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ORIGINAL REPORT

Association between gastrointestinal manifestations following acetaminophen poisoning and outcome in 291 acetaminophen poisoning patients

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SUMMARY

Background Acetaminophen poisoning is a common clinical problem, and early identification of patients with more severe poisoning is key to improving outcomes.

Purposes This study intends to document prevalence, clinical characteristics, and predictors of gastrointestinal (GI) manifestations and to assess the impact of these manifestations on outcome in patients with acetaminophen poisoning.

Methods This is a retrospective cohort study of hospital admissions for acute acetaminophen poisoning 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. Statistical Package for Social Sciences (SPSS) 15 was used for data analysis.

Results Two hundred and ninety-one patients were studied; their mean age was 23.01 ± 7.4 years and 76.6% had GI manifestations. Multiple logistic regression showed that significant risk factors for GI manifestations were present among patients who reported acetaminophen dose ingested ≥ 10 g ($p < 0.001$), and latency time more than 8 hours ($p = 0.030$). GI manifestations at first admission predicted poorer outcomes in terms of estimated acetaminophen levels to be a possible toxic ($p < 0.001$), elevated bilirubin levels ($p = 0.002$), prolonged prothrombin time (PT; $p = 0.002$), elevated creatinine level ($p = 0.028$), declination of potassium level ($p < 0.001$), and prolonged hospital stay ($p < 0.001$).

Conclusions GI manifestations were common among patients with acetaminophen poisoning. This study suggests that the presence of GI manifestations at first presentation appears to be an important risk marker of subsequent hepatotoxicity and nephrotoxicity. Copyright © 2010 John Wiley & Sons, Ltd.

KEY WORDS — acetaminophen; gastrointestinal manifestations; poisoning; outcome

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INTRODUCTION

The clinical course of poisoned patients is complicated frequently by gastrointestinal (GI) manifestations such as nausea and vomiting. Under normal circumstances, as toxicity resolves, these symptoms improve gradually. GI manifestations associated with certain poisons can be detrimental to the treatment of the patient. Although GI manifestations are observed among patients with acetaminophen poisoning,[1] there are no data concerning the prevalence of, and the relationship between, GI manifestations and outcome in patients presenting to the hospital with acetaminophen poisoning. To our knowledge, only one attempt has been made to identify GI manifestations as risk markers for hepatotoxicity in acetaminophen poisoning.[2] In that brief report, Knell listed clinical markers (rapid liver enlargement, abdominal pain, persistent nausea, jaundice) to be associated with hepatic encephalopathy. However, no data were provided to support these risk markers.

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Several criteria are used widely to predict outcome in more severely poisoned patients with acetaminophen.[3–11] 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 GI manifestations are an important component of the syndrome of severe acetaminophen poisoning, GI manifestations at the time of first admission might indicate more severe acetaminophen poisoning and poorer prognosis in those admitted to hospital.

To improve our knowledge about GI manifestations after acute acetaminophen poisoning, we carried out this 5-year, hospital-based study with the following objectives: (1) to document the prevalence and characteristics of GI manifestations on initial clinical presentation of acute acetaminophen poisoning during a defined study period; (2) to analyze the clinical, biochemical, and epidemiologic data recorded for these patients, all of whom were hospitalized specifically for this problem; (3) to determine which clinical findings would be most predictive of GI manifestations in hospitalized patients after acetaminophen poisoning; and (4) to assess the impact of these manifestations on outcome. The knowledge of prevalence, clinical characteristics, and predictors of GI manifestations, and relating it to final outcome in patients after acetaminophen poisoning, might contribute to reduced complication rates by enhancing the application of specific therapeutic and management strategies to patients with a high risk of hepatotoxicity.

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 this study.

Participants and data collection

Data were collected from 1 January 2004 to 31 December 2008. A computer-generated list was obtained 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 records of all patients with a discharge diagnosis of acetaminophen overdose were analyzed. 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 patient or the family. We went on to confirm that the patient had substantial acetaminophen ingestion by history, or by estimated serum acetaminophen level.

