Oxycodone Overdose in the Pediatric Population: Case Files of the University of Massachusetts Medical Toxicology Fellowship

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Case Presentation

A 7-year-old female, status post recent tonsillectomy, presented to the emergency department (ED) after an unintentional Roxicet® (oxycodone-acetaminophen coformulation) overdose. The patient weighed 19 kg and was prescribed 1.5 mL of Roxicet® 5/325 mg per 5 mL to take as needed for pain. Her mother misunderstood the dosing instructions and gave the patient 1.5 teaspoons (7.5 mL) of the medication, and immediately brought her to the ED.

On arrival, the patient was non-toxic-appearing with normal mental status, physical exam, and vital signs. She complained of a stomachache and nausea, but denied any vomiting or diarrhea. Her medical history was significant for tonsillectomy 3 days previously and a remote herniorrhaphy. Her only prescription or over-the-counter medication was Roxicet® as needed for pain.

What Is Known About the Use and Metabolism of Oxycodone?

Oxycodone (14-hydroxy-7,8-dihydrocodeinone) was discovered in 1916 as a semisynthetic derivative of thebaine, and it

has been in clinical use since 1917 [1, 2]. Oxycodone is one of the most common medications used to treat pain in both children and adults, but its use as a pediatric analgesic is off-label [1, 3]. Despite nearly 100 years of oxycodone's use as an analgesic, there is a dearth of pediatric pharmacokinetic and pharmacodynamic data [4]. In adults, oxycodone has 40–60 % oral bioavailability and less pharmacokinetic variability than morphine [3, 5]. Unlike other opioid analgesics, oxycodone does not release histamine and may be associated with a lower incidence of nausea, vomiting, pruritus, hallucinations, and sedation [2, 5]. Additionally, oxycodone has a more neutral taste than morphine when administered orally, which is a benefit in the pediatric population [2]. Unfortunately, there is little data available regarding the relationship of plasma oxycodone concentration and clinical effects, and pediatric dosing of oxycodone is largely based on local practice patterns instead of a standardized dosing regimen [5].

The majority of oxycodone metabolism occurs in the liver (via *N*-demethylation, *O*-demethylation, 6-ketoreduction, and conjugation with glucuronic acid), with only 10 % of the parent compound excreted in the urine unchanged [1, 4] (see Fig. 1). Oxycodone's primary active metabolites are noroxycodone and oxymorphone; however, neither of these compounds is thought to have significant opioid effects due to low plasma concentrations [2, 4]. Noroxycodone has a weak affinity for the mu opioid receptor, and it is produced by *N*-demethylation (CYP3A4) [1, 4]. More of this metabolite is produced after oral absorption of oxycodone (versus parenteral administration), which is thought to reflect a first-pass effect in the gastrointestinal mucosa [2]. Oxymorphone is produced through *O*-demethylation (CYP2D6), and in contrast to noroxycodone, has significant affinity for the mu opioid receptor. Oxymorphone has a 40-fold higher affinity for the mu opioid receptor compared to oxycodone; however, it is less lipophilic and may have reduced uptake in the CNS [4]. Noroxycodone and oxymorphone are then further

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Oxycodone Metabolism

Fig. 1 Metabolic pathways of oxycodone

metabolized or conjugated before excretion in the urine. Noroxycodone subsequently undergoes *O*-demethylation (CYP2D6) to form noroxymorphone, which has a two- to threefold higher affinity for the mu opioid receptor than oxycodone [2, 4]. The major determinant of oxycodone clearance in all age groups is CYP3A4 activity and not CYP2D6, which is the key factor in the metabolism of codeine [4].

What Data Exists About the Pharmacokinetics and Pharmacodynamics of Oxycodone in Children?

In children, the majority of pharmacokinetic and pharmacodynamic data exists for intravenous administration to patients aged 6 months to 7 years. When given parenterally, oxycodone's pharmacokinetic data in children mirrors that described in adults [5]. Intramuscular oxycodone has also been shown to have fairly constant drug absorption [5]. However, this route is painful and not convenient for outpatient therapy. By comparison, buccal and gastric administration in children has a less consistent rate and extent of absorption [5]. In children aged 6 months to 7 years, the bioavailability of oral oxycodone is 37 % [5]. The mean time to achieve maximal plasma concentration is 3 h, but can range up to 8 h [5]. Additionally, oxycodone is absorbed primarily in the small

intestine, so delayed gastric emptying may lead to delayed oxycodone absorption [5]. Due to inconsistent pharmacokinetics and pharmacodynamics in this age group using buccal and gastric administration, it is recommended that oxycodone dosing be individually titrated to achieve the desired clinical effect [5]. Little data exists regarding the use of oxycodone in children under the age of 6 months [1].

