Buprenorphine Ingestion in a 23-Month-Old Boy

Case: A previously healthy 23-month-old 12.6-kg boy presented to an outside community emergency department with vomiting and respiratory depression after a single episode of red-orange emesis that looked and smelled like his mother’s buprenorphine/naloxone tablets (8 mg/2 mg formulation). She reported slowed respirations, small pupils, and somnolence, but she denied witnessing any ingestion; therefore, the amount ingested and the time of ingestion remained unknown. At presentation to the emergency department, the patient’s respiratory rate was 14 per minute, with an oxygen saturation of 93% on room air; pupils were miotic, and the patient was described as lethargic. He was treated with 0.4 mg (0.03 mg/kg) of intravenous naloxone initially, without documented improvement in arousal or respiratory status. A second dose of naloxone 0.4 mg was administered intravenously immediately after the first dose. This second dose of naloxone resulted in arousal with crying and a respiratory rate of 18 per minute. At this time he was given 1 g/kg activated charcoal with sorbitol orally. A third dose of naloxone 0.4 mg was administered 20 minutes after the second dose, and at that time a naloxone infusion was initiated at 0.06 mg/hr. Approximately 15 minutes after initiation of the infusion he experienced recurrence of somnolence and bradypnea, and the naloxone infusion was increased to 0.2 mg/hr (0.015 mg/kg) with improvement. The patient was then transferred to the PICU.

Question: Why can it be more concerning to find buprenorphine pill fragments in the mouth than to have a known ingestion in which pills are swallowed?

Discussion: Buprenorphine is a semisynthetic opioid available in commercial form in the United States as a single tablet, a combination pill with naloxone, an injectable solution, a sublingual film with naloxone, and a topical patch. Suboxone (buprenorphine/naloxone) is a lemon–lime flavored, orange-colored tablet. Buprenorphine is a partial μ opioid receptor agonist and a weak κ antagonist that is both potent (25–40 times more potent than morphine) and long-acting; its high affinity for and slow dissociation from μ receptors is the reason for its long duration of action (half-life duration of 32 hours after therapeutic sublingual administration). Though not studied in children, buprenorphine, at doses >0.1 mg/70 kg, has μ opioid receptor antagonist activity, which limits sedation and respiratory depression without affecting analgesia. This ceiling effect has not been reported in children. Indeed, children may exhibit the typical dose-dependent respiratory depression observed with other opioids.

Like other opioids, buprenorphine is absorbed well through both gastric and buccal mucosa, although enteral bioavailability is <30% of its sublingual bioavailability. Sublingual absorption of buprenorphine is nearly complete within 2
Naloxone is included in a 4:1 ratio in this combination drug formulation to prevent the euphoric effects of buprenorphine in case the tablet is inappropriately crushed and injected. It might seem that naloxone would nullify the effects of the buprenorphine’s opioid activity, but naloxone undergoes extensive first-pass metabolism and therefore is not effective orally or sublingually. Naloxone may possess minimal opioid antagonist effect sublingually but if ingested completely, as is most likely in this case, there is no significant clinical effect.

**Case Continuation:** The patient’s initial serum chemistries were normal, without anion gap or acidosis. Serum acetonohpen and salicylate levels were below the detection limit. Serum ethanol level was <10 mg/dL. Urine immunoassay for drugs of abuse was negative for opioids (Dimension Vista 500; Siemens USA, Washington, DC). His chest radiograph showed no evidence of pulmonary edema, pneumonia, or other cause of hypoxia. A computed tomography scan of his head was not performed.

After transfer to our hospital and admission to our PICU, the naloxone infusion was increased to 0.04 mg/kg per hour because of respiratory depression and continued somnolence. The naloxone infusion was continued at 0.04 mg/kg per hour for 10 hours. The infusion was decreased to 0.02 mg/kg per hour for 3 hours, and then decreased to 0.01 mg/kg per hour for 7 hours. Twenty-three hours after the initial naloxone bolus, the patient was awake and alert with no signs of central nervous system or respiratory depression; the naloxone infusion was discontinued at that time. The patient was administered a continuous naloxone infusion for 23 hours after the initial doses of naloxone, for a total dose of 0.68 mg/kg. He was discharged from the hospital after 48 hours and at 6-month follow-up was doing well and appeared to have normal growth and development.

**Question:** How is it possible for a child to exhibit an opioid toxidrome in the setting of a negative result for opiates on a urine drug screen?

