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Assessing the Impact of Vomiting Episodes on Outcome after Acetaminophen Poisoning

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Abstract: Identifying indices of poor prognosis at first presentation after acetaminophen poisoning is the key to both improving clinical care and determining targets for intervention. This study intended to document the prevalence, clinical characteristics and predictors of vomiting and to investigate the relationship between episodes of vomiting at first hospital presentation and outcome in acetaminophen poisoning. This retrospective cohort study included patients who attended the emergency department and were admitted within 24 hr of acetaminophen ingestion. The study was conducted over a period of 5 years from 1 January 2004 to 31 December 2008. Parametric and non-parametric tests were used to test differences between groups depending on the normality of the data. SPSS 15 was used for data analysis. Data from 291 patients were included. Vomiting was present in 65.3% of patients with acetaminophen poisoning at the time of first presentation. Multiple logistic regression showed that significant risk factors for vomiting were present among patients who reported an ingested dose of acetaminophen ≥10 g ($p < 0.001$) and a latency time of more than 8 hr ($p = 0.030$). Overall, an increasing trend in prothrombin time ($p = 0.03$), serum bilirubin ($p < 0.001$), serum creatinine ($p = 0.005$), serum potassium ($p < 0.001$), length of hospital stay ($p < 0.001$) and the prevalence of patients who had a serum acetaminophen level above a 'possible toxicity' treatment line ($p = 0.001$) were associated with an increased number of episodes of vomiting. In conclusion, vomiting was common among patients with acetaminophen poisoning. This study suggests that an increase in episodes of vomiting at first presentation appears to be an important risk marker of subsequent nephrotoxicity and hepatotoxicity.

Vomiting is a common adverse effect following drug ingestion and other toxic exposure. Under normal circumstances, as toxicity resolves, these symptoms gradually improve. Vomiting associated with certain poisons can be detrimental to the treatment of the patient. Although vomiting is observed among patients with acetaminophen poisoning [1–3], there are no data concerning the prevalence of, and the relationship between, vomiting and outcome in patients presenting to hospital with acetaminophen poisoning [4]. Early markers of poor outcome are important both for acute physicians and liver units. In fact, in large doses, acetaminophen is capable of causing both hepatic necrosis and renal failure [5–10].

Several criteria are widely used to predict outcome in patients with more severe acetaminophen poisoning [11–20]. Despite this, comparatively little is known about the prognostic value of investigations performed at first admission to hospital after severe poisoning. We hypothesized that, since vomiting is an important component of the syndrome of severe acetaminophen poisoning, an increase in the number of episodes of vomiting from the time of acetaminophen ingestion to the time the patient was presented at the hospital might indicate more severe acetaminophen poisoning and a poorer prognosis.

To improve our knowledge about vomiting after acute acetaminophen poisoning, we carried out this 5-year, hospital-based study with the following objectives: (1) to document the prevalence of episodes of vomiting at the initial clinical presentation of acute acetaminophen poisoning during a defined study period; (2) to determine which clinical findings would be most predictive of vomiting in hospitalized patients after acetaminophen poisoning; and (3) to assess the impact of vomiting episodes on outcome. Knowledge of the prevalence, clinical characteristics and predictors of vomiting, and their relation to the final outcome in patients after acetaminophen poisoning, might contribute to reduced complication rates by improving clinical care and determining targets for intervention.

Methods

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

Participants and data collection. Data were collected from 1 January 2004 to 31 December 2008. A computer-generated list was obtained

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from the Hospital Records Office. We identified our cases according to the T-codes of the International Classification of Diseases – Tenth revision (ICD-10). All patients with diagnostic codes T 39.1 (acetaminophen poisoning) were included in the study.

