REVIEW ARTICLE

Opioid Use and the Risk of Respiratory Depression and Death in the Pediatric Population

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BACKGROUND Pediatric patients may be at an increased risk of adverse effects from various medications. Recently, there have been a number of serious adverse events, including several pediatric patients experiencing severe respiratory depression and death as a result of the use of codeine for pain control following tonsillectomy and adenoidectomy.

OBJECTIVE To assess the safety of opioid agonists in pediatric patients undergoing operative procedures or have experienced trauma and to evaluate the risk of respiratory depression and death among this population.

METHODS PubMed and Medline were searched to identify randomized controlled studies from 1994 to 2012 addressing postsurgery/trauma opioid use in pediatric patients. Relative risks and confidence intervals (CIs) were calculated using data available in clinical trials.

RESULTS A total of 16 clinical trials were evaluated for this review. Randomized controlled trials included studies comparing opioids versus non-opioids for a variety of painful conditions. The relative risk of respiratory depression associated with opioid use in 1 trial was 1.63 (95% CI: 0.64-6.13). The remaining 15 trials reviewed described no significant difference in respiratory depression or adverse effects associated with treatment. No deaths were attributed to opioid use in any of these studies.

CONCLUSION Opioid-associated respiratory depression was very rare and no deaths were reported in the reviewed studies. These findings under the well-defined conditions of controlled studies may not be the best means of determining overall opioid-associated side effects in pediatric patients.

INDEX TERMS children, clinical trial, codeine, opioid, pain

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INTRODUCTION

Acute and chronic pain management in the pediatric population is a challenging area of medicine and is a major public health concern in many countries.[1] The treatment of pain is often problematic due to the inherent difficulties of pain assessment in children. Maintaining adequate pain control while reducing adverse effects can be particularly challenging in preverbal and critically ill infants and children. Many patients also require several doses of an analgesic to achieve adequate pain control. A review published in 2005 reported that a single prophylactic dose of an analgesic is not sufficient to provide analgesia on the day of surgery.[2] Due to variable pharmacokinetics, lack of mature metabolic processes, coupled with dosing challenges, infants and children may be at increased risk of adverse effects. These adverse effects can then contribute to substantial morbidity and mortality in this population.[2] In 2012, an international evaluation of adverse drug reactions (ADRs) among children aged 0 to 18 years revealed that approximately 20% of all ADRs were attributable to cough and cold preparations containing analgesics or opioids.[3]

see Editorial on page 264

Within the past several years, an increasing number of case reports have illustrated clinically important respiratory depression and even death among infants and children receiving opioids for pain control particularly following tonsillectomy and adenoidectomy (T&A). In 2007, a previously healthy 29-month-old patient received acetaminophen and codeine after tonsillectomy and on post-op day 2, experienced severe apnea and subsequent brain injury.[4] Genetic testing in this patient revealed polymorphic expression of

Table 1. Prevalence of Ultra-Rapid Metabolic Activity of the Cytochrome P-450 isoenzyme 2D6 in Different Populations[10]

Population	UM Genotypes/Phenotypes (↑ Activity)	Prevalence % (UM/Total n)
African/Ethiopian	UM (active duplicate genes)	29 (35/122)
African American	UM (3 active duplicate genes)	3.4 (3/87) to 6.5 (60/919)
Asian	UM (active duplicate genes)	1.2 (5/400) to 2
Caucasian	UM (3 active duplicate genes)	3.6 (33/919) to 6.5 (18/275)
Greek	CYP2D6*2 × N/UM	6 (17/283)
Hungarian	UM (active duplicate genes)	1.9
Northern European	UM (active duplicate genes)	1-2

