PHARMACOEPIDEMIOLOGY AND DRUG SAFETY 2011; **20**: 203–208
Published online 23 December 2010 in Wiley Online Library (wileyonlinelibrary.com) **DOI**: 10.1002/pds.2060

BRIEF REPORT

Impact of serum acetaminophen concentration on changes in serum potassium, creatinine and urea concentrations among patients with acetaminophen overdose

Sa'ed H. Zyoud[1,2]*, Rahmat Awang[1], Syed Azhar Syed Sulaiman[3] and Samah W. Al-Jabi[2,3]

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

ABSTRACT

Background Acetaminophen overdose may be accompanied by electrolyte disturbances. The basis for electrolyte change appears to be due to increased fractional urinary electrolyte excretion.

Purpose This study investigated the impact of serum acetaminophen concentration on changes in serum potassium, creatinine and urea concentrations in patients with acetaminophen overdose.

Methods This was a retrospective cohort study which included patients admitted to the emergency department and hospital within 24 h of acetaminophen ingestion. The study was conducted over a period of 5 years from 1 January 2004 to 31 December 2008. Data are presented as mean ± SD and as medians (interquartile range) and groups were compared using independent two-tailed Student *t*-test. Statistical Package for Social Sciences (SPSS) 15 was used for data analysis.

Results Two hundred and eighty-three patients were studied (44 males and 239 females), mean age 23 ± 7.5 years. Patients who had a serum acetaminophen concentration above a 'possible toxicity' treatment line were associated with an elevation in serum creatinine concentration ($p = 0.044$) and a reduction in the serum potassium concentration ($p < 0.001$) but were not associated with a reduction in serum urea concentration ($p > 0.99$). During the study period, 63.3% (179 patients) had serum potassium concentrations less than the normal concentration (3.5 mmol/l) and 31.4% (89 patients) had serum urea concentrations less than the normal concentration (2.5 mmol/l). The serum creatinine concentration in all patients was within the normal range.

Conclusions Acetaminophen appears to cause a concentration-dependent reduction of potassium concentrations and an elevation of creatinine concentrations of short duration (<24 h) after overdose. Copyright © 2010 John Wiley & Sons, Ltd.

KEY WORDS — acetaminophen; potassium; creatinine; urea; overdose

Received 3 February 2010; Revised 10 August 2010; Accepted 6 September 2010

INTRODUCTION

Acetaminophen is one of the most common antipyretics and analgesics used all over the world. It is easily accessible over the counter and thus intentional acetaminophen overdose is common. In fact, acetaminophen in large doses is capable of causing both hepatic[1] and renal failure.[2]

The most effective way to diagnose toxicity is by obtaining a serum acetaminophen concentration. A drug nomogram developed in 1975, called the Rumack–Matthew nomogram, estimates the risk of toxicity based on the serum concentration of acetaminophen at a given number of hours after ingestion. This nomogram, called 'normal' treatment line, describes serum acetaminophen concentrations between 200 mg/l at 4 h and 30 mg/l at 15 h.[3] To determine the risk of potential hepatotoxicity, the acetaminphen concentration is traced along the nomogram. Use of a timed serum acetaminophen concentration plotted on the nomogram appears to be

* Correspondence to: S. H. Zyoud, Clinical Toxicology Program, National Poison Centre, Universiti Sains Malaysia (USM), Penang, Malaysia. E-mails: saedzyoud@yahoo.com; saedzyoud@najah.edu

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the best marker indicating the potential for liver injury.[4] An acetaminophen concentration drawn within the first 4 h after ingestion may underestimate the amount in the system because acetaminophen may still be in the process of being absorbed from the gastrointestinal tract. Therefore, a serum concentration taken within 4 h after ingestion is not recommended.[5] A similar nomogram, based on the previous one but extending the line to 24 h after ingestion, was also published (150 mg/l at 4 h and 5 mg/l at 24 h). The 'possible toxicity' line at 25% below the standard nomogram (Rumack–Matthew nomogram) has been proposed to allow for possible errors in plasma assays and ingestion times.[6]

Acetaminophen overdose may be accompanied by electrolyte disturbances.[7–11] The basis for electrolyte change appears to be due to increased fractional urinary electrolyte excretion but the underlying cellular mechanisms by which acetaminophen might change electrolyte transport are unidentified.[7–10] Recent prospective studies found inverse correlations between serum acetaminophen and electrolyte concentration.[9,10] However, a study on therapeutic doses of acetaminophen has found no effect on serum electrolytes.[12]

To improve our knowledge about changes in serum creatinine and electrolytes after acute acetaminophen overdose, we hypothesized that acetaminophen overdose might cause serum potassium, creatinine and urea concentration changes. To present this hypothesis, we carried out this 5-year hospital-based study to investigate the impact of serum acetaminophen concentration on changes in serum potassium, creatinine and urea concentrations in patients with acetaminophen overdose.