The primary outcome of interest was the prevalence rate of vomiting, and the secondary outcome were the association of vomiting episodes with outcome after acetaminophen poisoning. A vomiting episode was defined as the number of events of vomiting that occurred in a rapid sequence after ingestion of acetaminophen from the time of ingestion to the time the patient was presented at the hospital. The diagnosis of vomiting was based on the attending physicians' assessment of patients at the Accident and Emergency (A&E) Department, as reported in the medical records. All the patients were quizzed about the presence of vomiting. Clinical diagnosis of the presence of vomiting had been based on the patients' history and examination findings. Vomiting was graded as grade 0 – no vomiting, grade I – one episode of vomiting, grade II – two episodes of vomiting, and grade III – three or more episodes of vomiting.

Specially designed data collection forms were used to collect data concerning: age; gender; ethnicity; cause of overdose, including intentional or unintentional; history of psychiatric illness; history of chronic illness; history of alcohol intake; history of attempted suicide; stated date and time of poisoning for calculating the latency time (the time of ingestion to the time the patient was presented at the hospital); quantity of acetaminophen ingested; whether other drugs had been co-ingested; vomiting episodes at presentation; laboratory tests, including prothrombin time; alanine aminotransferase (ALT); pH; serum bilirubin; serum creatinine; serum acetaminophen concentration; and serum potassium concentrations during the first day of admission and after 4 hr of ingestion as a minimum time.

By convention from current practice, it has been recommended to obtain a serum acetaminophen level between 4 and 24 hr after ingestion [21,22], and the late time to analysis (>24 hr) would have low or undetectable acetaminophen levels, and therefore laboratory tests were performed immediately within the time range of acetaminophen analysis. Data on serum acetaminophen concentration were obtained from the hospital's therapeutic drug monitoring laboratory service. In addition, data related to psychiatric diseases were obtained. Psychiatric illness was defined as an existing cause of deliberate self-harm, such as depression, anxiety, adjustment disorders and impulsive behaviour; these causes were noted by the hospital psychiatric specialist report. Data related to length of hospital stay were also calculated based on the time of discharge minus the time of admission. Patients were categorized into two groups based on whether they were above or below the 'possible toxicity' treatment line (150 mg/L at 4 hr and 5 mg/L at 24 hr) [23]. The 'possible toxicity' treatment line, which is 25% below the standard nomogram (Rumack–Matthew nomogram) has been proposed to allow for possible errors in plasma assays and ingestion times [21,23]. As mentioned in a previous study, the reported dose of >10 g was a predictive of increased risk of hepatotoxicity [23], and so the best cut-off value for amount of acetaminophen ingested in predicting vomiting was 10 g.

The charts of all patients identified through the search were reviewed and the data were collected. Charts were excluded from analysis for the following reasons: (1) if the patients were discharged to another hospital; (2) the time of ingestion was not known; or (3) the time interval between ingestion and determination of serum acetaminophen concentration was more than 24 hr.

Statistical analysis. Data were entered and analysed using the Statistical Package for Social Sciences (SPSS; SPSS Inc., Chicago, IL, USA) program version 15. Continuous data are presented as mean ± S.D., and categorical data are expressed as numbers with percentages. Continuous data are also expressed as a median (lower – upper quartiles). Variables were tested for normality using the Kolmogorov–Smirnov test. Statistical significance for intergroup differences was assessed by the Pearson Chi-square or the Fisher exact test, whichever was appropriate, for categorical variables, and the Student's t-test for continuous variables. Outcome measures were analysed using ANOVA or a non-parametric Kruskal–Wallis test. Multiple logistic regression analysis was used to identify risk factors associated with vomiting. Variables included in the regression were those with significant p values (<0.05) in the univariate analysis.

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. Serum acetaminophen concentration was measured after 24 hr post-ingestion in 11 patients, and three patients were discharged to another hospital. The study population consisted of 291 patients.

During the study period, the overall incidence of vomiting after acetaminophen ingestion was about 65.3% (190 patients; 32 males and 185 females). Twenty (6.9%) patients reported having only one episode of vomiting, 10.6% of patients reported having two episodes of vomiting, and 47.8% of patients reported having three episodes or more of vomiting.

