Chronic Acetaminophen Exposure in Pediatric Acute Liver Failure

WHAT'S KNOWN ON THIS SUBJECT: Children with acute liver failure due to a single-dose acetaminophen exposure have a characteristic liver biochemistry profile of low conjugated bilirubin and high alanine aminotransferase, which is associated with a favorable clinical outcome when treated with N-acetylcysteine.

WHAT THIS STUDY ADDS: Children with acute liver failure associated with chronic acetaminophen exposure also have a similar liver biochemistry profile, but for unknown reasons, they have a poorer clinical outcome than patients with single-dose acetaminophen exposure.

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KEY WORDS

acute liver failure, acetaminophen, chronic drug-induced liver injury

ABBREVIATIONS

ALF—acute liver failure
ALT—alanine aminotransferase
APAP—N-acetyl-p-aminophenol or acetaminophen
CE—chronic exposure
HE—hepatic encephalopathy
NAC—N-acetylcysteine
NE—no exposure
PALF—Pediatric Acute Liver Failure
SE—single-dose exposure

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abstract

BACKGROUND: Acetaminophen (N-acetyl-p-aminophenol [APAP]) is a widely used medication that can cause hepatotoxicity. We examined characteristics and outcomes of children with chronic exposure (CE) to APAP in the multinational Pediatric Acute Liver Failure (PALF) Study.

METHODS: A total of 895 children enrolled from 2002 to 2009 were grouped by APAP exposure history as: CE (received multiple doses ≥ 2 days; $n = 83$), single dose exposure (SE; $n = 85$), and no exposure (NE; $n = 498$). CE was the reference group for pairwise comparisons. Median values are shown.

RESULTS: Patients with CE compared with those with SE were younger (3.5 vs 15.2 years, $P < .0001$), less likely to be female (46% vs 82%, $P < .0001$), and more likely to be Hispanic (25% vs 7%, $P = .001$), but they did not differ significantly from the NE group. At enrollment, total bilirubin was lower with CE than with NE (3.2 vs 13.1 mg/dL, $P < .001$). Alanine aminotransferase levels were higher with CE than with NE (2384 vs 855 IU/L, $P < .0001$), but lower than with SE (5140 IU/L, $P < .0001$). Survival without liver transplantation at 21 days was worse for CE than for SE (68% vs 92%, $P = .0004$) but better than for NE (49%, $P = .008$).

CONCLUSIONS: Children in the PALF study with CE had lower bilirubin and higher alanine aminotransferase than those with NE. Outcomes with CE were worse than with SE but better than with NE. Potential reasons for this outcomes advantage over non-APAP-exposed subjects should be explored. *Pediatrics* 2013;131:e740–e746

Acetaminophen (N-acetyl-p-aminophenol [APAP]) is one of the most widely used antipyretic and analgesic medications in children. It is available without prescription and is a trusted staple in most parents' medicine cabinets. APAP is considered safe when taken at the recommended dose (10–15 mg/kg) and frequency (≤ 5 doses/day) for a total recommended daily dose of 75 mg/kg per day.¹ However, caregivers may inadvertently overdose APAP if they do not measure the medication correctly, if they give the recommended single dose more frequently than is recommended over 24 hours, or if they are not aware that APAP is included in combination drug preparations to treat cold symptoms. Serious liver injury related to unintentional, multiple overdoses of APAP in adults has been the focus of multiple publications over the past 15 years.^{2,3} The highest recommended APAP dose for adults is 4 g/day; however, exposure to >6 –8 g/day for multiple days has been described as potentially toxic, especially in those with chronic ethanol use.² Concerns have also been raised that liver injury can occur in children who receive multiple days of APAP that exceed the recommended daily dose, but there is no consensus regarding the dosing exposure that is considered potentially toxic for pediatric patients.^{4,5}

After a single overdose, APAP toxicity can lead to the development of acute liver failure (ALF). N-acetylcysteine (NAC) is an effective treatment of patients with acute APAP-induced ALF.^{6,7} It is not clear if this therapy is also effective in treating patients with ALF who have liver injury initiated or exacerbated by chronic APAP exposure.

