CASE 2.3
Toxicology | Level 3

Mary A. Babico and Hanna Phan

1. What subjective and objective evidence supports the diagnosis of serotonin syndrome?

SUBJECTIVE FINDINGS: The patient arrived unresponsive and has a prescription for a chronic medication (fluoxetine) that can alter serotonin concentrations in the body. An empty bottle of fluoxetine and an empty box of guaifenesin/dextromethorphan extended-release were found on site according to report.

OBJECTIVE FINDINGS: The patient has measurable ankle clonus and presented with tachycardia. Increased body temperature (39°C) also is an objective finding of serotonin syndrome. On physical exam, the patient's skin is moist (likely diaphoresis), pupils are dilated, and lower extremities are noted to be rigid and positive for Babinski signs bilaterally. Although laboratory findings are nonspecific (i.e., elevated WBC count, elevated creatinine kinase, and decreased serum bicarbonate level), these are consistent with serotonin syndrome. The urine toxicology screen was positive for amphetamine, an agent with effects that alter serum serotonin concentrations, further predisposing the patient to serotonin syndrome.

Dextromethorphan exhibits its serotonergic activity at the 5-hydroxytryptophan-2 (5-HT2) receptor along with its antitussive effects by binding to sigma opioid receptors at recommended doses. At doses exceeding approximately 1.5 mg/kg/day (or 120 mg/day in older children and adults), dextromethorphan can also impair adrenergic neurotransmitter reuptake, leading to increased presynaptic serotonin concentrations. Amphetamine derivatives cause an increase in serotonin concentrations by acting as sympathomimetic agents, stimulating the release of catecholamines from their presynaptic terminal nerve storage sites.

2. What subjective and objective evidence supports toxicities due to other ingested agents?

SUBJECTIVE FINDINGS: The patient was found unresponsive. The mother reported that an empty vial of glipizide was found in the home. Guaifenesin overdoses can also cause central nervous system (CNS) depression.

OBJECTIVE FINDINGS: The patient's blood glucose was far below normal limits along with mildly decreased serum potassium, and the patient was tachycardic. A serum acetaminophen concentration was

detectable on lab work and dextromethorphan was found on thin layer chromatography.

An outcome of severe hypoglycemia is CNS depression due to the inadequate supply of glucose, and subsequently reduced intracellular ATP, as the brain's sole source of energy. Catecholamines, specifically epinephrine and norepinephrine, and cortisol are released in a state of hypoglycemia, which results in tachycardia. Along with cellular glucose intake, the release of insulin stimulated by sulfonylureas causes an intracellular shift of potassium resulting in low serum concentrations.

3. Devise a pharmacologic regimen for the treatment of this multiagent ingestion.

The management of serotonin syndrome involves discontinuation of all serotonergic agents and controlling precipitating symptoms. Treatment is generally aimed at eliminating neuromuscular abnormalities (e.g., muscle rigidity); controlling agitation; preventing or treating seizures; and normalizing elevations in body temperature, heart rate, and blood pressure. The administration of benzodiazepines is first-line therapy, regardless of severity, for agitation, prevention or treatment of seizures, and suppressing shivering, which can further prolong hyperthermia. Lorazepam is administered at 2 mg IV every 10 to 30 minutes as needed to control muscle rigidity, agitation, and seizure activity. Cyproheptadine, a 5-HT2A antagonist, can be utilized for additional symptom management, specifically neuromuscular abnormalities (such as muscle rigidity). Its use as an antidote has limited evidence for efficacy but is generally recommended at an initial dose of 12 mg orally, or in the case of our patient via nasogastric or orogastric tube, followed by 2 mg at 2-hour intervals until symptoms resolve. A maintenance dose of 4 to 8 mg every 6 hours has also been used until agitation improves, clonus/tremors are eliminated, and vital signs normalize along with overall clinical status. In younger children, 0.25 mg/kg/day (up to 12 mg/day) of cyproheptadine has been shown to eliminate symptoms. IV fluid replacement with boluses of 20 mL/kg isotonic solution followed by a calculated weight-based maintenance infusion can provide adequate hydration and help to prevent the acute renal dysfunction in the setting of rhabdomyolysis secondary to muscle rigidity, as indicated by patient's elevated creatinine kinase. Certain antipsychotics, specifically haloperidol and droperidol, should be avoided as these butyrophenones can both increase circulating catecholamines. This can prolong serotonin syndrome as well as inhibit diaphoresis to aid in dissipating body heat through its anticholinergic effects.

Symptomatic hypoglycemia, as seen in this patient, is generally treated with dextrose 0.5 to 1 g/kg as an IV bolus immediately. Dextrose 10% or 25% preparations are usually used in younger children and adolescents, whereas adults can be given 50%. Concentrations greater than 12.5% should be administered through a central IV line. A bolus of 500 mL dextrose 10% (D10W) can be given peripherally, or if patient has a central line, a bolus of 100 mL D25% or 50 mL D50% can be administered to this patient. Dextrose quickly raises blood glucose level and increases glucose delivery to the brain. Boluses can be repeated every 10 to 15 minutes with fingerstick blood glucose (FSBG) monitoring, and dextrose boluses may be repeated if serum glucose remains <60 mg/dL. Hypoglycemia can be prolonged and may require a continuous infusion of dextrose. Transient hyperglycemia from IV dextrose can trigger increased insulin release and recurrent episodes of hypoglycemia. To counteract this effect, octreotide, a somatostatin analog, reduces the calcium-induced release of insulin from pancreatic beta cells by inhibiting the voltage-gated calcium channel. The dosing for octreotide in the setting of sulfonylurea overdose has not been established, but studies have shown effective dosing at 1 to 1.5 mcg/kg subcutaneously every 6 to 8 hours to blunt the release of insulin until blood glucose remains stable above 70 mg/dL. Due to the long half-life of glipizide, octreotide therapy may be needed for greater than 24 hours. Glucagon is also another agent that has been used to treat hypoglycemia and can be given intravenously, intramuscularly, or subcutaneously at 0.025 to 0.1 mg/kg (maximum dose: 1 mg) every 20 minutes as needed. Glucagon has fallen out of favor due to its short duration of action as it depletes hepatic glycogen stores through