CYP2D6, cytochrome P-450 isoenzyme 2D6; UM, ultra-rapid metabolizer

the cytochrome P-450 2D6 (CYP2D6) isoenzyme responsible for the ultra-rapid metabolism of codeine. Three additional case reports were published in 2012 that involved 2 fatal cases and a severe case of life-threatening respiratory depression after codeine administration following tonsillectomy. All of these patients had functional gene duplications encoding for CYP2D6, which resulted in toxic levels of codeine's primary active metabolite, morphine.[5] A published case in 2009 reported the fatalities of 3-year-old twins given codeine as an antitussive agent every 6 hours.[6] Autopsy of one of the children revealed possible overdose, however, also revealed potential CYP2D6 polymorphism for ultra-rapid metabolism of codeine. In February 2013, the Food and Drug Administration (FDA) issued a drug safety communication to health care professionals and the public about a new boxed warning being added to the labels of codeine and codeine-containing products.[7] The warning contains information about the risk of codeine use in postoperative pain management in children following tonsillectomy and/or adenoidectomy. According to the FDA, codeine utilization in this population is now a contraindication.

Mortalities have also been reported following the administration of other opioids in pediatric patients. A study by the Researched Abuse, Diversion and Addiction-Related Surveillance System (RADARS) poison center investigators in 2009 reported 8 cases of death in infants and children aged 9 to 36 months following the ingestion of methadone (n=2), hydrocodone (n=2), and oxycodone (n=4).[8] Details on opioid dosing or the obtainment of genetic testing were not available for these cases. Metabolism of various medications occurs through the cytochrome P450 microsomal liver enzyme system. Approximately 10% to 25% of metabolized medications are processed by the CYP2C19 and CYP2D6 iso-enzymes.[9] Increasing evidence confirms the high degree of variability in polymorphically expressed enzymes responsible for drug metabolism. The prevalence of the CYP2D6 ultra-rapid metabolic genotype in various populations is shown in Table 1.[10] The incidence of toxic systemic concentrations with codeine or other opioids in specific pediatric population groups exhibiting ultra-rapid CYP metabolism is presently unknown.

Given the growing interest and concern regarding the reported morbidity and mortality among infants and children following the postoperative administration of opioids at appropriate doses, a review of the literature was conducted to determine if pediatric patients undergoing operative procedures or have experienced trauma are at risk of adverse opioid effects, mainly death and respiratory depression.

METHODS

Pertinent articles were searched using Medline and PubMed databases. Search terms included opioid, pain, all children 0 to 18 years, hydrocodone, hydromorphone, oxycodone, codeine, and clinical trial terms from 1994 to 2012. Randomized controlled trials (RCTs) studying any opioid versus a non-opioid with reported adverse effects in children were included in this review. Study data were used to calculate relative risks (RRs) and 95% confidence intervals (CIs) for adverse effects. The reported adverse effects that were analyzed included respiratory depression, defined as oxygen saturation below 95% or the requirement of supplemental oxygen, and use of rescue therapy such as naloxone during the trials. Reported deaths associated with opioid

administration in each trial were also included in the analysis.

RESULTS

A total of 16 clinical trials are included in this review. Details of each study are included in Table 2. One of the 16 studies included information regarding adverse effects to calculate RR. This study was a single-dose RCT examining the effectiveness of intravenous (IV) tramadol versus IV morphine following adenotonsillectomy in 66 pediatric patients 1 to 8 years old.[11] The RR of patients experiencing at least 1 desaturation episode was 1.63 times greater in patients who received morphine as compared to patients who received tramadol (95% CI: 0.64-6.13). An additional study by Zhuang and colleagues[12] reported no difference in the incidence of respiratory depression between patients receiving postoperative IV dexmedetomidine or IV morphine (p=0.85). Two different doses of IV tramadol compared to IV morphine were studied in a prospective, double-blind, RCT in children undergoing elective T&A.[13] Patients received analgesic study drug until hospital discharge and there were no episodes of respiratory depression described in either group. Ozalevli and colleagues[14] examined pain control differences between the administration of IV tramadol and IV morphine in the form of patient controlled analgesia (PCA) in pediatric patients who underwent T&A. Drug-associated adverse effects in patients receiving either therapy were monitored for 24 hours during PCA administration. There were no reported differences in oxygen saturation in this trial. Another RCT studied pain control in patients given IV tramadol, IV ketamine, or IV morphine following T&A.[15] This trial found no difference in oxygen saturation between groups. Lieh-lai and colleagues[16] evaluated the analgesic efficacy of IV ketorolac compared to IV morphine for the relief of postoperative pain in critically ill children. The authors state that "specific attention was given to a decrease in respiratory rate"; however, the results of this monitored adverse event following the dose of study medication were not reported.

