PEDIATRIC PHARMACOTHERAPY

A Monthly Newsletter for Health Care Professionals from the Children's Medical Center at the University of Virginia

• *celebrating 10 years of publication* •

Children's Medical Center
UVA HEALTH SYSTEM

Volume 10 Number 4 April 2004

Therapeutic Uses of Codeine in Pediatric Patients

Marcia L. Buck, Pharm.D., FCCP

The combination of acetaminophen and codeine is one of the most commonly used preparations for the treatment of moderate pain in children. Codeine is also used in a variety of antitussive preparations.[1,2] Despite the frequency of its use, there have been relatively few studies of codeine in the pediatric population. This issue of *Pediatric Pharmacotherapy* will review the pharmacology of codeine and highlight recent publications of its use in children.

Mechanism of Action

Codeine, also known as methylmorphine, is a naturally occurring alkaloid produced by the poppy plant, *Papaver somniferum*. It was first isolated from opium by the French pharmacist Robiquet in 1833. Although it may be obtained directly from the plant source, it is more commonly produced as a semisynthetic agent from the 3-O-methylation of morphine. Codeine is one of the phenanthrene opioids, a group with also includes morphine, hydrocodone, hydromorphone, oxycodone, oxymorphone, and levorphanol.[1,3]

Like other opioids, codeine binds to mu-opioid receptors to produce analgesia and euphoria, as well as respiratory depression, miosis, and reduced gastric motility. It also binds to kappa opioid receptors, producing spinally-mediated analgesia. Codeine has a low affinity for opioid receptors, however, making it a relatively weak analgesic with approximately 1/6th to 1/10th the potency of morphine.[3,4]

Pharmacokinetics and Pharmacodynamics

Codeine is well absorbed after oral administration, with a bioavailability of 60 to 90%. Peak plasma concentrations occur approximately 1 hour after an oral dose and 30 minutes after an intramuscular injection in children and adults. It is widely distributed throughout the body, with less than 10% bound to proteins. The volume of distribution in adults is 3.6 L/kg.

Codeine metabolism is a complex process, involving conjugation to codeine-6-glucuronide, O-demethylation via cytochrome P450 (CYP) 2D6, and N-demethylation through CYP3A3/4. Approximately 5 to 15% of a dose is metabolized to morphine through the CYP2D6 pathway. Genetic polymorphism of the CYP2D6 enzyme results in significant interpatient variability in the production of morphine, which may lead to differences in patient response. The primary metabolites, codeine-6-glucuronide, norcodeine, and morphine, as well as several minor metabolites, are excreted in the urine. Five to 15% of a dose is excreted unchanged. The average elimination half-life of codeine in children and adults is 2 to 4 hours. Infants have been reported to have a longer half-life, up to 6 hours, as a result of reduced glucuronidation.[2,3-6]

The onset of analgesic action with codeine is typically within 30 minutes after oral administration, with a maximum effect at 60 to 90 minutes. The duration of action is approximately 4 to 6 hours.[4]

Use as an Analgesic

Although codeine has a long history of use in children, there have been relatively few controlled trials published in the medical literature to support its efficacy as an analgesic. To further complicate assessment, these studies have produced mixed results. In 1995, Tobias and colleagues randomized 50 children, 7 months to 4 years of age, to receive a single dose of either acetaminophen (10 mg/kg) with codeine (1 mg/kg) or acetaminophen (15 mg/kg) alone prior

to myringotomy and placement of pressure equalization tubes.[7] Pain was assessed at four intervals following surgery by a nurse blinded to the medication. The patients receiving acetaminophen with codeine had lower pain scores at all four assessments prior to discharge. None of the patients receiving the combination product required supplemental analgesia during the observation period, compared to 12 of the 25 children given acetaminophen alone. Although not a significant difference, the time to discharge was shorter in patients given the combination. No adverse effects were noted in either group. Based on these results, the authors concluded that acetaminophen with codeine was superior to acetaminophen alone in this setting.

In contrast, Moir and colleagues found no significant difference in the pain scores of children receiving acetaminophen with codeine or acetaminophen alone after tonsillectomy.[8] In their prospective, randomized, double-blind trial, 51 children (ages 3 to 12 years) were given either 15 mg/kg acetaminophen elixir or acetaminophen (10 mg/kg) with codeine (1 mg/kg) elixir by their parents every 4 hours as needed after surgery, with pain assessed daily by the patients and parents using the Wong-Baker FACES scale. There were no differences in pain scores at any point during the 10-day assessment period. The combination group experienced more problems with nausea, emesis, and constipation, but the results were not statistically significant. The only significant finding of the study was greater oral intake in the acetaminophen group.

