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Dental pain as a risk factor for accidental acetaminophen overdose: A case control study

Jody Vogel, MD^{1,*}, Kennon J. Heard, MD^{2,*}, Catherine Carlson, MD³, Chad Lange, MD⁴, and Garrett Mitchell, MD¹

¹Denver Health Residency in Emergency Medicine, Denver CO

²Regions Hospital Emergency Medicine Residency, St Paul MN

³Department of Emergency Medicine, Maricopa Medical Center, Phoenix AZ

⁴Rocky Mountain Poison and Drug Center, Denver Health and Hospitals Denver CO; University of Colorado Department of Emergency Medicine and The Colorado Emergency Medicine Research Center, Aurora CO

Introduction

Dental pain affects 22 million adults in any given six month period and accounts for 738,000 emergency department visits annually.[1–2] In California, the visit rate for preventable dental conditions not requiring hospitalization exceeds the number of emergency department (ED) visits for diabetes.[3]

Acetaminophen decreases acute dental pain[4–5] and is frequently used by patients who have toothaches.[6] While acetaminophen is safe when used as directed, unintentional overdose of acetaminophen has serious consequences including hepatic injury and hepatic failure.[7] One prior study found that nonprescription analgesics are frequently overused by patients with dental pain.[8] However, this study did not compare the rate of overuse for dental conditions relative to overuse from other causes.

As patients with dental pain had a high rate of overuse of non-prescription analgesics and acetaminophen is commonly used to treat dental pain, we hypothesized that patients with dental pain may be at increased risk for unintentional acetaminophen overdose compared to patients using acetaminophen for other conditions.

METHODS

Study design

This was a case-control study of patients who were using nonprescription analgesics (or prescription products containing non-prescription ingredients) to control their pain. We selected this method as a preliminary investigation because the frequency of accidental

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Corresponding author Kennon Heard, Rocky Mountain Poison and Drug Center, 777 Bannock St MC 0180, Denver CO 80204, Phone 303 739-1264, Fax 303 739-1475, Kennon.heard@rmpdc.org.

*Drs Vogel and Heard contributed equally to this manuscript.

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acetaminophen overdose would make prospective study unfeasible without substantial resources. The local Institutional Review Board approved the retrospective portion of the study and deemed the survey portion exempt from review. Informed consent was waived for the retrospective data collection.

Setting

We conducted this study in two hospital systems; an urban university associated ED with 40,000 visits per year (University of Colorado Hospital-UCH), and an urban safety-net (>50% uninsured) hospital ED with 55,000 visits per year (Denver Health Medical Center-DHMC). The demographics for UCH are a median age of 40 years, 41% male, 46% white, 28% African American, 23% Hispanic and 6% other or unknown race. The demographics for DHMC are a median age of 36 years, 56% male, 41% white, 37% Hispanic, 14% African American and 9% other or unknown race.

Participant selection

Cases—Potential cases were identified by reviewing all records of patients evaluated 1/1/2006 thru 7/31/08 with a principal diagnostic code for acetaminophen overdose (*ICD-9-CM*, 965.4; *ICD-10*, T39.1). This strategy has been shown to highly sensitive and specific for acetaminophen poisoning and overdose.[9] We reviewed the records of these patients, to verify acetaminophen exposure and determine the reason for acetaminophen use. Patients who reported taking an excessive dose of acetaminophen to treat a medical condition *or* who had laboratory evidence of acetaminophen toxicity while reporting therapeutic use were included as cases. We excluded patients taking acetaminophen in a self-harm attempt, those using acetaminophen-opioid products for opioid abuse and those who had adverse events during therapeutic dosing (i.e. vomiting from while taking an acetaminophen-opioid combination product). Patients who were younger than 18 were also excluded.

Controls—Controls were identified from a survey conducted at the hospitals designed to measure the use of nonprescription analgesics (or prescription products with non-prescription ingredients) among adult (>17 years of age) ED patients. The survey was conducted during two months that overlapped with the case-collection period. During the survey, ED patients were approached and questioned about their use of products containing acetaminophen, ibuprofen, aspirin, ketoprofen, or naproxen. Subjects who reported using products containing acetaminophen for treatment of a medical symptom were included in this study as controls.

