
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

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 dysrhythmias; 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 Muhlen Dahl 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

Table 1. Summary of Methadone Ingestions Reported in Literature and Fatalities from AAPCC TESS Data

First author (Ref.)	No. cases	No. significant CNS/respiratory depression	No. deaths	Age(s)	Amount(s)	Reports of prolonged symptoms
Aronow (34)	18	9	1	<7 years	5–40 mg	Up to 13 h
Lee (35)	15	10	2	1–6 years	30–1120 mg	Yes*
Binchy (36)	44	20	2	11 months–7 years	Up to 200 mg	24–48 h†
DiMaio (37)	4	4	4	15 months–5.5 years	20–80 mg	>20 h
Robinson (38)	3	3	0	2–10 years	Up to 50 mg	8 h
Sey (39)	1	1	0	2 years	80 mg	48–72 h
Brooks (40)	1	1	0	30 months	Unknown	None
Sesso (41)	1	1	0	7 months	10–13 mg	5.5 h
McCurley (42)	1	1	0	21 months	20 mg	18 h
Schwab (43)	2	2	0	8 months–3 years	Unknown	Unknown
AAPCC 1987 (17)	1	1	1	12 months	35 mg	N/A
AAPCC 1989 (19)	1	1	1	5 years	10 mg	N/A
AAPCC 1994 (24)	1	1	1	4 years	Unknown	N/A
AAPCC 1995 (25)	3	3	3	19 months–3 years	Unknown	N/A
AAPCC 1997 (27)	1	1	1	2 years	12 mg	N/A
AAPCC 1999 (29)	1	1	1	5 years	Unknown	N/A
AAPCC 2000 (30)	2	2	2	8–22 months	Unknown	N/A
AAPCC 2001 (31)	1	1	1	4 years	Unknown	N/A
AAPCC 2002 (32)	1	1	1	17 months	Unknown	N/A

* Seven required multiple doses of opioid antagonists.

† Fourteen required continuous infusions of naloxone.

AAPCC TESS = American Association of Poison Control Centers Toxic Exposure Surveillance System.

(32). Lewis et al. reported a 31-month-old child who ingested approximately 10 mg/kg of codeine. The child developed respiratory depression requiring repeated doses and eventually a continuous infusion of naloxone (33).

No deaths have been documented from codeine ingestion in children under the age of 6 years in the AAPCC TESS data.

Methadone

There have been multiple case reports of methadone ingestions in children reporting significant toxicity from doses as low as 5 milligrams. Methadone is usually supplied as a 5-mg or 10-mg tablet or in a liquid concentration of 1 mg/mL mixed with a juice substitute. Symptoms lasting from 12 h to almost 3 days post-ingestion have been reported. Frequently, repeated doses of an opioid antagonist are required. Time to onset of initial symptoms was either unknown or unreported in most cases. The AAPCC TESS data also include multiple deaths after methadone ingestion. These cases are summarized in Table 1.

Tramadol

Spiller et al. reported 126 cases of tramadol exposures, 15 of which were in children under 6 years old. The most

common symptoms described were lethargy, nausea, tachycardia, agitation and seizures; coma, confusion and respiratory depression were also reported. No symptoms were reported in children under 6 years old who ingested less than 10 mg/kg. All symptomatic cases exhibited initial effects from tramadol within 4 h of ingestion (44).

Other Opioids

There are few data published reporting toxicity in the pediatric population with other commonly used opioid analgesics, such as hydrocodone, morphine, oxycodone and propoxyphene. Morrow and Faris reported a 3-year-old child weighing 26 kg who died after given multiple doses of a cough syrup containing hydrocodone, receiving a total of 15 mg (0.58 mg/kg) over 9 h. It was suspected that respiratory infection may have played a role in the death (45). Poklis et al. reported a fatality in an 8-year-old due to overdose of morphine; the amount ingested was estimated to be between 2.7 and 5.4 mg/kg (46).

There have been few deaths reported by the AAPCC TESS data in this age group. These are summarized in Table 2.

