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ORIGINAL REPORT

Reliability of the reported ingested dose of acetaminophen for predicting the risk of toxicity in acetaminophen overdose patients

Sa'ed H. Zyoud[1,2]*, Rahmat Awang[1] and Syed Azhar Syed Sulaiman[3]

[1] *WHO Collaborating Centre for Drug Information, National Poison Centre, Universiti Sains Malaysia, Penang, Malaysia*
[2] *Poison Control and Drug Information Center and College of Pharmacy, An-Najah National University, Nablus, Palestine*
[3] *Clinical Pharmacy Program, School of Pharmaceutical Sciences, Universiti Sains Malaysia, Penang, Malaysia*

ABSTRACT

Purpose The present study examines the relationship between the dose of acetaminophen reported to have been ingested by patients and the occurrence of serum acetaminophen levels above the 'possible toxicity' line in patients presenting at the hospital after acetaminophen overdose. The prognostic value of patient-reported dosage cut-offs of 8, 10 and 12 g was determined.

Methods This retrospective cohort study included patients admitted to the emergency department or hospital within 24 hours of acetaminophen ingestion. Serum acetaminophen concentrations were considered to be the gold standard, and specificity, sensitivity and positive/negative predictive values were calculated from the reported ingested dose, to predict toxicity using the Rumack–Matthew nomogram (i.e. the 'possible toxicity' treatment line) and standard equations.

Results Of 305 patients identified, 291 met the study inclusion criteria, and 121 (41.6%) had serum acetaminophen concentrations above the 'possible toxicity' treatment line. The range of patient-reported acetaminophen ingested was 1–75 g, with 185 patients (63.6%) reporting ≥8 g. One hundred eighteen patients (97.5%) who reported ingesting ≥8 g had serum acetaminophen concentrations above the '150-line', compared with only three patients (2.5%) who reported ingesting <8 g ($p < 0.001$). The positive predictive value of a patient-reported dose ≥8 g for predicting serum acetaminophen concentrations above the 'possible toxicity' treatment line was 63.78%, with a negative predictive value of 97.17%. The sensitivity of patient-reported doses ≥8 g was high (97.52%) but with low specificity (60.59%). The sensitivity of patient-reported doses ≥10 g also was high (89.26%) with low specificity (65.29%), whereas the sensitivity of ≥12 g dose was low (61.16%) with high specificity (86.47%).

Conclusions Patient-reported doses of acetaminophen are good risk indicators for acetaminophen overdose patients in Malaysia. Patient-reported ingestion of ≥8 g (as a cut-off dose) had a higher sensitivity than ≥10 g or ≥12 g. The results of this study have important implications for toxicity risk evaluations in areas with poor serum acetaminophen assay availability. Copyright © 2011 John Wiley & Sons, Ltd.

KEY WORDS — acetaminophen; patient-reported dosage; possible toxicity treatment line; sensitivity; specificity

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INTRODUCTION

Acetaminophen (paracetamol) is a very common cause of poisoning, which is widely used in deliberate self-poisoning[1,2] and is a leading cause of hospital admissions, delayed hepatotoxicity (including fulminant hepatic failure), renal failure and death following overdose in most countries.[3–5]

Since the early 1970s, *N*-acetylcysteine (NAC) has been used as an antidote for acetaminophen overdose.[6]

The risk of toxicity and need for antidote is normally determined by evaluating the extent of acetaminophen exposure, taking the following into consideration: patient-reported quantities of acetaminophen ingested, the elapsed time between ingestion and presentation at the hospital, patient susceptibility to hepatotoxicity, and evaluation of serum acetaminophen concentrations on the Rumack–Matthew nomogram.[6–8] Accordingly, NAC is normally administered if the patient is suspected to have ingested >12 g acetaminophen in the previous 24 hours.[8]

A drug nomogram developed in 1975, called the Rumack–Matthew nomogram, estimates toxicity risk