**Discussion:** The basic urine drug screen for the patient illustrated in this case was negative for opiates. Commercially available basic urine drug screens are enzyme-multiplied immunoassays designed for qualitative analysis of opiates in urine, most often morphine, morphine-3-glucuronide, and codeine. The test may be positive if certain synthetic or semisynthetic opioids structurally similar to morphine are present, such as hydromorphone. If an opioid structurally dissimilar to opiates is present, it is not expected to result in a positive test. Because of buprenorphine’s structural dissimilarity to morphine and codeine, it is not expected to produce a positive result. Specific immunoassays are available to detect other opioids such as methadone, propoxyphene, and buprenorphine. Although these results are unlikely to affect clinical management of the opioid toxidrome, they may assist in determining a safe disposition for the patient. In a patient with history or examination findings consistent with opioid toxicity, naloxone is indicated even in the absence of a positive urine or serum drug screen for opioids.

**Question:** What are current recommendations for management of pediatric buprenorphine toxicity?

**Discussion:** Children respond to buprenorphine ingestion with the classic signs of opioid toxicity but possibly with unique sensitivity, specifically manifested by significant respiratory depression. Buprenorphine was initially suggested to have minimal respiratory depression in pediatric patients, and this effect was attributed to its partial agonist activity at the µ receptor. Since 2004 there have been multiple reports of pediatric ingestions that resulted in significant toxicity, including death. Pediatric deaths caused by buprenorphine ingestion have prompted its US manufacturer to cease production of buprenorphine tablets.

To prevent endotracheal intubation and mechanical ventilation, our patient needed a continuous naloxone infusion for 23 hours after 3 initial bolus doses of naloxone on presentation, for a total dose of 0.68 mg/kg. Other case reports have indicated that high doses and prolonged duration of naloxone may be needed for children relative to treatment of ingestion of other opioids. Buprenorphine has high affinity for the µ receptor and a long half-life. Our patient’s clinical course was consistent with buprenorphine-induced opioid toxicity, and he received a prolonged continuous infusion of naloxone.

Pharmacokinetic data show that buprenorphine reaches peak plasma concentrations at 1 hour after sublingual administration. In a study evaluating the ceiling effect on respiratory depression, Dahan et al reported that peak respiratory depression occurred between 150 and 180 minutes after intravenous administration. Given buprenorphine’s rapid buccal and sublingual absorption, this time frame probably applies to oral exposures also.
These data suggest that a child who shows no signs of respiratory depression at 3 hours after ingestion is unexpected to develop toxicity. However, these data have significant limitations in pediatric patients. Therapeutic buprenorphine dosing is children ranges from 2 μg/kg to 6 μg/kg, and exposure to a single 2-mg tablet may represent a three- to fourfold increase over therapeutic dosing. This makes recommendations for disposition problematic. Pharmacokinetic data suggest that a child without any signs of central nervous system or respiratory depression 6 hours after exposure can be safely discharged from the hospital, and indeed some authors have recommended this approach. Some authors have recommended 24 hours of inpatient observation for all patients with buprenorphine exposures, regardless of the presence of clinical signs of central nervous system or respiratory depression.

Buprenorphine is being increasingly prescribed for opioid addiction. Subsequently, an exponential increase in pediatric exposures has been reported to poison centers. This recent phenomenon underscores the importance of clinicians understanding the diagnosis and management of buprenorphine exposures in pediatric patients.

Observation in a monitored setting is warranted for all pediatric patients with suspected exposure to buprenorphine. The clinical presentation described herein is consistent with classic opioid toxicity, despite a urine drug screen with a negative result for urinary opiates. Pediatric patients may need higher dosages and repeated doses or prolonged infusion after buprenorphine ingestion. Prompt naloxone dosing, airway management, and after care are vital components of treatment.

**LEARNING POINTS**

- Buprenorphine has potential to cause significant toxicity, even if the tablet is in the mouth for a short period of time.
- Pediatric patients who may have been exposed to buprenorphine should be observed for 6 to 8 hours, and if they remain asymptomatic and need no antidotal therapy, they may be safely discharged from the hospital.
- Pediatric patients who have been exposed to buprenorphine and exhibit any symptoms should be admitted to a monitored setting for 24 hours because the severity of potential adverse effects.
- Pediatric patients presenting with examination findings consistent with opioid toxicity should receive empirical naloxone, even in the presence of a negative urine drug screen.

**REFERENCES**