Fentanyl

Fentanyl is available for parenteral, dermal and oral use. Oral products include lozenges (200, 300, 400 µg) and a

Table 2. Pediatric Deaths Reported by AAPCC TESS Data from Ingestions of Hydrocodone, Morphine, Oxycodone, Propoxyphene

Opioid	Year (Ref.)	Age	Amount	Comment
Hydrocodone	1997 (27)	6 years	Unknown	
Hydrocodone	1999 (29)	2 years	Unknown	Given 3 doses of cough syrup containing hydrocodone
Morphine	1996 (26)	2 years	Unknown	Long-acting preparation
Morphine	2001 (31)	9 months	10 mg	Two doses of 5 mg taken 2 h apart
Oxycodone	1997 (27)	6 years	15–20 mg	
Oxycodone	2001 (31)	22 months	Unknown	Long-acting preparation
Oxycodone	2001 (31)	13 months	Unknown	Long-acting preparation; had seizures and respiratory arrest
Propoxyphene	1989 (19)	20 months	Unknown	
Propoxyphene	1991 (21)	19 months	Unknown	Respiratory difficulty noted 3.5 h post-ingestion

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transmucosal lozenge (Actiq®) on an attached handle that looks like a lollipop. Transdermal fentanyl (patches are available in doses of 25, 50, 75, 100 µg/h) is used for the management of chronic pain and has been shown to be safe and effective in older children (47). Hardwick et al. reported on a 2-year-old child who became unresponsive and developed agonal respirations approximately 2 h after the inadvertent application of a fentanyl patch at a dose of 50 µg/h. There was immediate reversal of symptoms after administration of 0.5 mg of intravenous naloxone. Approximately 5.5 h after initial application of the patch, the child again developed repeated respiratory depression. This resolved after repeat administration of naloxone (48).

The 2002 AAPCC TESS data reported the death of a four year old girl who was found asystolic after her grandmother had applied transdermal fentanyl to relieve pain. It is unknown how many patches had been applied and over what time frame this was done (29).

RECOMMENDATIONS

Symptomatic Patients

Any patient exhibiting symptoms of respiratory depression should be treated with appropriate airway manage-

ment and opioid antagonism. Due to the short half-life of the commonly used opioid antagonist naloxone, there is a high risk that respiratory depression will recur. All of these patients should be admitted to the hospital in an intensive care unit for further monitoring. Those exhibiting central nervous system (CNS) symptoms should be cared for according to the severity of their symptoms. Mild sedation will most likely only require observation. The obtunded, comatose or seizing child will require more significant support and treatment; opioid antagonism may be considered and hospital admission will be required.

Children who are symptomatic after taking an extended-release preparation or one of the opioids with a longer half-life, such as methadone, propoxyphene or tramadol, may be candidates for a continuous infusion of naloxone. Table 3 lists properties of common opioids (2,7,49).

Asymptomatic Patients

Determining the disposition of an asymptomatic child provides a significant challenge for the clinician. Most asymptomatic children may be observed for a period of

Table 3. Properties of Common Opioids*

Drug	Onset (min)	Duration (h)	Half-life (h)	Analgesic dose equivalent to 10 mg parenteral morphine	Analgesic dose equivalent to oral 5 mg/kg codeine
Codeine	10–30	4–6	2–4	120 mg p.o.	5 mg/kg
Hydrocodone	–	4–6	3.3–4.5	10 mg p.o.	0.42 mg/kg
Hydromorphone	15–30	4–5	2–3	7.5 mg p.o.	0.31 mg/kg
Meperidine	15–60	1.5–3	3–4	300 mg p.o.	12.5 mg/kg
Methadone	30–60	4–6	15–40	10 mg p.o.	0.42 mg/kg
Morphine	15–60	3–7	1.5–2	60 mg p.o.	2.5 mg/kg
Oxycodone	15–30	4–6	–	10 mg p.o.	0.42 mg/kg
Propoxyphene	30–60	4–6	6–12	65 mg p.o.	2.7 mg/kg
Tramadol	30–60	4–6	6 (7.5 for active metabolite)	50–100 mg p.o.	2–4 mg/kg

* From references (2,7,49).