*Correspondence to: S. H. Zyoud, Clinical Toxicology Program, National Poison Centre, Universiti Sains Malaysia, 11800 Penang, Malaysia. E-mail: saedzyoud@yahoo.com, saedzyoud@najah.edu

based on the serum acetaminophen concentration at a given number of hours after ingestion. Serum acetaminophen levels at or above a line connecting 200 μg/mL at four hours postingestion and 30 μg/mL at 15 hours postingestion were found to consistently predict hepatotoxicity.[6] When the nomogram was introduced in the USA, the FDA required an alteration of the original nomogram as part of the NAC protocol, resulting in a 25% reduction of the NAC treatment threshold. A line connecting 150 μg/mL at four hours and 4.7 μg/mL at 24 hours was defined as the 'possible toxicity' line, to allow for possible errors in plasma assays and ingestion times.[9] After an acute ingestion, serum acetaminophen levels should be measured four hours postingestion or at any time up to 24 hours postingestion and plotted on the nomogram. Patients with acetaminophen levels above the 'possible toxicity' line should be treated with NAC.[10,11] Acetaminophen concentrations measured within the first four hours of ingestion may underestimate the amount of drug in the system because acetaminophen may still be in the process of being absorbed from the gastrointestinal tract. Therefore, serum concentration measurements within the first four hours postingestion are not recommended.[12]

There is little consensus concerning the usefulness of patient-reported quantities of acetaminophen ingested versus measured serum acetaminophen concentrations as prognostic indicators in acute acetaminophen overdose patients. In addition, it is unclear which patient-reported dosage cut-off (e.g. 8, 10 or 12 g) would be preferable. Furthermore, a common perception is that patient-reported dosage quantities are unreliable in the context of acute acetaminophen overdose; thus, the validity of this approach has received relatively little attention. A literature search using PubMed (http://www.ncbi.nlm.nih.gov/pubmed/) for keywords 'acetaminophen' or 'paracetamol' and 'overdose' or 'toxicity', 'poisoning' or 'ingestion' and 'dose', retrieved only a few studies in the English language, which have examined the validity of patient-reported dosages.[8,13–16]

To improve our knowledge about outcomes after acetaminophen overdose, we hypothesised that the occurrence of serum acetaminophen levels above the 'possible toxicity' line after acetaminophen overdose during hospitalisation could be predicted by patient-reported dosage on admission. To present this hypothesis, we carried out this five-year hospital-based study to examine the relationship between the dose of acetaminophen reported to have been ingested by patients (patient-reported dosage) and the occurrence of serum acetaminophen levels above the 'possible toxicity' line in patients presenting at the hospital after acetaminophen overdose. In addition, the patient-reported dosage cut-off (e.g. 8, 10 or 12 g) found to be a good prognostic indicator for poor outcome was determined. The ability to identify poor prognostic indicators during the initial hospital evaluation is crucial for both improving clinical care and determining targets of intervention for prevention, early detection, diagnosis and treatment. During the present study, we also explored the relationships between serum acetaminophen concentrations and other known factors associated with patient outcome.

METHODS

Study setting and design

This study is an observational, retrospective case-review of all patients admitted to a 1200-bed hospital located in the northern region of Malaysia for acute acetaminophen poisoning. The hospital provides healthcare and emergency treatment for all illnesses and accidents. All aspects of this study protocol, including access to and use of patients' clinical information, were authorised by the local health authorities before initiation of the study.

Study participants and data collection

The present work is a secondary analysis of data on acetaminophen overdoses reported previously using different approaches in different studies.[2,17,18] Data were collected from 1 January 2004 to 31 December 2008. A computer-generated list was obtained from the Hospital Records Office. The cases were identified according to T-codes of the International Classification of Diseases–10th Revision. All patients with diagnostic codes T 39.1 (acetaminophen poisoning) were included in the study. The records of all patients with a discharge diagnosis of acetaminophen overdose were analysed. Patients who were not admitted to the hospital after being assessed in the accident and emergency department were excluded from this study. We included patients who had a history of acetaminophen ingestion reported by either the patients or their families. We went on to confirm that patients included in this study had substantial acetaminophen ingestion by examination of patient histories or by estimated serum acetaminophen levels. The charts of all patients identified through the above search were reviewed, and data were collected. All patient data were ascertained by careful review of all pre-hospital, emergency department and in-patient records. Charts were excluded from analysis for the following reasons:

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(i) serum acetaminophen concentration was not measured; (ii) the time of ingestion was not known; (iii) the time interval between ingestion and serum acetaminophen concentration determination was more than 24 hours; or (iv) the patient presented to the hospital more than 24 hours after the overdose. After acute acetaminophen ingestion, serum acetaminophen levels should be measured between 4 and 24 hours postingestion and plotted on the nomogram. Acetaminophen concentrations measured within the first four hours postingestion may underestimate the amount of acetaminophen in the system because acetaminophen may still be in the process of being absorbed by the gastrointestinal tract. Therefore, a serum concentration taken within four hours of ingestion is not recommended.[12]

Specially designed data-collection forms were used to collect data concerning the following: age; gender; ethnicity; circumstances surrounding the ingestion (e.g. suicide attempt); latency time (calculated as the elapsed time between acetaminophen ingestion and the time the patient presented at the hospital); quantity of acetaminophen ingested; laboratory tests, including prothrombin time; alanine aminotransferase (ALT); and serum acetaminophen concentration during the first day of admission and after four hours of ingestion (minimum). Data on serum acetaminophen concentration measurements were obtained from the hospital's therapeutic drug monitoring laboratory service.

