The Clinical Value of Routine Acetaminophen Level Screening in Pediatric Patients Presenting to the Emergency Department

Anna Shklovsky-Kordi MD[1]*, Renana Gelernter MD[1,2]*, Matitiahu Berkovitch MD[1,2], Zahi Dagan MD[1] and Eran Kozer MD[1,2]

[1]Department of Pediatrics, Shamir Medical Center (Assaf Harofeh), Zerifin, Israel
[2]Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

ABSTRACT **Background:** Acetaminophen is the most common drug involved in pediatric poisonings, both intentionally and accidentally, and is the leading cause of acute liver failure among all age groups.

Objectives: To define the characteristics of patients admitted to a pediatric emergency department (ED) where serum acetaminophen concentrations were measured, and to determine which variables are associated with significant risk of acetaminophen toxicity.

Methods: Acetaminophen serum concentrations were taken from a retrospective case series of patients younger than 18 years who had been admitted to the ED at Shamir Medical Center between 1 January 2008 and 31 December 2015.

Results: During the study period 180,174 children were admitted to the ED. Acetaminophen serum concentrations were measured in 209 (0.12%) patients. Mean age was 12.4 ± 5.9 years. Elevated liver enzymes were found in 12 patients, 5 of whom had documented acute liver injury. All five were older than 11 years of age. Two cases of acute liver injury were attributable to acetaminophen ingestion. In both cases the cause was intentional overdose. Univariate analysis showed a significant ($P < 0.05$) correlation between detectable acetaminophen blood level and a positive history of drug or acetaminophen ingestion, and suicide attempt. A positive history of acetaminophen ingestion was associated with a 28-fold higher risk for detectable acetaminophen blood level.

Conclusions: In the absence of a positive history of acetaminophen ingestion and in young children with accidental intoxication, the risk of hepatotoxicity is relatively low.

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KEY WORDS: acetaminophen, emergency department (ED), intentional overdose, poisoning

Acetaminophen is the most common medication used in the pediatric population in the United States [1]. Although considered a safe medication in recommended doses [1-3], overdose can cause liver damage and even death. [2,4-7]. Acetaminophen is the drug most frequently involved in pediatric poisonings [2,3,5-9] and is one of the most frequently used drugs in intentional overdoses.

Acetaminophen poisoning has no specific clinical features in the early phase. As a consequence, diagnosis is usually based on a history of ingestion and measurement of plasma acetaminophen concentrations related to the estimated time of ingestion. In patients presenting with acute overdose of acetaminophen, treatment with N-acetylcysteine can prevent severe liver damage [10]. The decision to treat with N-acetylcysteine is usually based on plotting measured acetaminophen plasma levels against the Rumack–Matthew nomogram [11]. Due to the potential for severe toxicity after acetaminophen overdose, the high prevalence of acetaminophen poisoning, and the availability of an effective antidote, many clinicians routinely take blood samples for estimation of plasma acetaminophen concentrations in all patients presenting after an acute drug overdose, regardless of the history of acetaminophen ingestion [12-14].

The aim of this study was to define the characteristics of patients for whom acetaminophen blood concentrations were measured and to determine which variables are associated with a significant risk of acetaminophen toxicity.

PATIENTS AND METHODS

STUDY DESIGN

This retrospective case series was conducted at Shamir Medical Center, a university-affiliated hospital in central Israel. The center serves a population from urban and suburban areas of diverse ethnic groups, mainly Jews and Arabs. The hospital ethics board approved the study protocol.

*The first and second authors contributed equally to this study

PATIENTS AND MEASUREMENTS

The cohort comprised a convenient sample of all patients younger than 18 years ofage who had been admitted to the pediatric emergency department (ED) between 1 January 2008 and 31 December 2015 and whose acetaminophen serum concentration was measured. Serum acetaminophen concentration was assayed by the enzymatic reaction CONTAB INTEGRA 400 plus system (Roche Instrument Center, Rotkreuz, Switzerland)

The medical records were reviewed and the following data were recorded: age, gender, reason for request of acetaminophen concentration measurements (intentional overdose, accidental ingestion, impaired liver function), ingested drugs, time elapsed from ingestion to acquisition of blood sample, type of regimen (acute or chronic), blood acetaminophen concentration, blood liver enzymes, and presence of acute liver injury. Data regarding level of consciousness, therapy given, and outcome were also recorded.

