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ORIGINAL ARTICLE

Evaluation of a Food and Drug Administration Mandate to Limit Acetaminophen in Prescription Combination Products

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Abstract
Introduction In 2014, the US Food and Drug Administration limited the production of prescription acetaminophen-opioid combination products to 325 mg per dose unit. The goal of this mandate was to decrease the likelihood of unintentional acetaminophen hepatotoxicity. This study was designed to determine if this federal regulation has succeeded in reducing unintentional acetaminophen-induced hepatotoxicity from opioid combination products.
Methods Using data from the National Poison Data System (NPDS), we analyzed all calls to US Poison Control Centers in the years 2013 and 2015 for acetaminophen-opioid combination product exposures. We then excluded cases that were classified as intentional and those aged 12 years and younger. We used a primary endpoint of *N*-acetylcysteine administration; secondary endpoints included evidence of hepatotoxicity as aspartate aminotransferase elevation, opioid antagonist administration and severity of overall medical outcome.
Results A total of 18,259 calls between the two yearlong periods met inclusion criteria. 5.16 and 5.01% of calls resulted in *N*-acetylcysteine administration in 2013 and 2015, respectively. 3.63 and 4.02% received naloxone in 2013 and 2015, respectively, and 0.9% in each year developed hepatotoxicity. Rates of *N*-acetylcysteine administration, naloxone administration, and hepatotoxicity did not differ significantly between 2013 and 2015. Severity of medical outcome was worse in 2015 as compared to 2013 with more cases being categorized as "major effect" and fewer cases being categorized as "no effect."
Conclusions The Food and Drug Administration limitation on acetaminophen content per dose unit in opioid combination products did not reduce the occurrence of unintentional acetaminophen-induced hepatotoxicity or *N*-acetylcysteine administration as reported to NPDS.

Keywords Acetaminophen · Hepatotoxicity · Food and Drug Administration · Drug dosing limits

Introduction

Over the past several decades, the most frequent calls to US Poison Control Centers (PCC) has been for acetaminophen (APAP) exposures, with over 100,000 recorded annually. Approximately 42% of these calls pertain to APAP-opioid combination products [1]. Acetaminophen-induced hepatotoxicity is a significant public health concern, resulting in over 26,000 hospitalizations and over 450 deaths annually, with approximately 20–25% of these deaths attributed to unintentional exposures [2]. Half of US cases of acute liver failure (ALF) are associated with acetaminophen use [3]. According to a 2005 study, 63% of unintentional overdoses that resulted in ALF involved acetaminophen-opioid combination formulations [4, 5].

In 2011, a Food and Drug Administration (FDA) advisory committee recommended limiting the APAP content of prescription combination products to 325 mg per dose unit, with a maximum of 650 mg per dosing interval. The goal of this mandate was to reduce the risk of unintentional APAP hepatotoxicity "if [one] mistakenly takes too many doses of acetaminophen-containing products." This regulation went into effect in early January 2014 [6, 7].

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When the mandate went into effect, pharmacies and manufacturers were permitted to distribute and sell any remaining pre-mandate APAP combination products in their stocks. At that time, APAP was available in combination tablets containing one or more of the following products: aspirin, butalbital, caffeine, codeine, hydrocodone, oxycodone, pentazocine, and tramadol. Quantities as high as 750 mg of APAP per dose unit were present in commercially available APAP-hydrocodone products, 650 mg in APAP-pentazocine products, and 650 mg in APAP-oxycodone products [7].

The FDA has had previous success with introduction of regulations to reduce unintentional poisoning from pharmaceutical products. Prior to 1997, iron toxicity was responsible for nearly half of all pediatric poisoning fatalities in the USA [8]. In 1997, the FDA mandated that iron supplements be sold in unit-dose blister packs. This intervention has been reported to reduce the risk of iron poisoning resulting in death for children 6 years and younger by an odds ratio of 13.56 [9].

