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Selected Topics: Toxicology

ARE ONE OR TWO DANGEROUS? OPIOID EXPOSURE IN TODDLERS

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□ **Abstract—Ingestions of opioid analgesics by children may lead to significant toxicity as a result of depression of the respiratory and central nervous systems. A review of the medical literature was performed to determine whether low doses of opioids are dangerous in the pediatric population under 6 years old. Methadone was found to be the most toxic of the opioids; doses as low as a single tablet can lead to death. All children who have ingested any amount of methadone need to be observed in an Emergency Department (ED) for at least 6 h and considered for hospital admission. Most other opioids are better tolerated in ingestions as small as one or two tablets. Based on the limited data available for these opioids, we conclude that equianalgesic doses of 5 mg/kg of codeine or greater require 4 to 6 h of observation in the ED. Data for propoxyphene and all extended-release preparations are limited; their prolonged half-lives would suggest the need for longer observation periods. All opioid ingestions leading to respiratory depression or significant central nervous system depression require admission to an intensive care unit. © 2005 Elsevier Inc.**

□ **Keywords—opioid; pediatric; overdose; toxicity; narcotics**

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INTRODUCTION

For centuries, opium and its derivatives have been used for their analgesic properties. Today, the multiple forms of opioids, including natural (e.g., morphine, codeine), semi-synthetic (e.g., oxycodone, hydrocodone), and synthetic (e.g., methadone, meperidine) are commonly prescribed analgesics. Their properties also make them effective agents for sedation, gastrointestinal slowing, and cough suppression. The ready availability of opioid analgesics in combination with other analgesic groups (e.g., acetaminophen, salicylates) further increases their popularity with physicians.

This article focuses on the ingestion of prescription opioids by the pediatric population. A common scenario presenting to Poison Centers and Emergency Departments (EDs) everywhere is that of a toddler who has swallowed a known or unknown number of tablets of a prescription medication belonging to an adult member of the household. We review the existing literature to determine whether doses as low as one or two tablets pose a health risk to children under 6 years old and the most appropriate management of such patients.

Pathophysiology and Clinical Manifestations

The clinical manifestations of opioids result from their actions on specific receptors within the brain, spinal cord, and various peripheral nerves. The three receptor

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types, *mu, kappa* and *delta* modulate the clinical effects of opioid analgesics and are differentially activated by various drugs. The mu receptor is the most clinically significant of the three receptor types, being responsible for analgesia, respiratory depression, gastrointestinal dysmotility, and inhibition of the cough reflex (1).

Death from an overdose of opioids usually results from respiratory failure. Respiratory depression is mediated through reduction of the patient's sensitivity to both hypoxia and hypercarbia, with apnea being the terminal event (2). Eckenhoff and Oech reported that equianalgesic doses of different opioids will elicit approximately the same degree of respiratory depression (3). This is an important concept when examining data comparing different opioids to determine toxic doses.

Non-cardiogenic pulmonary edema has been described in patients after acute opioid overdose, most commonly with injection of heroin (4). Mental status changes may include mild sedation, lethargy or coma, but are rarely life-threatening. Seizures can occur at very high doses; they tend to be more common with certain drugs, such as propoxyphene and meperidine (5,6).

In general, opioid intoxication has only mild impact on the cardiovascular system (7). The exception to this is propoxyphene overdose. Propoxyphene may induce a sodium channel blockade similar to quinidine, leading to widening of the QRS complex on electrocardiogram (EKG), AV block, and dysrythmias; these may be treated by the administration of sodium bicarbonate, lidocaine, atropine or isoproterenol (8).

Tramadol has a slightly different mode of action from the other opioids reviewed. It is a centrally acting analgesic that possesses both opioid and non-opioid properties. It seems to have a low overall affinity for opioid receptors but may have some selectivity for the mu receptor (9). A frequent clinical manifestation of tramadol overdose is seizures. Tramadol and its active metabolite (O-demethyl tramadol) both have long half-lives (5–9 h); an overdose requiring prolonged opioid antagonism has been reported in an adult (10).

LITERATURE REVIEW

From 1983 to 2000, there were over 75,000 exposures to opioids and opioid-analgesic combinations in children under 6 years old reported to poison control centers throughout the United States, as documented by the American Association of Poison Control Centers (AAPCC) Toxic Exposure Surveillance System (TESS).

Codeine was the most commonly ingested opioid, comprising over 44% of all exposures in this age group. Since 1997, the number of oxycodone ingestions has risen dramatically to the point where it is now the second most commonly reported opioid ingestion in children under the age of 6 years. Morphine ingestions have also increased in the past few years. The rates of ingestion of meperidine and propoxyphene have shown little or no change.

The majority of exposures (almost 54,000) were to opioid-analgesic combinations. Acetaminophen-opioid combinations were the most common, comprising more than half of all exposures to opioids in this age group. Reported exposures to opioid combinations with aspirin are much less common and have fallen in number since peaking between 1988 and 1990. Toxicity from acetaminophen or aspirin must therefore be considered when evaluating a patient.

Pediatric exposures to opioids as street drugs (e.g., heroin) were omitted in our analysis of the data. Also, diphenoxylate was omitted from our data as it is discussed in a separate article in this series.

The following data were obtained from a literature search performed on MEDLINE as well as from AAPCC TESS data from 1983 to 2002 (11–30). Search terms in MEDLINE were: pediatrics, opioids, opiates, narcotics, and overdose. References from articles discovered by this search were reviewed to expand our database.

Codeine

Von Muhlendahl et al. performed a retrospective review on 430 children between the ages of 1 and 6 years after acute exposure to codeine. One hundred ninety-six children presented with ingestions estimated to be less than 5 mg/kg; few in this group exhibited any symptoms and none were clinically significant. Two hundred thirty-four children presented with ingestions estimated to be greater than 5 mg/kg; eight children in this group developed significant symptoms, including respiratory failure requiring mechanical ventilation. There were two deaths. In this symptomatic subset of patients, the smallest ingestion reported was 5 mg/kg and the highest was 12 mg/kg. Seven of the eight developed respiratory symptoms within 6 h of ingestion. In the one remaining case, onset to respiratory failure was noted to be 15 h, but time to onset of initial symptoms is unclear and co-ingestants may have been involved. Of note, 15 children ingested more than 15 mg/kg, none of whom required respiratory support. The primary limitation of this study is that the weights of the children were not measured; instead, they were estimated from growth charts at the 50th percentile for their respective age groups (31).

Tong et al. reported a 17-day-old infant who had three episodes of respiratory depression and cyanosis after receiving 18 mg of codeine over a 2-day period for cold-like symptoms. The child recovered uneventfully