Clinical and Translational Science Institute

Centers

6-1-2018

Indications for Use of Combination Acetaminophen/Opioid Drugs in Infants <6 Months>Old

William T. Basco Jr
Medical University of South Carolina

James R. Roberts
Medical University of South Carolina

Myla Ebeling
Medical University of South Carolina

Sandra S. Garner
University of South Carolina

Thomas C. Hulsey
West Virginia University

See next page for additional authors

Follow this and additional works at: https://researchrepository.wvu.edu/ctsi

Authors

William T. Basco Jr, James R. Roberts, Myla Ebeling, Sandra S. Garner, Thomas C. Hulsey, and Kit Simpson

Indications for Use of Combination Acetaminophen/Opioid Drugs in Infants <6 Months Old

William T. Basco Jr, MD, MS[1], **James R. Roberts, MD, MPH**[1], **Myla Ebeling**[1], **Sandra S. Garner, PharmD**[2], **Thomas C. Hulsey, MSPH, ScD**[3], and **Kit Simpson, DrPH**[1]

[1]The Medical University of South Carolina, Charleston, SC, USA

[2]South Carolina College of Pharmacy, Charleston, SC, USA

[3]West Virginia University, Morgantown, WV, USA

Introduction

Opioid analgesics are potentially hazardous medications in young children. During the past 5 years, much attention has been drawn to the safety concerns of these medications.[1–6]

Data evaluating pain control after injury among older children suggest that opioid drugs are not more effective than nonopioids in treating pain secondary to acute traumatic injury.[7,8] Postsurgical data evaluating children who underwent palatoplasty demonstrated that children treated with nonopioid pain regimens did as well as subjects treated with morphine.[9] More concerning, opioid analgesics have been consistently demonstrated to be among the most common drugs involved in accidental ingestions prompting emergency department visits and rank consistently high as contributors to medication-related death in children.[1] Data from nonopioid medication studies have demonstrated that young children, particularly infants, are at higher risk for experiencing drug errors and experiencing adverse outcomes should they experience a dosing error.[10] In previous studies, we demonstrated that children 0 to 36 months old who received opioid drugs received a potential overdose approximately 1.6% to 2.7% of the time, and the frequency of potential opioid overdose may be as high as 11.8% among children 0 to 2 months old.[11,12] In this brief report, we examined South Carolina Medicaid data to determine the indications for receipt of opioid analgesics among subjects 0 to <6 months old.

Method

The study retrospectively evaluated pharmacy claims from South Carolina Medicaid prescriptions from January 1, 2011, through August 30, 2012, dispensed to subjects 0 to <6 months old. The unit of analysis for this study was the dispensed prescription. We studied 2 preparations—acetaminophen/codeine and acetaminophen/hydrocodone—the most common opioid preparations prescribed to children aged 0 to 36 months.[11] The data were provided to the investigators in de-identified format, consisting of 3 Medicaid files: a pharmacy file (dispensed prescriptions), enrollee file (with limited demographic data), and an outpatient visit file that includes ambulatory surgeries (with visit diagnoses), all matched one to another utilizing a unique identifier provided by the South Carolina Revenue and Fiscal Affairs Office.

Demographic data included race/ethnicity (ethnicity is not entered as a separate category but is entered as a "racial" category, so Hispanic ethnicity was utilized as a "racial" category), gender, and age in months. Enrollee demographic data were linked to each prescription. In order to assess indications, we then linked prescriptions to corresponding diagnoses from the visit data. We began with the date of the dispensed medication in the prescription file, and then matched each prescription to the closest visit date in the outpatient visit data file. We first began by searching for any outpatient visit in the 30 days prior to the prescription dispensing date, then for 30 days after the prescription date, as described previously.[13] Any prescription for which we could not identify a corresponding outpatient visit was dropped from analyses.

