

Buprenorphine May Not Be as Safe as You Think: A Pediatric Fatality From Unintentional Exposure

abstract

Buprenorphine is a partial μ -opioid receptor agonist that is approved for the treatment of opioid dependency. It is generally believed to be safer than methadone because of its ceiling effect on respiratory depression. As more adults in US households use buprenorphine, an increasing number of children are being exposed. We report a fatal exposure to buprenorphine in a small child that occurred after ingestion of a caretaker's buprenorphine/naloxone. Postmortem toxicology analysis showed free serum concentrations of 52 ng/mL and 39 ng/mL for buprenorphine and norbuprenorphine, respectively. No other drugs were detected. Autopsy did not find signs of injury or trauma. The theoretical safety provided by the ceiling effect in respiratory depression from buprenorphine may not apply to children, and buprenorphine may cause dose-dependent respiratory depression. *Pediatrics* 2012;130:e1700–e1703

AUTHORS: Hong K. Kim, MD, MPH,^{a,b} Monica Smiddy, MD, MPH,^c Robert S. Hoffman, MD,^{a,b} and Lewis S. Nelson, MD^{a,b}

^aNew York University Langone Medical Center/Bellevue Hospital Center, New York City Poison Control Center, New York, New York; ^bDepartment of Emergency Medicine, New York University School of Medicine, New York, New York; and ^cOffice of Chief Medical Examiner, City of New York, Department of Forensic Pathology, New York, New York

KEY WORDS

buprenorphine, pediatric poisoning, suboxone, respiratory depression

Drs Kim and Nelson were involved in the case as medical toxicology consultants; Dr Kim drafted and revised the article as the primary author; Dr Smiddy contributed to the autopsy and toxicology finding sections and contributed to the draft revisions; Dr Nelson contributed to the conception of the case report, draft revision, and final approval of the version to be published; and Dr Hoffman contributed to draft revisions and finalization of the version to be published.

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Address correspondence to Hong K. Kim, MD MPH, New York City Poison Control Center, 455 First Ave, Room 123, New York, NY 10016. E-mail: hongkimmd@gmail.com

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Buprenorphine is a partial μ -opioid receptor agonist and κ -opioid receptor antagonist that has been available for decades for the treatment of acute and chronic pain. It gained wide acceptance in Europe as an alternative to methadone maintenance for patients with opioid dependence and has been used for this indication in the United States since 2002.¹ Buprenorphine has the theoretical advantage of having a "ceiling effect" on its ability to produce respiratory depression.²⁻⁵ Moreover, unlike methadone maintenance programs that require daily, supervised visits and dispensing by a federally certified clinic, buprenorphine/naloxone is prescribed by certified physicians for unsupervised use outside of a health care facility.

The number of unintentional buprenorphine exposures in children is increasing. According to data from the American Association of Poison Control Centers, reported buprenorphine exposures in children younger than 6 years old increased dramatically between 2002 (2 cases) and 2008 (907 cases). Meanwhile, exposures to methadone in the same age group doubled from 155 cases to 332 cases during the same 6-year period.⁴ In 2010, the number of buprenorphine exposures again exceeded methadone exposure in children <6 years old.⁵ Such data highlight the growing public health problem of buprenorphine in children and likely reflects the increasing number of children who are at risk for exposure in a home in which an adult family member is using buprenorphine.

Despite the theoretical safety of the ceiling effect in healthy adults, buprenorphine-associated deaths among adults are reported.⁶⁻⁸ Many of these cases may be related to drug interactions with other abused or therapeutic drugs. In children, central nervous system depression, miosis, and vomiting are the most commonly reported clinical

findings after buprenorphine ingestion.⁹⁻¹² Cases of significant respiratory depression requiring naloxone administration and intubation have occurred, even after ingestion of only 1 or 2 tablets.^{4,12,13} Here, we report a confirmed buprenorphine-associated fatality in a young child.

CASE DESCRIPTION

A healthy, 13 month-old boy (10.2 kg) was found unresponsive at home ~8 hours after exposure to an adult family member's sublingual buprenorphine/naloxone (8 mg/2 mg). By report, the child was discovered with a pill in his mouth, which was subsequently removed. The child was fed and put to sleep in his crib. Neither direct medical attention nor a call to the regional poison control center was made. The following morning, the child was found unresponsive in his crib and emergency medical services was notified. Upon arrival, paramedics found the child apneic and pulseless. The child received 4 mg of naloxone intravenously without any response and resuscitative efforts were initiated. Assisted ventilation and chest compression were performed and epinephrine administered without success. The child was pronounced dead on arrival to the nearest emergency department. No other medication exposure was reported.