Table 4. Recommendations for Opioid Ingestions in Asymptomatic Children Under 6 Years Old

Drug	Amount ingested	Recommendation
Codeine	<5 mg/kg ≥5 mg/kg	Observe at home Observe in ED for 4–6 h
Fentanyl* (transdermal)	Any exposure	Observe in ED for 4 h
Hydrocodone*	<0.42 mg/kg ≥0.42 mg/kg	Observe at home Observe in ED for 4–6 h
Hydromorphone*	<0.31 mg/kg ≥0.31 mg/kg	Observe at home Observe in ED for 4–6 h
Meperidine*	<12.5 mg/kg ≥12.5 mg/kg	Observe at home Observe in ED for 4–6 h
Methadone	Any amount	Observe in ED for 6 h, consider hospital admission
Morphine*†	<2.5 mg/kg ≥2.5 mg/kg	Observe at home Observe in ED for 4–6 h
Oxycodone*†	<0.42 mg/kg ≥0.42 mg/kg	Observe at home Observe in ED for 4–6 h
Propoxyphene*	Any amount	Observe in ED for 6 h
Tramadol	<10 mg/kg ≥10 mg/kg	Observe at home Observe in ED for 4 h

* Limited information available; use clinical judgment.

† Consider longer period of observation or hospital admission if extended-release preparation is ingested.

time before discharge to home. This length of time is not always well defined. In this literature review, we found that the time to onset of initial symptoms was frequently unreported or unknown. However, in the cases in which they were reported, symptoms almost always occurred within 4 to 6 h of ingestion.

Hollander et al. studied 260 patients (37 of whom were 2 years old or younger) with potentially toxic oral ingestions of all types. They found that all of the 109 patients who were medically cleared for discharge after 6 h of observation could have been identified at either 2 or 4 h of observation. The main limitation of this study was the small sample size, as only 14 of the patients had ingested opioids (50).

The following are discussions of the care of asymptomatic patients after the ingestions of different opioids (see Table 4).

Codeine

Despite the large number of exposures reported, AAPCC TESS data documented no pediatric deaths from codeine. This would indicate that codeine ingestion is very well tolerated. Von Muhlendahl et al. demonstrated that an acute ingestion of less than 5 mg/kg of codeine is non-toxic; these children may be observed at home. Significant respiratory symptoms developed in 3.4% of children with ingestions of ≥5 mg/kg. Time to onset of respiratory symptoms occurred within 6 h of ingestion in virtually all cases (31). Given the relatively short half-life of codeine (2.5–3 h), an observation period in the ED of 4 to 6 h should be sufficient after a codeine ingestion of 5 mg/kg or more.

There exist many preparations of codeine-containing medications (49). The most commonly used tablets contain 30 mg of codeine. Given an average weight of 10–15 kg in a toddler, a single tablet represents a dose range of 2–3 mg/kg and should not pose a risk to the child. However, two or more of these tablets may exceed 5 mg/kg, which can cause significant toxicity; these cases should be observed in the ED.

Methadone

Methadone is clearly the most toxic of the opioids reviewed in this article. Methadone is usually supplied as a 5-mg or 10-mg tablet or in a liquid concentration of 1 mg/mL mixed with a juice substitute. Given that life-threatening toxicity in children with exposures as low as 0.5 mg/kg have been reported, even a single tablet of methadone may be dangerous to a toddler.

Many of the cases involving methadone that were reviewed did not report time to onset of symptoms; of the cases that did specify the time to onset of symptoms, all reported initial onset of CNS or respiratory depression to occur within the first 4 to 6 h. There were no documented cases of symptoms beginning after this time period.

We recommend that any child who has ingested any amount of methadone be sent to the ED for at least 6 h of observation. Due to potential toxicity of methadone ingestion and limited data regarding optimal length of observation, we suggest consideration of hospital admission for extended monitoring. This decision should be based on several factors, such as the age and size of the child, amount ingested, time of day, and reliability of those who would observe the child at home.

Tramadol

Although the analgesic equivalence to 5 mg/kg of codeine is 2–4 mg/kg of tramadol, data by Spiller et al. show that higher doses of tramadol are well tolerated. Based on these data, we recommend that children under 6 years old who have ingested less than 10 mg/kg can be observed at home; asymptomatic children who have ingested more than 10 mg/kg should be monitored in the ED for 4 h (44). Tramadol is supplied in 50-mg tablets. An ingestion of one or two tablets by a 10–15 kg toddler (3.3–10 mg/kg) should be non-toxic.