Other countries have also introduced legislation or regulations to reduce the risk of APAP poisoning. In 1998, the UK passed legislation limiting over the counter (OTC) sales of APAP to 8 g per package and those obtained by prescription to 16 g. This legislation was associated with a 15% decrease in median dose of APAP exposure; however, there was no proven benefit as the prevalence of APAP toxicity resulting in death was unaffected [10]. In 1999, six Canadian providences repealed legislation that limited OTC sales of acetaminophen to 24-count packages. The lifting of this restriction did not alter the rate of APAP-related hospitalizations [11]. Many members of the European Union place limits on the amount of APAP per package and/or reserve APAP products to be available through pharmacies only.

The purpose of this study was to determine if limiting the content of acetaminophen in opioid-acetaminophen combination products has been effective in reducing the incidence of unintentional acetaminophen hepatotoxicity.

Methods

Data was obtained by querying the National Poison Data System (NPDS), a database of all calls placed to US Poison Control Centers. Data was entered to NPDS by certified specialists in poison information (CSPI), which are specially trained nurses or pharmacists. Each call to a PCC for a suspected poisoning or exposure is identified by substance using a unique numeric code determined by the American Association of Poison Control Centers (AAPCC). Other information that is typically collected is date and time of initial call, age, gender, geographical information, route of exposure, reason for exposure (intentional, occupational, environmental, etc.), chronicity, symptoms, medical outcome, and medical interventions. Data was obtained from two yearlong periods before and after the 2014 mandate. Pre-mandate data included all calls to the PCC from the calendar year 2013. Post-mandate data included all calls from the calendar year 2015. The calendar year 2014 was excluded as a washout period, during which higher concentration products remaining in manufacturer and pharmacy stocks could still be dispensed even after the mandate went into effect.

The NPDS database was queried for all calls pertaining to APAP-opioid combination products that were commercially available in the USA at that time. We used AAPCC generic category codes to identify relevant cases. We searched for codes 0201063, 0072700, 0072702, 0072703, and 0072704, which correspond respectively to "APAP with hydrocodone," "APAP with codeine," "APAP with oxycodone," "APAP with propoxyphene," and "APAP with other narcotics or narcotic analogs." We included all patient taking acetaminophen/opioid combination products, not just single substance exposures, as this was the patient population specifically addressed in the FDA statement.

Inclusion criteria consisted of those aged 13 years or greater (including adults of unknown age), human species, unintentional ingestions, adverse reactions, or unknown intents as classified by the CSPI at the time of consultation. Collected data included month and year of the call to the poison center, age, gender, medical outcome (none, minor, moderate, major, or death), clinical effect (symptoms), substance(s) ingested, and therapies given. A sensitivity analysis was then performed by using the same data and analytical methods as above with the additional exclusion criteria of unknown intent of ingestion. Institutional review board approval was obtained for this study protocol.

We defined our primary endpoint as initiation of *N*-acetylcysteine (NAC) therapy, which served as a surrogate marker for potential APAP-induced hepatotoxicity. Secondary endpoints included APAP-induced hepatotoxicity as defined by aspartate aminotransferase (AST) concentration greater than or equal to 1000 units/L, administration of an opioid antagonist, liver transplantation, and severity of overall medical outcome. Actual APAP-induced hepatotoxicity was not utilized as a primary endpoint as timely initiation of NAC effectively prevents this outcome, additionally in the acute overdose setting there is a well-defined point for initiation of NAC therapy based on serum APAP concentration and time since ingestion as defined by the Rumack-Matthew Nomogram 12.

Overall severities of medical outcome based on AAPCC definitions are reported using descriptive statistics. "No effect" are cases without any medical complications or the case was not followed by the PCC as the exposure was determined to be medically insignificant. A minor effect is a patient that developed some signs or symptoms that rapidly resolved without sequelae. A moderate effect is a patient that had symptoms that were more pronounced or prolonged, those were

non-life threatening and had no sequelae; however, treatment was typically indicated. A major effect involved either life-threatening symptoms or the development of permanent sequelae.

Testing for statistical significance was performed using Welch's two-proportion *t* test to compare proportion of NAC administration between the pre-mandate and post-mandate periods. Descriptive statistics were used to compare severity of overall medical outcome between the two periods. A p value <0.05 was considered statistically significant. All statistical calculations were performed in SPSS version 23 (IBM, Armonk, NY).