The presence of toxic acetaminophen plasma concentration was plotted against the Rumack–Matthew nomogram in all patients for whom the time of ingestion was known. Acetaminophen concentrations were measured in children presenting with suspected acetaminophen overdose or ingestion of unknown drugs or in cases of liver injury of unknown etiology. Urine and blood were tested for toxins based on history and clinical presentation. The outcome measures were acute liver injury and exposure to acetaminophen. A toxic dose of acetaminophen was defined as a single ingestion of more than 150 mg/kg in a single dose for acute poisoning or in repeated doses in a 24-hour period for chronic poisoning. A detectable level was defined as above the lower level of detection (≥ 2 μg/ml).

Elevated liver enzymes were defined as aspartate transaminase (AST) or alanine transaminase (ALT) levels at least twice the levels of the upper normal value, and acute liver injury was defined as AST or ALT higher than 1000 units/L. Other etiologies of liver damage were excluded before attributing it to acetaminophen overdose.

STATISTICAL ANALYSIS

Descriptive statistics were used to describe the study population. Patients who tested positive for acetaminophen in the blood and patients with liver injury were compared with all other patients using the Fisher exact test or the Chi-square test (as appropriate) for categorical variables and Student's *t*-test or Mann-Whitney test (as appropriate) for continuous variables. A stepwise logistic regression model was used to determine the effect of different variables (including a positive history of acetaminophen ingestion and age) on the risk for detectable acetaminophen levels and acute liver injury. Demographic and clinical variables were included in the model based on data from previous studies. A P value < 0.05 was considered statistically significant. Statistical analyses were performed using IBM Statistical Package for the Social Sciences statistics software, version 25 (SPSS, IBM Corp, Armonk, NY, USA).

RESULTS

During the study period 180,174 children were admitted to the ED. Of them 209 patients (0.12%) fulfilled the inclusion criteria. The mean age of patients was 12.4 ± 5.9 years. Overall patient characteristics and results are described in Table 1.

A history of drug or substance ingestion was noted in 159 patients. Of them, 98 had a positive history of acetaminophen ingestion (64 cases of acetaminophen as a single drug and 34 cases of co-ingestion of acetaminophen with other drugs). Acetaminophen serum concentrations were obtained at 5.2 ± 3.0 hours after ingestion. In only 37 cases there was a recorded ingestion dose with a median of 5.5 grams (interquartile range [IQR] 2.25–10 grams, mean 9.7 ± 16.1 grams). Acetaminophen concentrations ≥ 2 μg/ml were detected in 69 of the 98 (70%) patients with a positive history of acetaminophen ingestion, with a median of 23 μg/ml (IQR 2–378 μg/ml).

Among the 111 patients who denied acetaminophen exposure there were 8 patients (7.2%) with detectable acetaminophen levels (4–22 μg/ml), all of whom were above 11 years of age. There was an intentional drug overdose in six patients without elevation of liver enzymes. In the other two cases there was no intentional ingestion. Both patients were evaluated for elevated liver enzymes, and in both cases the disturbance in liver enzymes was not attributable to acetaminophen toxicity. One 11-year-old patient had acute liver failure that was attributed to antihistamine toxicity (by history and pathologic results). The other patient, a 15-year-old female, had clinical course and laboratory results that suggested a viral disease. The adverse drug reaction (ADR) probability score (Naranjo), designed for determining if a clinical syndrome is due to an ADR, was 0 (doubtful); that is, the reaction was unlikely due to acetaminophen. Liver enzymes were obtained for 163 patients (77%). Twelve patients (5.7%) had elevated liver enzymes. For eight patients, acetaminophen concentration was measured because of liver involvement, and the workup diagnosis was not acetaminophen exposure. Four patients had a positive history of acetaminophen exposure, two with intentional overdose and liver injury, and two with acute non-toxic accidental overdose with no liver injury.

Of the 12 patients with elevated liver enzymes, 5 had documented acute liver injury. Two cases of acute liver injury were attributable to acetaminophen ingestion, the cause of which was intentional overdose [Table 2]. Of the other three patients, two underwent extensive investigation with no etiology and had a suspected viral infection. The Naranjo score in both cases was zero or lower. Both recovered uneventfully. The third case was of girl with antihistamine toxicity as mentioned earlier. No patient younger than 11 years had liver injury.