Trials that studied caudal and epidural solutions containing an opioid versus a non-opioid were also reviewed to determine risk of serious adverse effects. One study that compared the efficacy of IV clonidine or fentanyl in conjunction with ropivacaine given caudally for postoperative pain relief resulted in no significant difference in oxygen saturation (Spo_2) (p>0.05).[17] An RCT studied caudal blockade with single dose clonidine, hydromorphone, or morphine combined with ropivacaine with epinephrine in children undergoing ureteral implantation.[18] No postoperative respiratory events were identified in this patient population. Another RCT compared morphine or clonidine with bupivacaine for caudal analgesia in children undergoing upper abdominal surgery.[19] In this investigation, no respiratory depression was reported in any patients throughout the postoperative study time periods. Epidural administration of clonidine or morphine plus ropivacaine was described in children who underwent various abdominal surgeries.[20] Adverse effects were evaluated during the first 48 hours after the end of surgery. Results of this trial did not include reports of respiratory depression or death. The comparison of bupivacaine plus clonidine or morphine administered caudally for orchidopexy, hernia repair, or circumcision was assessed for postoperative respiratory depression.[21] There was no difference in respiratory rates between the 2 treatment groups. Ozcengiz and colleagues[22] evaluated the effects of a single caudal administration of either tramadol or morphine on the requirement of perioperative sevoflurane and the preemptive analgesic efficacy of morphine in children undergoing inguinal herniorrhaphy. Oxygen saturation and respiratory rates were similar between the groups.

Randomized trials including oral opioid analgesics were also evaluated. During the trial period of an RCT examining oral administration of acetaminophen, ibuprofen, and codeine for acute pain relief in children with musculoskeletal trauma, no respiratory depression, or serious adverse events were reported.[23] Evaluation of a randomized, double-blind trial that examined the oral administration of ibuprofen versus acetaminophen with codeine for pediatric arm fracture revealed a 4.1% difference in adverse effects between the 2 interventions; however, respiratory depression was not separately stratified.[24] A comparison of oral acetaminophen with codeine versus ibuprofen for pain in postoperative tonsillectomy patients was performed.[25] No respiratory effects were reported during the trial. Moir and colleagues[26] measured the effectiveness

Table 2. Summary of Studies Examining Opioid Versus Non-opioid Pain Control and Associated Adverse Effects

Reference	Age (n)	Procedure/type of Pain	Interventions	Route	Study Duration	Adverse Effects Outcomes
Hullett et al[11]	1-8 yr (n=66)	T&A postoperative pain	Tramadol 2 mg/kg vs. morphine 0.1 mg/kg	IV	6 hr	24% more morphine patients with 1 desaturation episode (p=0.13)
Zhuang et al[12]	2-13 yr (n=60)	T&A	Dexmedetomidine 1 mcg/kg vs. morphine 100 mcg/kg	IV	1 hr	No difference in S_{PO_2}[c] between groups (p=0.85)
Engelhardt et al[13]	3-8 yr (n=60)	T&A	Tramadol 1 mg/kg vs. tramadol 2 mg/kg vs. morphine 0.1 mg/kg	IV	Every 4 hr until discharge	Respiratory depression and death were not present during study period
Ozalevli et al[14]	6-12 yr (n=60)	T&A	Morphine PCA vs. tramadol PCA	IV	24 hr during PCA administration	No significant differences in S_{PO_2} between groups
Umuroglu et al[15]	5-12 yr (n=60)	T&A	Ketamine 0.5 mg/kg vs. morphine 0.1 mg/kg vs. tramadol 1.5 mg/kg vs. placebo	IV	6 hr	No significant differences in S_{PO_2} between groups
Lieh-Lai et al[16]	5.6-14.8 yr (n=102)	Cardiovascular, spinal fusion, neurosurgical, reconstructive	Morphine 0.1 mg/kg vs. ketorolac 0.6 mg/kg	IV	6 hr	Respiratory depression and death not reported during study period
Shukla et al[17]	3-8 yr (n=90)	Infraumbilical surgical procedures	Ropivacaine 0.25% 1 mL/kg + clonidine 2 mcg/kg vs. ropivacaine 0.25% 1 mL/kg + fentanyl 1 mcg/kg	Caudal	6 hr	No difference in postop S_{PO_2}[c] (p>0.05)
Vetter et al[18]	0.5-6 yr (n=60)	Ureteral reimplantation	Clonidine 2 mcg/kg vs. hydromorphone 10 mcg/kg vs. morphine 50 mcg/kg*	Caudal	24 hr	Respiratory depression and death not reported during study period