The majority (73.4%) of cases of acetaminophen ingestion presented within 8 hr. The median (interquartile range) quantity of acetaminophen ingested was 10 g (6–15 g). Initial management included stomach wash, which was performed in 195 (67.0%) cases. Activated charcoal was given while patients were in the Accident and Emergency department; it was given as single or multiple doses in 188 cases (64.6%). Intravenous *N*-acetylcysteine (NAC) was given to 139 patients (47.8%) after acetaminophen levels were estimated. The current protocol in Malaysia for the management of acetaminophen overdose involves an intravenous NAC infusion of 150 mg/kg in 200 mL 5% dextrose over 15 min., followed by 50 mg/kg in 500 mL 5% dextrose over 4 hr, and 100 mg/kg in 1000 mL 5% dextrose over 16 hr. The median (interquartile range) serum acetaminophen concentration was 56 mg/L (14.6–122.7 mg/L). Overall, two patients were admitted to the intensive care unit but no patient died or needed liver transplant as a result of acetaminophen poisoning.

The demographic data and characteristics related to vomiting after acetaminophen poisoning are shown in table 1. There were significant differences between vomiting and non-vomiting groups in patients with intentionally ingested acetaminophen ($p = 0.003$), presence of psychiatric illness ($p < 0.001$), reported acetaminophen dose ingested ≥10 g ($p < 0.001$), and a latency time of more than 8 hr ($p < 0.001$). Other factors such as age, ethnicity, history of alcohol intake, history of chronic illness, history of psychiatric illness, history of attempted suicide, and co-ingestion of other agents did not have a statistically significant influence on vomiting.

Table 2 shows the multivariate logistic regression analysis of risk factors related to vomiting. All included variables had a significant p value in the univariate analysis between vomiting and non-vomiting groups. Multiple logistic regression showed that significant risk factors for vomiting were present among patients who reported an ingested acetaminophen

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Table 1.

Analysis of risk factors for vomiting after acetaminophen poisoning.

Variable	Total (N = 291)	Vomiting (N = 190)	Non-vomiting (N = 101)	p-Value
Age (year)[1], Mean ± S.D.	23 ± 7.4	23.25 ± 6.9	22.54 ± 8.3	0.233
Gender, n (%)				
Male	46 (15.8)	32 (16.8)	14 (13.9)	0.314
Female	245 (84.2)	158 (83.2)	87 (86.1)	
Ethnic group, n (%)				
Malay	145 (49.8)	93 (48.9)	52 (51.5)	0.689
Indian	72 (24.8)	48 (25.3)	24 (23.8)	
Chinese	67 (23)	43 (22.6)	24 (23.8)	
Other	7 (2.4)	6 (3.2)	1 (1.0)	
Cause of intent, n (%)				
Intentional (suicide)	243 (83.5)	168 (88.4)	75 (74.3)	0.003
Unintentional (accidental)	48 (16.5)	22 (11.6)	26 (25.7)	
History of alcohol intake, n (%)				
Yes	25 (8.6)	16 (8.4)	9 (8.9)	0.89
No	266 (91.4)	174 (91.6)	92 (91.1)	
History of chronic illness, n (%)				
Yes	10 (3.4)	7 (3.7)	3 (3.0)	>0.99
No	281 (96.6)	183 (96.3)	98 (97.0)	
History of psychiatric illness, n (%)				
Yes	9 (3.1)	8 (4.2)	1 (1.0)	0.170
No	282 (96.9)	182 (95.8)	100 (99.0)	
No. of co-ingested agents, n (%)				
Single agent	23 (7.6)	18 (9.5)	5 (5.0)	0.257
Multiple agents	268 (92.1)	172 (90.5)	96 (95.0)	
History of suicide attempt, n (%)				
Yes	7 (2.4)	4 (2.1)	3 (3.0)	0.697
No	284 (97.6)	186 (65.5)	98 (97.0)	
Presence of psychiatric illness, n (%)				
Yes	155 (53.3)	120 (63.2)	35 (34.7)	<0.001
No	136 (46.7)	70 (36.8)	65 (65.3)	
Reported dose ingested, n (%)				
≥10 g	167 (57.4)	132 (69.5)	35 (34.7)	<0.001
<10 g	124 (42.6)	58 (30.5)	66 (65.3)	
Latency time, n (%)				
>8 hr	69 (23.8)	59 (31.1)	10 (9.9)	<0.001
≤8 hr	222 (76.3)	131 (68.9)	91 (90.1)	

[1]Significance of differences estimated with Student's t-test.