Results

The NPDS data contained a total of 37,668 calls to all US Poison Control Centers in 2013 for exposures to acetaminophen-opioid combination products and a total of 31,810 calls in 2015. A total of 23,248 and 19,957 calls in 2013 and 2015, respectively, were excluded for being of intentional nature. Also, 4538 and 3476 calls in 2013 and 2015, respectively, were excluded for being non-human species or children 12 years and younger. This left a total of 18,259 (9882, and 8376 in 2013 and 2015, respectively) calls available for analysis (Fig. 1). Demographic characteristics are given in Table 1. In both pre-mandate and post-mandate periods, females and persons aged 21–40 years of age were overrepresented. For 10–11% of calls, the age and/or gender was unavailable.

The primary endpoint of *N*-acetylcysteine (NAC) administration as well as the secondary endpoints of opioid antagonist administration and liver transplantation are found in Table 2. There was no significant difference between the pre-mandate and post-mandate periods for each of those endpoints. The percent of patients whom received NAC therapy was 5.16% in 2013 compared to 5.01% in 2015. Only 3.63% of patients received an opioid antagonist in 2013 compared to 4.02% receiving it in 2015. There was only one patient who received a liver transplant, which occurred in the pre-mandate period.

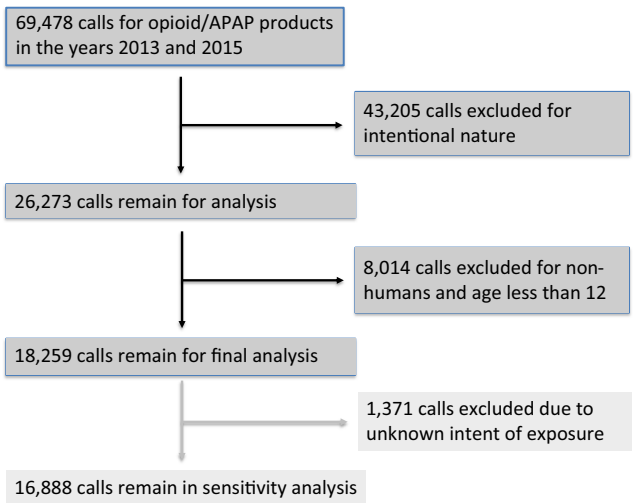

Fig. 1 Flow chart depicting exclusion criteria

Table 1 Demographics

	2013 *n* (%)	2015 *n* (%)
Totals	9882 (100)	8377 (100)
Gender *n* (%)		
Female	6158 (62.3)	5251 (62.7)
Pregnant	15 (0)	11 (0)
Male	3559 (36.0)	3031 (36.2)
Unknown/not listed	165 (1.7)	95 (1.1)
Age *n* (%)		
13–20 years	837 (8.4)	680 (8.1)
21–40 years	3127 (31.6)	2512 (30.0)
41–60 years	2468 (25.0)	2060 (24.6)
≥61	2386 (24.1)	2294 (27.4)
Unknown/not listed	1064 (10.8)	831 (9.9)

When those cases with unknown intent are excluded, the pre-mandate and post-mandate datasets become more similar (Table 3). An additional 752 and 619 (from 2013 and 2015, respectively) met exclusion criteria, leaving 9130 and 7758 cases for analysis. In these datasets, 294 (3.2%) and 253 (3.3%) of cases received NAC therapy compared to the 5.16 and 5.01% when the unknown intents were included.

The severities of overall medical outcomes are listed in Table 4. The majority of cases in each cohort had no effect from their exposure. More exposures resulted in major and minor effects in the post-mandate group and fewer exposures resulted in no adverse effect. There was an absolute risk reduction of −0.4% in major medical outcomes. The mortality rate was 0.3% in both periods.

