Respiratory Failure Leading to Intubation in the Setting of Flibanserin Ingestion in a Toddler

Neil D. Fernandes, MD[a,b,*]; Catherine Naber, MD[a,b]; Shreedhar Paudel, MD, MPH[c]; Carlos Duran MD[a,b]; Erica Swartz, MD[b]; Erika Cornell, MD[b]; Theodore A. Stern, MD[c]; and Michael Flaherty, DO[a,b]

LESSONS LEARNED AT THE INTERFACE OF MEDICINE AND PSYCHIATRY

The Psychiatric Consultation Service at Massachusetts General Hospital sees medical and surgical inpatients with comorbid psychiatric symptoms and conditions. During their twice-weekly rounds, Dr Stern and other members of the Consultation Service discuss diagnosis and management of hospitalized patients with complex medical or surgical problems who also demonstrate psychiatric symptoms or conditions. These discussions have given rise to rounds reports that will prove useful for clinicians practicing at the interface of medicine and psychiatry.

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[a]Division of Pediatric Critical Care Medicine, Massachusetts General Hospital, Boston, Massachusetts

[b]Department of Pediatrics, Massachusetts General Hospital, Boston, Massachusetts

[c]Department of Psychiatry, Massachusetts General Hospital, Boston, Massachusetts

**Corresponding author:* Neil D. Fernandes, MD, Department of Pediatrics, Massachusetts General Hospital, 55 Fruit St, Boston, MA 02114 (ndfernandes@mgh.harvard.edu).

Have you ever seen a toddler who ingested a potentially toxic agent? Have you been uncertain about the dangers of psychotropics and other agents in the pediatric population? Have you wondered whether antidotes exist to reverse such toxidromes? If you have, then the following case vignette and discussion should prove useful.

CASE VIGNETTE: PART 1

A 22-month-old boy was brought to an outside emergency department (ED) after having ingested an unknown amount of flibanserin (a new psychotropic) approximately 30–40 minutes before his arrival. He had been found by his father lying behind a curtain with an open bottle of his mother's medication and some pills on the floor. His father noted some foaming at the mouth. The child was unresponsive and his eyes were rolling back, but no associated tonic-clonic activity was evident. Emergency medical services (EMS) was called, and the child was taken to the ED, where he was noted to have vomited and had ongoing foaming at his mouth. Given his poor respiratory effort and decreased mental status, the child was intubated for airway protection. On further questioning of his parents, he most likely consumed a maximum of 4 flibanserin tablets (100 mg each).

The child's past medical history was unremarkable. Initial assessment included an electrocardiogram and chest x-rays to rule out aspiration and to confirm adequate endotracheal tube placement. Initial laboratory studies revealed the following levels: serum sodium: 136 mEq/L, potassium: 7.4 mEq/L (hemolyzed sample), chloride: 104 mEq/L, bicarbonate: 17 mEq/L, blood urea nitrogen: 12 mg/dL, creatinine: 0.26 mg/dL, and glucose: 91 mg/dL. Albumin was 3.9 g/dL and calcium was 9 mg/dL. His direct bilirubin was < 0.2 mg/dL, total bilirubin was 0.3 mg/dL, aspartate aminotransferase was 86 U/L, and alkaline phosphatase was 183 U/L. A respiratory viral panel, including influenza A/B and respiratory syncytial virus, was checked given his recent upper respiratory tract infection; they were negative. To rule out coingestion of acetaminophen, ethanol, and salicylate, levels of those substances were obtained, and all were negative. An initial venous blood gas test showed a pH level of 7.32 with a pCO_2 level of 50 mm Hg and a HCO_3 level of 25 mmol/L with a FiO_2 level of 0.25. The complete blood count (CBC) was notable for a white blood cell count of 18.08 K/uL. His hemoglobin was 10.2 g/dL, hematocrit was 32.4%, and platelet count was 264 K/uL. Urine toxicology was positive for benzodiazepines; however, he was being

Clinical Points

- Unintentional ingestion of household medications is common in children.
- Supportive management of flibanserin overdose is the mainstay of treatment.
- Filing with the Department of Children and Families and involvement with social services is necessary in cases in which neglect could be a cause for an unintentional ingestion in a child.

maintained on a midazolam infusion for sedation. The rest of his urine panel was negative for 6-monoacetylmorphine, amphetamines, barbiturates, buprenorphine, cocaine, methadone, opiates, oxycodone, and tetrahydrocannabinol/cannabinoids. He was transferred to the pediatric intensive care unit (PICU) on midazolam and fentanyl drips. On examination, he had "posturing" of both upper extremities, but there was no obvious limb jerking during transport.