There are few reports of accidental overdose due to chronic ingestion of APAP in children leading to severe hepatotoxicity.^{5,8,9} These and other studies suggest that risk factors for developing severe hepatotoxicity include

concomitant use of multiple APAP-containing products or other medications that alter hepatic metabolism, delays in getting appropriate medical care, younger age, and a prodromal illness associated with periods of fasting.^{4,5,8} Although the magnitude of this clinical problem in children is not well defined, 48% of APAP-induced ALF in adults in the United States is due to unintentional overdoses of APAP, often with the chronic use of ethanol or concomitant use of opioids or other potentially hepatotoxic medications, reinforcing the concept that accidental misuse of this medication leading to serious liver injury is a significant problem.¹⁰

The Pediatric Acute Liver Failure (PALF) study group is a multinational collaboration of pediatric tertiary health care centers that has been examining the epidemiology and outcomes of children with ALF since December 1999. In the current study, we report the characteristics and clinical outcomes of a subgroup of 895 consecutive patients enrolled in the PALF registry over a 10-year interval who were retrospectively selected and stratified primarily according to APAP exposure history. We hypothesized that PALF patients with chronic exposure (CE) to APAP would have clinical features and outcomes more similar to PALF patients with single-dose exposure (SE) to APAP than to patients with no exposure (NE) to APAP but outcomes that were not as favorable as those in patients with acute toxicity.

METHODS

Study Design

This was an observational cohort study conducted through the PALF Consortia, which enrolls eligible children with ALF. Patient enrollment began in December 1999. During the period of this study, the PALF study group consisted of 22 pediatric sites: 19 centers in the United States, 1 in Canada, and 2 in the United

Kingdom. Working groups of pediatric hepatologists established definitions for ALF in children and for various diagnostic categories. Representatives from all participating centers approved final recommendations from the working groups. The study was approved by the institutional review boards from all of the institutions, and the National Institutes of Health provided a Certificate of Confidentiality to the study. Written informed consent was obtained from the parents or guardians of the children in the study. At some sites, deceased children could be enrolled, with data collection via chart review, if consent had not been refused.

After enrollment, demographic, clinical, and diagnostic data are recorded daily for up to 7 days; 21-day outcomes were determined as death without transplantation, transplantation, or alive without transplantation. Patients in this study were enrolled under 2 protocols coinciding with the study periods of 1999–2005 and 2005–2010. The 1999–2005 protocol requested the investigator to note on the case report form whether an APAP overdose occurred, and if so, whether it was in the setting of a suicide attempt or an accidental ingestion. The total APAP dose ingested was requested for all patients. In addition, if a history of a “single dose” was obtained, the date and time of ingestion were to be recorded; if a history of “chronic use” of APAP was obtained, the investigator was to indicate the number of days of use. In the case of APAP exposures not considered by the investigator to lead to overdose, APAP dosage history (total reported dose per day, duration, date last taken) was recorded under medications taken before admission.

In the revised protocol implemented from 2005 to 2010, investigators were instructed to document if any APAP exposure was elicited from the patient's

history, and if so, was the exposure a “single dose” or “chronic use.” If the APAP taken was a single dose, then the total dosage and date and time of the dosing were requested. If the APAP taken was chronic use, then the average daily reported dose was estimated by the site investigator, and the number of days that it was taken over the preceding month was recorded if the history was available.

Diagnostic evaluation and medical management were under the direction of the attending physician and consistent with the standard of care at each site. A final diagnosis for the cause of PALF was assigned by the primary physician at each study site, as summarized previously.¹¹

Subjects of the Study

Patients <18 years of age were eligible for enrollment into the PALF registry if they met the following entry criteria: no known evidence of chronic liver disease, biochemical evidence of acute liver injury, and hepatic-based coagulopathy (not corrected with vitamin K) defined as a prothrombin time ≥ 15 seconds or an international normalized ratio ≥ 1.5 in the presence of clinical hepatic encephalopathy (HE) or a prothrombin time ≥ 20 seconds or an international normalized ratio ≥ 2.0 regardless of the presence or absence of HE. A clinical coma grade scale was used for infants and children as previously reported.¹¹

