American Journal of Emergency Medicine (2011) **29**, 1125–1129

The American Journal of Emergency Medicine

www.elsevier.com/locate/ajem

Original Contribution

Dental pain as a risk factor for accidental acetaminophen overdose: a case-control study☆,☆☆

Jody Vogel MD[a,1], Kennon J. Heard MD[a,d,e,*,1], Catherine Carlson MD[b], Chad Lange MD[c], Garrett Mitchell MD[a]

[a]*Denver Health Residency in Emergency Medicine, Denver, CO, USA*
[b]*Regions Hospital Emergency Medicine Residency, St Paul, MN, USA*
[c]*Department of Emergency Medicine, Maricopa Medical Center, Phoenix, AZ, USA*
[d]*Rocky Mountain Poison and Drug Center, Denver Health and Hospitals, Denver, CO*
[e]*Department of Emergency Medicine, University of Colorado, and The Colorado Emergency Medicine Research Center, Aurora CO, USA*

Received 3 June 2010; revised 19 August 2010; accepted 29 August 2010

Abstract Patients frequent take acetaminophen to treat dental pain. One previous study found a high rate of overuse of nonprescription analgesics in an emergency dental clinic.
Objectives: The purpose of this study is to determine if patients with dental pain are more likely to be treated for accidental acetaminophen poisoning than patients with other types of pain.
Methods: We conducted a case-control study at 2 urban hospitals. Cases were identified by chart review of patients who required treatment for accidental acetaminophen poisoning. Controls were self-reported acetaminophen users taking therapeutic doses identified during a survey of emergency department patients. For our primary analysis, the reason for taking acetaminophen was categorized as dental pain or not dental pain. Our primary outcome was the odds ratio of accidental overdose to therapeutic users after adjustment for age, sex, alcoholism, and use of combination products using logistic regression.
Results: We identified 73 cases of accidental acetaminophen poisoning and 201 therapeutic users. Fourteen accidental overdose patients and 4 therapeutic users reported using acetaminophen for dental pain. The adjusted odds ratio for accidental overdose due to dental pain compared with other reasons for use was 12.8 (95% confidence interval, 4.2-47.6).
Conclusions: We found that patients with dental pain are at increased risk to accidentally overdose on acetaminophen compared with patients taking acetaminophen for other reasons. Emergency physicians should carefully question patients with dental pain about overuse of analgesics.

1. Introduction

Dental pain affects 22 million adults in any given 6-month period and accounts for 738 000 emergency department (ED) visits annually [1,2]. In California, the visit rate for preventable dental conditions not requiring hospitalization exceeds the number of ED visits for diabetes [3].

☆ The project described was supported by Award Number K08DA020573 from the National Institute on Drug Abuse.
☆☆ The content of this article is solely the responsibility of the authors and does not necessarily represent the official views of the National Institute on Drug Abuse or the National Institutes of Health.
* Corresponding author. Rocky Mountain Poison and Drug Center, Denver CO 80204, USA. Tel.: +1 303 739 1264; fax: +1 303 739 1475.
E-mail address: kennon.heard@rmpdc.org (K.J. Heard).
[1] Drs Vogel and Heard contributed equally to this manuscript.

0735-6757/$ – see front matter © 2011 Elsevier Inc. All rights reserved.
doi:10.1016/j.ajem.2010.08.006

Acetaminophen decreases acute dental pain [4-5] and is frequently used by patients who have toothaches [6]. Although 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.

Because patients with dental pain had a high rate of overuse of nonprescription 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 (UAO) compared with patients using acetaminophen for other conditions.

2. Methods

2.1. Study design

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

2.2. Setting

We conducted this study in 2 hospital systems: an urban university–associated ED with 40 000 visits per year (University of Colorado Hospital, or UCH), and an urban safety-net (>50% uninsured) hospital ED with 55 000 visits per year (Denver Health Medical Center, or DHMC). The demographics for UCH are as follows: 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 as follows: a median age of 36 years, 56% male, 41% white, 37% Hispanic, 14% African American, and 9% other or unknown race.