Data collection

In the case group data were abstracted retrospectively from the hospital records. A standardized case report form was used to collect demographic and clinical data. For each case we collected the following data: age, sex, reason for analgesic use, therapeutic intent, product(s) ingested, alcoholism, peak alanine aminotransferase (ALT), and medical outcome (survival, liver transplant, death). Key variables (therapeutic intent, reason for use and outcome) were determined by two independent abstractors to assure accuracy. The abstractors were trained in record review prior to onset of the study. These data were entered into a formatted Microsoft Excel spreadsheet.

The survey as data collection for control subjects was conducted on a convenience sample of adult emergency department patients. Research assistants were trained in the administration by the primary investigator. They attempted to interview all patients in the ED and recorded the reason that nonparticipants were excluded. The researchers collected the following information: age, gender, and analgesic or cough/cold product use in the 72 hours preceding their ED visit. Those who reported taking a product containing a non-prescription analgesic

(including non-prescription and opioid combination products) were asked to provide this additional information: reason for analgesic use, specific products used in the three days preceding the ED visit (up to 4 products) and if they drink an average of more than 3 alcoholic drinks per day. The ingredients in the products was determined by searching in Micromedex (Thompson Inc, Greenwood Village, CO)

Data analysis—In both the cases and the control group, the reason for acetaminophen use was categorized as back pain, dental pain, headache, other musculoskeletal pain, fever/illness, other pain, and not specified. For the controls this was self-reported in a closed-ended questionnaire. For the cases, it was determined by two investigators based on record review of the case notes. Any disagreement regarding the reason for therapeutic use was resolved by a second review of the medical record and discussion between the two abstractors. When there were irresolvable differences, we categorized the case as not dental pain. We coded products as single ingredient acetaminophen product, acetaminophen-opioid combination, sleep aid, or cough/cold preparations.

The primary outcome of interest was the risk of unintentional acetaminophen overdose (UAO) compared to therapeutic use (TU) for the conditions of interest. To determine if individuals taking acetaminophen for dental pain were at increased risk of overdose we collapsed the reasons for use to dental pain and not dental pain. We determined the odds ratio (with 95% confidence intervals) as: [(UAO dental pain)/(TU dental pain)]/[(UAO other pain)/(TU other pain)]. Logistic regression was used to adjust for age, sex, alcoholism and use of combination products. As ALT was not normally distributed, the median of the peak ALT of dental patients was compared to non-dental pain patients using a Shapiro-Wilk test with a $p < 0.05$ considered significant.

Results

During the 18 month study period we identified 278 patients who had relevant diagnostic codes for acetaminophen poisoning at the two hospitals. Of these, 73 cases were identified as patients who received treatment or evaluation for acetaminophen overdose or poisoning that occurred with therapeutic intent.

During the survey at the two hospitals we approached 1185 patients. Of these, 876 agreed to participate. Two hundred and two (23%) reported taking an acetaminophen-containing product. One patient was excluded because he took acetaminophen in a self-harm attempt leaving 201 who were taking acetaminophen to treat a medical symptom.

The cases and controls had similar characteristics for most conditions (Table). The unadjusted odds ratio for accidental overdose on acetaminophen for dental pain was 11.4 (3.6 to 35.9) compared to all other reasons for use. In our logistic model, the adjusted odds ratio for accidental overdose was elevated for alcoholics (8.4, 3.1 to 25.3) but not for use of combination products (1.1, 0.61 to 2.0) or male sex (0.97, 0.51 to 1.8). After adjustment for age, sex, alcoholism and the use of combination products, the odds ratio for accidental acetaminophen overdose due dental pain was 12.8 (4.2 to 47.6) times higher than for other types of pain.

The overall survival of cases was 70/73. The deaths were a 77 year old male taking acetaminophen for musculoskeletal pain, an 18 year old male taking a combination product for fever/illness, and a 47 year old female taking an opioid combination product for flank pain. We did not have a pre-defined definition for acetaminophen related fatalities. All subjects had detectable serum acetaminophen concentrations at presentation and had liver injury consistent with acetaminophen toxicity at the time of death.

