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Buprenorphine: Can It Be Deadly in a Dose?

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Pediatric exposures to buprenorphine are on the rise, due to increasing use of the drug as a treatment for adult opioid dependence. This case of a 13-month-boy with worsening respiratory depression demonstrates buprenorphine's toxic effects in children.

Case

A 13-month-old boy with an unremarkable medical history is found lethargic in his crib and is brought to the emergency department. Approximately 2 hours prior to presentation, the child was discovered with an open container of buprenorphine/naloxone. The parent notes that pill fragments were present in the child's mouth; these were removed immediately. In the emergency department, his vital signs are as follows: blood pressure, NA; heart rate, 120 beats/min; respiratory rate, 10 breaths/min; temperature, 98.2°F. His oxygen saturation is 94% on room air. The physical examination is notable for lethargy, but the child is arousable to tactile stimuli. There are no signs of trauma. His pupils are pinpoint. The cardiovascular and pulmonary examinations are normal. The patient is able to move all of his extremities spontaneously.

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What is buprenorphine and how is it used?

Buprenorphine is a partial μ-opioid receptor agonist and κ-opioid receptor antagonist that is increasingly being used as an alternative to methadone as maintenance therapy for opioid dependence. Although buprenorphine has been available for decades for the treatment of pain, it has been used for this new indication only since 2002 in the United States. Buprenorphine has approximately a 1,000-fold greater receptor affinity compared to morphine and is 20 to 50 times more potent than morphine.[1] Several properties of buprenorphine contribute to its long duration of action, including the presence of active metabolites, slow dissociation from the receptor, and a prolonged elimination half-life (mean, 37 hours).[1-3] These characteristics of buprenorphine also explain the higher naloxone dose requirement for clinical reversal of respiratory depression.[4,5]

A theoretical advantage of buprenorphine is its "ceiling effect" in producing respiratory depression.[6] This means that excessive dosing of buprenorphine may be safer than excessive dosing of full opioid agonists, such as methadone. In one study, increasing the dose of buprenorphine in healthy adult volunteers decreased ventilation by 50%.[6,7] Administration of higher buprenorphine doses did not cause further ventilatory depression. In comparison, fentanyl caused dose-dependent respiratory depression and apnea.[6,7]

Buprenorphine is available in a combined formulation with naloxone in a 4 to 1 ratio (buprenorphine to naloxone: 2 mg/0.5 mg and 8 mg/2 mg). The combined formulation with naloxone deters intravenous

misuse.[4,8] Moreover, while methadone maintenance treatment programs require daily visits to a federally certified clinic, buprenorphine/naloxone can be prescribed by certified physicians for less stringently monitored use. The buprenorphine/naloxone combination is available in a sublingual formulation in the United States. Naloxone is not systemically bioavailable by this route. In children, buccal absorption is the major route of exposure for buprenorphine, and bioavailability with this route is believed to be similar to that with sublingual administration.[8,9]

What is the risk of buprenorphine exposure in children?

The number of unintentional buprenorphine exposures in children is increasing along with the availability of buprenorphine. According to data from the American Association of Poison Control Centers (AAPCC), reported buprenorphine exposures in children younger than 6 years increased exponentially between 2002 (2 cases) and 2008 (907 cases).[8] Meanwhile, exposures to methadone in the same age-group doubled (155 to 332 cases) during the same 6-year period.[8]

Although the theoretical "ceiling effect" in respiratory depression has been demonstrated in small studies with healthy adults, there are reports of buprenorphine-associated deaths among adults with opioid abuse history.[10] Many of these cases may be related to drug interactions with other abused or therapeutic drugs. In the pediatric population, cases of significant respiratory depression requiring naloxone administration and intubation have occurred after exposure to one or two tablets.[2,4,8,9] There is no evidence to support the possibility of a "ceiling effect" for the pediatric population.

What common medications are dangerous to a child after ingestion of a single adult dose?

Several types of medication pose this risk. For instance, exposure to a single therapeutic adult dose of a phenothiazine, such as chlorpromazine, can cause central nervous system (CNS) depression and hypotension in children. However, the danger to children depends not only on the dose itself but also on the pharmacokinetic and pharmacodynamic properties of the individual agent. For example, antihypertensives and antidiabetic agents are among the most commonly prescribed medications in adults, yet not all of these medications are dangerous in a single adult dose in a child. Some, such as sustained-release calcium channel and β-adrenergic antagonists, can result in cardiovascular collapse even hours after ingestion. Clonidine, an imidazoline derivative that stimulates central α_2-adrenergic receptors, may cause bradycardia, hypotension, and opioid-like CNS and respiratory depression in children with a single tablet. Among the antidiabetic agents, a single adult dose of a sulfonylurea can cause severe and protracted hypoglycemia in children and—notably—in adults.