Patients were categorised into two groups, based on whether they were above or below the 'possible toxicity' line (150 μg/mL at 4 hours and 4.7 μg/mL at 24 hours).[9] The 'possible toxicity' line is 25% below the standard nomogram toxicity line (Rumack–Matthew nomogram), to allow for possible errors in plasma assays and ingestion times.[6,9]

Statistical analysis

Collected data were analysed using the Statistical Package for Social Sciences (SPSS) program version 15. Continuous variables that were normally distributed were expressed as means with 95%CI to describe the spread of the data and proportions for categorical variables. Variables were tested for normality using the Kolmogorov–Smirnov test. Data that were not normally distributed were expressed as median (lower-upper quartiles). Student's *t*-test was used to compare the means of continuous variables. If assumptions of equality of variance and normality (assumed for the *t*-test) were not met, the Mann–Whitney *U* test (a non-parametric equivalent of the *t*-test) was performed as appropriate. A chi-squared test was used to test for statistical significance between categorical variables. Multiple logistic regression analysis was used to identify factors associated with serum concentrations above the '150-line' (i.e. the 'possible toxicity' treatment line). Variables with significant p values (<0.05) in the univariate analysis were included in the regression analysis. The correlation between patient-reported ingested acetaminophen dose and serum acetaminophen concentration was tested using Pearson's correlation coefficient.

Serum acetaminophen concentrations were considered to be the gold standard, and specificity, sensitivity and positive/negative predictive values were calculated for the reported ingested dose to predict toxicity using the Rumack–Matthew nomogram (the 'possible toxicity' treatment line) and standard equations (Accessed December 25, 2010, at http://www.hpa-midas.org.uk/sensitivity_calculator.asp). The best predictors of increased toxicity risk were obtained from cut-off values of 8, 10 and 12 g of acetaminophen ingested.

RESULTS

A total of 305 patients with a diagnosis of acetaminophen poisoning were admitted to the hospital during the study period; of these, 14 (4.6%) were excluded because they did not meet study criteria. Of these 14 patients, serum acetaminophen concentrations were measured >24 hours postingestion for 11 patients, and acetaminophen concentrations were not measured for three patients. Thus, the final study population consisted of 291 patients.

Demographic and clinical characteristics of these 291 patients, including patient status at the time of admission and during hospitalisation, are shown in Table 1. Serum acetaminophen concentrations were below the 'possible toxicity' treatment line for 170 (58.4%) cases and above the 'possible toxicity' treatment line for 121 (41.6%) cases. Patients with serum acetaminophen concentrations above the 'possible toxicity' treatment line in comparing to patients with serum acetaminophen concentrations below the 'possible toxicity' treatment line were more likely to be male subjects (20.7% versus 12.4%; $p=0.052$), Chinese (33.9% versus 15.3%; $p=0.002$), have intentional drug ingestion (93.4% versus 76.5%; $p<0.001$), have high estimated acetaminophen level (median [lower quartile–upper quartile (Q1–Q3)]=143 [73.2–185.0] versus 26.5 [4.9–59.5]; $p<0.001$), have high reported dose ingested (median [Q1–Q3]=15 [10–20] versus 6.5 [5–10]; $p<0.001$) and have long latency time (median [Q1–Q3]=6 [3.5–10] versus 4 [2.5–7]; $p<0.001$), respectively. Multiple logistic

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Table 1. Demographic and clinical characteristics of the 291 acetaminophen overdose patients included in this study upon admission and during hospitalisation

