

Potential Acetaminophen and Opioid Overdoses in Young Children Prescribed Combination Acetaminophen/Opioid Preparations

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Abstract

Introduction: Combination preparations of acetaminophen/opioid are the most common opioid form prescribed to children. We tested the hypothesis that dispensed prescriptions of acetaminophen/opioid preparations more appropriately match acetaminophen dosing parameters than opioid dosing parameters. We also hypothesized that the frequency of potential overdose was inversely related to subject age. **Methods:** Using 2011 to 2012 South Carolina outpatient Medicaid data, the authors identified acetaminophen/opioid preparations dispensed to children 0 to 36 months. Utilizing Centers for Disease Control and Prevention (CDC) data to impute subject weights as the 97th percentile for age and gender, the authors used imputed weights to calculate the maximum recommended daily dose (expected dose) of each component. We calculated the dose delivered per day (observed dose) based on drug concentration, volume dispensed, and days' supply and then calculated the frequency of overdose (observed dose/expected dose, >1.10) by each component, comparing overdose frequency of acetaminophen to the overdose frequency of opioid using a risk ratio. Logistic regression evaluated differences in potential overdose by age, controlling for race/ethnicity and gender. **Results:** Among 2,653 dispensed prescriptions of study drugs to 2,308 children 0 to 36 months old, the frequency of potential overdose was 0.7% for acetaminophen and 1.6% for opioid (risk ratio, 2.28). Age less than 3 months was associated with a greater frequency of potential overdose of either acetaminophen or opioid, even after controlling for gender and race/ethnicity. **Conclusions:** Prescriptions of acetaminophen–opioid drugs dispensed to children 0 to 36 months old contained potential overdoses of opioid at greater than twice the frequency of acetaminophen and were more likely to occur in infants less than 3 months old.

Keywords: Child, children, medication errors, overdose, patient safety

INTRODUCTION

Acetaminophen is the most common pharmaceutical involved in calls to poison control centers about infants, and acetaminophen

followed by opioids is the drug most commonly involved in emergency department (ED) visits for overdose by children.^{1,2} US adult data demonstrated a tripling in fatal poisonings by opioid analgesic products between 1992 and 2006,³ and opioids accounted for more than 75% of deaths because of pharmaceuticals in 2010.⁴ Pediatric data from the National Poison Database System demonstrate that analgesics are the most common cause of medication error, accounting for approximately 25% of errors.⁵ Other authors found that opioids demonstrated a steady increase as the cause of ED visits between 2001 and 2008, with ED visits because of opioid adverse events more than doubling during the study period.⁶ Opioids were also involved in 35% of the child deaths from prescription medications in that sample.⁶

Combination products of acetaminophen with codeine or hydrocodone were each dispensed to more than 1.9 million children from US retail pharmacies in the calendar year 2010.⁷ More recent data suggest that there has been little change in prescribing opioids for children with upper respiratory tract infections hovering at 0.4% to 0.5% of ED visits.⁸ The end result is that opioids and opioid-containing combination products are still commonly prescribed medications for children despite strong statements

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Supported by grant number K08HS015679 from the Agency for Healthcare Research and Quality, WT Basco, Jr, PI. Additional research support was provided by award numbers UL1RR029882 and UL1TR000062 from the National Center For Research Resources.

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PQS 2016;1:e007

Received for publication 15 July 2016; Accepted 20 October 2016

Published online December 1, 2016

DOI: 10.1097/pq9.000000000000007



from the American Academy of Pediatrics and the Food and Drug Administration that opioids should not be prescribed for children for cough⁹ and even for some post-operative conditions.¹⁰ Although opioids are a drug class with considerable risk, younger children are particularly vulnerable to experiencing overdose errors of any drug and experiencing adverse outcomes for any overdose.^{5,11} Even with national concerns regarding the safety of opioid products for children, recent survey data suggest that pediatric providers are still likely to prescribe opioids to children for pain.¹² For the current study, we used dispensed prescription data from 1 state to evaluate acetaminophen/opioid combination prescribing to children, with a focus on children 0 to 36 months old. We tested the primary hypotheses that dispensed prescriptions of acetaminophen/opioid combination drugs more appropriately matched acetaminophen dosing parameters than opioid dosing parameters. Our secondary hypothesis was that age was inversely related to the frequency of potential overdose, with younger children being at greater risk.