The ALT was not measured in 2 dental pain cases and 2 non-dental pain cases. The median (10–90th percentiles) for the ALT was 26 (13 to 10880) IU/L for the dental pain cases and 231 (12 to 7143) IU/L for the non-dental pain cases ($p=0.05$).

In a secondary analysis we determined the adjusted odds ratios of accidental overdose for back pain, musculoskeletal pain, headache and fever (each specific cause compared to all other causes). The odd ratio of accidental overdose was not statistically different from 1.0 for back pain (OR=1.8), headache (OR=0.58) or musculoskeletal pain (OR=0.48) but was less than 1.0 for fever (OR=0.33; 95% CI 0.09 to 0.91).

Discussion

Patients taking acetaminophen for dental pain are at increased risk for being diagnosed with accidental acetaminophen overdose compared to those using acetaminophen for other reasons. While the interpretation of our findings must be tempered by the limitations of our study design, this study clearly supports the hypothesis that dental pain patients are a high risk group for accidental acetaminophen overdose.

There are several potential reasons that patients with dental pain may be at increased risk for accidental overdose of acetaminophen. Patients with dental pain may take more medication than those with other conditions. For example, a headache, acute injury or illness is likely to be self-limited and improve over a few days, while a dental infection is likely to get worse if it is not treated. This may lead to longer dosing, and if the symptoms worsen, an escalation of dosage, frequency or both to attempt to treat the pain.

Another possible explanation is that patients with dental pain are at greater risk for acetaminophen toxicity from a dose of acetaminophen that would not cause toxicity in patients with other causes of pain. As patients with toxicity are more likely to be identified than asymptomatic over-users, increased susceptibility would produce diagnostic workup bias for dental pain patients. One previously described risk factor for acetaminophen toxicity is starvation,[10] and it is plausible that dental pain may be associated with starvation. However, the median ALT in this study was slightly (although not statistically significant) lower for dental pain patients than for other patients, suggesting a lesser degree of toxicity.

There are several potential limitations that may bias the results of case-control studies and invalidate our conclusions regarding the association between dental pain and acetaminophen. The first is selection bias. Selection bias would occur if patients taking acetaminophen for dental pain were more or less likely to be selected into either the case or control groups than patients taking acetaminophen for another type of pain. As cases were identified using a standardized search of ICD codes for acetaminophen poisoning or overdose, it seems unlikely that cases due to a particular painful condition would be over or under-represented. This is further supported by the similar distribution of painful conditions found at the two hospitals; it is unlikely that both institutions would miscode these cases in the same manner. As patients in the control group were selected by researchers who were not aware of the study purpose, it is unlikely that they would differentially approach patients with dental pain compared to those with pain from other causes. Our controls were selected as a convenience sample, and it is possible that our sample may not reflect the ED population.

Another threat to the validity of a case-control study is misclassification bias. This would occur in cases if patients thought to have overdosed on acetaminophen actually did not. The diagnosis of acetaminophen overdose was based on self-report (which may be inaccurate) and it is possible that some cases that appeared to be acetaminophen toxicity may have been due to other causes (such as viral hepatitis or other poisons). While there is a potential for

bias in the classification of cases, we attempted to minimize this bias by having two reviewers independently abstracting the cases and then discussing cases where the reason for reviewers did not agree. We had no cases where we could not agree on the reason for use. Misclassification could also occur if cases or controls stated that they were taking acetaminophen when they were actually using another analgesic. However, there is no obvious reason that either of these misclassifications would occur more or less frequently in patients who reported taking acetaminophen for dental pain than in those taking acetaminophen for other reasons. Thus any misclassification would be non-differential. When non-differential misclassification occurs, the main effect is to bias the odds ratio towards 1.0.[11] Therefore if non-differential misclassification occurred, the strength of association we observed is an underestimate.

With any observational study it is possible that unmeasured factors may differ between the cases and controls and that these unmeasured risk factors may be the “true” causative factor for the observed association. We attempted to account for several of variables that have been associated with acetaminophen overdose, including alcoholism, age, gender, and the use of acetaminophen-combination products. The adjusted odds ratios were similar to the unadjusted odds ratio suggesting that the association with dental pain is not due these factors. However, we cannot exclude the possibility that one or more unmeasured risk factors differed between cases and controls and that these variables account for the observed association.