METHODS

Settings and study design

This study was 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. The cases were identified 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 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 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 charts of all patients identified through the search were reviewed and the data were collected. Charts were excluded from analysis for the following reasons: (i) baseline serum potassium, urea and/or creatinine concentrations were not measured; (ii) the time of ingestion was not known; or (iii) the time interval between ingestion and determination of serum acetaminophen concentration was more than 24 h or presentation to the hospital was more than 24 h after overdose.

A data collection sheet was used to record patient age, gender, date and time of overdose, stated acetaminophen dose and serum acetaminophen concentration. Laboratory tests, including serum acetaminophen concentration, serum creatinine, serum urea and serum potassium concentrations, were collected between 4 h after ingestion up to 24 h after presentation to hospital. Data on serum acetaminophen concentration measurements were obtained from the hospital's therapeutic drug monitoring laboratory service. Patients were categorized into two groups based on whether they were above or below the 'possible toxicity' treatment line (150 mg/l at 4 h and 5 mg/l at 24 h).[6] The 'possible toxicity' line 25% below the standard nomogram (Rumack–Matthew nomogram), which has been proposed to allow for possible errors in plasma assays and ingestion times, was used.[3,6]

Statistical analysis

Data were entered and analysed using SPSS program version 15. Continuous data are presented as mean $\pm$ SD, and categorical data are expressed as a number with its per cent. Also, continuous data are expressed as median and interquartile ranges (lower–upper quartiles). Variables were tested for normality using the Kolmogorov–Smirnov test. Statistical significance for intergroup differences was assessed by an independent two-tailed Student *t*-test. Confidence

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DOI: 10.1002/pds

intervals of 95% were determined for each mean serum concentration of potassium, creatinine and urea for all patients.

RESULTS

A total of 305 patients with a diagnosis of acetaminophen overdose were admitted to the hospital during the study period; of these, 22 (7.2%) were excluded. Serum acetaminophen concentration was measured 24 h post-ingestion in 11 patients, and baseline potassium, urea, creatinine and acetaminophen concentrations were not measured in six patients. The study population consisted of 283 patients.

Two hundred and thirty-nine (84.4%) patients of the study population were female. The average age of the study population was 23 ± 7.48 years (range: 4.4–53 years). The majority (76%) of patients in the study population were presented within 8 h after acetaminophen ingestion. The median (interquartile range) quantity of acetaminophen ingested was 10 g (5.75–15 g). The median (interquartile range) serum acetaminophen concentration was 56.6 mg/l (14.6–122 mg/l). Overall, two patients were admitted to the intensive care unit but no patient died or needed a liver transplant as a result of acetaminophen overdose. Also, only two patients with acetaminophen overdose were presented to the hospital with impairment in the concentration of consciousness upon admission. Acetaminophen concentrations were below the 'possible toxicity' treatment line and above the 'possible toxicity' treatment line in 165 (58.3%) and 118 (41.7%) cases, respectively. The mean serum potassium concentration of the patients was 3.35 ± 0.43 mmol/l (95% CI = 3.3–3.4). The mean serum creatinine concentration of the patients was 69.56 ± 12.29 mmol/l (95% CI = 68.1–71), while the mean serum urea concentration was 3 ± 0.92 (95% CI = 2.83–3.1). During the study period, 63.3% (179 patients) had serum potassium concentrations less than normal (3.5 mmol/ l) and 31.4% (89 patients) had serum urea concentrations less than normal (2.5 mmol/l). Serum creatinine concentrations in all patients were within the normal range.