METHODS

We utilized South Carolina paid Medicaid pharmacy administrative data from January 1, 2011, through August 30, 2012. We identified dispensed prescriptions for acetaminophen/codeine or acetaminophen/hydrocodone products among subjects 0 to 36 months old. The data were provided to the investigators in deidentified format, and the limited demographic data in the enrollee files were matched to the pharmacy data utilizing a unique identifier provided by the South Carolina Revenue and Fiscal Affairs Office. The Institutional Review Board of the Medical University of South Carolina approved the use of these data for the study. The limited demographic data available included a race/ethnicity variable (Hispanic ethnicity is not entered separately, so it was used as a “racial” category), gender, and age.

We identified 2 liquid formulations of acetaminophen in combination with an opioid: acetaminophen/codeine (120 mg/12 mg per 5 mL) and acetaminophen/hydrocodone (167 mg/2.5 mg per 5 mL). The maximum recommended daily doses and frequencies were based on the *Pediatric Dosage Handbook*, 17th edition.¹³ The maximum acetaminophen dose recommended is 15 mg/kg per dose, given up to every 4 hours, for a maximum daily dose of 90 mg/kg. The maximum recommended dose for codeine is 1 mg/kg per dose, given up to every 4 hours, for a maximum daily dose of 6 mg/kg. The maximum recommended dose for hydrocodone is 0.2 mg/kg per dose, given up to every 3 hours, for a maximum daily dose of 1.6 mg/kg. The Medicaid file provides the volume dispensed (quantity dispensed) and the days’ supply (number of days) the drug was to be administered. If the “days’ supply” is not indicated on a prescription, the pharmacist calculates the value based on the frequency prescribed and number of doses or volume indicated on the prescription.

By dividing the volume dispensed by the days’ supply, one can calculate the daily volume dispensed. Knowing the daily volume dispensed and the concentration of the preparation, one can then calculate the “observed” daily dose. Drug concentrations were identified by matching the national drug code for each prescription in the data set to its formulary concentration.

To calculate the “expected” maximum dose, we estimated weights. Downloadable tables from the CDC provided the 97th percentile weight for each subject based on his or her gender and age in months at each prescription. This estimated weight was utilized to calculate the expected daily dose for each prescription. Ages for children who were between whole months (eg, 2 months, 9 days) were rounded to the next highest whole month to use the CDC charts, again serving to conservatively estimate weight-based expected doses.

The unit of analysis was the prescription. A prescription was deemed to represent a potential overdose if the observed daily dose of either the acetaminophen or opioid exceeded the expected daily dose by more than 10% (ratio observed/expected, >1.10). The percentage overdose for the prescriptions that contained an overdose amount represents the amount dispensed over what was expected (eg, observed/expected ratio of 1.35 = 35% potential overdose amount). We assessed the primary hypothesis by calculating the risk ratio of opioid overdose to acetaminophen overdose for all children in the sample. We completed descriptive analyses of the sample and then bivariate comparisons of associations of age, race/ethnicity, and gender with potential overdose prescriptions. Finally, regression analyses examined adjusted relationships among independent and outcome variables in order to assess the secondary hypothesis that potential overdose frequency was inversely associated with age. Employing all subjects, logistic regression evaluated adjusted relationships between age category and frequency of potential overdose of acetaminophen or opioid, adjusted for race/ethnicity and gender. Linear regression assessed adjusted relationships between age and percentage overdose (the excess volume dispensed) among those who received a potential overdose, adjusted for race/ethnicity and gender.