Oxycodone has been used as an alternative analgesic to codeine in nursing women since 2007 when the US Food and Drug Administration (FDA) published a warning regarding the safety of codeine in nursing mothers. The warning was in response to the death of a 13-day-old breastfed infant whose morphine levels were significantly elevated due to the mother being an ultrarapid metabolizer of codeine [6]. However, the neonatal safety of maternal oxycodone use while breastfeeding has never been established, and limited information is available regarding the amount of oxycodone in breast milk and its subsequent effects on the neonate [7]. It has been shown that maternal oxycodone and codeine use have the same incidence of central nervous system depression in neonates, so oxycodone is unlikely to be a safer alternative in this clinical setting [7].

What Is the Recommended Length of Observation in Children After Overdose of Oxycodone?

Limited data exists regarding the pharmacokinetic and pharmacodynamic properties of oxycodone in children when given in therapeutic doses, and even less evidence-based medicine is available concerning the toxicokinetics and toxicodynamics. It has taken as long as 8 h to reach a maximal plasma concentration after oxycodone is given by the gastric route in therapeutic doses, and other factors such as delayed gastric absorption may contribute to delays in reaching the peak concentration [5]. In overdose, normal pharmacokinetics is altered, leading to potentially prolonged toxicity and clinical effects [8].

Generally, asymptomatic patients with exposure to short-acting opioids should be observed in the emergency department for at least a 4- to 6-h period [9, 10]. Longer observation periods or admission (for at least 24 h) should be considered in methadone, buprenorphine, and delayed-release preparations of opioids due to the potential for prolonged respiratory depression and CNS depression [9, 11, 12]. These recommendations are based on patients who are asymptomatic with an exposure to an opioid medication, not on children with a known overdose. Insufficient data and clinical experience are available to recommend a safe time period for observation of children after a supratherapeutic ingestion of oxycodone.

Case Continuation

The patient was admitted to the pediatric floor overnight for observation and respiratory monitoring. The acetaminophen

level drawn 4 h after the medication error occurred was 12 mcg/mL, which was within the therapeutic range. Her transaminases were within normal limits.

Why Is There a Black Box Warning for Codeine in Children After Tonsillectomy?

In August of 2012, the FDA released a safety announcement regarding the use of codeine in pediatric patients with a diagnosis of obstructive sleep apnea (OSA) status post tonsillectomy or adenoidectomy [13]. The announcement came in the setting of pediatric fatalities attributed to codeine use in this population [14, 15]. After a full investigation by the FDA, a boxed warning and contraindication was published in February 2013 [16]. The investigation revealed that codeine is a widely used analgesic in the pediatric population, with 1.7 million children (age 0–17 years) receiving a prescription for the medication in 2011 [16]. A review of their Adverse Event Reporting System (AERS) database from 1969 to 2012 revealed 13 pediatric fatalities or overdose involving codeine, 7 of which are described in the medical literature [16]. Although the warning specifically addresses the pediatric population status post tonsillectomy or adenoidectomy, children who are at risk for adverse effects due to codeine administration likely extends beyond the postoperative population included in the FDA-boxed warning [17].

What Is Understood About Codeine and Its Metabolism?

Codeine is a widely used analgesic and antitussive medication that is a naturally occurring opium alkaloid [18, 19]. It was first isolated in 1832 from the opium poppy *Papaver somniferum*, but is now mostly synthesized from morphine via *O*-methylation [19–21]. Compared to morphine, codeine is a weak opioid with a potency ratio of 1:10 at the mu opioid receptor [19, 21]. Codeine has variable and adverse effects that range from ineffective analgesia to respiratory depression and death [19, 20]. However, it is still widely used and is recommended as a step 2 medication in the World Health Organization Pain Ladder for the treatment of pain [17, 19, 20].