Variable	Above the 'possible toxicity' treatment line, $n=121$	Below the 'possible toxicity' treatment line, $n=170$	p-value
Gender, n (%)*			
Male	25 (20.7)	21 (12.4)	0.052
Female	96 (79.3)	149 (87.6)	
Ethnic group, n (%)*			
Malay	51 (42.1)	95 (55.9)	0.002
Chinese	41 (33.9)	26 (15.3)	
Indian	25 (20.7)	46 (27.1)	
Other	4 (3.3)	3 (1.8)	
Cause of intent, n (%)*			
Intentional (suicide)	113 (93.4)	130 (76.5)	<0.001
Unintentional (accidental)	8 (6.6)	40 (23.5)	
Estimated acetaminophen level (mg/L); median (Q1–Q3)†	143 (73.2–185)	26.5 (4.9–59.5)	<0.001
Age (years); mean (95%CI)‡	23.6 (22.2–24.9)	22.6 (21.5–23.7)	0.27
Reported dose ingested (g); median (Q1–Q3)†	15 (10–20)	6.5 (5–10)	<0.001
Latency time (hours); median (Q1–Q3)†	6 (3.5–10)	4 (2.5–7)	<0.001
Hospital stay (hours); median (Q1–Q3)†	59.5 (43–82)	22 (17–35)	<0.001
prothrombin time (second); mean (95%CI)‡	14.3 (13.7–14.9)	12.9 (12.7–13.1)	<0.001
ALT (IU/L); median (Q1–Q3)†	13.5 (10–30)	10 (7–14.8)	<0.001

*The statistical significance of differences was estimated with the chi-squared test.
†The statistical significance of differences was estimated with the Mann–Whitney U test.
‡The statistical significance of differences was estimated with Student's t-test.

regression analysis demonstrated that significant risk factors associated with serum acetaminophen concentrations above the '150-line' were present in patients who reported higher acetaminophen dose ingestion (p 0.001) and longer latency times ($p=0.001$). The model was significant, with a chi-squared value of 140.4, d.f. =5; $p<0.001$ (data not shown). Also, patients with serum acetaminophen concentrations above the 'possible toxicity' treatment line were significantly associated with long hospital stay (median [Q1–Q3]=59.5 [43–82]; $p<0.001$), long prothrombin time (mean=14.3, 95%CI: 13.7–14.9; $p<0.001$) and high ALT levels (median [Q1–Q3]=13.5 [10–30]; $p<0.001$).

In addition, the median length of stay in the hospital was longer for patients with serum acetaminophen concentrations above the 'possible toxicity' treatment line ($p<0.001$) (Table 1). There was a significant positive correlation ($r=0.57$; $p<0.001$) between patient-reported ingested dose and serum acetaminophen concentration.

Patient-reported acetaminophen ingestion ranged from 1 to 75 g, with 185 patients (63.6%) reporting ingestion of ≥8 g. One hundred eighteen (97.5%) of the patients who reported ingestion of ≥8 g had serum acetaminophen concentrations above the '150-line', compared with only three patients (2.5%) who reported ingestion of <8 g ($p<0.001$). The positive predictive value of a patient-reported dose of ≥8 g for predicting serum acetaminophen concentrations above the 'possible toxicity' treatment line was 63.78%, with a negative predictive value of 97.17%. In addition, the sensitivity of a patient-reported dose of ≥8 g was high (97.52%), although with low specificity (60.59%) (Table 2).

One hundred sixty-seven patients (57.4%) reported acetaminophen ingestion doses ≥10 g. One hundred eight (89.3%) of the patients who reported ingestion of ≥10 g had serum acetaminophen concentrations above the '150-line', compared with only 13 patients (10.7%) who reported ingestion of <10 g ($p<0.001$). The positive predictive value for a patient-reported dose of ≥10 g for predicting serum acetaminophen concentrations above the 'possible toxicity' treatment line was 64.67%, with a negative predictive value of 89.52%. The sensitivity of a ≥10-g patient-reported dose was high (89.26%) but with low specificity (65.29%) (Table 2).