APAP, acetaminophen; PCA, patient controlled analgesia; S_{PO_2}, oxygen saturation; T&A, tonsillectomy and adenoidectomy
**All treatments were combined with ropivacaine 0.2% with epinephrine 1:200,000 1 mL/kg*
†Both treatments were combined with bupivacaine 0.2% 1.25 mL/kg
‡Both treatments were followed by continuous infusion of either ropivacaine 0.08% and clonidine 0.6 mcg/mL or ropivacaine 0.08% and morphine 10 mcg/mL at 0.4 mL/kg/hr
§Both treatments were combined with bupivacaine 0.18% 1.5 mL/kg
¶Dosing based on treatment protocol according to age

Table 2. Summary of Studies Examining Opioid Versus Non-opioid Pain Control and Associated Adverse Effects (*cont.*)

Reference	Age (n)	Procedure/type of Pain	Interventions	Route	Study Duration	Adverse Effects Outcomes
Singh et al[19]	1-6 yr (n=50)	Abdominal surgery	Clonidine 2 mcg/kg vs. morphine 30 mcg/kg†	Caudal	Until child awake	Respiratory depression was not present during study period
Cucchiaro et al[20]	3-12 yr (n=26)	Abdominal surgery	Clonidine 1 mcg/kg + ropivacaine 2.5 mg/kg vs. morphine 40 mcg/kg + ropivacaine 2.5 mg/kg‡	Epidural	48 hr	Respiratory depression and death not reported during study period
Luz et al[21]	0.5-6 yr (n=36)	Abdominal surgery	Clonidine 1 mcg/kg vs. morphine 30 mcg/kg§	Epidural	24 hr	No significant differences in respiratory rates between groups
Ozcengiz et al[22]	5-9 yr (n=116)	Inguinal herniorrhaphy	Tramadol 2 mg/kg vs. morphine 0.03 mg/kg	Caudal	24 hr	Respiratory depression and death not reported during study period
Clark et al[23]	6-17 yr (n=300)	Musculoskeletal trauma	APAP 15 mg/kg vs. ibuprofen 10 mg/kg vs. codeine 1 mg/kg	Oral	48 hr	Respiratory depression and death not reported during study period
Drendel et al[24]	4-18 yr (n=336)	Arm fracture	Ibuprofen 10 mg/kg vs. APAP w/codeine 1 mg/kg	Oral	72 hr	Respiratory depression and death not reported during study period
St. Charles et al[25]	1.3-14 yr (n=110)	T&A	APAP w/codeine versus ibuprofen¶	Oral	Every 4 hr until discharge	Respiratory depression and death not reported during study period
Moir et al[26]	3.1-7.9 yr (n=51)	T&A	APAP 15 mg/kg versus APAP w/codeine 1 mg/kg	Oral	10 days	Respiratory depression and death not reported during study period

APAP, acetaminophen; PCA, patient controlled analgesia; SpO_2, oxygen saturation; T&A, tonsillectomy and adenoidectomy
**All treatments were combined with ropivacaine 0.2% with epinephrine 1:200,000 1 mL/kg*
†Both treatments were combined with bupivacaine 0.2% 1.25 mL/kg
‡Both treatments were followed by continuous infusion of either ropivacaine 0.08% and clonidine 0.6 mcg/mL or ropivacaine 0.08% and morphine 10 mcg/mL at 0.4 mL/kg/hr
§Both treatments were combined with bupivacaine 0.18% 1.5 mL/kg
¶Dosing based on treatment protocol according to age

of acetaminophen versus acetaminophen with codeine after pediatric T&A. Respiratory effects were not captured by parental questionnaires during postoperative follow-up. Of the 16 trials analyzed for review, no deaths were reported among any of the patients included in the studies.