Metabolism of codeine takes place primarily in the liver by glucuronidation and the cytochrome P450 enzyme system. The majority of codeine (50–70 %) is converted by the enzyme uridine diphosphate glucuronosyltransferase 2B7 (UGT2B7) into codeine-6-glucuronide [17, 21] (see Fig. 2). A smaller proportion (10–15 %) of codeine is *N*-demethylated via CYP3A4 to form norcodeine. Although genetic variants of CYP3A4 are common, they do not seem to influence drug metabolism [22]. Both codeine-6-glucuronide and norcodeine have the same affinity for the mu opioid receptor as codeine. A small amount of codeine (5–15 %) is excreted unchanged into the urine, and the rest undergoes *O*-demethylation to form morphine by the CYP2D6 pathway [18, 20]. Morphine is the

Fig. 2 Metabolic pathways of codeine

most active metabolite, with a 200-fold greater affinity for the mu opioid receptor than codeine [17, 21]. Although *O*-demethylation accounts for the minority of codeine metabolism, the morphine it produces is thought to be responsible for codeine's analgesic activity [18, 22]. Morphine is further metabolized in the liver and brain to form morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G). M3G has a low affinity for the mu opioid receptor, but M6G is metabolically active with a two- to fourfold greater affinity for the mu opioid receptor than morphine [21]. However, despite its potency, M6G is not thought to play a large role in codeine's analgesic activity due to its low blood concentrations [21].

How Does the Cytochrome P450 2D6 (CYP2D6) Pathway Influence the Effects of Codeine?

CYP2D6 is an important polymorphic enzyme involved in the oxidative metabolism of nearly 25 % of pharmaceuticals on the market [23, 24]. Of these drugs, nearly 50 % have altered metabolism as a result of the polymorphisms, making the CYP2D6 genes extremely relevant to drug metabolism [24]. In addition to its many polymorphisms, CYP2D6 is generally regarded as the only drug metabolizing enzyme system that is non-inducible, leading its genetic variations to have the most

significant impact on its enzyme activity [24]. The two alleles responsible for CYP2D6 have over 100 variants and subvariants with a variety of functional capabilities [17, 21]. These combinations account for its diverse phenotypes and wide spectrum of metabolic activity [17, 19, 21]. Additionally, children may have higher rates of drug metabolism via the CYP450 system due to their larger liver mass per kilogram body weight compared to adults [25].

This diversity in the function of CYP2D6 is responsible for the wide variation in the metabolism of codeine, leading to its considerable spectrum of clinical effects at therapeutic doses [17, 26]. A patient's CYP2D6 activity directly correlates with the expected effect of codeine, and individuals are phenotypically classified as poor metabolizers (PM), intermediate metabolizers (IM), extensive metabolizers (EM), and ultrarapid metabolizers (UM) [17, 27]. Due to homozygosity for nonfunctional mutant CYP2D6 alleles, PMs lack metabolic activity [18, 22]. As a result, PMs are unable to demethylate codeine to form morphine, and these individuals do not obtain adequate analgesia from codeine.

In contrast, CYP2D6 gene duplication leads to increased CYP2D6 activity and increased metabolism of codeine to morphine in UMs [18, 23]. As a result, UMs have 50 % higher plasma concentrations of morphine metabolite than EMs, which can lead to significant toxicity from morphine, even at therapeutic doses of codeine [17, 23].

CYP2D6 polymorphisms vary in frequency by ethnicity and are believed to be a result of unequal crossover events during homologous recombination [21, 23]. Poor metabolizers are prominent in white Caucasian populations (7–10 %) and are common in North America and Europe [20, 24]. Asia has a large number of IMs, and the most common allele of CYP2D6 in the Chinese population contains a mutation in a well-conserved region of the enzyme, leading to lower activity and slower metabolism via CYP2D6 [24, 28]. Ultrarapid metabolizers account for 3 % of the North American Caucasian population, 1 % of Swedish, 5–10 % of Southern Europeans, 10 % of Saudi Arabians, and 29 % of the Ethiopian population [18, 23]. The Greek population has a high prevalence of CYP2D6 gene duplication, supporting the belief that there may be a north/south gradient in the occurrence of UMs in European populations [26].

What Opioid Analgesics are Available for Pain Control for Pediatric Patients Status Post Tonsillectomy?