All patients enrolled in the PALF registry at the time of analysis (ie, 895 patients) were included in this study. Patients were retrospectively classified into 1 of the 3 following patient groups on the basis of APAP exposure history, serum APAP level, and final PALF diagnosis: CE group (history of multiple-dose exposure to APAP over ≥ 2 days; $n = 83$); SE group (history of a single-dose APAP exposure; $n = 85$); NE group (no history of APAP exposure, no evidence of de-

tectable serum APAP levels, and no final diagnosis of APAP-induced PALF; $n = 498$). The remaining 229 patients did not meet the criteria for 1 of the 3 groups. These patients had various forms of documented APAP exposure, including exposure anytime in the 2 months preceding enrollment in the study ($n = 143$), documentation of receiving an APAP dose ($n = 22$) or of a detectable level of APAP in their serum within the first week of presentation ($n = 106$) without a quantified exposure documented, or were ascribed a final diagnosis of APAP-induced PALF by the primary physician ($n = 11$) without a documented history of exposure that would allow them to be categorized into groups CE or SE. These patients were not included in this analysis given the heterogeneity and unclear APAP exposure history of this group.

Statistical Methods

The CE group was the reference group for all pairwise group comparisons. Pearson's χ^2 test was used for categorical data, and the Wilcoxon rank-sum test was used for continuous data. Results were considered significant if $P \leq .05$. Statistical analyses were performed by using SAS 9.2 (SAS Institute, Cary, NC).

RESULTS

APAP Exposure Characteristics

Of the 666 patients included in this analysis (Table 1), 83 (12%) met the criteria for inclusion in the CE reference group. There were 85 patients (13%) classified into the SE group and 498 patients (75%) in the NE group. A history of APAP toxicity was identified in all 85 SE patients with 65 of 85 being a suicide attempt. A history of APAP toxicity was not known in 60 of 83 patients with CE, and for those where it was known 20 of 23 cases were characterized as an accidental overdose. The majority (51%) of patients in the CE

group had 3 to 7 days of exposure to APAP, 36% had 2 days of exposure, 4% had 8 to 14 days of exposure, and 9% had >15 days of APAP exposure. The median reported dose of APAP in the CE group was significantly less than that of SE patients (31 vs 258 mg/kg per day, respectively; $P < .0001$). However, among patients with APAP levels recorded, there was not a significant difference between the CE and SE groups in the proportion of patients who had serum APAP levels ≥ 10 mg/L (66% in SE patients versus 68% in CE patients, $P = .87$). Exposure to other APAP-containing medications was common: 65% of patients in the CE group and 35% in the SE group.

Twenty-two percent of CE patients were assigned a final diagnosis of APAP toxicity by their primary physician, compared with 97% in the SE group ($P < .0001$). The most common final diagnosis was indeterminate in CE (37%) and NE (47%) patients.

Demographic and Baseline Clinical Characteristics

The demographic characteristics of the CE patients did not differ significantly from those of the NE group (Table 2). SE patients were significantly older than the CE patients (median = 15.2 vs 3.5 years, $P < .0001$), and a larger percentage were non-Hispanic/Latino (93% vs 75%, $P = .001$) and female (82% vs 46%, $P < .0001$).

The distribution of HE grades at study entry for NE patients did not significantly differ from that for CE patients. SE patients had lower HE grades at presentation. SE patients also had significantly lower maximum grades of HE within the first 7 days postenrollment compared with CE patients ($P = .003$; data not shown).

Comparisons of laboratory results at study enrollment are reported in Table 3. Of these results, the most striking observation is that, compared with CE patients who had relatively low total