Table 2.

Independent factors associated with vomiting after acetaminophen poisoning using multiple logistic regression analysis (enter method).

Variable	β	S.E.	Wald Test	p-Value	Exp(β) [95% CI]
Cause of intent (Intentional)	0.51	0.38	1.2	0.264	1.53 [0.72–3.24]
Presence of psychiatric illness	0.43	0.32	2.7	0.109	1.66 [0.89–3.09]
High stated acetaminophen dose (≥10 g)	1.18	0.29	16.9	<0.001	3.26 [1.85–5.71]
Long latency time (≥8 h)	1.24	0.39	10.3	0.001	3.44 [1.62–7.32]

CI, confidence interval; β, the coefficient of the predictor variables.

dose ≥10 g ($p < 0.001$), and a latency time of more than 8 hr ($p = 0.001$). The model was significant, with a Chi-square of 53.86, DF = 4; $p < 0.001$.

The median (interquartile range) quantity of acetaminophen ingested was 6.25 g (5–10 g) for patients without vomiting, 10 g (5–10 g) for patients with one episode of vomiting, 10 g (5–10 g) for patients with two episodes of vomiting, and 12 g (10–15 g) for patients with three episodes or more of vomiting. Overall, an increasing trend in the number of episodes of vomiting ($p < 0.001$) was noted as the quantity of acetaminophen ingested increased.

Table 3 shows clinical and laboratory variables and data on outcome between the four groups (grades) in terms of number of episodes of vomiting. Overall, an increasing trend in prothrombin time ($p = 0.03$), serum bilirubin ($p < 0.001$), serum creatinine ($p = 0.005$), length of hospital stay ($p < 0.001$), and the prevalence of patients who had a serum acetaminophen level above a 'possible toxicity' treatment line

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Table 3.
Final outcome among patients with or without vomiting after acetaminophen poisoning.