RESULTS

During the 17 months of study data collection, there were 51,292 total subjects 0 to 36 months old and 325,886 total prescriptions. There were 2,308 subjects who received 2,653 prescriptions for acetaminophen/opioid preparations (Table 1). There were 1,808 prescriptions for acetaminophen/codeine and 845 prescriptions for acetaminophen/hydrocodone. The mean age at which the subjects received the prescriptions was 21.2 months, and 62.3% of the subjects were males. Subject race and ethnicity breakdown was 45.7% whites, 27.5% blacks, 10.2% Hispanic, and 16.6% others. Among prescriptions to subjects 0 to 36 months, 1.6% of prescriptions contained a potential overdose quantity of opioid compared with 0.7% of the

prescriptions containing a potential overdose quantity of acetaminophen, resulting in a risk ratio of 2.28.

Table 1 illustrates differences in the frequency of potential overdose among different age groups. Among prescriptions to subjects less than 3 months, 11.8% ($n = 2$ prescriptions) contained a potential overdose of acetaminophen and 11.8% ($n = 2$) contained a potential overdose of opioid. For prescriptions to older age groups such as 3 to less than 6 months, 6 to less than 12 months, and 12 to 36 months, the frequency of potential overdose of acetaminophen was less than 1%. However, for the same age groups, the frequency of potential opioid overdose remained fairly constant, ranging from 1.5% to 2%. In other bivariate analyses, neither race/ethnicity nor gender was related to the frequency of potential acetaminophen or opioid overdose. For all age groups, those who received a potential opioid overdose on average received approximately 49% more than expected. Age was associated with the percentage of overdose, with an observed/expected ratio of 2.2 among those who received a potential overdose at less than 3 months compared to 1.4 to 1.5 for those 3 to less than 6 months, 6 to less than 12 months, or 12 to 36 months ($P = 0.02$).

Table 2 displays the regression analyses to evaluate associations between age and acetaminophen and opioid potential overdose, controlling for race/ethnicity and gender. In logistic regression predicting acetaminophen potential overdose, age less than 3 months was significantly associated with the frequency of potential acetaminophen overdose compared with children 12 to 36 months old ($P < 0.001$). Age less than 3 months was also associated with the frequency of potential opioid overdose compared with children 12 to 36 months ($P = 0.01$). Finally, the degree of potential opioid overdose was inversely associated with age, with prescriptions to children less than 3 months old containing a greater ratio of observed/expected opioid than did prescriptions to children 12 to 36 months ($P = 0.03$).

DISCUSSION

Unacceptable numbers of prescriptions to very young infants contained potential overdose quantities of both acetaminophen and opioids in these data, with 1.5% to 2% of all acetaminophen/opioid prescriptions to children 0 to 36 months containing potential overdoses of the opioid component. Because the risk ratio for opioid versus acetaminophen potential overdose is more than 2, these data suggest that practitioners are prescribing these combination products based on the acetaminophen component, thus supporting our primary hypothesis. The findings also confirmed our secondary hypothesis that potential overdoses of the two-drug components were inversely associated with age. After controlling for other demographic variables, subjects in the youngest age stratum (<3 months old) were much more likely than older subjects to receive potential

overdose quantities of opioid (adjusted OR, 7.5) and acetaminophen (adjusted OR, 16.9). Although only 2 total prescriptions to children in this age stratum received overdose quantities, they did so for both drugs and received more than 200% of the expected amount, suggesting that these were true overdoses. None of the children who had received a potential opioid overdose had received morphine (for neonatal abstinence syndrome), suggesting that the excess opioids dispensed were not because of opioid tolerance. Acetaminophen is one of the most commonly prescribed medications to children. We believe it likely, therefore, that acetaminophen dosing is one of the dosing parameters most commonly recalled by pediatric providers. Opioid preparation dosing, in part, by nature of the fact that opioids are less often prescribed and come in more variable dosing preparations than does acetaminophen, is likely less familiar to many pediatric practitioners. It is possible that practitioners make an assumption that the relative concentrations of the 2 drugs are appropriate, such that if one calculates the desired dose based on the acetaminophen component, one would also prescribe an appropriate opioid dose. That assumption is not the case, demonstrated by the fact that the risk ratio of opioid overdose is twice that of acetaminophen.

These estimated frequencies of potential overdose are very conservative given our methodology assigned the 97th percentile weight to every child and included rounding of ages up to whole months, thereby biasing toward estimating dosing with higher weights. The analytic approach also assumed the highest recommended dose and the most frequent recommended frequency of administration when calculating expected doses. This conservative approach undertaken for these analyses suggests the true frequency of potential overdoses is likely much higher, making the inverse association with age even more concerning.