Effective pediatric pain management has been challenging since before the FDA released the boxed warning on codeine. Multiple studies demonstrate the need for significant improvement and changes in practice to obtain effective analgesia in pediatric populations [3, 17]. However, limited data exists regarding the pharmacokinetics, pharmacodynamics, efficacy, and safety of most analgesics in children [3]. As a result, off-

label use of analgesics occurs frequently in the pediatric population [29].

More than 5 million children undergo surgery annually in the USA, and one of the most common operations is tonsillectomy [20, 30]. Patients who underwent otolaryngologic, orthopedic, and urologic procedures have been found to be the most likely group to experience significant pain postoperatively compared with other surgeries [31]. Children who undergo tonsillectomy have been shown to experience pronounced pain for 7 days, and to have difficulty performing regular activities up to 2 weeks postoperatively [32].

Opioids are generally considered to be the most effective analgesics, but they also carry the greatest risk of adverse effects [33]. Recommendations to improve safety while using opioid analgesics include dosing them by ideal body weight instead of actual body weight, and using opioids such as oxycodone and hydrocodone that do not rely on metabolism to achieve their analgesic effect [17, 34, 35].

Hydrocodone is a semisynthetic opioid with analgesic and antitussive properties. It is 12 times more active at the mu opioid receptor than codeine [36]. Hydrocodone is primarily metabolized by CYP3A4 to norhydrocodone and by CYP2D6 to hydromorphone. These metabolites subsequently undergo conjugation by uridine diphosphate glucuronosyltransferases before being excreted in the urine [36]. Although both hydrocodone and oxycodone undergo metabolism via CYP2D6 to active metabolites, their analgesic effects are not as variable as codeine's because both parent compounds are pharmacologically active [35]. However, little data exists exploring the dose–toxicity relationship in the pediatric population [36].

Morphine is the most frequently used opioid in pediatric palliative care, but its use is not as prevalent for outpatient postoperative pediatric patients [37]. It is inexpensive and widely available, but is unpopular for its bitter taste. Morphine clearance varies with age, but it appears to function similarly to adults starting between 6 and 12 months of age [37]. As with hydrocodone, little is known about its dose–response relationship in children.

Methadone is a synthetic opioid that is long-acting, has an unpredictable and varied half-life, no known active metabolites, and is an NMDA antagonist [38]. Methadone is not generally used in the postoperative setting, but it is beginning to play a role in the outpatient treatment of pediatric oncology patients [38]. However, literature is limited about the pharmacokinetics and pharmacodynamics of methadone in the pediatric and neonate populations [39].

Hydromorphone is a semisynthetic opioid that has five to seven times the affinity for the mu opioid receptor compared with morphine [37]. It is metabolized to inactive metabolites by the liver and has a 50–60 % bioavailability when given enterally [37]. Use of hydromorphone in the pediatric literature is limited to case reports in the palliative care settings.

Limited data is available regarding its pharmacokinetics and pharmacodynamics in children [37].

Tramadol is a lipophilic opioid agonist with serotonergic activity. It has 1/6,000th the affinity of morphine at the mu opioid receptor [37]. Tramadol is metabolized by CYP2D6 to *O*-desmethyl-tramadol, an active metabolite with 200 times greater affinity for the mu opioid receptor than tramadol [37]. Its effects have been shown to vary with phenotypically different CYP2D6 metabolizers in adults, but little information exists regarding these potential effects in children [37].

Although the FDA-boxed warning only applies to codeine use, it is not clear that the use of any opioids is safe in children with OSA postoperatively [40]. Pediatric OSA has an incidence of 2–3.5 %, and up to 33 % of these individuals are not cured of OSA after surgery [40]. Additionally, it may take days to weeks for OSA to improve after surgery, and up to 10 % of patients are at risk for perioperative respiratory complications status post tonsillectomy and adenoidectomy [40]. Obesity, young age (especially children less than 3 years old), severe preoperative OSA, and other comorbidities place children at increased risk for perioperative respiratory events in the setting of surgery to treat OSA [40].

Case Conclusion

The patient was monitored overnight with no signs of respiratory depression or mental status changes. After remaining asymptomatic for 10 h after receiving the erroneous dose of Roxicet®, she was discharged home with her family in good condition.

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