Other Opioids

Limited information exists for many other commonly used opioids, such as hydrocodone, hydromorphone, meperidine, morphine, oxycodone and propoxyphene, making it difficult to form specific recommendations regarding management for exposures to these agents in the pediatric population. Eckenhoff and Oech determined that equianalgesic doses of two different opioids will elicit approximately the same degree of respiratory depression (3). Using this information, we can extrapolate data from other opioids for which we have more information to construct guidelines for these opioids.

Table 3 compares doses equivalent in analgesia to 5 mg/kg of oral codeine. This table may be used as a guideline for the clinician. Asymptomatic children who have ingested less than the equivalent of 5 mg/kg of codeine may be observed at home; those who have ingested an amount equal to or greater than 5 mg/kg of codeine should be observed for at least 4 h in the ED.

There is potential for delayed onset of symptoms and respiratory depression in children who have ingested an extended-release preparation, usually of either morphine or oxycodone. These products may contain large doses of drug in each tablet or capsule. Not enough data exist regarding ingestion of these agents to make a specific recommendation. However, a longer observation period and probable hospital admission seem warranted.

The equianalgesic dose range for propoxyphene is large (5 mg/kg of codeine is equivalent to 2.7–10 mg/kg of propoxyphene), making it difficult to assess the usefulness of this table. Besides respiratory and central nervous system depression, seizures and ventricular dysrhythmias may occur, usually within the first hour of overdose (2). Because of the long half-life of propoxyphene (6–12 h) and the lack of data regarding overdose in children, we recommend that any propoxyphene ingestion be observed in the hospital setting for at least 6 h.

Exposure to transdermal fentanyl has been shown to be potentially fatal. Data on the oral dosage forms (loz-

enges, transmucosal) are lacking. Given the short half-life of fentanyl, we believe a short observation period of 4 h should be sufficient once the patch has been removed or activated charcoal has been administered.

Combination Analgesics

These recommendations do not take into account other compounds present in combination analgesics, such as aspirin or acetaminophen; these need to be evaluated separately. One or two tablets of a combination analgesic should not provide toxic doses of aspirin or acetaminophen to the average 10–15-kg toddler; therefore, the clinician can focus on the opioid that is in the combination analgesic. In larger ingestions, toxicity from acetaminophen or aspirin must be considered.

CONCLUSION

Opioid analgesics are a popular and versatile class of drugs that, because of their widespread use, have been increasingly implicated in exposures to toddlers and young children under 6 years old. To date, there have been no specific recommendations about the evaluation and treatment of ingestion in this pediatric population. After review of the literature, it is clear that the ingestion of as few as one or two tablets, although potentially dangerous, is usually well tolerated, depending on the weight of the child and the type and dose of the opioid ingested. The exception is methadone, which has clearly demonstrated significant morbidity and mortality in this age group.

A child who demonstrates respiratory depression or significant mental status changes, such as coma or seizures, should be treated with an appropriate dose of an opioid antagonist, such as naloxone, and admitted to the hospital in an intensive care setting.

Asymptomatic children who have ingested a short-acting opioid in a dose less than the equivalent of 5 mg/kg codeine may be observed at home, provided there are no co-ingestants and the amount of opioid ingested can be established. Reliability of the home environment should be considered. Asymptomatic children who have ingested the equivalent of 5 mg/kg or more of codeine should be treated as a significant exposure and be observed for a period of at least 4 to 6 h after ingestion.

The exceptions to the above are 1) methadone, for which any ingestion requires a minimum of 6 h of ED observation and consideration of inpatient hospital admission; 2) tramadol, which does not seem to cause toxicity at less than 10 mg/kg; 3) propoxyphene, for which we recommend at least 6 h of observation due to

its long half-life and lack of data regarding ingestion in the pediatric population; and 4) extended-release preparations of medications such as oxycodone or morphine, which should be considered for hospital admission. Although data are limited regarding time to onset of symptoms, it seems that children who become symptomatic tend to do so quickly. Table 4 summarizes our recommendations for opioid ingestions. Clinical judgment should always prevail when making treatment and disposition decisions.

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