Two investigators (WTB and JRR) viewed all of the diagnoses in the administrative record that corresponded to the visit date. The authors classified each diagnosis based on a grouping that included surgical diagnoses (eg, "talipes equinovarus," "unilateral cleft lip"), trauma/ trauma-related pain diagnoses (eg, "fracture"), respiratory diagnoses (eg, "bronchiolitis," "URI"), and "other" diagnoses (eg, well child check, any missing diagnosis). Any visit that lacked a diagnosis was assigned as "other" diagnosis. The authors classified each opioid prescription as "appropriate" (surgical and trauma/pain diagnoses) and "inappropriate" (respiratory or "other" diagnoses). We calculated raw agreement between the 2 reviewers on the question of whether the indication was appropriate or not, and we also calculated the kappa statistic for agreement. Differences between the 2 reviewers were addressed by discussion between the 2 reviewers and consensus. The analyses included a description of the prescriptions, the recipients, and the diagnoses along with the frequency of appropriate and inappropriate indications. The Institutional Review Board of the Medical University of South Carolina approved the study.

Results

In the 17 months of data reviewed, there were 67 opioid prescriptions prescribed to children 0 to <6 months old. The large majority of these prescriptions were for acetaminophen/ codeine (97%), with 3% for acetaminophen/hydrocodone. The mean age of the subjects dispensed one of these preparations was 4.0 months, and 80.6% of the prescriptions were to

male subjects. The race ethnicity breakdown of the subjects receiving the prescriptions was 47.8% white, 28.4% black, 13.4% Hispanic, and 10.2% other.

The 2 reviewers' raw agreement on the determination of whether a prescription was appropriate or not was 91%, with a kappa of 0.75. This falls into the classification of "substantial" agreement. Review of the data revealed that 20.9% of the indications were inappropriate, consisting of 9% respiratory diagnoses and 11.9% "other" diagnoses. However, 79.1% of the indications were considered to be appropriate, with 73.1% of the total being for surgical diagnoses and 6% being due to trauma/pain diagnoses. See Table 1 for a further breakdown of the distribution of the diagnostic categories by age, gender, and race/ethnicity.

The sample size was too small to allow rigorous statistical comparisons, but review of Table 1 reveals that no child <1 month old received one of the combination opioid drugs. While surgical and other diagnoses were relatively evenly spread among the age categories, 100% of the patients who received opioid for trauma/ pain and 83.3% of those who received opioid for a respiratory diagnosis were in the oldest age stratum. While males comprised 80.6% of the total subjects, they were 93.9% of those who received opioid for a surgical diagnosis but only 33.3% of those who received opioid for a respiratory diagnosis. Urological diagnoses were common in the data, representing 42% of all diagnoses among subjects prescribed one of the acetaminophen/opioid drugs in this data set (data not separately shown in Table 1).

Discussion

In this brief report reviewing acetaminophen/opioid prescriptions dispensed to subjects <6 months old, 1-in-5 prescriptions was for an inappropriate indication, and almost 1-in-10 were for respiratory diagnoses. While opioid products are approved by the US Food and Drug Administration for cough suppression, use of opioids in this context is strongly discouraged by professional organizations such as the American Academy of Pediatrics owing to concerns about the safety of the drug class.[14] In addition to safety concerns, opioids have limited effectiveness controlling cough and other respiratory symptoms, yet respiratory indications comprised 9% of the indications for opioid prescription in this sample of infants <6 months old.[15] Finally, the fact that combination opioids with acetaminophen were prescribed for respiratory indications is particularly troubling given the potential toxicities and risk of overdosing depending on which drug component and respective range is used for dose calculations.[12]

The large majority (79.1%) of the prescriptions to the subjects in this study were for appropriate indications, either related to surgical indications (presumably to treat pain after a surgical procedure for the surgical diagnosis) or posttraumatic pain. While opioids have US Food and Drug Administration indications for treatment of pain in this population, there is a concerning lack of research on their effectiveness compared to other analgesics in infants. Randomized trials suggest that nonsteroidal anti-inflammatory medications may be equally effective or even superior to opioids for pain control for fractures, but these studies evaluated older patients (4–18 years) after emergency department evaluation for injury, whereas most of the subjects in this study received opioids after surgery.[7,8] We believe there is a striking

need for similar research in infants after injury or planned surgery, especially given the mounting concerns about the safety of opioids in this age group.