Patients with acetaminophen concentrations above the 'possible toxicity' treatment line in comparison to patients with acetaminophen concentrations below the 'possible toxicity' treatment line were more likely to have a significant reduction in serum potassium concentrations [3.23 ± 0.47 (95% CI = 3.14–3.31) versus 3.43 ± 0.39 (95% CI = 3.37–3.49) $p < 0.001$) and an elevation in serum creatinine clearances [71.3 ± 12.4 (95% CI = 69–73.5) versus 68.3 ± 12.14 (95% CI = 66.4–70.2) $p = 0.044$], respectively. There was no difference in either group with respect to serum urea concentrations ($p > 0.99$; Table 1).

DISCUSSION

Previously, we reported the prevalence, clinical characteristics, and predictors of gastrointestinal

Table 1. Impact of serum acetaminophen concentration on changes in serum potassium, creatinine and urea concentrations among patients with acetaminophen overdose

Variable	Total ($n = 283$)	Above the 'possible toxicity' treatment line ($n = 118$)	Below the 'possible toxicity' treatment line ($n = 165$)	p-Value
Serum potassium (mmol/l)				
Mean ± SD	3.35 ± 0.43	3.23 ± 0.47	3.43 ± 0.39	<0.001
95% CI	3.3–3.4	3.14–3.31	3.37–3.49	
Median	3.3	3.2	3.5	
Q1–Q3	3.1–3.6	2.9–3.4	3.2–3.65	
Range	2–5.8	2–5.8	2–4.8	
Serum creatinine (mmol/l)				
Mean ± SD	69.56 ± 12.29	71.3 ± 12.4	68.3 ± 12.14	0.044
95% CI	68.1–71	69–73.5	66.4–70.2	
Median	68	69	68	
Q1–Q3	62–72	64–78.25	61–74	
Range	38–116	38–105	40–116	
Serum urea (mmol/l)				
Mean ± SD	3 ± 0.92	3 ± 0.92	3 ± 0.92	>0.99
95% CI	2.83–3.1	2.83–3.16	2.85–3.13	
Median	2.8	2.8	2.8	
Q1–Q3	2.3–3.6	2.4–3.6	2.3–3.5	
Range	1.2–6.6	1.2–6.6	1.3–6	

SD, standard deviation; CI, confidence interval; Q1–Q3, lower quartile–upper quartile.

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DOI: 10.1002/pds

manifestations and the impact of these manifestations on outcome in patients with acetaminophen overdose. And also, we reported the impact of vomiting episodes on outcome after acetaminophen poisoning.[13,14] This study is one of the few papers to shed light on the impacts of serum acetaminophen concentrations on changes in serum potassium, creatinine and urea concentrations among patients with acetaminophen overdose. This study is also believed to be one of the largest of its kind, with nearly 283 patients included in the study.

In the current study, a reduction in potassium concentration was associated with patients who had acetaminophen concentrations above the 'possible toxicity' treatment line. This finding is in agreement with another published study which showed an inverse relationship between acetaminophen exposure and serum potassium concentrations, which was strongly suggestive of a dose-dependent effect of acetaminophen.[9] Another study showed that acetaminophen overdose is associated with a reduction in serum potassium proportional to the dose ingested, and that this reduction is of a relatively short duration.[8] This study showed a reduction in serum potassium of not longer than 24 h post-ingestion.[8] A reduction in potassium concentration is also recognized after non-steroidal anti-inflammatory drug overdose, suggesting that cyclo-oxygenase (COX) inhibition might be relevant to the effects of acetaminophen.[15] The effect of high acetaminophen concentrations on COX activity offers a feasible mechanism by which acetaminophen overdose might exert effects on potassium homeostasis while therapeutic doses do not.[9] A previous study has suggested a specific renal effect of acetaminophen in overdose.[8] This suggestion might be consistent with an increasing aldosterone action on the distal tubules as renal perfusion falls due to acetaminophen-induced renal vasoconstriction consequent upon COX inhibition, and hence reduced production of vasodilator prostaglandins.[8] A reduction in serum potassium concentration might also arise due to an association between high acetaminophen concentrations and hypokalaemia might be due to potassium wasting in the setting of acute tubular dysfunction.[16,17]

In the current study, the mean serum creatinine changes were significantly different between the patients who had acetaminophen concentrations above the 'possible toxicity' treatment line versus patients who had acetaminophen concentrations below the 'possible toxicity' treatment line (71.3 ± 12.4 versus 68.3 ± 12.14 mmol/l, $p = 0.044$). Serum creatinine in these cases was within the normal range. This finding is in agreement with another published study which showed that serum creatinine did not change significantly after 12 or 24 h.[8] 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.[18,19] Other mechanisms of nephrotoxicity have been proposed, including oxidative stress and lipid peroxidation, through which acetaminophen is capable of evoking tubular epithelial degeneration and cortical interstitial congestion.[20] A recent study in the UK suggested that nephrotoxicity may be delayed after acetaminophen overdose and a significant rise in serum creatinine concentrations might not be detectable until more than 2 days after ingestion.[2] Our results could therefore be consistent with the early effects of acetaminophen toxicity due to consequent renal haemodynamic changes.