Eleven patients were treated with N-acetylcysteine. Three of these patients had acetaminophen concentrations above the treatment line on the Rumack–Matthew nomogram. In the re-

Table 1. Patient characteristics and results

Variables	Features	n	%
Median age (range), years	15 (0–18)	209	100
Gender	Male	56	26.8
	Female	153	73.2
History of drugs ingestion	Acetaminophen only	64	30.6
	Acetaminophen and other drugs/substances	34	16.2
	Other drugs or substances without acetaminophen	61	29.1
	No history of drug or substance ingestion	50	23.9
Alcohol ingestion		17	8.1
Reason for requested acetaminophen level measurements	Intentional overdose	79	37.7
	Accidental	79	37.7
	Liver enzyme disorder	8	3.8
	Altered consciousness	7	3.3
	Unknown	36	17.2
Type of regimen	Acute	204	97.6
	Chronic	5	2.3
Acetaminophen dose, grams	Median 5.5 (interquartile range 2.25–10)	37	
Acetaminophen concentrations > 2 µg/ml		77	36.8
Liver enzymes obtained		163	77
Elevated liver enzymes		12	5.7
N-acetylcysteine treatment		11	5.3
Acute liver injury		5	2.4

maining eight patients, the antidote was used due to a reported ingested dose of above 300 mg/kg.

The primary reasons for requesting acetaminophen levels were intentional overdose and accidental ingestion (79 patients each, 37.7%), followed by elevated liver enzymes (8 patients, 3.8%) and altered level of consciousness (7 patients, 3.3%). The reason was unknown in 36 patients (17.2%), and none of them had detectable acetaminophen blood levels. Among the 79 patients with intentional overdose, 46 patients (58.2%) had a history of acetaminophen ingestion, two of these had elevated liver enzymes and subsequent acute liver injury.

VARIABLES ASSOCIATED WITH SIGNIFICANT RISK OF ACETAMINOPHEN TOXICITY

Univariate analysis showed a significant association between detectable acetaminophen blood level and a positive history of drug/substance ingestion ($P < 0.01$, odds ratio [OR] 43.42, 95% confidence interval [95%CI] 5.81–322.32), a positive history of acetaminophen ingestion ($P < 0.01$, OR 30.63, 95%CI 13.22–70.95), and suicide attempt ($P = 0.021$, OR 2.08, 95%CI 1.15–3.77). There was no significant association between acute liver injury and a positive history of drug or acetaminophen ingestion.

The regression model for the risk of detectable acetaminophen levels correctly classified 82% of the cases with R^2 of 55%. The model showed significant correlation between detectable acetaminophen blood levels and a positive history of acetaminophen ingestion (OR 28.8, 95%CI 10.6-78.3) and age; for each year the risk for detectable acetaminophen blood levels was increased by 7% (95%CI 1%–14%). There was no significant association between any of the variables and liver injury in the model for liver injury.

Table 2. Characteristics of patients with acute liver injury

Cases	1	2	3	4	5
Age, years	11	15	11	14	17
Gender	Male	Male	Female	Female	Female
History of acetaminophen ingestion	No	No	No	Yes	Yes
Reason for requested acetaminophen level	Elevated liver enzymes	Elevated liver enzymes	Elevated liver enzymes	Intentional overdose	Intentional overdose
Regimen	Acute	Acute	Acute	Acute	Acute
Dose, grams	Unknown	Unknown	Unknown	12	15
Acetaminophen level, µg/ml	0	0	4	0	97
AST, units/L	1440	194	1187	2382	977
ALT, units/L	2210	1928	1532	2610	3340

ALT = alanine transaminase, AST = aspartate transaminase

DISCUSSION

In our study, only two patients (< 1%) whose acetaminophen serum concentration was measured, had acute liver injury attributable to acetaminophen ingestion, secondary to intentional overdose. These patients were 14 and 17 years old. In both cases, the reported ingested dose was high, 12 grams and 15 grams, respectively. Among the 111 patients who denied acetaminophen use 8 (7.2%) were found with detectable but non-toxic acetaminophen level. Five of them with multidrug ingestion and one with insufficient history, both factors were used in a previous study as additional criteria for identifying unreliable deniers of acetaminophen ingestion [15]. A positive history of acetaminophen ingestion was associated with a 28-fold higher risk for detectable acetaminophen blood level. As for age, the risk for detectable acetaminophen blood level was increased by 7% each year.