One potential area of focus going forward may be urological surgeries. We were surprised to find that 42% of all indications were for urological diagnoses. Given the limited amount of diagnostic data available in the administrative data sets, it is impossible to determine whether any individual prescription might have been for a procedure to correct a major urologic malformation or for something less complicated, such as circumcision. Many of the diagnoses in the data set included "phimosis" or "redundant foreskin," which may indicate a simple circumcision, but the limited diagnostic information in these data limit detailed conclusions. Regardless of the indication, the overrepresentation of urological procedures in these infants who received opioids suggests a population of high priority for comparative effectiveness research of opioid vs other pain control postprocedure.

This study has notable limitations, including the fact that we only evaluated diagnoses among 67 subjects. Nevertheless, these data are hypothesis-generating and suggest avenues of future investigation. These data are from only one state, and adult data suggest wide variation in opioid prescribing from state to state.[16] For that reason, it is unclear how generalizable these data are to other states. Not all diagnoses for a given visit may be present in the administrative data. For example, several of the "other" category diagnoses included "well child visit," suggesting that a diagnosis that prompted the prescription of the opioid may have been dealt with at the visit, but the diagnoses were not included because the visit was billed as a health maintenance exam. While many of the visits had surgical diagnoses, we were unable to tell if the patient actually had a procedure on that date. However, prescription of an opioid linked to a visit with "inguinal hernia," for example, suggests that the opioid was prescribed after a procedure to correct the hernia.

Conclusions

Among subjects <6 months old who received a combination acetaminophen/opioid drug, 79.1% were for appropriate indications, primarily surgical diagnoses. The percentage of prescriptions given for respiratory conditions is concerning. Given the safety concerns of administering opioid drugs in infants, there appears to be an opportunity to conduct comparative effectiveness studies that would evaluate the relative pain control and safety of opioid versus nonopioid pain medications among infants.

Acknowledgments

References

1. Bond GR, Woodward RW, Ho M. The growing impact of pediatric pharmaceutical poisoning. J Pediatr. 2012; 160:265–270. [PubMed: 21920539]

2. Dowell D, Kunins HV, Farley TA. Opioid analgesics: risky drugs, not risky patients. JAMA. 2013; 309:2219–2220. [PubMed: 23700072]

3. Groenewald CB, Rabbitts JA, Gebert JT, Palermo TM. Trends in opioid prescriptions among children and adolescents in the United States: a nationally representative study from 1996 to 2012. Pain. 2016; 157:1021–1027. [PubMed: 26716995]

4. Kelly LE, Rieder M, van den Anker J, et al. More codeine fatalities after tonsillectomy in North American children. Pediatrics. 2012; 129:e1343–e1347. [PubMed: 22492761]

5. Kuehn BM. FDA: no codeine after tonsillectomy for children. JAMA. 2013; 309:1100. [PubMed: 23512037]

6. Prows CA, Zhang X, Huth MM, et al. Codeine-related adverse drug reactions in children following tonsillectomy: a prospective study. Laryngoscope. 2014; 124:1242–1250. [PubMed: 24122716]

7. Clark E, Plint AC, Correll R, Gaboury I, Passi B. A randomized, controlled trial of acetaminophen, ibuprofen, and codeine for acute pain relief in children with musculoskeletal trauma. Pediatrics. 2007; 119:460–467. [PubMed: 17332198]

8. Drendel AL, Gorelick MH, Weisman SJ, Lyon R, Brousseau DC, Kim MK. A randomized clinical trial of ibuprofen versus acetaminophen with codeine for acute pediatric arm fracture pain. Ann Emerg Med. 2009; 54:553–560. [PubMed: 19692147]

9. Pierson BW, Cardon BS, Anderson MP, Glade RS. A comparison of nonopioid and opioid oral analgesia following pediatric palatoplasty. Cleft Palate Craniofac J. 2017; 54:170–174. [PubMed: 26882023]