The primary outcomes of interest were the prevalence rate and types of GI manifestations, and the secondary outcomes were the relationship between GI manifestations and final outcome. Clinical diagnosis of the presence of GI manifestations had been based on the history, and patients' examination findings. All patients were observed in the Accident and Emergency Department of our hospital by specialists in emergency medicine. The data related to GI manifestations were collected from the Accident and Emergency Department medical records and hospital admission records. All the patients were quizzed about the presence of GI manifestations. Such GI manifestations included nausea, vomiting, diarrhea, and abdominal pain.

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 suicide attempt; stated date and time of poisoning to calculate the latency time (the time of ingestion to the time patient was presented at the hospital); quantity of acetaminophen ingested; whether other drugs had been co-ingested; presenting syndromes, such as vomiting and diarrhea; laboratory tests, including prothrombin time (PT) (normal, 11.0–13.1 seconds); alanine aminotransferase (ALT) (normal, 7–56 IU/L); pH (normal, 7.35–7.45); serum bilirubin (normal, 3.4–22 mmol/L); serum creatinine (normal, 61–150 mmol/L); serum acetaminophen concentration; and serum potassium concentrations (normal, 3.5–5.5 mmol/L) during the first day of admission and after 4 hours of ingestion as a minimum time. Data on serum acetaminophen concentration measurements were obtained from the hospital's therapeutic drug monitoring laboratory service. In most patients, laboratory parameters were repeated and for that we took the peak of each during the first 24 hours. In addition, data related to psychiatric diseases were obtained. Psychiatric illness was defined as present

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cause of deliberate self-harm, such as depression, anxiety, adjustment disorders, and impulsive behavior; these causes were noted by the hospital psychiatric specialist report. Also, data related to length of hospital stay were calculated as the hour of discharge minus the hour 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 hours and 5 mg/L at 24 hours).[12] A 'possible toxicity' line 25% below the standard Rumack–Matthew nomogram was proposed to allow for possible errors in plasma assays and ingestion times.[12,13]

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 hours.

Statistical analysis

Data were entered and analyzed using Statistical Package for Social Sciences (SPSS) program version 15. Data were expressed as mean ± SD for continuous variables and as frequency for categorical variables. Variables that were not normally distributed were expressed as a median (lower–upper quartiles). Variables were tested for normality using the Kolmogorov–Smirnov test. χ^2 or Fisher exact test, whichever was appropriate, was used to test significance between categorical variables. Student *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. Multiple logistic regression analysis was used to identify factors associated with the GI manifestations. 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 hours' post-ingestion in 11 patients, and three patients were discharged to another hospital. The study population consisted of 291 patients.

Of the 291 patients in the study population, 223 (76.6%) developed GI manifestations, which included nausea in 69 (23.7%), vomiting in 190 (65.3%), abdominal pain in 75 (25.8%), and diarrhea in 7 patients (2.4%). One hundred and thirty-two (45.4%) patients reported having only one type of GI manifestations, 22.7% of patients reported having two different types of GI manifestations, and 8.6% of patients reported having three or more different types of GI manifestations. A total of 341 GI manifestation episodes were reported by all the patients, giving a mean 1.17 ± 0.9 (median: 1, range: 0–4) GI manifestations per patient.

Results of analysis of 291 patients according to demographic and clinical characteristics status at admission are shown in Table 1. Patients with GI manifestations were significantly associated with intentionally ingested drugs ($p = 0.008$), presence of psychiatric illness ($p < 0.001$), reported acetaminophen dose ingested ≥10 g ($p < 0.001$), and latency time of more than 8 hours ($p = 0.003$).

Table 2 shows the multivariate logistic regression analysis of factors related to GI manifestations. All included variables had a significant *p* value in the analysis between patients with the presence or absence of GI manifestations (Table 1). Multiple logistic regression showed that significant risk factors for GI manifestations were present among patients who reported acetaminophen dose ingested ≥10 g ($p < 0.001$), and latency time more than 8 hours ($p = 0.030$). The model was significant, with a χ^2 of 38.18, DF = 4; $p < 0.001$.

Table 3 shows clinical and laboratory variables and data on outcomes. Patients with GI manifestations had more overall liver and kidney manifestations, as indicated by elevated levels of serum bilirubin ($p = 0.002$) and creatinine ($p = 0.028$), significantly. Measures of severity of illness (estimated acetaminophen levels to be a possible toxic, elevated bilirubin levels, prolonged PT, elevated creatinine level, and declination of potassium level) were all more pronounced in patients with GI manifestations than in patients without GI manifestations. Median length of stay was higher in patients with GI manifestations ($p < 0.001$). Overall, two patients were admitted to the intensive care unit but no patient died or needed liver transplant as a result of acetaminophen poisoning.