The secondary endpoint of hepatotoxicity, as evident by an elevation in serum AST concentration, is listed in Tables 5 and 6. There was no statistically significant difference between the pre-mandate and post-mandate periods in APAP-induced hepatotoxicity (AST >1000 units/L) or in an AST elevation of

Table 2 Initiation of antidotal therapies: analysis of initial dataset

	2013 *n* = 9882 (%)	2015 *n* = 8377 (%)	*p* value
Received NAC	510 (5.16)	423 (5.01)	0.733
Received naloxone	359 (3.63)	337 (4.02)	0.170
Received both (NAC+ naloxone)	89 (0.90)	91 (1.09)	0.206
Liver transplantation	1	0	n/a

p values obtained by Welch's *t* test

NAC N-acetylcysteine, *n/a* not available

Table 3 Initiation of antidotal therapies: after exclusion of unknown intents

	2013 *n* = 9130 (%)	2015 *n* = 7758 (%)	*p* value
Received NAC	294 (3.2)	253 (3.3)	0.881
Received naloxone	200 (2.2)	182 (2.3)	0.498
Received both (NAC+ naloxone)	30 (0.3)	37 (0.5)	0.127

lesser extent. However, in the sensitivity analysis, AST elevation was significantly worse in the post-mandate period. This was likely a type I error as there were no subsets of hepatotoxicity that reached statistical significance.

Discussion

There was no difference in the primary endpoint of NAC administration or the secondary endpoint of APAP-induced hepatotoxicity (AST >1000 IU/L) between the pre-mandate and post-mandate periods. This suggests that the FDA mandated decrease in APAP content per dose unit has not yet demonstrated an effect in preventing clinically significant, unintentional APAP poisoning. There was no change in NAC administration or in the utilization of naloxone. It is possible that these differences might meet significance if these trends are followed over a longer period of time.

Despite the lack of change in the primary and secondary endpoints of APAP-induced hepatotoxicity, there was a seemingly worse severity of overall medical outcome in the post-mandate period with a negative absolute risk reduction. We cannot definitively state why medical outcomes were more severe in the post-mandate period due to limitations in the data collected by NPDS. However, 28.1% of cases in the post-mandate period were coded as at least minor adverse effect, while only 5.01% received NAC, which suggests that the increase in medical outcome severity in the post-mandate

Table 4 Severity of medical outcomes as defined by the American Association of Poison Control Centers

	2013 *n* (%)	2015 *n* (%)
No effect[a]	6509 (65.7)	5404 (64.5)
Minor	1666 (16.9)	1531 (18.3)
Moderate	761 (7.7)	649 (7.7)
Major	136 (1.4)	153 (1.8)
Death[b]	26 (0.3)	27 (0.3)
Unable to follow	784 (7.9)	613 (7.3)

[a] Includes cases listed as not followed due to minimal exposure, non-exposure, or unrelated effect

[b] Includes all causes of death, not just acetaminophen or opiate related

Table 5 Prevalence of hepatotoxicity: analysis of initial dataset

	2013 *n* = 9882 (%)	2015 *n* = 8377 (%)	*p* value
AST elevation	309 (3.1)	295 (3.5)	0.137
AST >100 but <1000	187 (1.9)	181 (2.2)	0.198
AST ≥1000	90 (0.9)	79 (0.9)	0.820
Other LFT disturbances	32 (0.3)	35 (0.4)	0.295

period is most related to co-ingestants, but possibly in part due to opioid toxicity.

There are several potential explanations for this phenomenon:

1. The decrease in the APAP content in each dose unit may decrease the pain relieving potential obtained per dose unit, causing patients to take additional doses. The higher opioid to APAP ratio in the post-mandate period may predispose individuals to opioid toxicity.
2. Patients in the post-mandate period may feel it is safe to take larger doses of the combination product due to the lower APAP content per dose unit.
3. The increase in severity is unrelated to the change in combination product formulation and instead is due to some other difference between the 2013 and 2015 cohorts. NPDS annual reports document that overall medical outcome severity for all exposures has gradually worsened each year since 2000 5, 13.
4. An overwhelming increase in opioid deaths relating to the opioid epidemic was occurring over the same period, which may cofound our results.