TABLE 1 Features of APAP Exposure Groups

APAP Characteristics and Diagnosis	Chronic APAP Exposure (CE Group; <i>n</i> = 83 [Reference Group])	Single Toxic APAP Exposure (SE Group; <i>n</i> = 85)	<i>P</i> ^a	No APAP Exposure (NE Group; <i>n</i> = 498)	<i>P</i> ^a
History of APAP toxicity, <i>n</i> (%)					
Unknown	60 (—)	0			
Suicide attempt	3 (13.0)	65 (76.5)	<.0001	NA	—
Accidental overdose	20 (87.0)	20 (23.5)			
Reported APAP dose, mg/kg per day	63	70			
Median (25th, 75th)	30.8 (15.1, 52.4)	258.1 (135.9, 378.4)	<.0001	NA	—
Exposure to other APAP-containing medications, <i>n</i> (%)	54 (65.1)	30 (35.3)	<.001	NA	
Serum APAP level, <i>n</i> (%)					
Missing	52 (—)	38 (—)			
<10 mg/L	10 (32.3)	16 (34.0)	.87	NA	—
≥10 mg/L	21 (67.7)	31 (66.0)			
Final diagnosis, <i>n</i> (%)					
APAP overdose	18 (21.7)	82 (96.5)		0 (0.0)	
Metabolic	4 (4.8)	0 (0.0)		72 (14.5)	
Autoimmune	6 (7.2)	0 (0.0)	<.0001	34 (6.8)	<.0001
Infection	7 (8.4)	0 (0.0)		51 (10.2)	
Indeterminate	31 (37.3)	3 (3.5)		234 (47.0)	.37 ^b
Other	17 (20.5)	0 (0.0)		107 (21.5)	

NA, not applicable.

^a χ^2 or rank-sum test comparing with the CE group (unless otherwise indicated).^b χ^2 test comparing with the CE group after excluding the APAP overdose group.

bilirubin levels (median = 3.2 mg/dL), NE patients had high total bilirubin levels (median = 13.1 mg/dL, $P < .0001$). SE patients also exhibited a relatively low total bilirubin level (median = 2.0 mg/dL), which was similar to, but statistically lower than, that of the CE

patients ($P = .002$). Serum alanine aminotransferase (ALT) levels in CE patients (median = 2384 IU/L) were intermediate in value compared with SE (5140 IU/L, $P < .0001$) and NE (855 IU/L, $P < .0001$) patients. The remaining initial laboratory values were not

significantly different between the CE and NE groups. However, SE patients differed significantly from CE patients in most other measured laboratory variables. Similar differences between groups were observed when comparing maximum laboratory values (data not shown).

TABLE 2 Demographic and Baseline Characteristics by APAP Exposure Group

	Chronic APAP Exposure (CE Group [Reference Group])	Single Toxic APAP Exposure (SE Group)	<i>P</i> ^a	No APAP Exposure (NE Group)	<i>P</i> ^a
<i>n</i>	83	85		498	
Age, median (25th, 75th)	3.5 (1.2, 10.1)	15.2 (14.3, 16.3)	<.0001	3.2 (0.1, 10.1)	.04
Gender, <i>n</i> (%)					.79
Male	45 (54.2)	15 (17.6)		278 (55.8)	
Female	38 (45.8)	70 (82.4)		220 (44.2)	
Ethnicity, <i>n</i> (%)			.001		.28
Not Hispanic or Latino	62 (74.7)	79 (92.9)		398 (79.9)	
Hispanic or Latino	21 (25.3)	6 (7.1)		100 (20.1)	
Race, <i>n</i> (%)			.45		.47
Unknown	0 (—)	0 (—)		3 (—)	
White	61 (73.5)	58 (68.2)		350 (70.7)	
Nonwhite	22 (26.5)	27 (31.8)		145 (29.3)	
Encephalopathy at study entry, <i>n</i> (%)			.053		.16
Missing	5 (—)	2 (—)		36 (—)	
Grade 0	30 (38.5)	51 (61.4)		247 (53.5)	
Grade I	27 (34.6)	16 (19.3)		119 (25.8)	
Grade II	9 (11.5)	5 (6.0)		46 (10.0)	
Grade III	7 (9.0)	6 (7.2)		33 (7.1)	
Grade IV	5 (6.4)	5 (6.0)		17 (3.7)	

^a χ^2 or rank-sum test comparing with the CE group.

Clinical Outcomes

Clinical outcomes are reported in Table 4. At 21 days after enrollment, 68% of CE patients were alive without liver transplantation, which was significantly worse than SE patients (92% alive without liver transplantation; $P = .0004$) and better than those with NE (49% alive without liver transplantation; $P = .008$).