Variables[1]	Total (*N* = 291)	Grade 0 Non-vomiting (*N* = 101)	Grade I 1 episode of vomiting (*N* = 20)	Grade II 2 episodes of vomiting (*N* = 31)	Grade III ≥3 episodes of vomiting (*N* = 139)	*p*-Value
Estimated acetaminophen level, n (%)[2]						
Above the 'possible toxicity' treatment line	121 (41.6)	30 (29.7)	7 (35)	11 (35.5)	73 (52.5)	0.001
Below the 'possible toxicity' treatment line	170 (58.4)	71 (70.3)	13 (65)	20 (64.5)	66 (47.5)	
Peak ALT (IU/L)[3]						
Mean ± S.D.	68.4 ± 350	25.7 ± 41	99.1 ± 580	106.5 ± 492.5	79.5 ± 338.5	0.259
Median	12	12	10	10	13	
[Q1–Q3]	[9–19]	[8–26]	[8.75–14]	[8.75–20]	[8.75–29.25]	
Peak prothrombin time (sec.)[4]						
Mean ± S.D.	13.5 ± 2.5	12.95 ± 1.48	13.44 ± 3.21	13.65 ± 3.91	13.84 ± 2.36	0.030
Median	13.1	13.2	13.3	13.45	13.7	
[Q1–Q3]	[12.2–14]	[11.6–14.2]	[12.15–14.3]	[12.2–14.5]	[12.8–15.6]	
Peak serum bilirubin (mmol/L)[3]						
Mean ± S.D.	13.4 ± 9.5	11.2 ± 9.1	12.1 ± 9.2	13.1 ± 9.5	14.8 ± 9.4	<0.001
Median	11	9	10	11	12	
[Q1–Q3]	[8–16]	[6–16.5]	[6–14]	[6.5–15]	[9.75–20.25]	
Peak pH[4]						
Mean ± S.D.	7.34 ± 0.3	7.36 ± 0.06	7.36 ± 0.05	7.37 ± 0.05	7.39 ± 0.07	0.054
Median	7.38	7.38	7.35	7.35	7.4	
[Q1–Q3]	[7.35–7.4]	[7.33–7.4]	[7.33–7.39]	[7.33–7.39]	[7.36–7.4]	
Bicarbonate (mmol/L)[4]						
Mean ± S.D.	20.37 ± 4	20.4 ± 4.6	20.6 ± 3.3	20.3 ± 3.9	20.4 ± 3.9	0.951
Median	20.1	20.55	21	21	19.8	
[Q1–Q3]	[18.4–23]	[17.5–24.7]	[17.8–23]	[17.8–23]	[18.4–22]	
Peak serum creatinine (mmol/L)[4]						
Mean ± S.D.	69.6 ± 12.3	66.74 ± 11.48	67.2 ± 9.23	69.15 ± 8.74	71.9 ± 13.41	0.005
Median	68	67.5	69	70	71	
[Q1–Q3]	[62–75]	[62.75–75.75]	[62–73]	[63.5–73.25]	[66–82.5]	
Peak serum potassium (mmol/L)[4]						
Mean ± S.D.	3.34 ± 0.43	3.55 ± 0.43	3.53 ± 0.41	3.52 ± 0.45	3.14 ± 0.28	<0.001
Median	3.3	3.5	3.4	3.3	3.2	
[Q1–Q3]	[3.1–3.6]	[3.15–3.7]	[3.15–3.6]	[3.15–3.6]	[2.9–3.3]	
Length of stay in hospital (hr)[3]						
Mean ± S.D.	45.07 ± 36.8	36.02 ± 28.9	42.32 ± 30.2	45.55 ± 35.1	51.94 ± 40.5	<0.001
Median	35	39.5	45	47	49.5	
[Q1–Q3]	[20–59.5]	[29–57.5]	[21–78.2]	[21.25–80]	[29.75–69]	

ALT, alanine aminotransferase; Q1–Q3: lower quartile – upper quartile.
[1]Serum creatinine, potassium, and bicarbonate levels were not determined in eight patients; and serum bilirubin and alanine aminotransferase levels were not determined in five patients.
[2]Significance of differences estimated with Chi-square test.
[3]Significance of differences estimated with Kruskal–Wallis test.
[4]Significance of differences estimated with ANOVA test.

($p = 0.001$), and a decreasing trend in serum potassium ($p < 0.001$) were noted as the number of episodes of vomiting increased.

Discussion

This study is the first of its kind to obtain initial data regarding the prevalence of vomiting, and to assess the relationship between episodes of vomiting and outcome in in-patients presenting to hospital after acetaminophen poisoning.

In the present study, vomiting was identified in 190 patients, and the prevalence of vomiting among hospitalized patients with acetaminophen poisoning was 65.3%. In a study by Rumack, vomiting occurred in 33.3% of 662 patients with an acetaminophen overdose [21]. Another study in the United Kingdom showed that the prevalence of vomiting among 392 patients with acetaminophen overdose, of whom 120 took acetaminophen alone, was 11.7% [24]. Because the UK study did not report the incidence of vomiting in the acetaminophen alone group and could not exclude the confounding influence of co-ingestants (e.g. dextropropoxyphene in 112 patients), the true incidence of vomiting in acetaminophen overdose patients during this study period cannot be determined. A study in the USA that investigated the prevalence of vomiting in 1009 adult patients with an acetaminophen overdose, who were reported to a poisons centre, found the prevalence of vomiting to be 12.5% in all patients. Because the USA study only included patients who