AUTOPSY FINDINGS

This 13 month-old child appeared well nourished and hydrated. He was normally developed for age and was within the 25th percentile for height and weight. A full forensic autopsy, including full-body x-rays, neuropathology, and postmortem laboratory testing, was performed. There were no injuries found on external or internal examination. There were no congenital abnormalities. Gross and histopathologic examination and radiographs of all major organs revealed no significant findings. Gastric contents consisted of ~40 mL of tan-white liquid.

No discrete pills or capsules were visible in the gastric contents. Nonspecific pulmonary congestion and dilation of the urinary bladder were noted.

TOXICOLOGY FINDINGS

Postmortem specimens were submitted for toxicologic analysis by liquid chromatography tandem mass spectrometry. Free buprenorphine, free norbuprenorphine, and free naloxone were detected in samples of internal pooled blood and in gastric contents. The results are summarized in Table 1. Elevated concentrations of free buprenorphine (52 ng/mL) and norbuprenorphine (39 ng/mL) were detected in the blood. Elevated concentrations of free buprenorphine (7400 ng/mL) and norbuprenorphine (84 ng/mL) were also detected in the gastric contents. No other prescription drugs, over-the-counter medications, ethanol, or drugs of abuse were detected in postmortem samples of blood, urine, or gastric contents.

DISCUSSION

Buprenorphine is 20 to 50 times more potent as an analgesic than morphine and has ~1000-fold greater μ - and κ -opioid receptor affinity.^{1,14} Buprenorphine's high receptor affinity is also reflected by its slow dissociation from μ -receptors (dissociation half-time is 166 minutes compared with 7 minutes for fentanyl).¹⁵ In the United States, buprenorphine is available in a combined formulation with naloxone in a 4:1 ratio for sublingual administration (buprenorphine:naloxone: 2 mg/0.5 mg and 8 mg/2 mg). Formulation of buprenorphine with naloxone (Suboxone) is intended to deter intravenous misuse and abuse.¹⁶

TABLE 1 Postmortem Analysis

	Pooled Blood (ng/mL)	Gastric (ng/mL)
Buprenorphine	52	7400
Norbuprenorphine	39	84
Naloxone	39	970

Buprenorphine is typically administered sublingually, where it is rapidly absorbed, can achieve its peak concentration in 1 hour (Table 2), and has a bioavailability of ~50%.^{13,17} In contrast, orally administered (ingested) buprenorphine has poor bioavailability (<15%) owing to significant first-pass hepatic metabolism.^{13,17,18} In children, buccal absorption is likely to be the major route of exposure, as it is more common for children to either chew or suck on tablets. The bioavailability from the buccal route is lower than by the sublingual route (28% vs 51%).^{13,17,18} In 1 study, average peak plasma buprenorphine concentrations of 3.31 ng/mL and 1.98 ng/mL were achieved within 1 hour in healthy adult volunteers who were administered 4 mg buprenorphine via sublingual and buccal routes, respectively.¹⁸ Given that the estimated therapeutic buprenorphine concentration in adults ranges from 1 ng/mL to 5 ng/mL, it is likely that a child would absorb a consequential quantity of buprenorphine from buccal exposure to a single adult dose.²¹

Results from several small studies suggest that unlike full μ -agonists,

such as methadone, excessive dosing of the partial μ -agonist buprenorphine may be safe because of the ceiling effect in respiratory depression.^{2,3,14,22} In 1 study, increasing the dose of buprenorphine (range: 0.05 to 0.60 mg) decreased the minute ventilation of healthy adult volunteers by 50% from the baseline; administration of higher doses did not cause further respiratory depression. In contrast, fentanyl caused dose-dependent respiratory depression and apnea.¹⁴ The existence of the ceiling effect from buprenorphine in children is not defined. Postoperative pain management studies using buprenorphine in children showed that administration of buprenorphine (3 μ g/kg) decreased the ventilatory rate more significantly and for longer duration than an equi-analgesic dose of morphine (100 μ g/kg)^{23,24}; however, there are no studies formally investigating a dose-response relationship.