DISCUSSION

This report describes a group of pediatric patients with ALF associated with a history of chronic APAP exposure and a clinical phenotype that may be distinct from other children presenting with ALF. Children with ALF and a history of CE have serum ALT levels that are significantly greater than, and serum total bilirubin levels that are significantly

TABLE 3 Clinical Laboratory Results on Study Enrollment Day by APAP Exposure Group

	Chronic APAP Exposure (CE Group; <i>n</i> = 83 [Reference Group])	Single Toxic APAP Exposure (SE Group; <i>n</i> = 85)	<i>P</i> ^a	No APAP Exposure (NE Group; <i>n</i> = 498)	<i>P</i> ^a
Arterial blood pH			.0003		.09
<i>n</i>	42	40		230	
Median (25th, 75th)	7.4 (7.3, 7.4)	7.4 (7.4, 7.5)		7.4 (7.4, 7.4)	
INR			.10		.54
<i>n</i>	72	79		389	
Median (25th, 75th)	2.6 (1.9, 4.0)	2.2 (1.7, 3.3)		2.7 (2.1, 3.8)	
Prothrombin time			.02		.71
<i>n</i>	74	74		356	
Median (25th, 75th), s	27.1 (22.0, 35.4)	22.9 (17.9, 31.9)		25.9 (22.0, 35.0)	
Serum creatinine			<.0001		.29
<i>n</i>	74	74		425	
Median (25th, 75th), mg/dL	0.5 (0.3, 0.9)	0.7 (0.6, 1.0)		0.5 (0.4, 0.8)	
Total bilirubin			.002		<.0001
<i>n</i>	76	75		420	
Median (25th, 75th), mg/dL	3.2 (1.6, 12.8)	2.0 (1.1, 3.5)		13.1 (5.7, 19.7)	
ALT			<.0001		<.0001
<i>n</i>	77	75		363	
Median (25th, 75th), IU/L	2384.0 (1038.0, 4344.0)	5140.0 (2600.0, 7050.0)		855.0 (149.0, 2067.0)	
Serum phosphate			.005		.32
<i>n</i>	55	56		330	
Median (25th, 75th), mg/dL	3.1 (2.4, 4.0)	2.6 (1.8, 3.4)		3.5 (2.5, 4.2)	
WBC count			.06		.37
<i>n</i>	71	67		430	
Median (25th, 75th), 1000/mm ³	7.8 (5.2, 11.8)	9.4 (6.8, 12.1)		8.7 (5.6, 12.2)	
Platelets			.0004		.67
<i>n</i>	70	66		433	
Median (25th, 75th), 1000/mm ³	148.5 (90.0, 201.0)	188.0 (149.0, 242.0)		134.0 (77.0, 217.0)	

INR, international normalized ratio; WBC, white blood cell.

^a Wilcoxon rank-sum test comparing with the CE group.

less than, those in patients with NE. This pattern of “high ALT, low total bilirubin levels” observed in PALF patients with CE is similar to the pattern seen in PALF and adult patients with SE. Although there is overlap between the bilirubin and ALT ranges between children with CE and those with NE, this pattern may help distinguish patients who warrant further consideration for APAP-related liver injury (eg, ascertainment of a serum APAP level).

Although CE patients shared biochemical similarities with SE patients, patients with CE had significantly worse 21-day outcomes compared with those

with SE. We can only speculate why CE patients were more likely to die or undergo liver transplantation compared with the SE cohort. One factor might include a higher use of NAC at the referral hospital among the SE group, because APAP toxicity might not have been suspected in the CE cohort, and NAC is not approved for use in patients with chronic APAP exposure. Our case report form did not include a specific question to properly address NAC use before enrollment for all patients; therefore, its use before entry into the PALF study cannot be analyzed. Another factor may be that 37% of CE patients had

an indeterminate diagnosis. Patients with an indeterminate diagnosis are more likely to undergo liver transplantation than those with other known diagnoses.¹¹ Alternatively, a significant number of patients in the CE group may have had a multifactorial liver injury, with APAP toxicity being 1 component of the liver injury.