Ninety-seven patients (33.3%) reported ingestion of ≥12 g acetaminophen. Seventy-four (61.2%) of the patients who reported ingestion of ≥12 g acetaminophen had serum acetaminophen concentrations above the '150-line', compared with only 47 patients (38.8%) who reported ingestion of <12 g ($p<0.001$). The positive predictive value of a patient-reported dose of ≥12 g for predicting serum acetaminophen concentrations above the 'possible toxicity' treatment line was 76.29%, with a negative predictive value of 75.77%. The sensitivity of a ≥12-g patient-reported dose was

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Table 2. Validity parameters of patient-reported acetaminophen dosages cut-offs of 8, 10 and 12 g and the proportion of patients with serum acetaminophen levels above the 'possible toxicity' line

	Detectable acetaminophen level (expected result)		
	Positive	Negative	
History of acetaminophen ingestion cut-offs of ≥8 g (observed results)			
Positive	TP $n=118$	FP $n=67$	Predictive value of positive test‡ 0.6378 (95%CI: 0.5641–0.7071)
Negative	FN $n=3$	TN $n=103$	Predictive value of negative test** 0.9717 (95%CI: 0.9195–0.9941)
	Sensitivity* 0.9752 (95%CI: 0.9293–0.9949)	Specificity† 0.6059 (95%CI: 0.5282–0.6798)	
History of acetaminophen ingestion cut-offs of ≥10 g (observed results)			
Positive	TP $n=108$	FP $n=59$	Predictive value of positive test‡ 0.6467 (95%CI: 0.5691–0.7190)
Negative	FN $n=13$	TN $n=111$	Predictive value of negative test** 0.8952 (95%CI: 0.8274–0.9430)
	Sensitivity* 0.8926 (95%CI: 0.8233–0.9415)	Specificity† 0.6529 (95%CI: 0.5763–0.7242)	
History of acetaminophen ingestion cut-offs of ≥12 g (observed results)			
Positive	TP $n=74$	FP $n=23$	Predictive value of positive test‡ 0.7629 (95%CI: 0.6658–0.8434)
Negative	FN $n=47$	TN $n=147$	Predictive value of negative test** 0.7577 (95%CI: 0.6912–0.8162)
	Sensitivity* 0.6116 (95%CI 0.5187–0.6988)	Specificity† 0.8647 (95%CI: 0.8039–0.9123)	

FN, false negative; FP, false positive; TN, true negative; TP, true positive.
*Sensitivity=TP/(TP+FN).
†Specificity=TN/(TN+FP).
‡Positive predictive value (PPV)=TP/(TP+FP).
**Negative predictive value (NPV)=TN/(TN+FN).

low (61.16%) but with high specificity (86.47%) (Table 2).

DISCUSSION

Identification of rapid prognostic indicators for acetaminophen overdose is critical; therefore, several criteria are commonly used to predict outcomes in patients with severe acetaminophen overdoses.[8,17] In spite of their importance, relatively little prognostic value is attributed to preliminary evaluations performed upon initial admission to the hospital after severe poisoning.[8,14] In the current study, concerning patients who were presented to the hospital following an acute acetaminophen overdose, patient-reported ingested acetaminophen doses significantly and positively correlated ($r=0.57$; $p<0.001$) with serum acetaminophen concentrations above the 'possible toxicity' line. Importantly, patient-reported dosages correlated with both the extent of acetaminophen exposure and the probability of subsequent hepatotoxicity. This shows the potential validity of patient histories for rapidly estimating the quantity of acetaminophen ingested by poisoned patients presented to the hospital for treatment. A study in the USA showed that there is a positive correlation between patient-reported acetaminophen ingested doses and the risk of hepatotoxicity in staggered overdose cases.[15] Another study in the UK showed that there was a positive correlation between patient-reported ingested doses and estimated four-hour serum acetaminophen concentrations in both men ($r=0.654$) and women ($r=0.667$).[8]

The current study found that 118 patients (97.5%) who reported ingestion of ≥8 g of acetaminophen had serum acetaminophen concentrations above the '150-line', compared with only three patients (2.5%) who reported ingestion of <8 g ($p<0.001$). The sensitivity of a patient-reported dose of ≥8 g (97.52%) was higher than the sensitivity of ≥10-g (89.26%) or ≥12-g (61.16%) patient-reported dose. A study in the UK showed that there was a positive dose–exposure relationship determined by the proportion of patients with serum acetaminophen concentrations higher than the '200-line' for the following patient-reported acetaminophen ingestion subgroups: 0–4, 4.1–8, 8.1–12, 12.1–16, 16.1–24 and >24 g.[8]

Our results show a positive correlation between patient-reported ingested dose and 4- to 24-hour serum acetaminophen levels; patient-reported dosages <10 and ≥10 g were associated with serum