DISCUSSION

The focus of this review was to determine if pediatric patients undergoing surgical procedures and those with trauma are at an increased risk of developing respiratory depression when receiving opioids for pain control. The results of this review are inconclusive. In the studies analyzed, there were no reported deaths associated with study treatments. Limitations to this review include the lack of published RCTs comparing opioids versus non-opioids that critically assessed all types of expected/unexpected adverse effects. Unfortunately, the published RCTs analyzed contained small sample sizes and their study periods for most trials were short in duration, thus severely limiting any critical assessment of opioid associated respiratory depression and death.

In 2012 the World Health Organization published guidelines on the assessment and management of pain in the pediatric population. Recommendations include appropriate assessment of pain and utilizing analgesic therapy in 2 steps according to the child's level of pain severity. Acetaminophen and ibuprofen should be administered for mild pain, whereas for more moderate to severe pain, an opioid should be considered.[1] When an opioid is used, particularly in the outpatient setting, education on adverse effects provided to parents and caregivers is paramount. As a result of the recent case reports with the use of codeine, the FDA has changed the labeling of codeine and codeine-containing products. For children undergoing tonsillectomy and/or adenoidectomy, the FDA recommends health care professionals prescribe an alternate analgesic for postoperative pain control.[8] The FDA also recommends that codeine should be reserved for children experiencing pain only when the benefits are anticipated to outweigh the risks.[8] For these reasons, pharmacy and therapeutic committees for many hospitals and health systems have resisted the use of codeine use or discontinued its use altogether. Autopsy results of fatal codeine cases have revealed genetic polymorphisms of the CYP2D6 enzyme. Since these reports, knowledge about the frequency of, but more importantly the clinical consequences of ultra-rapid metabolism has emerged. Other opioids, such as hydrocodone, oxycodone, and tramadol are metabolized to active metabolites through CYP2D6; however, the frequency of serious and/or fatal adverse effects as observed with codeine is unknown. Furthermore, the frequency of ultra-rapid CYP2D6 metabolism is present in various ethnic populations (Table 1), and the studies assessed in this review did not focus on genotype or phenotype for medication therapy and associated adverse effects.

A paucity of data exists addressing the use of opioids linked to CYP genotype in certain populations. Focused areas for future research should include randomized trials to adequately evaluate differences in adverse effects with specific attention to analgesic-induced respiratory depression between opioids and non-opioids in pediatric patients with a high prevalence of ultra-rapid metabolism genotype. Studies analyzing metabolic gene mutations for all affected opioids administered to infants and children will better delineate the concern surrounding the use of opioids in this population fostering optimal analgesic safety and efficacy.

CONCLUSION

Respiratory depression was very rare and no deaths were described in the reviewed trials. It is important to note that the patient populations included in these trials were at very low risk for serious opioid-associated adverse events with their use. Additional RCTs evaluating opioid-associated adverse effects over longer study periods are warranted to determine if certain patients have a greater risk of respiratory depression and death associated with the use of opioids with a focus on ultra-rapid metabolism among this population.

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ABBREVIATIONS ADR, adverse drug reaction; APAP, acetaminophen; CI, confidence interval; CYP2D6, cytochrome P-450 isoenzyme 2D6; FDA, Food and Drug Administration; IV, intravenous; PCA, patient controlled analgesia; RCT, randomized controlled trial; RR, relative risk; SpO_2, oxygen saturation; T&A, tonsillectomy and adenoidectomy; UM, ultra-rapid metabolizer

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