Strengths of our study include the use of a national dataset and a large number of subjects, which has the potential to generate considerable statistical power. However, there are still inherent limitations associated with use of NPDS data. The Poison Center System has had a steady decline in the number of calls over the last several years [13]. A large portion of this decline is likely related to the general population and

Table 6 Prevalence of hepatotoxicity: analysis with exclusion of unknown intent

	2013 *n* = 9130 (%)	2015 *n* = 7758 (%)	*p* value
AST elevation	175 (1.92)	183 (2.36)	0.047
AST >100 but <1000	111 (1.22)	117 (1.51)	0.101
AST ≥1000	49 (0.54)	42 (0.54)	0.967
Other LFT disturbances	15 (0.16)	21 (0.27)	0.135

AST aspartate aminotransferase

healthcare providers obtaining poisoning data from alternate and/or on-line sources [14]. This decline in call volume could account for a decrease in the "no effect" patients in the post-intervention group. A selection bias is created in which providers are less likely to call the PCC if they have no concerns or are comfortable with patient management. Over the 5 years prior to the FDA mandate, there had been a steady decrease in the number of calls to poison centers both overall as well as in regard to APAP exposures. From 2009 through 2013, there had been a steady decline in exposures to opioid-APAP combination products with 48,051 calls in 2009 to 38,142 calls in 2013 [13, 15–18]. This correlates to a 20.6% reduction in the 5 years prior to the FDA intervention as compared to an 11.8% reduction in exposure calls of all types to poison centers in the same period [19].

Another limitation to our study was the incompleteness of records in the database. In both the pre-mandate and post-mandate periods, 7–8% of cases were lost to follow-up. We believe that the proportion of cases lost to follow-up are unlikely to differ between the pre-mandate and post-mandate periods; hence, the presence of incomplete records is unlikely to significantly confound our findings. In addition, poison specialists codify data input to the NPDS system at the time the call is received. Intent of the patient may not be known and is often inferred by the specialists. Also, information relayed to Poison Control Centers can originate from any source: patients, their family members, or medical personnel. This may skew data toward the extremes of the worried well and the extremely ill. This relayed information is often incomplete. Collection of data is of a passive nature, requiring providers to initiate a call to the PCC; this leads to underestimation of total exposures.

In addition, NAC is not a good surrogate for hepatotoxicity. While appropriate NAC therapy prevents the outcome of AST >1000 IU/L, we thought the best way to include all potential cases of hepatotoxicity was to use NAC therapy. We do realize that many patients whom would have never obtained hepatotoxicity were treated with NAC. We feel that initiation of NAC therapy is an indication that the patient was hospitalized and that is an outcome worth preventing.

We included cases coded as unknown intent in our initial analysis, which may include some intentional exposures, especially for cases that were critically ill, where a history may be difficult to obtain or patients were unwilling to divulge their self-injurious behavior. Inclusion of these cases biased our study away from the null hypothesis, as self-injurious ingestions were more likely to have resulted in clinical toxicity than unintentional ingestions. Despite the inclusion of these cases, we still failed to find a significant difference in APAP-induced hepatotoxicity before and after the mandate. Analysis with the unknown intents excluded more so confirms the null hypothesis.

There were other factors affecting APAP consumption, which occurred during the study period. There was a reduction in the maximum daily dose of APAP on OTC preparations, as well as a standardization in the concentration of liquid children's APAP. Neither of these were likely to have had an effect on our study as neither of the targeted groups met our inclusion criteria.

A 2013 study of the same NPDS database analyzed deaths from all acetaminophen combination products. That study excluded cases in which there were non-acetaminophen containing co-ingestants. It was determined that only 35% of deaths were due to the APAP component when in combination with an opioid [20]. When considering that the acetaminophen is to work synergistically with the opioid, it raises the concern that each tablet offers less pain relief, which adds support to the theory that patients may be more likely to take additional doses.

A 2016 position statement from the American College of Medical Toxicology (ACMT) supported the FDA decision to limit the APAP content in APAP-opioid combination products but further recommends use of APAP-free opioid analgesics when available [21]. Despite warning statements from medical expert groups (ACMT) and actions by both federal regulatory agencies (FDA) and APAP manufacturers, APAP-induced hepatotoxicity remains an important public health concern.

Conclusion

The FDA action to limit APAP content in APAP-opioid combination products to 325 mg per dose unit has not yet been effective in this cohort of unintentional poisonings in reducing the risk of APAP-induced hepatotoxicity. Overall severity of medical outcome was slightly worse after implementation of the FDA regulation, although the reason for this change is not clear. APAP-induced hepatotoxicity remains a significant public health concern and further steps should be undertaken to address this issue.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflicts of interest.

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