It has been suggested by many investigators that the primary analgesic response from codeine results from its conversion to morphine, and that patients with reduced CYP2D6 function may not achieve adequate morphine concentrations to provide analgesia.[2,4,9] This may explain, in part, the lack of response seen in some studies. In 2002, Williams and colleagues compared the analgesic efficacy of codeine, at a dose of 1.5 mg/kg, versus morphine 0.15 mg/kg, both given intramuscularly after adenotonsillectomy in 96 children (ages 3 to 12 years).[5] Genetic analysis and plasma morphine concentrations were evaluated in both groups to ascertain the degree of codeine metabolism to morphine. Forty-seven percent of the children were found to have reduced CYP2D6 function. There was a significant relationship between enzyme function and plasma morphine concentrations after administration of codeine; however, neither enzyme function nor morphine concentrations were correlated with pain scores or the need for supplemental analgesia. Overall, more children in the codeine group required additional analgesia at both 2 and 4 hours after surgery than in the morphine group. Based on their results, the authors concluded that reduced codeine metabolism may be more common than previously reported, but that response was not well correlated to phenotype.

Use as an Antitussive

Codeine is also commonly used as an antitussive in cough and cold preparations. Codeine suppresses the cough reflex through a direct effect on the cough center in the medulla. There is little evidence in the medical literature to support this use. Several studies comparing codeine to placebo have failed to show a statistically significant reduction in cough frequency, intensity, or duration.[10,11] In a trial of 49 children randomized to receive codeine, hydrocodone, or placebo at bedtime for 3 days, Taylor and colleagues found no differences in parental report of cough frequency or sleep duration.[11]

In addition to questions regarding their efficacy, there is concern for the risk of toxicity with inappropriate administration of codeine-containing preparations in infants and young children. In 1999, Magnani and Evans reported a fatal case of codeine intoxication in a 29-day old term infant given 1 ml Novahistine DH® (providing a dose of 0.63 mg/kg) every 6 hours.[12] The dose had been prescribed in the emergency department for presumed viral tracheitis. The patient was found not breathing by a parent approximately one hour after the second dose. Resuscitation attempts failed. Postmortem findings suggested acute opiate intoxication, compounded by severe bronchitis/bronchiolitis. Although the dose did not appear excessive in this case, the immaturity of metabolic enzyme function in the newborn likely led to drug accumulation resulting in respiratory depression.

In a 1997 statement from the American Academy of Pediatrics, the Committee on Drugs found insufficient evidence to support either the safety or efficacy of codeine or dextromethorphan as antitussive agents in children.[13] The Committee concluded that patients and parents should be educated about the lack of proven benefit of antitussives, as well as their potential risks.

Drug Interactions

Codeine should be used with caution in patients receiving other central nervous system and respiratory depressants, including other opioids, barbiturates, benzodiazepines, and phenothiazines.[4]

Adverse Effects

Codeine, like other opioids, may produce severe respiratory depression and hypotension with excessive doses. More commonly, opioids are associated with dizziness, sedation, altered mental status or mood, miosis, dry mouth, nausea, emesis, constipation, urinary retention, pruritus, and diaphoresis. Severe hypersensitivity reactions are uncommon, but are more likely to occur in patients known to react to other phenanthrene-derived opioids. As with other opioids, long-term administration of codeine may result in the development of tolerance and physiologic dependence.[4]

Intravenous (IV) administration of codeine is not recommended. Use of this route has been associated with severe hypotension, resulting from excessive histamine release. In addition, it has been suggested that codeine may produce a direct depression of myocardial function.[14-16] Intravenous codeine administration has also been linked with seizures in children. In 2001, Zolezzi and Al Mohaimeed reported a case of a seven year old child with sickle cell disease who developed tonic-clonic seizures after receiving IV codeine (2 mg/kg) for a pain crisis.[17] The seizures responded to diazepam and naloxone, and the patient experienced a full recovery within 24 hours.