10. Alexander DC, Bundy DG, Shore AD, Morlock L, Hicks RW, Miller MR. Cardiovascular medication errors in children. Pediatrics. 2009; 124:324–332. [PubMed: 19564316]

11. Basco WT Jr, Ebeling M, Garner SS, Hulsey TC, Simpson K. Opioid prescribing and potential overdose errors among children 0 to 36 months old. Clin Pediatr (Phila). 2015; 54:738–744. [PubMed: 25971461]

12. Basco WT Jr, Garner SS, Ebeling M, Hulsey TC, Simpson K. Potential acetaminophen and opioid overdoses in young children prescribed combination acetaminophen/ opioid preparations. Pediatr Qual Saf. 2016; 1:e007.doi: 10.1097/pq9.0000000000000007

13. Basco WT Jr, Ebeling M, Hulsey TC, Simpson K. Using pharmacy data to screen for look-alike, sound-alike substitution errors in pediatric prescriptions. Acad Pediatr. 2010; 10:233–237. [PubMed: 20541485]

14. American Academy of Pediatrics. Committee on Drugs. Use of codeine- and dextromethorphan-containing cough remedies in children. Pediatrics. 1997; 99:918–920. [PubMed: 9190557]

15. Goldman RD. Codeine for acute cough in children. Can Fam Physician. 2010; 56:1293–1294. [PubMed: 21156892]

16. Kuehn BM. CDC: major disparities in opioid prescribing among states: some states crack down on excess prescribing. JAMA. 2014; 312:684–686. [PubMed: 25099564]

Table 1

Indications for Use of Acetaminophen/Opioid Drugs by Infants 0 to < 6 Months Old, South Carolina Medicaid Data, 2011–2012.

	Prescriptions, n (%)	Surgical Indication[a], n (%)	Trauma/Pain Indication[b], n (%)	Respiratory Indication[c], n (%)	"Other" Indication[d], n (%)
Age in months					
0 to <1	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	—
1 to <2	4 (6.0%)	3 (6.1%)	0 (0.0%)	0 (0.0%)	1 (12.5%)
2 to <3	13 (19.4%)	9 (18.4%)	0 (0.0%)	1 (16.7%)	3 (37.5%)
3 to <4	7 (10.5%)	7 (14.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
4 to <5	17 (25.4%)	14 (28.6%)	0 (0.0%)	0 (0.0%)	3 (37.5%)
5 to <6	26 (38.8%)	16 (32.7%)	4 (100.0%)	5 (83.3%)	1 (12.5%)
Race/ethnicity[e]					
Black	19 (28.4%)	13 (26.5%)	2 (50.0%)	2 (33.3%)	2 (25.0%)
Hispanic	9 (13.4%)	6 (12.2%)	0 (0.0%)	1 (16.7%)	2 (25.0%)
Other	7 (10.5%)	6 (12.2%)	0 (0.0%)	0 (0.0%)	1 (12.5%)
White	32 (47.8%)	24 (49.0%)	2 (50.0%)	3 (50.0%)	3 (37.5%)
Gender					
Male	54 (80.6%)	46 (93.9%)	2 (50.0%)	2 (33.3%)	4 (50.0%)
Female	13 (19.4%)	3 (6.1%)	2 (50.0%)	4 (66.7%)	4 (50.0%)
Total	67 (100%)	49 (73.1%)	4 (6.0%)	6 (9.0%)	8 (11.9%)

[a] Surgical Indication examples include "cleft lip," "hypospadias," and "hydrocephalus with VP shunt" among others.

[b] Trauma/pain Indication examples include "fracture" and "accident" among others.

[c] Respiratory indication examples include "URI," "strep pharyngitis," and "acute bronchiolitis" among others.

[d] Other indication examples include "health maintenance visit" and "routine visit dermatitis" among others.

[e] In South Carolina Medicaid data, Hispanic ethnicity is treated as a separate category, equal to race, rather than an ethnicity descriptor of the races.