DISCUSSION

This study is the first of its kind to obtain an initial data regarding the prevalence rate and types of GI manifestations, and to assess the relationship between

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Table 1. Baseline characteristics based on the presence or absence of gastrointestinal manifestations in patients with acetaminophen poisoning ($n = 291$)

Variable	Total $n = 291$	Presence of GI manifestations $n = 223$	Absence of GI manifestations $n = 68$	p value
Age (year)*, Mean ± SD	23.01 ± 7.39	23.52 ± 7.18	21.32 ± 7.86	0.06
Gender, *n* (%)**				
Male	46 (15.8)	33 (14.8)	13 (19.1)	0.249
Female	245 (84.2)	190 (85.2)	55 (80.9)	
Ethnic group, *n* (%)**				
Malay	145 (49.8)	110 (49.3)	35 (51.5)	0.533
Indian	72 (24.8)	55 (24.7)	17 (25)	
Chinese	67 (23)	51 (22.9)	16 (23.5)	
Other	7 (2.4)	7 (3.1)	0 (0.0)	
Cause of intent, *n* (%)**				
Intentional (suicide)	243 (83.5)	194 (87.0)	49 (72.1)	0.008
Unintentional (accidental)	48 (16.5)	29 (13.0)	19 (27.9)	
History of alcohol intake, *n* (%)†				
Yes	25 (8.6)	18 (8.1)	7 (10.3)	0.574
No	266 (91.4)	205 (91.9)	61 (89.7)	
History of chronic illness, *n* (%)†				
Yes	10 (3.4)	8 (3.6)	2 (2.9)	0.794
No	281 (96.6)	215 (96.4)	66 (97.1)	
History of psychiatric illness, *n* (%)†				
Yes	9 (3.1)	9 (4.0)	0 (0.0)	0.088
No	282 (96.9)	214 (96.0)	68 (100.0)	
Co-ingested agents, *n* (%)†				
Single agent	23 (7.6)	18 (8.1)	5 (7.4)	0.846
Multiple agents	268 (92.1)	205 (91.9)	63(92.6)	
History of suicide attempt, *n* (%)†				
Yes	7 (2.4)	6 (2.7)	1 (1.5)	0.544
No	284 (97.6)	217 (97.3)	67 (98.5)	
Presence of psychiatric illness, *n* (%)**				
Yes	155 (53.4)	133 (59.6)	22 (32.4)	$p < 0.001$
No	136 (46.6)	90 (40.4)	46 (67.6)	
Reported dose ingested, *n* (%)**				
≥10 g	167 (57.4)	146 (65.5)	21 (30.9)	$p < 0.001$
<10 g	124 (42.6)	77 (34.5)	47 (69.1)	
Latency time, *n* (%)†				
>8 hours	69 (23.8)	62 (27.8)	7 (10.3)	0.003
≤8 hours	222 (76.3)	161 (72.2)	61 (89.7)	

Abbreviation: GI: gastrointestinal; SD: standard deviation.
*Significance of differences estimated with Student's *t* test.
**Significance of differences estimated with Fisher's exact test.
†Significance of differences estimated with the χ^2 test.

GI manifestations and outcome inpatients presenting to hospital after acetaminophen poisoning.

In this study, GI manifestations were identified in 223 patients, and the prevalence of GI manifestations among hospitalized patients with acetaminophen poisoning was 76.6%. Many authors described the GI manifestations in patients with acetaminophen poisoning, especially in the course of management, with symptoms and signs of nausea and vomiting and in acetaminophen poisoning patients secondary to *N*-acetylcysteine (NAC) administration.[14–18] The prevalence and characteristics of GI manifestations in initial clinical presentation of acetaminophen poisoning patients have not been reported before. In the current study, patients who reported acetaminophen dose ingested ≥10 g, and latency time more than 8 hours were identified as predictors for high-prevalence GI manifestations. In this study, we also showed that the

Table 2. Independent factors associated with gastrointestinal manifestations after acetaminophen poisoning using multiple logistic regression analysis (enter method)

Variable	β	S.E	Wald Test	p value	Exp(β) (95%CI for Exp(β))
Cause of intent (Intentional)	0.50	0.4	1.6	0.207	1.64 (0.76–3.55)
High stated acetaminophen dose (≥10 g)	1.24	0.33	14.2	<0.001	3.44 (1.81–6.55)
Long latency time (≥8 hours)	0.97	0.44	4.8	0.030	2.63 (1.11–6.28)
Presence of psychiatric illness	0.37	0.36	1.1	0.298	1.45 (0.72–2.94)

Abbreviations: CI: confidence interval; β: the coefficient of the predictor variables; S.E: standard error.