Availability and Dosing Recommendations

Codeine is available in a wide variety of dosage forms, including 30 mg/ml and 60 mg/ml injectable products, as well as 15, 30, and 60 mg tablets, and a 15 mg/5ml oral solution. In addition, codeine is available in many combination products with acetaminophen. The most frequently prescribed products include tablets (300 mg acetaminophen with 15, 30, or 60 mg codeine) and an oral elixir with 120 mg acetaminophen and 12 mg codeine per 5 ml.[4]

The recommended oral analgesic dose for codeine in children is 0.5 to 1 mg/kg administered every 4 to 6 hours as needed, to a maximum of 60 mg/dose. The same dose may be used for intramuscular or subcutaneous administration, although not commonly used. As stated previously, IV administration of codeine is not recommended because of the risk for hypotension and seizures. In adults, the analgesic dose ranges from 15 to 60 mg/dose every 4 to 6 hours.[4]

As discussed previously, there is little information to support the use of codeine as an antitussive. If it is used for antitussive effects, a lower codeine dose of 0.25 to 0.5 mg/kg is generally recommended for children. Alternatively, dosing may be based on age, with children 2 to 6 years receiving 2.5 to 5 mg and children 6 to 12 years receiving 5 to 10 mg orally every 4 to 6 hours. The use of codeine in children less than 2 years of age is not recommended. The antitussive dose for adults is typically 10 to 20 mg given every 4 to 6 hours.[4]

In patients with moderate renal dysfunction, the dose of codeine should be reduced by 25%. In those with severe renal dysfunction, the dose should be reduced by 50%.[4] Failure to adjust dosing in children with renal dysfunction may lead to severe opioid intoxication. Talbott and colleagues reported apnea and respiratory arrest in a 5 year old child with chronic renal failure who was given four standard doses of acetaminophen with codeine after adenotonsillectomy.[18] Although no specific dosing recommendations are available for patients with hepatic dysfunction, smaller doses and prolonged dosing intervals should be considered to avoid drug accumulation.[4]

Summary

Codeine has a long history of use as both an analgesic and antitussive in children. Despite the frequency of its use, there have been few studies of its efficacy and safety. Recent studies of codeine as an analgesic in children have provided mixed results, while the limited research on its efficacy in reducing cough has failed to demonstrate significant benefit. More controlled clinical trials, as well as pharmacokinetic studies, are needed to better define the utility of codeine in the pediatric population.

References

1. Cunliffe M. Codeine phosphate in children: time for re-evaluation? [editorial] Brit J Anaesth 2001;86:329-31.
2. Williams DG, Hatch DJ, Howard RF. Codeine phosphate in paediatric medicine. Brit J Anaesth 2001;86:413-21.
3. Reisine T, Pasternak G. Opioid analgesics and antagonists. In: Hardman JG, Limbird LE, eds. Goodman and Gilman's The Pharmacological Basis of Therapeutics. 9th ed. New York: McGraw-Hill, 1996: 521-55.
4. Narcotic agonist analgesics. *Drug Facts and Comparisons*. EFacts [online]. 2004. Available from Wolters Kluwer Health, Inc. Accessed 4/6/04.
5. Williams DG, Patel A, Howard RF. Pharmacogentics of codeine metabolism in an urban population of children and its implications for analgesic reliability. Br J Anaesth 2002;89:839-45.
6. Quiding H, Olsson GL, Boreus LO, et al. Infants and young children metabolise codeine to morphine. A study after single and repeated rectal administration. Br J Clin Pharmacol 1992;33:45-9.
7. Tobias JD, Lowe S, Hersey M, et al. Analgesia after bilateral myringotomy and placement of pressure equalization tubes in children: acetaminophen versus acetaminophen with codeine. Anesth Analg 1995;81:496-500.
8. Moir MS, Bair E, Shinnick P, et al. Acetaminophen versus acetaminophen with codeine after pediatric tonsillectomy. Laryngoscope 2000;110:1824-7.