Acetaminophen and opioids are both potentially problematic medications for young children. The excess opioids prescribed in these subjects could lead to overdoses in individual patients or, at a minimum, allow excess opioids to be available in the home. In a 2014 study of subjects undergoing surgical procedures, 76% of patients who received a postoperative morphine prescription filled the prescription. However, the median number of doses administered was less than 2 for 63% of the sample, presumably leaving excess morphine available in the home.¹⁴ Opioids are the most common drug class involved in accidental ingestions among young children,^{6,15} and diversion for use by adolescents and young adults is a real concern. National data demonstrated that the nonmedical use of prescription opioids is associated with an increased frequency of subsequent initiation of heroin (hazard ratio, 13.1).¹⁶ Even appropriate use of opioids in adolescents correlates with a 33% higher frequency of future opioid abuse.¹⁷ For these reasons, opioid “stewardship” and

Table 1. Bivariate Comparisons of Frequency of Potential Overdoses of Acetaminophen/Opioid Combination Drugs, January 2011 to August 2012, South Carolina Medicaid Data (n = 2,653 Prescriptions)

	Prescriptions, n (%)	Potential Acetaminophen Overdose,* n (%)	Potential Opioid Overdose,* n (%)	Opioid Overdose Ratio† (Mean Observed/Expected)
Age, mo				
<3	17 (0.6)	2 (11.8)	2 (11.8)	2.2
3–5	51 (1.9)	0 (0.0)	1 (2.0)	1.5
6–11	418 (15.7)	1 (0.2)	7 (1.7)	1.4
12–36	2167 (81.7)	15 (0.7)	33 (1.5)	1.5
		<i>P</i> = 0.006‡	<i>P</i> = 0.03‡	<i>P</i> = 0.02‡
Race/ethnicity				
Black	730 (27.5)	3 (0.4)	13 (1.8)	1.40
Hispanic §	270 (10.2)	3 (1.1)	6 (2.2)	1.45
Other	441 (16.6)	0 (0.0)	6 (1.4)	1.26
White	1212 (45.7)	12 (1.0)	18 (1.5)	1.63
		<i>P</i> = 0.1¶	<i>P</i> = 0.6	<i>P</i> = 0.09¶
Gender				
Male	1652 (62.3)	13 (0.8)	30 (1.8)	1.49
Female	1001 (37.7)	5 (0.5)	13 (1.3)	1.47
		<i>P</i> = 0.5	<i>P</i> = 0.3	<i>P</i> = 0.9

*Overdose = observed/expected amount >1.10 for respective component.

†Opioid overdose ratio = ratio of observed/expected amount among those who received overdose quantity, corresponding to the excess amount dispensed (eg, ratio, 2.2 = 220% of expected amount).

‡*P* value comparing <3 months with all other age categories.

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

¶*P* value comparing white with all other races.

attempts to refine use even in appropriate conditions remain important goals.

Patient safety options to reduce excess opioid exposure to children are multiple and include limiting opioid prescriptions and insuring proper prescribing when used. Although national attention currently focuses on adult opioid use,^{18–20} the American Academy of Pediatrics

and other organizations have been forceful in urging practitioners to limit the use of opioids especially in young children.^{9,10,21} Computerized physician order entry with decision support offers the promise of calculating proper opioid doses for children, but the ability of various electronic health record products to do this is uneven.^{22,23} Safe prescribing and dispensing would be

Table 2. Adjusted Associations between Patient Demographics and Potential Overdoses of Acetaminophen and Opioid Components in Acetaminophen/Opioid Combination Drugs, January 2011 to August 2012, South Carolina Medicaid Data