DISCUSSION

What Is Flibanserin?

Flibanserin was initially identified as a potential antidepressant compound with rapid onset of action.[1,2] It was developed as a serotonin-modulating antidepressant before efforts were redirected toward its use as a treatment for hypoactive sexual desire disorder (HSDD).[3,4] Flibanserin was approved by the US Food and Drug Administration in August 2015 and by Health Canada in February 2018 for the treatment of acquired, generalized HSDD in premenopausal women.[5]

Flibanserin is commercially available as 100-mg tablets that are taken orally once daily at bedtime (qhs).[5] Maximum plasma concentrations (Cmax) occur 45 to 60 minutes after oral dosing with a half-life ($T_{1/2}$) of approximately 11 hours. Steady state is achieved within 3 days. Food moderately affects its rate and extent of absorption. Peak plasma concentrations occur between 1.75 and 4 hours postdosing with food; the duration of exposure is increased up to 56% after a high-fat, high-caloric meal. Flibanserin undergoes extensive first-pass metabolism and is primarily metabolized to inactive metabolites by the hepatic isoenzyme cytochrome (CYP) 3A4 and to a lesser extent by CYP2C19.[5,6]

Filbanserin's mechanisms of action include effects on serotonin receptors and increased levels of norepinephrine and dopamine. Specifically, flibanserin acts predominantly at 5-HT_{1A} receptors as an agonist and secondarily at 5-HT_{2A} receptors as an antagonist, resulting in overall decreased levels of serotonin in the prefrontal cortex. In this region of the brain, there is an increase in norepinephrine and dopamine levels in response to flibanserin administration.[7] The exact mechanism by which this agent treats HSDD is not fully understood at this time[8,9]; however, it is thought to be due to the combination of removing the sexually inhibitory effects of serotonin while simultaneously providing excitatory norepinephrine and dopamine effects in the prefrontal cortex.[7] The primary metabolic pathway of flibanserin involves action by CYP3A4 in the liver.

What Other Agents, When Taken in Overdose, Might Look like a Flibanserin Overdose?

Trifluoromethylphenylpiperazine (TFMPP) has been identified as an active metabolite of flibanserin, and it is detectable via a gas chromatography-mass spectrometry assay.[10,11] TFMPP was identified in the 1970s as a serotonergic metabolite of antrafenine, which was previously developed as an analgesic and anti-inflammatory agent.[12] TFMPP is used recreationally as a stimulant and hallucinogen that is often used in combination with a benzylpiperazine analog.[12] These drugs are known colloquially as "Legal X" or more generally as "Molly" or "Ecstasy."[13] They are used as alternatives to 3,4-methylenedioxymethamphetamine.[12]

As a class, piperazine compounds, such as TFMPP, have been associated with hyperthermia, muscle rigidity, brain edema, seizures, hallucinations, psychosis, tachycardia, hypertension, and nausea.[14,15] Serotonin syndrome and increases in norepinephrine levels have also been described following piperazine use.[16,17]

With an elevated TFMPP concentration in the context of flibanserin overdose, clinical effects typical of the piperazine class may develop and could have caused our patient to have seizure-like activity, mild hypertension, mydriasis, and drug-induced hyperthermia. Alternatively, other possible etiologies of his increased temperature could have included an occult infectious process or a stress response (eg, to emergency hospitalization).

Who Is at Risk for Overdose?