9. Poulsen L, Riishede L, Brosen K, et al. Codeine in post-operative pain: study of the influence of sparteine phenotype and serum concentrations of morphine and morphine-6-glucuronide. Eur J Clin Pharmacol 1998;54:451-4.
10. Herbert ME, Brewster GS. Myth: codeine is an effective cough suppressant for upper respiratory tract infections. West J Med 2000;173:283.
11. Taylor JA, Novack AH, Almquist JR, et al. Efficacy of cough suppressants in children. J Pediatr 1993;122(pt 1):799-802.
12. Magnani B, Evans R. Codeine intoxication in the neonate. Pediatrics 1999;104(6):e75. Accessed 4/6/04.
13. Committee on Drugs, American Academy of Pediatrics. Use of codeine- and dextromethorphan-containing cough remedies in children. Pediatrics 1997;99:918-20.
14. Shanahan EC, Marshall AG, Garrett CP. Adverse reactions to intravenous codeine phosphate in children. A report of three cases. Anaesthesia 1983;38:40-3.
15. Parke TJ, Nandi PR, Bird KJ, et al. Profound hypotension following intravenous codeine phosphate. Three reports and some recommendations. Anaesthesia 1992;47:852-4.
16. Cox RG. Hypoxaemia and hypotension after intravenous codeine phosphate. Can J Anaesth 1994;41:1211-3.
17. Zolezzi M, Al Mohaimeed SA. Seizures with intravenous codeine phosphate. Ann Pharmacother 2001;35:1211-3.
18. Talbott GA, Lynn AM, Levy FH, et al. Respiratory arrest precipitated by codeine in a child with chronic renal failure. Clin Pediatr 1997;36:171-3.

Pharmacology Literature Review

Pharmacokinetics of antiretrovirals in children

The pharmacokinetic effects of drug interactions among the antiretrovirals has not been well studied in pediatric patients. In this open-label multicenter study, 21 children infected with human immunodeficiency virus (HIV) were randomized to receive one of three treatment regimens: 1) zidovudine plus lamivudine, 2) ritonavir with zidovudine and lamivudine, or 3) ritonavir plus stavudine. Following the first stage of the study, all patients were given a regimen of ritonavir plus stavudine and nevirapine. Overall, the concentrations achieved with these regimens in children were comparable to those observed in adults. Pharmacokinetic analysis revealed a slower clearance of oral ritonavir in children who received stavudine, compared to those receiving zidovudine and lamivudine. Stavudine oral clearance was slightly faster when combined with ritonavir and nevirapine, compared to the combination of stavudine and ritonavir. Fletcher CV, Yogev R, Nachman SA, et al. Pharmacokinetic characteristics of ritonavir, zidovudine, lamivudine, and stavudine in children with human immunodeficiency virus infection. **Pharmacotherapy 2004;24:453-9.**

Formulary Update

The following actions were taken by the Pharmacy and Therapeutics Committee during their meeting on 3/26/04:

1. Bevacizumab (Avastin®) was added to both the Inpatient and Outpatient Formularies. This product is a humanized monoclonal antibody to vascular endothelial growth factor (VEGF), which prevents VEGF from binding to its receptor sites. It is used in combination with 5-fluorouracil for the first-line treatment of metastatic carcinoma of the colon or rectum.
2. Cetuximab (Erbitux®), a recombinant human/mouse chimeric monoclonal antibody that binds to epidermal growth factor receptors to cause apoptosis, inhibit cell proliferation and angiogenesis, was also added to both Formularies. Cetuximab is used in conjunction with irinotecan for the treatment of patients with EGFR-expressing metastatic colorectal cancer. It may be used as a single agent in patients intolerant of irinotecan.
3. The polifeprosan 20 with carmustine implant (Gliadel wafer®) was added to the Inpatient Formulary. It is indicated in newly diagnosed high-grade malignant glioma patients and patients with recurrent glioblastoma multiforme.
4. Omalizumab (Xolair®) was added to both Inpatient and Outpatient Formularies, with restriction to Allergy/Immunology, Pediatric Immunology, and Pulmonary/Critical Care services. This recombinant humanized monoclonal anti-IgE antibody is used in the treatment of moderate to severe persistent asthma. It is currently indicated for use in patients 12 years of age and older.
5. Pemetrexed (Alimta®), an antifolate medication that is used in combination with cisplatin for the treatment of malignant pleural mesothelioma, was added to both Inpatient and Outpatient Formularies.
6. The etonogestrel/ethinyl estradiol vaginal ring (NuvaRing®) was added to the Outpatient Formulary.
7. The restriction on the use of darbepoetin (Aranesp®) was amended to include use in hematology/oncology patients, as well as patients with anemia resulting from chronic renal failure.

Contributing Editor:Marcia L. Buck, Pharm.D.
Editorial Board: Anne E. Hendrick, Pharm.D.
Michelle W. McCarthy, Pharm.D.
Kristi N. Hofer, Pharm.D.
If you have comments or suggestions for future issues, please contact us at Box 800674, UVA Health System, Charlottesville, VA 22908 or by e-mail to mlb3u@virginia.edu. This newsletter is also available at www.healthsystem.virginia.edu/internet/pediatrics/pharma-news/home.cfm