Clinical experience and data suggest higher doses of naloxone are often required to reverse the adverse effects of buprenorphine intoxication compared with that needed for other opioids.^{10,12,13,25} A small adult volunteer study, however,

showed that administration of high doses of naloxone (>4 mg) resulted in a paradoxical decrease in reversal activity.²⁵ In children, several reports suggest that 0.04 to 0.10 mg/kg of naloxone successfully reverses buprenorphine-induced respiratory depression, and up to 5 mg of naloxone have been administered with success.^{10,12,13}

The history and postmortem toxicologic analysis confirmed that this child was only exposed to buprenorphine/naloxone (Table 1). In some cases, the interpretation of postmortem drug concentrations as they relate to the cause of death may be difficult. Serum concentrations of drugs may be higher postmortem compared with antemortem owing to postmortem redistribution of drugs from tissue to serum. To date, no data are available regarding the extent to which buprenorphine redistributes from tissue to plasma after death. Reported postmortem concentrations of buprenorphine and norbuprenorphine among adult fatalities with a history of buprenorphine misuse (Table 3) range postmortem from 3.5 to 10.2 ng/mL and 2.6 to 8.2 ng/mL, respectively.^{6–8,26,27} In comparison, this case had postmortem buprenorphine and norbuprenorphine concentrations (52 and 39 ng/mL respectively) that are more than fivefold higher. Most of the reported deaths in adults note coexposure to psychotropic agents, however, most commonly benzodiazepines, which may result in

TABLE 2 Peak Serum Concentrations in Adults Given Single Sublingual Buprenorphine Tablets

Buprenorphine Dose	Peak Serum Buprenorphine Concentration, ng/mL	Time to Peak, h	Peak Serum Norbuprenorphine Concentration, ng/mL	Time to Peak, h
2 mg ¹⁹	1.6	1.3		
4 mg ^{18,20}	1.94–3.30	1	0.31–0.83	4
8 mg ²⁰	3	1	1.48	1
16 mg ²⁰	5.47–5.95	0.8–1.0	2.54–3.50	0.98–1.44

TABLE 3 Mean Postmortem Buprenorphine and Norbuprenorphine Concentrations From Case Reports

	All Cases		Buprenorphine Only	
	Buprenorphine, ng/mL	Norbuprenorphine, ng/mL	Buprenorphine, ng/mL	Norbuprenorphine, ng/mL
Kintz et al 2001 ⁸ (n = 117) ^a	Site A: 10.2 (range: 0.5–51.0) Site B: 12.6 (range: 0.1–76.0)	Site A: 8.2 (range: 0.2–47.1) Site B: 10.6 (range: <0.1–65.0)	0.8 (n = 1)	
Tracqui et al 1998 ⁶ (n = 20)	8.4 (range: 1.1–29.0)	2.6 (range: 0.2–12.6)	3.1 (n = 1)	6.2 (n = 1)
Kintz et al 2002 ⁷ (n = 13)	3.5 (range: 0.3–7.7)	2.9 (range: 0.3–16.2)		
Lai 2006 ²⁸ (n = 12)	3.2 (range: 0.7–17.1)	2.1 (range: 0.8–3.4) ^b		
Ferrant et al 2011 ²⁷ (n = 3)	5.0 (range: 3.8–6.1)	1.0 (range: 0.56–1.5)		
Kintz 2003 ²⁶ (n = 1)	1.1			

^a Site A: Strasbourg; Site B: other 13 French sites.

^b Norbuprenorphine detected in 2 deaths only.

additive ventilator depression.^{6–8} The serum buprenorphine concentration in the present case (52 ng/mL) is more than 15 times greater than the concentrations found in 2 adults with isolated buprenorphine fatalities (0.8 and 3.1 ng/mL) (Table 3).^{6,8} These data support that the mechanism of death is likely attributable to ventilatory depression from exposure to buprenorphine.

When caring for children with unintentional drug exposure, clinicians

must ask both caretakers and parents about all prescription medication in the household, including methadone and buprenorphine. Routine toxicologic testing usually assesses common drugs of abuse, alcohol, and several over-the-counter medications, such as aspirin and acetaminophen. Buprenorphine is not detected in routine urine toxicology testing. The duration of buprenorphine toxicity in children can be prolonged or the onset can be delayed

up to 6 hours.^{4,9,12,13,23,24} Thus, it may be prudent to admit children for 24 hours of observation after buprenorphine exposure.⁴ Prescribers should ask about the presence of children in the household and emphasize medication safety.

In summary, this case illustrates that the theoretical safety of the ceiling effect in respiratory depression from buprenorphine may not apply to children and that buprenorphine may cause dose-dependent respiratory depression.

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