Other medications that are dangerous in children after exposure to a single adult dose are listed in the Table. In general, exposure to sustained-release agents poses a particular concern, as clinical signs and symptoms of toxicity can be delayed in onset and prolonged in duration. Moreover, agents with active metabolites or a slow elimination can produce prolonged clinical toxicity. Appropriate gastrointestinal decontamination, antidote administration, or other clinical interventions should be performed in conjunction with a regional poison control center or medical toxicologist consultation.

Table. Selected Medications That Can Cause Serious Toxicity in Children After Exposure to a Single Adult Dose

Benzocaine
β-adrenergic antagonists (sustained release)
Calcium channel antagonists (sustained release)
Clonidine
Diphenoxylate and atropine
Monoamine oxidase inhibitors
Opioids
Phenothiazines
Quinine or chloroquine
Sulfonylureas
Theophylline
Tricyclic antidepressants

What is the spectrum of buprenorphine toxicity in children?

Buprenorphine can induce substantial toxicity in children, even with single- or partial-tablet exposure (0.07 to 0.4 mg/kg).[2,9] In a study of pediatric patients with buprenorphine exposure reported to the RADARS (Researched Abuse, Diversion, and Addiction-Related Surveillance) system, approximately 90% of symptomatic patients experienced CNS depression, miosis, and/or vomiting.[2,4] In a case series of children younger than 2 years who had been exposed to one or two tablets, all patients required naloxone administration or intubation.[9] Additionally, there are reports of delayed onset of respiratory depression in toddlers, as late as 6 hours post exposure.[8,9] Therefore, clinicians must rely on the history, clinical findings, and understanding of the pharmacology of buprenorphine to determine the appropriate course of management. Although there is limited evidence to guide the management of buprenorphine exposure in children, it is prudent to admit children with such exposure for 24 hours of clinical observation.

Can naloxone reverse the CNS and respiratory effects of buprenorphine toxicity?

Naloxone is a competitive μ-opioid receptor antagonist that is commonly used to reverse the ventilatory depressant effects of opioids. Although small doses of naloxone administered intravenously will readily reverse most opioid-induced clinical effects, naloxone does not predictably reverse those of buprenorphine. In a small prospective study of healthy adult volunteers, administration of 0.8 mg of naloxone did not reverse the respiratory depression caused by 0.2 mg of buprenorphine.[5] Full reversal of respiratory depression was achieved only when 2 to 4 mg of naloxone was administered. Furthermore, in children, the onset of naloxone reversal of buprenorphine-induced respiratory depression has appeared to be delayed.[9] Interestingly, administration of high doses of naloxone (> 4 mg) resulted in decreased reversal activity in the adult volunteers, creating an inverse U-shaped dose-response curve.[5] A limitation of this study was that half of the naloxone dose was administered as a bolus and the remaining half as a continuous infusion over 30 minutes, instead of a more customary intravenous bolus administration. In summary, naloxone appears to reverse the effects of buprenorphine, but higher naloxone doses may be required. The exact reason remains unclear, but buprenorphine's high receptor affinity and slow dissociation may play a role.

Several reports of pediatric buprenorphine intoxication have suggested that 0.04 to 0.1 mg/kg of naloxone (the currently recommended initial pediatric dose) successfully reversed respiratory depression.[2,9] Despite a lack of evidence and limited clinical experience using naloxone to reverse buprenorphine-induced respiratory depression, it seems reasonable to start by administering up to 0.1 mg/kg until the dose-reversal relationship is better characterized. More naloxone may be required, but it is important to keep in mind that doses greater than 4 mg may result in reduced reversal activity.

Case Conclusion

Despite the administration of two bolus doses of 0.4 mg of naloxone, the patient's respiratory rate continued to decrease. As hypoxemia developed, the emergency physician intubated the patient for ventilatory support. The child remained on ventilatory support for 16 hours and was subsequently extubated without complications. No additional naloxone was administered during the hospital stay, and the patient recovered without any complications. The state child protective services agency was contacted. **EM**

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