Not all patients underwent a toxic screen. The role of drug screening in the ED is controversial. Studies in pediatric EDs [16,17] have shown that toxicological screening results rarely necessitate a change in medical management. In Shamir Medical Center the urine toxicology screen is an immune-based test with low sensitivity and specificity. Universal screening would not have had a major effect on our results. Univariate and multivariate analysis failed to demonstrate significant association between acute liver injury and potential risk factors such as older age or a positive history of drug or acetaminophen ingestion. This result can be attributed to the small number of cases of acute liver injury in the study.

Our results concur with previous studies reported in the literature, showing that there is a very low rate of liver damage due to acetaminophen ingestion in young children and in patients who deny acetaminophen ingestion. We think that acetaminophen serum concentration in children younger than 11 years should be obtained only in special circumstances, such as suspected multiple supra-therapeutic doses, deliberate administration of overdose by a caregiver, and patients with elevated liver enzymes with no other diagnosis. In older patients with intentional overdose, acetaminophen serum concentration should be obtained in every case of a positive history of acetaminophen exposure, insufficient history, and in cases of multidrug ingestion. Validation of these findings could be useful for developing clinical rules in cases where acetaminophen measurements of pediatric patients are not indicated (e.g., less than 6 years of age, no history of accidental or intentional ingestion, and no suspicion for abuse).

Hewett et al. [13] preferred the routine screening for acetaminophen poisoning. However, there have been only a few systematic studies performed to evaluate this common practice worldwide and only a few of them focus on the pediatric population. In fact, these studies showed that elevated acetaminophen blood levels are uncommon among suicidal patients reporting not to have ingested acetaminophen [7,8,12,14,18-20], and the rate of consequent hepatotoxicity is even lower. In a prospective open study [15] none of the suicidal patients who denied both acetaminophen and multidrug ingestions had a detectable acetaminophen level. Waring et al. [21] demonstrated a positive correlation between the stated doses ingested and estimated 4-hour acetaminophen concentration.

These few studies focusing on the pediatric population demonstrate that, although ingestion of acetaminophen containing products may be frequent, the majority of cases will be toxicologically insignificant [22-25]. Rumack [22] showed that of 417 pediatric patients younger than 5 years of age with a positive history of acetaminophen ingestion, 55 had toxic plasma levels, of which only

3 (< 1%) had acute liver injury. Kumar et al. [24] reported 140 cases of acetaminophen ingestion, 130 accidental and 10 intentional. They found that serious poisoning due to acetaminophen overdose is uncommon. Caravati and colleagues [25] studied a prospective cohort of children aged 1–72 months with single ingestions of acetaminophen-containing products. They demonstrated that of 1015 patients, the overall incidence for potential hepatotoxicity was 0.59% (6/1015, 95%CI 0.12%–1.16%). All had ingested more than 200 mg/kg or an unknown amount.

LIMITATIONS

This study has some limitations. It is a retrospective study and thus some data may have been missed. Also, the study was based on the presence of acetaminophen blood concentration tests. In this method, cases with acetaminophen poisoning, for which an acetaminophen blood level was not taken, could have been missed, resulting in biased results. However, this underestimation of acetaminophen poisoning is believed to be low due to the screening protocol mentioned earlier. The association between variables measured and significant risk of acetaminophen toxicity should be interpreted with caution, due to the retrospective nature of the study and the fact that many children with non-severe acetaminophen poisoning may not have been diagnosed during the study period. We did not include children with toxicity that might have presented late and so by-passed the ED. We did not investigate how this would affect the results. There were 36 patients with an unknown reason for measuring acetaminophen serum levels. However, none of them had detectable acetaminophen blood level. We assume that this unique group did not affect the results. Last, in this single center study, we did not perform a power analysis. Therefore, a multicenter study with a larger cohort of patients could provide more robust results.

CONCLUSIONS

In the absence of a positive history of acetaminophen ingestion and in young children with accidental intoxication, the risk of hepatotoxicity is relatively low. Further studies in large cohorts are required to define the prevalence of hepatotoxicity in children exposed to acetaminophen and to draw recommendations for management, based on risk for significant acetaminophen toxicity.

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Correspondence

Dr. R. Gelernter
Dept. of Pediatrics, Shamir Medical Center (Assaf Harofeh), Zerifin 70300, Israel
Phone: (972-8) 977-9916
Fax: (972-8) 977-9914
email: grenana@gmail.com

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