10–100 mg daily) are generally required because the reactivation of inactive vitamin K is interrupted by the anticoagulant rodenticides, and physiologic quantities of vitamin K depend on the normal ability to recycle the inactivated vitamin. Monitoring of INR or clotting factor levels is generally recommended to determine the progress of therapy.⁵ The empiric prescribing of vitamin K to LAA-exposed patients without documentation of a coagulopathy is not ideal. Since the parent (or patient) is unlikely to properly continue therapy for the required month or longer, a covert and delayed rise in INR with sequelae is possible. Those who ingest LAA-type rodenticides rarely develop clinical anticoagulation, and

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several days of oral vitamin K1 should allow the rodenticide to be eliminated and coagulation to normalize. Thus, in these patients, there is no need for testing.

Case conclusion

The boy had a normal baseline INR and was discharged to follow-up with his pediatrician. The parents were given clear instructions on limiting the child's activities to minimize the risk of injury until follow-up (eg, limiting playground time). They were given poison-prevention information and advised to return to the ED if any bleeding occurred. The pediatrician reported a normal INR drawn at approximately 48 hours after exposure.

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