2.3. Participant selection

2.3.1. Cases

Potential cases were identified by reviewing all records of patients evaluated January, 1, 2006, through July 31, 2008, with a principal diagnostic code for acetaminophen overdose (*International Classification of Diseases* (*ICD*)*, Ninth Revision*, 965.4; *ICD, Tenth Revision*, 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 (TU) 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 (ie, vomiting while taking an acetaminophen-opioid combination product). Patients who were younger than 18 were also excluded.

2.3.2. Controls

Controls were identified from a survey conducted at the hospitals designed to measure the use of nonprescription analgesics (or prescription products with nonprescription ingredients) among adult (>17 years of age) ED patients. The survey was conducted for 2 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.

2.4. 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 2 independent abstractors to assure accuracy. The abstractors were trained in record review before the 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 ED 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, sex, and analgesic or cough/cold product use in the 72 hours preceding their ED visit. Those who reported taking a product containing a nonprescription analgesic (including opioid combination products that have a non-prescritpion ingredient) were

asked to provide this additional information: reason for analgesic use, specific products used in the 3 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, Col).

2.4.1. 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 2 investigators based on record review of the case notes. Any disagreement regarding the reason for TU was resolved by a second review of the medical record and discussion between the 2 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 UAO compared with 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 (OR; with 95% confidence intervals) as follows: [(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. Because ALT was not normally distributed, the median of the peak ALT of dental patients was compared with nondental pain patients using a Shapiro-Wilk test, with a $P < .05$ considered significant.

3. Results

During the 18-month study period, we identified 278 patients who had relevant diagnostic codes for acetaminophen poisoning at the 2 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 2 hospitals, we approached 1185 patients. Of these, 876 agreed to participate. Two hundred 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 1). The unadjusted OR (95% confidence interval) for accidental overdose on acetaminophen for dental pain was 11.4 (3.6-35.9) compared with all other reasons for use. In our logistic model, the adjusted OR for accidental overdose was elevated for alcoholics (8.4; 95% confidence interval, 3.1-25.3) but not for use of combination products (1.1; 95% confidence interval, 0.61-2.0) or male sex (0.97; 95% confidence interval, 0.51-1.8). After adjustment for age, sex, alcoholism, and the use of combination products, the OR (95% confidence interval) for accidental acetaminophen overdose due dental pain compared to other types of pain was 12.8 (4.2-47.6).

The overall survival of cases was 70 of 73. Those who died were a 77-year-old man taking acetaminophen for musculoskeletal pain, an 18-year-old young man taking a combination product for fever/illness, and a 47-year-old woman taking an opioid combination product for flank pain. We did not have a predefined definition for acetaminophen-related fatalities. All fatal cases had detectable serum acetaminophen concentrations at presentation

Table 1 Characteristics of cases and controls who were using acetaminophen to treat medical symptoms

	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	43	7	33	29	67
Age [a]	30 (21-49)	23 (18-28)	45 (23-87)	47 (25-64)	38 (18-43)	38 (18-55)	51 (24-77)	52 (20-85)	23 (20-55)	41 (18-85)	40 (20-81)	42 (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)	23 (34)
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)	35 (52)
Opioid [b], n (%)	1 (7)	3 (75)	7 (70)	9 (53)	1 (20)	3 (10)	3 (38)	19 (44)	2 (29)	1 (2)	15 (52)	32 (48)
Cold [c] (%)	0	1 (25)	0	0	4 (80)	23 (73)	0	3 (7)	0	1 (2)	3 (11)	5 (7)
Sleep [d], n (%)	1 (7)	0	0	0	1 (20)	1 (3)	0	1 (2)	1 (15)	1 (2)	0	1 (2)
EtOH [e], n,(%)	2 (14)	0	2 (20)	0	0	1 (3)	1 (13)	1 (2)	0	11 (33)	9 (31)	3 (4)

The condition was unknown for 6 controls.