Another consideration is that we evaluated acetaminophen overdose rather than acetaminophen toxicity. An overdose that does not produce liver injury is of little clinical relevance. It is possible that patients with dental pain take excessive acetaminophen but do not go on to develop liver injury from the overdose. This is somewhat supported by the slightly lower peak ALT observed in the dental patients. However, 25% of dental pain patients developed a peak ALT above 1000 U/L so at least some develop clinically significant liver injury from their overdose. Therefore we believe identifying dental pain as a high risk condition has clinically relevant implications.

There are several implications of this study for clinical practice. The first is that patients with dental pain should be questioned about the amount of nonprescription analgesics they are using. While our study focused on acetaminophen, overuse of other non-prescription analgesics such as ibuprofen or aspirin may also cause toxicity. Earlier identification of these patients would allow intervention and may prevent more severe toxicity. The second implication is that health care providers should educate patients with dental pain about appropriate use of non-prescription medications. This could occur during routine dental care, during ED visits, during interactions with a pharmacist or if the patient contacts a nurse advice line. Other measures such as product labeling changes or warnings in precautions on medical websites could also be used. However, it seems unlikely that changes in labeling would be effective since the current label clearly states that users should not exceed 8 tablets/day and not to take these products with other acetaminophen containing products.

Our findings suggest that there is a need for better overall dental care. While not systematically studied, it is logical that routine preventative dental care would decrease the incidence of painful dental conditions. Increased access to emergency dental care would provide patients with definitive treatment of their dental conditions and decrease the need to rely on self-medication to treat dental symptoms.

Conclusions

We found patients with dental pain are a high risk group for accidental acetaminophen overdose. Emergency physicians must be aware of the increased risk for unintentional therapeutic overdose in dental pain patients. Dental pain patients should be questioned about analgesic use and educated on the appropriate use of non-prescription analgesics.

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Table

Characteristics of cases and controls who were using acetaminophen to treat medical symptoms. The condition was unknown for 6 controls.

	Dental		Back		Fever		Musculoskeletal		Headache		Other	
	Case	Control	Case	Control	Case	Control	Case	Control	Case	Control	Case	Control
N	14	4	10	17	5	31	8	42	7	33	29	68
Age¹	30	23	45	47	38	38	51	52	23	41	40	42
	(21–49)	(18–28)	(23–87)	(25–64)	(18–43)	(18–55)	(24–77)	(20–85)	(20–55)	(18–85)	(20–81)	(18–81)
Male n (%)	4 (28%)	1 (25%)	3 (30%)	10 (59%)	2 (40%)	10 (32%)	3 (38%)	14 (33%)	4 (57%)	9 (28%)	11 (38%)	24 (35%)
DHMC n (%)	5 (36%)	2 (50%)	3 (30%)	7 (41%)	2 (40%)	21 (55%)	3 (38%)	10 (23%)	2 (29%)	11 (33%)	11 (38%)	32 (47%)
UCH n (%)	9 (64%)	2 (50%)	7 (70%)	10 (59%)	3 (60%)	10 (32%)	5 (63%)	33 (77%)	5 (71%)	22 (66%)	18 (62%)	36 (53%)
Opioid² n (%)	1 (7%)	3 (75%)	7 (70%)	9 (53%)	1 (20%)	3 (10%)	3 (38%)	19 (44%)	2 (29%)	1 (2%)	15 (52%)	32 (47%)
Cold³ (%)	0	1 (25%)	0	0	4 (80%)	23 (73%)	0	3 (7%)	0	1 (2%)	3 (11%)	5 (7%)
Sleep⁴ n (%)	1 (7%)	0	0	0	1 (20%)	1 (3%)	0	1 (2%)	1 (15%)	1 (2%)	0	1 (2%)
EtoH⁵ n (%)	2 (14%)	0	2 (20%)	0	0	1 (3%)	1 (13%)	1 (2%)	0	11 (33%)	9 (31%)	3 (4%)

¹Median and range in years

²Acetaminophen-opioid combination product

³Multi-ingredient cold product containing acetaminophen

⁴Sleep product containing acetaminophen

⁵EtoH = self report of drinking > 3 drinks/day for controls and documentation of alcoholism in the medical record for cases.