Frequency of Poison Center Exposures for Pediatric Accidental Unsupervised Ingestions of Acetaminophen after the Introduction of Flow Restrictors

Eric P. Brass, MD, PhD[1], Kate M. Reynolds, MPH[2], Randy I. Burnham, MS[2], and Jody L. Green, PhD[2]

Objective To assess the temporal association of flow restrictor introduction and the rate of accidental unsupervised ingestions (AUIs) of liquid acetaminophen products.

Study design The National Poison Data System was used to identify AUIs of single ingredient acetaminophen in patients aged <12 years reported between 2007 and 2015. Six regional poison centers obtained additional information using a structured telephone survey.

Results Pediatric AUIs involving acetaminophen averaged 30 000 exposures per year between 2007 and 2012. From 2012 to 2015, after flow restrictor introduction, exposures steadily decreased at a rate of 2400 fewer exposures annually, reaching 21 877 exposures in 2015. Normalized to sales volume, exposures involving liquid acetaminophen products decreased by 40% from 2010 to 2015. Exposures involving products with flow restrictors tended to have a lower estimated ingestion per exposure, fewer exposures exceeding a 150 mg/kg acetaminophen threshold, and were associated with lower rates of hospital admissions when compared with products without restrictors. Caregivers reported improper storage and child confusion of the medicine with treats as common contributing factors to exposures.

Conclusions The introduction of flow restrictors was associated with a decrease in pediatric AUIs of liquid acetaminophen products. Decreases in the dose ingested and risk of hospital admission per exposure may also have resulted. Efforts to optimize flow restrictors and increase their use with medicines associated with high pediatric overdose risk should be encouraged. *(J Pediatr 2018;■■:■■-■■).*

Acetaminophen is widely used as a pediatric analgesic and antipyretic. Although safe and effective when used as directed, acetaminophen is also associated with a large number of unintentional overdoses. Acetaminophen overdoses can result in acute liver failure and were responsible for 14% of all cases of pediatric acute liver failure in 1 large cohort,[1] and 19% of pediatric liver transplant cases in another series.[2] These overdoses may result from unintentional medication errors or from accidental unsupervised ingestions (AUI) by children. Emergency department visits for unintentional acetaminophen overdoses in children under the age of 6 years are 10-fold more likely to be due to AUIs than medication errors, with visit rates for AUIs of acetaminophen estimated at 42.5 visits per 100 000 population per year.[3] In the US from 2010 to 2013, AUIs in children less than 6 years old of liquid acetaminophen products led to an estimated 2607 emergency visits per year.[4] Thus, pediatric AUIs of acetaminophen continue to represent personal and public health burdens.

Initiatives have been launched to decrease the number of pediatric acetaminophen overdoses and their severity, including safety awareness campaigns and packaging innovations.[5-9] In 2011, nonprescription acetaminophen manufacturers voluntarily introduced flow restrictors into pediatric liquid acetaminophen products.[10] Flow restrictors have been shown to be effective in reducing liquid medication access in the research setting.[9] The introduction of flow restrictors was coupled with the standardization of pediatric liquid acetaminophen concentrations at 160 mg per 5 mL and the inclusion of an in-package dosing device to decrease medication dosing errors.[11]

The current study assessed the temporal relationship between introduction of flow restrictors and pediatric AUIs of single ingredient acetaminophen products from 2007 to 2015 using National Poison Data System (NPDS) data.

AUI	Accidental unsupervised ingestion
NPDS	National Poison Data System
RPC	Regional poison center

From the [1]Department of Medicine, David Geffen School of Medicine at UCLA, Los Angeles, CA; and [2]Rocky Mountain Poison and Drug Center, Denver Health and Hospital Authority, Denver, CO

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Methods

This was a study of exposures reported to the NPDS, a repository for all exposures received by regional poison centers (RPCs) throughout the US and maintained by the American Association of Poison Control Centers. RPC staff collect information using standardized data systems designed to obtain key information, including patient's age, products involved, circumstances of the exposure, and estimated amount ingested. Exposures are followed until no further follow-up or recommendations are required or no further information is available.[12] All exposures are assigned a "reasons" code based on the history provided (eg, medication error, AUI). Case follow-up is done to obtain the medical outcome and is completed in an average of 46.8% of exposures reported to the NPDS.[12] Details on NPDS methodologies can be found in their annual report.[12]