Variable	Potential Acetaminophen Overdose*,†	Potential Opioid Overdose*,†	Opioid Overdose Ratio (Mean)‡,§
	OR (95% CI)	OR (95% CI)	Parameter Estimate (β)
	<i>P</i>	<i>P</i>	
Age, mo			
0–2	16.9 (3.4–85.2)	7.5 (1.6–34.6)	0.718
	0.0006	0.01	0.03
3–5	NA¶	1.2 (0.2–9.1)	–0.081
		0.8	0.9
6–11	0.3 (0.04–2.3)	1.0 (0.4–2.3)	0.01
	0.3	1.0	1.0
12–36	Reference	Reference	Reference
Race/ethnicity			
Black	0.4 (0.1–1.5)	1.2 (0.6–2.5)	–0.25
	0.2	0.6	0.1
Hispanic	1.0 (0.3–3.8)	1.5 (0.6–3.7)	–0.14
	1.0	0.4	0.5
Other	NA¶	0.9 (0.4–2.4)	–0.35
		0.9	0.09
White	Reference	Reference	Reference
Gender			
Male	1.5 (0.5–4.3)	1.3 (0.7–2.6)	–0.58
	0.5	0.4	0.7
Female	Reference	Reference	Reference

*Overdose = observed/expected amount >1.10 for respective component.

†Logistic regression, predicting “overdose” (observed/expected amount, >1.10) for each demographic variable.

‡Opioid overdose ratio = ratio of observed/expected amount among those who received overdose quantity, corresponding to the excess amount dispensed (eg, rate, 2.2 = 220% of expected amount).

§Linear regression on the ratio of observed/expected for each demographic variable.

¶OR not calculable because of the lack of observations.

CI, confidence interval; OR = odds ratio.

improved by requiring weights to appear on opioid prescriptions for children less than 12 to 24 months old, thus allowing pharmacists to calculate dose appropriateness.²⁴ In the end, improving the safety of prescribing of opioids and opioid combination products to children will involve a multipronged approach, including policy interventions, provider education, and technology-based interventions.^{22,24,25}

The safety of combination acetaminophen/opioid preparations could be improved by making sure that the opioid concentration matches the acetaminophen concentrations better such that if the practitioner prescribes the maximum acetaminophen dose, they would also prescribe an appropriate opioid dose. Although this study involved only liquid preparations, recent changes in tablet formulations have actually reduced the amount of acetaminophen in opioid combination products owing to concerns that chronic use exposes patients to excessive acetaminophen. That formulation change will be effective in reducing acetaminophen exposure if practitioners calculate doses based only on the opioid component. If practitioners calculate doses based on acetaminophen, however, then the changed ratios in the formulations will actually result in greater opioid delivery. The problematic nature of dosing 2 drugs at once, particularly in children, then raises the question of whether combination opioid products should be used at all in young children.

There are several limitations to the study. First, we used estimated weights for study subjects, but the study choices provide conservative weight estimates and therefore likely underestimate potential overdoses. Second, these data are from 1 state's Medicaid population, and adult data demonstrate considerable variation in opioid prescribing among states.²⁰ It is unclear whether there is similar variation in opioid prescribing for children. Third, it is also not clear how well these data from a Medicaid population would compare with non-Medicaid pediatric cohort; however, because Medicaid insures approximately 50% of South Carolina children, this study outlines the potential risk for a large cohort of children. Fourth, we were unable to determine whether the children actually ingested potential overdose quantities. Finally, these data are from 2011 to 2012, but nationally representative data from 1996 to 2012 suggest that opioid prescribing for children changed little during that time period, ranging from 2.68% to 2.91% of subjects.²⁶

CONCLUSIONS

In children 0 to 36 months evaluated for this study, prescriptions for acetaminophen/opioid combination products contained potential overdose quantities of the opioid component 1.6% of the time, occurring more than twice as commonly as potential acetaminophen overdoses. Potential overdose frequencies occurred in 11.8% of prescriptions to subjects less than 3 months old, with the risk of both acetaminophen and opioid overdose being higher

in this group compared with older subjects. Given other data demonstrating that opioids are commonly involved in adverse drug events, ED visits, and child death, we should strive for greater opioid stewardship in the care of children.

ACKNOWLEDGMENT

The authors thank James R. Roberts, MD, MPH, for his advice and collaboration during the formulation of the analysis approach, presentation of the results, and for input on the manuscript.

DISCLOSURE

The authors have no financial interest to declare in relation to the content of this article.

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