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Table 3. Final outcomes associated with presence or absence of gastrointestinal manifestations in patients with acetaminophen poisoning ($n = 291$)

Variables[‡]	Total n (%) $n = 291$	Presence of GI manifestations $n = 223$	Absence of GI manifestations $n = 68$	p value
Estimated acetaminophen level, n (%)[*]				
Above the 'possible toxicity' treatment line.	121 (41.6)	105 (47.1)	16 (23.5)	<0.001
Below the 'possible toxicity' treatment line.	170 (58.4)	118 (52.9)	52 (76.5)	
Peak acetaminophen (mg/L)[**]				
Mean ± SD	75.7 ± 67.9	78.6 ± 60	66.2 ± 49	0.154
Median	56	60	49	
(Q1–Q3)	(14.6–122.7)	(18.5–134.2)	(11.5–84.75)	
Peak ALT (IU/L)[**]				
Mean ± SD	68.4 ± 350	78.02 ± 390	29.7 ± 47.1	0.181
Median	12	11	13	
(Q1–Q3)	(9–19)	(8–18.5)	(9.25–23.75)	
Peak prothrombin time (second)[†]				
Mean ± SD	13.5 ± 2.5	13.68 ± 2.7	12.88 ± 1.52	0.002
Median	13.1	13.2	12.6	
(Q1–Q3)	(12.2–14)	(12.4–14.05)	(11.7–13.7)	
Peak serum bilirubin (mmol/L)[**]				
Mean ± SD	13.4 ± 9.5	13.93 ± 9.2	11.25 ± 10.30	0.002
Median	11	11	8.5	
(Q1–Q3)	(8–16)	(8–17)	(5–13.75)	
Peak pH[†]				
Mean ± SD	7.34 ± 0.3	7.35 ± 0.28	7.3 ± 0.36	0.280
Median	7.38	7.38	7.37	
(Q1–Q3)	(7.35–7.4)	(7.35–7.4)	(7.33–7.4)	
Bicarbonate (mmol/L)[†]				
Mean ± SD	20.37 ± 4	20.4 ± 3.8	20.3 ± 4.6	0.880
Median	20.1	20.05	20.5	
(Q1–Q3)	(18.4–23)	(18.6–22.7)	(17.4–23)	
Peak serum creatinine (mmol/L)[†]				
Mean ± SD	69.6 ± 12.3	70.32 ± 12	66.9 ± 13	0.028
Median	68	69	66	
(Q1–Q3)	(62–75)	(63–75)	(60–73.5)	
Peak serum potassium (mmol/L)[†]				
Mean ± SD	3.34 ± 0.43	3.28 ± 0.42	3.55 ± 0.42	<0.001
Median	3.3	3.3	3.6	
(Q1–Q3)	(3.1–3.6)	(3–3.5)	(3.35–3.8)	
Length of stay in hospital (hour)[**]				
Mean ± SD	45.07 ± 36.8	48.78 ± 39.31	32.9 ± 23.61	<0.001
Median	35	38	22	
(Q1–Q3)	(20–59.5)	(22–62)	(16–42.75)	

Abbreviations: GI: gastrointestinal; SD: standard deviation; Q1–Q3: lower–upper quartile.
[*]Significance of differences estimated with χ^2.
[**]Significance of differences estimated with Mann–Whitney U test.
[†]Significance of differences estimated with Student's t test.
[‡]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.

patients with GI manifestations had more overall liver and kidney manifestations, as indicated by elevated levels of serum bilirubin and creatinine. Measures of severity of illness (estimated acetaminophen levels to be a possible toxic, elevated bilirubin levels, prolonged PT, elevated creatinine level, and declination of potassium level) were all more pronounced in patients with GI manifestations than in patients without GI manifestations. This finding is in agreement with a previous, published study that showed that large doses of acetaminophen (>10 g) and delays in presentation to hospital were more likely to be associated with hepatotoxicity.[19]

None of the patients in the current study developed fulminant hepatic failure or required liver transplantation. All patients with signs of hepatotoxicity (elevated bilirubin levels, prolonged PT) recovered with supportive care.