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concentrations above the '150-line' in 13 (4.5%) and 108 (37.1%) of cases, respectively ($p<0.001$). A retrospective study in Sydney, Australia, found that patient-reported doses >10 g were predictive of increased risk for hepatotoxicity.[19] A similar study in Israel showed that patient-reported dosages <10 and ≥10 g also were associated with similar serum acetaminophen concentrations and outcome. However, these authors concluded that information concerning ingested dosages given by patients admitted to the hospital for self-poisoning is inaccurate and often overstated and that management of acute acetaminophen overdose must be based on serum acetaminophen concentration measurements and not on patient-reported ingested doses.[13]

A study in the UK found a correlation between patient-reported ingested dosages and four-hour serum acetaminophen levels; patient-reported dosages <12 and ≥12 g correlated with serum concentrations above the '200-line' in 3% and 20% of cases, respectively.[20] Another study in the UK showed that a patient-reported ingested dose >12.5 g correlated with a 4.5-fold higher risk of hepatotoxicity.[21] Our results show a correlation between patient-reported ingested dose and 4- to 24-hour serum acetaminophen levels; patient-reported doses <12 and ≥12 g correlated with serum concentrations above the '150-line' in 47 (16.2%) and 74 (25.4%) of cases, respectively ($p<0.001$).

Multiple logistic regression analysis demonstrated that significant risk factors associated with serum acetaminophen concentrations above the '150-line' were present among patients who reported ingesting a high acetaminophen dose and a long latency time. Previously, we extensively reported and discussed the prevalence, clinical characteristics and predictors of gastrointestinal manifestations, as well as the impact of these manifestations on outcomes for acetaminophen overdose patients.[18] We also extensively reported and discussed the impact of vomiting on patient outcomes following acetaminophen poisoning.[17] In these previous studies, we found that gastrointestinal manifestations or vomiting are associated with patients who reported ingesting an acetaminophen dose ≥10 g. These previous studies suggest that, during initial evaluation, increased vomiting or gastrointestinal manifestations following acetaminophen ingestion appear to be important risk markers for the following: increased prevalence of serum acetaminophen levels above the 'possible toxicity' treatment line, prolonged prothrombin times, elevated serum creatinine levels, reduced serum potassium levels, and elevated serum bilirubin levels.[17,18]

To the best of our knowledge, this is the first study, which examined the correlation between patient-reported dosages in patient histories and serum acetaminophen levels above the 'possible toxicity' line and evaluated the prognostic value of patient-reported dose cut-offs (8, 10 or 12 g) for predicting outcomes in patients presenting to the hospital following acetaminophen overdose. Limitations of this study include its retrospective nature and the fact that sensitivity and specificity values associated with the screening of other outcomes were not presented. Further research is needed to present sensitivity and specificity values associated with patient-reported dosages in patient histories and specific outcomes in patients with acetaminophen poisoning.

CONCLUSIONS AND RECOMMENDATIONS

In conclusion, the results of this study support the hypothesis that patient-reported acetaminophen dosages are a good toxicity risk indicator for patients presenting with acetaminophen overdose in Malaysia. Patients reported ingestions ≥8 g (as a cut-off dose) had a higher sensitivity than ≥10 or ≥12 g. Our results have important implications for the evaluation of toxicity risk in areas with poor availability of serum acetaminophen assays. Furthermore, the present data are directly applicable to the clinical treatment of poisoned patients for whom conventional methods are inappropriate, for example, patients who were presented to the hospital late, because the risk nomogram is only valid for serum measurements taken between four and 24 hours postingestion.[9] However, careful interpretation is essential on the individual patient level because of reporting variability, possibly because of altered mental status or the effects of coingested sedative medications or ethanol. To improve patient outcomes after acetaminophen overdose, it is suggested that the usual protocol of waiting to obtain the serum acetaminophen level from the hospital's therapeutic drug monitoring laboratory service may not be required. NAC administration should be commenced immediately if the patient-reported dose exceeds the threshold for possible toxicity. If the serum acetaminophen level is subsequently found to be below the nomogram line, NAC therapy may be ceased, whereas if it is above the line, it should be continued.

CONFLICT OF INTEREST

The authors have declared that there is no conflict of interest.

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KEY POINTS

- Identifying indicators of poor prognosis at the time of initial hospital evaluation is critical for both improving clinical care and determining targets of intervention for prevention, early detection, diagnosis and treatment.
- Patient-reported acetaminophen dosages are a good toxicity risk indicator for patients presenting with acetaminophen overdose.
- Patients reported ingestions $\geq$8 g (as a cut-off dose) had a higher sensitivity than $\geq$10 or $\geq$12 g.

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