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had documented acetaminophen toxicity and vomiting secondary to the ingestion of an adult-strength, acetaminophen-only product, and did not include patients who may have developed acetaminophen toxicity from a combination product, the true incidence of vomiting in acetaminophen overdose patients during the study period cannot be determined [2]. It is likely that the differences in the prevalence of vomiting reported are due to the different study populations, differences in the inclusion criteria, and oversight or accuracy in documentation in the medical records. Another explanation for this difference might be related to patients who reported an ingested acetaminophen dose ≥10 g, and whose latency time was more than 8 hr, both of which were identified as strong independent predictors for vomiting.

In the current study, an increasing trend in prothrombin time was noted as the number of episodes of vomiting increased. A previous study retrospectively studied the prolongation of prothrombin time in 143 patients admitted for acetaminophen poisoning without hepatic injury (i.e. normal transaminase levels) and found a small rise in the prothrombin time in most patients [25].

In the present study, a decline in potassium level was associated with an increased number of episodes of vomiting. It is true that much of the potassium secreted in the gastric juice, together with potassium ingested in the diet, may be lost following persistent vomiting, and this can also contribute to hypokalemia [26,27]. Vomiting is known to cause hypokalemia as a consequence of metabolic alkalosis [27,28]. In our study, vomiting did not show a relationship with serum bicarbonate, which would be expected if vomiting was related to metabolic alkalosis. This finding is consistent with another published study, which showed that hypokalemia is not related to metabolic alkalosis [29]. A study in Canada demonstrated that patients (i.e. pregnant women) with severe vomiting showed dehydration, acid-base disturbances and electrolyte imbalances, especially hypokalemia [30].

In the current study, the creatinine concentration was significantly higher in patients with an increased number of episodes of vomiting. Risk factors such as glutathione depletion in the kidney and dehydration at presentation (excessive vomiting), may increase the risk of renal injury after acetaminophen poisoning [20,31]. A recent study in the UK showed that peak serum creatinine concentrations did not occur until 5.5 days after acetaminophen ingestion. Serum creatinine concentrations were slowly restored to normal, and renal replacement was not required. In this study, rising serum creatinine concentrations only became detectable more than 48 hr after acetaminophen ingestion [10]. Our results could therefore be consistent with early effect of acetaminophen toxicity being due to renal haemodynamic change consequent.

The data in our study also show that patients with an increased number of episodes of vomiting had other markers of worse outcome, as indicated by the increasing trend in length of hospital stay. This is almost certainly due to the presence of other markers that worsen outcome among this group of patients, such as elevated bilirubin levels, prolonged prothrombin time, elevated creatinine level, and the lower potassium level. These signs need to remain under observation until they have recovered to normal.

To the best of our knowledge, this is the first study comparing the relationship between episodes of vomiting at first hospital presentation and outcome in acetaminophen poisoning. Overall, this study was subject to a few limitations. A first limitation was its retrospective nature. Second, we can only suggest, rather than prove, that the increase in episodes of vomiting at first presentation appears to be an important risk marker of subsequent nephrotoxicity and hepatotoxicity. Further studies of the pathophysiology and clinical consequences of vomiting after acetaminophen poisoning are required.

Conclusions

We conclude that the prevalence of vomiting is high in patients with acetaminophen poisoning and is associated with patients who reported an ingested acetaminophen dose ≥10 g and whose latency time was more than 8 hr, both of which were identified as strong independent predictors for vomiting. In addition, we have demonstrated that patients with a higher frequency of vomiting episodes after acetaminophen poisoning tend to have a worse general condition than patients with a low frequency of vomiting episodes or without vomiting. This study suggests that an increased number of episodes of vomiting after acetaminophen ingestion, at first presentation, appears to be an important risk marker of prolonged prothrombin time, elevated serum creatinine, reduced serum potassium and elevated serum bilirubin.

Conflict of interests

We would like to declare that there was no conflict of interest in conducting this research.

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