NPDS exposures included in the current analysis involved ≥1 single ingredient acetaminophen product, with or without other substances, categorized as an AUI, and occurring in a child <12 years of age (or an estimated age of ≤5 years if the exact age could not be determined). In addition, all NPDS pharmaceutical exposures were extracted from the 2007-2015 NPDS annual reports to provide context for trends in reported exposures.[12-20]

Six RPCs collected follow-up information on exposures involving single ingredient acetaminophen products between August 2013 and January 2016. Information on the specific product(s) involved, awareness of medication safety, and possible contributing factors were obtained using a custom designed survey tool. Information was obtained only if the individual making the original call to the RPC was the child's caregiver (eg, not a healthcare provider), and was available and agreed to participate.

Survey personnel were trained to assess the presence or absence of new packaging features using questions such as, "When you look at the bottle, is there a restricted or smaller opening which you have to use a syringe to get the medication out?", "Do you have to squeeze the bottle to get any medicine out?", "Does the top of the bottle have an opening that allows the medication to flow out freely without squeezing?", and "Did the medication come with a syringe?".

RPCs received ethics approval by their local institutional review board to conduct the surveys and submit deidentified case narratives. Survey participants provided verbal consent.

Unit sales (ie, bottles or blister packs) from food, drug, and other major retailers were obtained from Information Resources, Inc (Chicago, Illinois) from 2010 to 2015. These data were used to generate annual rates of exposure per million units sold.

Statistical Analyses

The data presented are descriptive; no prospective inferential hypothesis testing was defined. Therefore, no *P* values were calculated and data are presented as observed absolute values, means with SDs, or medians with IQR. Time trends were estimated using linear regression. Although changes in acetaminophen packaging was introduced in 2011, 2012 was used as the transition year for assessments owing to the time required to introduce manufacturing changes, turnover of store shelf product, and turnover of home product stocks. An iterative fitting technique of single breakpoint piecewise linear regression models was used post hoc to analyze the best fit of a transition year by comparing mean squared error values. Analyses were completed in 2017 and were conducted using SAS (version 9.4; SAS Institute, Cary, North Carolina).

Results

From 2007 to 2015, the NPDS received approximately 1.5 million reports of pharmaceutical exposures, with little year-to-year variation (minimum of 1.451 million exposures in 2014 and maximum of 1.564 million exposures in 2009). From 2007 to 2012 the number of exposures involving AUIs of single ingredient acetaminophen products (including both liquid and solid formulations) also remained relatively stable at approximately 30 000 per year (**Figure**, A). In contrast, beginning in 2012 (after the 2011 introduction of flow restrictors), the number of acetaminophen exposures per year decreased, reaching 21 877 in 2015. The trend in exposures per year from 2007 to 2012 was a decrease of 520 exposures per year ($r^2 = 0.28$; 95% CI, −1688 to 648). In contrast, for the period 2012-2015 the trend was a decrease of 2401 exposures per year ($r^2 = 0.99$; 95% CI, −2980 to −1822).

A breakpoint analysis confirmed that 2012 was the optimal transition year in the time series. In contrast, total AUIs including all substances decreased at a slow, relatively consistent rate for the period 2007-2015 without evidence of a change in rate after 2011 (**Table I**).

The age distribution of patients exposed via AUI of single ingredient acetaminophen products was stable over the 9 years of observation (**Table II**). The median age was 2 years and 96.3% of exposures involved children <6 years of age. Approximately 52.0% of the patients were male and 96.9% of exposures occurred in the child's own residence. The vast majority (93.4%) of the exposures involved only a single product.

Exposures involved ingestion of liquid or solid single ingredient acetaminophen formulations, and rarely (0.1% of all exposures) both. Annual exposure counts decreased over the

Table I. Total NPDS AUI exposures in children ≤5 years of age

Years	AUIs in children ≤5 years of age	Percent change from previous year
2007	1 165 797	
2008	1 193 318	+2.36
2009	1 185 714	−0.64
2010	1 112 098	−6.21
2011	1 051 342	−5.46
2012	1 011 485	−3.79
2013	963 535	−4.74
2014	950 216	−1.38
2015	933 157	−1.80

Annual numbers of AUIs involving any substance in children ≤5 years of age were tabulated and the percent change from the previous year calculated.

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