[a] Median and range in years.

[b] Acetaminophen-opioid combination product.

[c] Multi-ingredient cold product containing acetaminophen.

[d] Sleep product containing acetaminophen.

[e] EtOH: self-report of drinking more than 3 drinks/d for controls and documentation of alcoholism in the medical record for cases.

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 nondental pain cases. The median (10th-90th percentiles) for the ALT was 26 (13-10 880) IU/L for the dental pain cases and 231 (12 to 7143) IU/L for the nondental pain cases ($P = .05$).

In a secondary analysis, we determined the adjusted ORs of accidental overdose for back pain, musculoskeletal pain, headache, and fever (each specific cause compared with all other causes). The OR 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% confidence interval, 0.09-0.91).

4. Discussion

Patients taking acetaminophen for dental pain are at increased risk for being diagnosed with accidental acetaminophen overdose compared with those using acetaminophen for other reasons. Although 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, whereas 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. Because patients with toxicity are more likely to be identified than asymptomatic overusers, 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. Because 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 overrepresented or underrepresented. This is further supported by the similar distribution of painful conditions found at the 2 hospitals; it is unlikely that both institutions would miscode theses cases in the same manner. Because 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 with 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). Although there is a potential for bias in the classification of cases, we attempted to minimize this bias by having 2 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 nondifferential. When nondifferential misclassification occurs, the main effect is to bias the OR toward 1.0 [11]. Therefore, if nondifferential 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, sex, and the use of acetaminophen-combination products. The adjusted ORs were similar to the unadjusted OR suggesting that the association with dental pain is not due to 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. Although our study focused on acetaminophen, overuse of other nonprescription 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 nonprescription 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 Web sites could also be used. However, it seems unlikely that changes in labeling would be effective because the current label clearly states that users should not exceed 8 tablets/d and not to take these products with other acetaminophen-containing products.

Our findings suggest that there is a need for better overall dental care. Although 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.

5. Conclusions

We found that 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 nonprescription analgesics.

References

[1] Lewis C, Lynch H, Johnston B. Dental complaints in emergency departments: a national perspective. Ann Emerg Med 2003;42:93-9.
[2] Lipton JA, Ship JA, Larach-Robinson D. Estimated prevalence and distribution of reported orofacial pain in the United States. J Am Dent Assoc 1993;124:115-21.
[3] Maiuro, L. Emergency department visits for preventable dental conditions in California: California HealthCare Foundation.
[4] Korberly BH, Schreiber GF, Kilkuts A, et al. Evaluation of acetaminophen and aspirin in the relief of preoperative dental pain. J Am Dent Assoc 1980;100:39-42.
[5] Weil K, Hooper L, Afzal Z, et al. Paracetamol for pain relief after surgical removal of lower wisdom teeth. Cochrane Database Syst Rev 2007:CD004487.
[6] Preshaw, P. M., Meechan, J. G. and Dodd, M. D.: Self-medication for the control of dental pain: what are our patients taking?, Dent Update 1994; 21:299-301, 304.
[7] Daly FF, O'Malley GF, Heard K, et al. Prospective evaluation of repeated supratherapeutic acetaminophen (paracetamol) ingestion. Ann Emerg Med 2004;44:393-8.
[8] Heard KJ, Ries NL, Dart RC, et al. Overuse of non-prescription analgesics by dental clinic patients. BMC Oral Health 2008;8:33.
[9] Myers RP, Leung Y, Shaheen AA, et al. Validation of ICD-9-CM/ICD-10 coding algorithms for the identification of patients with acetaminophen overdose and hepatotoxicity using administrative data. BMC Health Serv Res 2007;7:159.
[10] Whitcomb DC, Block GD. Association of acetaminophen hepatotoxicity with fasting and ethanol use. JAMA 1994;272:1845-50.
[11] Gordis L. Epidemiology. Philadelphia (Pa): Saunders; 2000.