Concern that therapeutic doses of APAP may contribute to ALF in some children has been a topic of considerable interest.^{5,8,9} Alonso et al⁵ reported a series of 7 children with a history of chronic (>2 days) exposure to therapeutic dosing of APAP and PALF of unknown

TABLE 4 Outcome for the First 21 Days by APAP Exposure Group

	Chronic APAP Exposure (CE Group; <i>n</i> = 83)	Single Toxic APAP Exposure (SE Group; <i>n</i> = 85)	<i>P</i> ^a	No APAP Exposure (NE Group; <i>n</i> = 498)	<i>P</i> ^a
Death without transplantation, <i>n</i> (%)	10 (12.0)	2 (2.4)	.0004	78 (15.7)	.008
Transplantation, <i>n</i> (%)	17 (20.5)	5 (5.9)		174 (34.9)	
Alive without transplantation, <i>n</i> (%)	56 (67.5)	78 (91.8)		246 (49.4)	

^a χ^2 test comparing with the CE group.

etiology, with liver histology consistent with APAP-induced injury showing zone 3 necrosis in all 5 patients who underwent biopsy. Serum bilirubin levels ranged from 1.5 to 9.4 mg/dL and serum ALT levels were all >2630 IU/L, which is consistent with the pattern observed in the CE patients with PALF reported here. Miles et al⁹ also reported on 8 children with ALF and chronic APAP exposure of ≥ 4 days, with reported doses ranging from 20 to 200 mg/kg per day; of note, one of these PALF patients was reported to have received 71 mg/kg per day of APAP over 4 days and a second was reported to have received 20 mg/kg per day of APAP over a 7-day period of time. Likewise, most of these patients had low serum bilirubin and high ALT levels. Thus, ours is not the first report to recognize this clinical phenotype. We now affirm these findings in a large, multicenter cohort of children with ALF and present data that suggest that chronic APAP toxicity may contribute to liver injury in at least 10% of these patients. These observations need to be further validated in the future: for example, by future analysis of serum specimens from these patients for APAP protein adducts, which is a sensitive measure and specific indicator of APAP-induced metabolism and hepatocyte injury.^{12,13} However, because adduct testing is not yet clinically available, recognition of this clinical profile may help clinicians identify patients who are likely to have chronic APAP toxicity.

Three-quarters of the patients in the CE group were reported to have received <52 mg/kg per day of APAP for >2 days, a daily dose that is within the recommended dose range. Unfortunately, serum APAP levels were missing in 52 of 83 (62.7%) of the CE cohort. Yet, 21 of 31 CE patients with measured APAP concentrations had a level >10 mg/L, with 3 patients having levels >100 mg/L. Although we do not know the actual dose

or dosing interval or serum APAP levels for all of our patients, it is important to recognize that many of the CE patients had markedly elevated serum APAP levels outside of the range that would be considered therapeutic. Further research characterizing the pharmacokinetics of APAP in the setting of CE in ill children is necessary to determine the significance of elevated APAP levels in patients with evidence of hepatocellular injury.

An important limitation of this observational study is the difficulty inherent in obtaining accurate and a complete dosage history from patients and caregivers who are overwhelmed and preoccupied as they struggle to assimilate information regarding their child's acute illness. Incomplete diagnostic evaluations have also been identified as a problem within this study cohort.¹⁴ Other limitations of the current study are that the data are based on a case registry and complete medical records of study subjects were not available, as well as the fact that only select centers (both in the United States and internationally) were involved in patient accrual, which introduces the possibility of tertiary care selection bias.

CONCLUSIONS

The clinical phenotype of a younger patient with ALF, a low serum bilirubin and a high ALT, should raise the suspicion of CE. PALF patients with CE do not appear to have the same favorable outcomes as the majority of children with SE. Rather, the results of our study suggest that a child with a history of CE is more likely to die or require liver transplantation, similar to PALF patients with other etiologies. APAP protein adduct testing in a large cohort of children with ALF is warranted to further define the importance of CE in this population. In addition, with respect to anticipatory preventive guidance for families and physicians, we recommend the following:

1. Full disclosure of use of all over-the-counter medications, including any and all APAP-containing products, by caretakers for their children at the time of the office visit. This disclosure would be facilitated by clear and prominent labeling of all over-the-counter products that they contain APAP, which should not be coadministered with other APAP-containing products.
2. The need for better communication between physicians and families about the risks and benefits of extended and prolonged use of APAP-containing products in children.
3. The need for educational initiatives aimed at preventing APAP dosing misadventures in infants, children, and adolescents.

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