In the current study, hepatic transaminase levels did not differ between patients with or without GI manifestations, although serum bilirubin was elevated significantly in patients with GI manifestations ($p = 0.002$). This finding is in agreement with previous, published studies that noted a distinctive clinical pattern with mildly elevated bilirubin level and disproportionately high transaminase levels. This is

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probably due to differences in the rapidity and duration of hepatocyte injury, together with variations in net hepatic regeneration.[20,21]

In the current study, PT was prolonged significantly in patients with GI manifestations ($p = 0.002$). PT prolongation in acetaminophen poisoning without hepatotoxicity has already been reported.[22,23] In these cases, the prolongation was attributed to a reduction in functional levels of the vitamin K-dependent clotting factors due to acetaminophen poisoning itself.[22] A previous study retrospectively studied the PT prolongation in 143 patients admitted for acetaminophen poisoning without hepatic injury (i.e., normal transaminase levels) and found a small rise in the PT prolongation of most patients.[22]

In this study, creatinine concentration was significantly higher in patients presenting with GI manifestations after ingestion than in those presenting without GI manifestations ($p = 0.028$). 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.[11,24] A recent study in the UK showed that peak serum creatinine concentrations did not occur until 5.5 days (4.4–5.9 days) after acetaminophen ingestion ($p = 0.031$ by Wilcoxon test). Serum creatinine concentrations slowly restored to normal, and renal replacement was not required. In this study, rising serum creatinine concentrations only became detectable after more than 48 hours after acetaminophen ingestion.[25]

In the present study, declination of potassium level was associated with GI manifestations after acetaminophen ingestion. It is true that, in potassium secreted in gastric juice, much of this, 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, serum potassium did not show a relationship with serum bicarbonate, which would be expected if vomiting was a factor related to metabolic alkalosis. This finding is in agreement with another published study, which showed that hypokalemia is not related to metabolic alkalosis.[29] The data also show that patients with GI manifestations had other markers of worse outcome, as indicated by longer stay in hospital ($p < 0.001$). 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 PT, elevated creatinine level, and declination of potassium level. These signs need to be under observation until recovered to normal. In addition, all patients with a high serum acetaminophen concentration or/and above the 'possible toxicity' treatment line might have received intravenous NAC, so those patients needed a time to complete the administration of antidote course.

Although this study is the first one of its type in Malaysia, there were some limitations in this study. They include the retrospective nature and lack of structured interview assessment of the subjects. Another limitation of this study is that it does not present sensitivity and specificity of the screening outcomes. Further research is needed to present sensitivity and specificity associated with the incidence of different types of GI manifestations and specific type of outcomes in patients with acetaminophen poisoning.

Conclusions and recommendations

GI manifestations were common among patients with acetaminophen poisoning. This study suggests that the presence of GI manifestations, at first presentation, appears to be an important risk marker of subsequent hepatotoxicity and nephrotoxicity. NAC should be commenced immediately if the patient shows clinical signs suggestive of acetaminophen toxicity (nausea, vomiting, abdominal pain, or tenderness). Evaluation of serum acetaminophen and ALT levels should then be performed as soon as possible. If the serum acetaminophen level is found subsequently to be below the nomogram line, NAC may be ceased; if above the line, it should be continued.

KEY POINTS

- This study is the first of its kind to obtain an initial data regarding the prevalence rate and types of GI manifestations.
- The prevalence of GI manifestations among hospitalized patients with acetaminophen poisoning was 76.6%.
- Patients who reported acetaminophen dose ingested = 10 grams, and latency time more than 8 hours were identified as predictors for high-prevalence GI manifestations.
- This study suggests that the presence of GI manifestations, at first presentation, appears to be an important risk marker of subsequent hepatotoxicity and nephrotoxicity.

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CONTRIBUTORS

All authors supervised several parts of the study, analyzed and interpreted the data, and helped develop and edit the report.

CONFLICT OF INTEREST

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

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