From these data, we have demonstrated that acute renal failure might easily be missed if patients are discharged within 24 h of acetaminophen overdose. The diagnosis of acute renal failure relies on serial measurements of serum creatinine concentrations, although this is of limited value for detection of an early acute decline in kidney function. A study in the USA suggested that since *N*-acetylcysteine may not prevent acetaminophen-induced renal toxicity in humans,[21] the importance of nephrotoxicity in the long-term prognosis of acetaminophen-overdosed patients needs to be further evaluated, as does the use of oral *N*-acetylcysteine as the standard acetaminophen antidote.[22]

The present study found no relationship between serum acetaminophen and serum urea concentrations. These data demonstrate that a dose-dependent effect on serum urea concentration after acetaminophen overdose is absent. This finding is in agreement with another published study which showed that low serum urea concentrations do not independently predict an increased risk of hepatotoxicity after acetaminophen overdose.[10] The present study found the baseline urea concentrations were normal in 194 (68.6%) patients, whereas 89 (31.4%) patients had concentrations <2.5 mmol/l. A previous study found that a low serum urea concentration was common in medical inpatient settings. About 14.8% of acute acetaminophen overdose patients suffered from low serum urea concentrations.[10] A study in the UK showed that the major associated clinical condition, common to a third of patients who had a low urea concentration, was hepatobiliary disease without liver failure. Half of the patients with low urea concentrations had a history of alcohol abuse, 14.8% of patients had various psychia-

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DOI: 10.1002/pds

KEY POINTS

- An elevation in serum creatinine concentration and a reduction in the serum potassium concentration were associated with patients who had a serum acetaminophen concentration above a 'possible toxicity' treatment line.
- A reduction in serum urea concentration was not associated with patients who had a serum acetaminophen concentration above a 'possible toxicity' treatment line.
- Patients (63.3%) had serum potassium concentrations less than the normal concentration (3.5 mmol/l) and 31.4% of patients had serum urea concentrations less than the normal concentration (2.5 mmol/l). The serum creatinine concentration in all patients was within the normal range.

tric disorders and 12.3% of patients had taken intravenous fluids.[23]

The UK study showed that 15% of their patients had various psychiatric disorders, ranging from neurosis, depression and psychosis to anxiety states.[23] Another study reported the association of low urea concentration and high albumin concentrations during states of anxiety and depression.[24] In a previous study[11], we reported that 232 (82.9%) of 280 acetaminophen poisoning patients were diagnosed with different psychiatric illnesses. The high per cent of psychiatric illness could be related to the high per cent of low serum urea concentration. A study in the UK showed that patients can refuse to eat or drink due to psychiatric illnesses such as severe depression and psychosis.[25] The consequence of starvation can be progress to low serum urea concentration.[26]

We conclude that serum acetaminophen concentration is associated with a reduction in serum potassium concentration and an elevation of serum creatinine concentration. Additionally, there was no correlation between changes in serum urea concentration and serum acetaminophen concentration. Overall, this study was subject to a few limitations. Firstly, further risk factors for electrolyte changes were not taken into account in the analysis. A second limitation was its retrospective nature and the lack of a structured interview assessment of the subjects. Thirdly, we can only suggest, rather than prove, that the serum acetaminophen concentration is responsible for the reduction in serum potassium concentration and the elevation of serum creatinine concentration diagnosed in our population.

CONFLICT OF INTERESTS

The authors would like to declare that there was no conflict of interests in conducting this research.

ACKNOWLEDGEMENTS

The authors would like to thank the Universiti Sains Malaysia (USM) and Islamic Development Bank (IDB) for the financial support provided for their research. The assistance of the medical and records office staff is gratefully acknowledged.

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DOI: 10.1002/pds