Children, especially toddlers, are at increased risk of unintentional poisonings. Toddlers are explorers; they learn about their physical environment by touching, tasting, and interacting with their surroundings. This exploratory phase makes it essential to "child proof" the home when children become mobile and can enter dangerous situations. Unintentional medication ingestions/overdoses are particularly prevalent during this time, as small pills left accessible can be tempting for children to ingest; unfortunately, they can also be fatal. Children in homes with parents or other caregivers who take medications on a regular basis are particularly prone to unintentional ingestions. In these homes, pills should remain in their child-proof bottles out of reach; other medication dispensers, including non–child-proof daily dispensers, should be avoided.

How Should Health Care Providers Respond After an Unintentional Overdose in a Child?

Was our case a clear example of neglect by the child's parents? Not necessarily, but the possibility of neglect needs to be considered given mandatory reporting statutes. Our patient was found unresponsive by his father, with a medication bottle in his hand. On the basis of state laws, neglect is defined as "failure by a caretaker, either deliberately or through negligence or inability, to take

those actions necessary to provide a child with minimally adequate food, clothing, shelter, medical care, supervision, emotional stability and growth, or other essential care; provided, however, that such inability is not due solely to inadequate economic resources or solely to the existence of a handicapping condition."[18] Given the unintentional overdose in our patient, there was reason to suspect inadequate supervision of the child and inappropriate storage of a medication bottle. As per state law, physicians and social workers are mandated reporters and should notify the Department of Children and Families (DCF) when they suspect a child has been neglected.[18] DCF decides if there is an immediate child safety issue after initial screening and determines if further investigation is necessary. The DCF evaluation outcome outlines allegations, persons involved, and the appropriate DCF interventions for the child's safety. In our case, social work was involved and the DCF was contacted. Following discussion with providers and persons involved, it was deemed that the child was in no immediate danger and a case for neglect was not filed.

Parental distress caused by witnessing serious injury or an accident involving their children is common and can lead to depression and symptoms of posttraumatic stress disorder that impacts the health of the child and the parents themselves.[19] The parental responses to a traumatic event can influence a young child's psychological recovery.[20] To reduce the impact of emotional trauma on parents, our social worker provides brief counseling to family members.

Where Are Toddlers Who Overdose Best Treated?

Toddlers who suffer an ingestion/overdose need rapid assessment of their neurologic, cardiovascular, and respiratory systems in the ED. Once these systems have been evaluated, the local poison control center should be contacted to discuss appropriate monitoring and to provide possible treatments. If the identity and quantity of the toxic ingestion is known, the decision to admit the child to the ICU can be straightforward. Important pharmacologic factors, such as half-life, often determine the need for ICU monitoring. If the ingested substance is unknown, one must rely on the bedside examination. If there is any concern that the neurologic, cardiovascular, or respiratory systems may deteriorate, the child should be monitored in the ICU. Of note, flibanserin overdose is generally managed by use of supportive care.

CASE VIGNETTE: PART 2

On arrival to the PICU, the child was noted to have spontaneous movement of all 4 extremities as his sedation was lightened. Given the unclear initial history, a brain magnetic resonance imaging scan was done to rule out nonaccidental trauma but was unrevealing. Given concern for possible seizures, he was placed on overnight long-term electroencephalographic monitoring, which failed to uncover seizure activity. In the morning, sedation (midazolam and fentanyl infusions) was turned off, and he awoke prior to extubation. During his hospitalization, he had a Tmax of 38.9°C. While intubated, thick mucus plugs were removed; given concern for aspiration, he was started on ampicillin-sulbactam that was switched to amoxicillin-clavulanate once oral feeds were initiated. The child was transferred to the pediatric floor on hospital day 2 and discharged to his home on the third hospital day.

SUMMARY

Flibanserin is an uncommonly prescribed medication; this makes accruing a large case series and data analysis regarding its use challenging. Furthermore, interactions with other agents and the effects of unknown metabolites may result in unexpected clinical presentations. Our report involved a toddler's suspected flibanserin ingestion/overdose and proposed a pathophysiology based on the drug's piperazine metabolite.

This is the first case report, to our knowledge, of a toddler who required intubation for airway protection in the setting of flibanserin ingestion. Although benzodiazepines were present on the drug screen, we believe this was due to his benzodiazepine infusion; it was iatrogenic. Therefore, we believe that flibanserin was the causative agent of the patient's altered mental status and possible seizure-like activity.

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