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High prevalence of hypokalemia after acute acetaminophen overdose: Impact of psychiatric illness

Sa’ed H Zyoud¹,², Rahmat Awang¹, Syed Azhar Syed Sulaiman³ and Samah W Al-jabi²,³

Abstract
Background: Hypokalemia is not an isolated disease but an associated finding in a number of different diseases. It is also a commonly neglected condition among patients with acute acetaminophen overdose. Objectives: This study intended to determine the prevalence of hypokalemia and its clinical correlates in acute psychiatric illness among hypokalemic and normokalemic patients after acetaminophen overdose. Methods: This is a retrospective cohort study of hospital admissions for acute acetaminophen overdose conducted over a period of 5 years from 1 January 2004 to 31 December 2008. Demographic data and different types of psychiatric illness were compared between hypokalemic and normokalemic patients. Hypokalemia was predefined by a serum concentration <3.5 mmol/L. Statistical Package for Social Sciences (SPSS) 15 was used for data analysis. Results: Two hundred and eighty patients out of 305 admissions were studied. Hypokalemia was found in 63.6% of patients with a higher prevalence in the presence of psychiatric illness (67.7%). Hypokalemic patients were significantly associated with the presence of major depression (p = .04), adjustment disorder (p < .001), anxiety (p = .01), and suicidal attempts (p = .04). Conclusion: Hypokalemia was common among patients with psychiatric illness and acute acetaminophen overdose.

Keywords
acetaminophen, hypokalemia, overdose, potassium, psychiatric illness

Introduction
Deliberate self-poisoning (DSP) is recognized as a major cause of suicide around the world.¹ Acetaminophen (Paracetamol) is the most common drug employed in DSP in many countries,²,³ including Malaysia.⁴ Despite excellent safety in therapeutic doses of acetaminophen, it is also one of the leading causes of severe hepatic necrosis.⁵

Acetaminophen overdose may be accompanied by electrolyte disturbances including hypokalemia, and these appear to be independent of the hepatotoxic effects.⁶ These electrolyte changes appear to be due to the increase in fractional renal excretion of potassium, but the underlying cellular mechanisms by which acetaminophen might alter electrolyte transport are still unknown.⁶-⁹ In some cases, hypokalemia may be severe, reaching a level of 2.3 mmol/L after reported ingestion of 48 g of acetaminophen.⁸

Hypokalemia, an easily identifiable and clinically important condition in clinical settings, has received little attention from researchers worldwide. Not only is hypokalemia associated with frequent cardiac and neuromuscular complications, but its effect on mental function may also exacerbate psychiatric disturbances.¹⁰,¹¹ Both anxiety¹² and intense exercise¹³

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increase circulating epinephrine, which induces a β2-receptor-mediated influx of potassium into skeletal muscle.14 As this condition may be similar to the acute psychotic state, it was hypothesized that the decline in serum potassium concentration could be associated with the presence of psychiatric illness during acetaminophen overdose.

To improve our knowledge of hypokalemia after acute acetaminophen overdose, we carried out a 5-year, hospital-based study with the following objectives: (1) to determine the prevalence of hypokalemia in patients presenting to hospital after acetaminophen overdose and (2) to investigate the clinical correlates in acute psychiatric illness among hypokalemic and normokalemic patients after acetaminophen overdose.

**Methods**

**Settings and study design**

This is an observational retrospective case review of all patients with acute acetaminophen overdose 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 Record 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 overdose) were included in the study.

Specially designed data-collection forms were used to collect data concerning age, gender, circumstances of overdose (accidental or suicidal), stated date and time of poisoning to calculate the latency time (the time of ingestion to the time the patient was presented at the hospital), quantity of acetaminophen ingested, GI decontamination such as stomach wash, laboratory tests including serum acetaminophen concentration, and serum potassium concentrations during the first day of admission and after a minimum of 4 hours of ingestion. Data on serum acetaminophen concentration measurements were obtained from the hospital’s therapeutic drug monitoring laboratory service. In addition, data related to the presence of psychiatric illness were obtained. Psychiatric illness was defined as the presence of any disturbance of emotional equilibrium, as manifested in maladaptive behavior and impaired functioning, caused by genetic, physical, chemical, biological, psychological, or social and cultural factors such as depression, anxiety, adjustment disorders, impulsive behaviors and stress reactions, either emotional or behavioral; these causes were noted by the hospital psychiatric specialist report.

Hypokalemia was defined as a serum potassium level of less than 3.5 mmol/L.11 Patients with hypokalemia were classified into three groups based on potassium levels: (1) mild/grade 1 (3.0–3.4 mmol/L), (2) moderate/grade 2 (2.5–2.9 mmol/L) and, (3) severe/grade 3 (<2.5 mmol/L).

The charts of all patients identified through the search were reviewed and the data collected. Charts were excluded from analysis for the following reasons: (1) baseline potassium concentrations were not measured, (2) if patients had taken acetaminophen but the cause of ingestion was unknown or undetermined, (3) the time of ingestion was not known or (4) the patients were on regular prescribed drugs that lead to hypokalemia, such as furosemide, and (5) the patients were children under 13 years of age. Charts of patients who had laboratory tests at or more than 4 hours post-ingestion were extracted for further analysis.

**Statistical analysis**

Data were entered and analyzed using the Statistical Package for Social Sciences program version 15 (SPSS). Data were expressed as mean ± SD for continuous variables and as frequency for categorical variables. The chi square or Fischer’s exact test, as appropriate, was used to test the significance between categorical variables. The independent samples t-test was used to compare means of continuous variables. Variables were tested for normality using the Kolmogorov-Smirnov test. Variables that were not normally distributed were expressed as a median (lower–upper quartiles). Statistical significance was considered at p < .05.

**Results**

Three hundred and five cases of acetaminophen overdose were identified. Of these, 25 patients (8.2%) were excluded. Baseline potassium concentrations were not measured in eight patients, one patient was...
given furosemide at admission, five patients were less than 13 years old, the cause of ingestion was unknown or undetermined in 11 patients, and therefore, the study population consisted of 280 patients (45 male and 235 female patients with a mean age of 23.4 ± 7.1, giving a female: male ratio of 5.22:1).

The majority (72.1%) of cases of acetaminophen ingestion were presented within 8 hours. The median (interquartile range) quantity of acetaminophen ingested was 10 g (6–15 g). Initial management included stomach wash, which was performed in 181 (64.6%) cases. Activated charcoal was given while patients were in the Accident and Emergency department; it was given as single or multiple doses in 173 cases (61.8%). Intravenous N-acetylcysteine (NAC) was given to 140 patients (50%) after acetaminophen levels were estimated. The median (interquartile range) serum acetaminophen concentration was 55.6 mg/L (14–120 mg/L).

During the study period, 63.6% (178 patients; 33 males and 145 females) had potassium levels of less than 3.5 mmol/L. For the hypokalemic patients, the mean potassium level was 3.1 ± 0.26 mmol/L, while that for the normokalemic patients was 3.76 ± 0.35 mmol/L. Most of the patients (129) were in mild-stage hypokalemia and 45 patients were in moderate-stage hypokalemia. Few patients (4) were in severe-stage hypokalemia. Psychiatically ill subjects were found to have hypokalemia, and the prevalence was higher than that in non-psychiatically ill subjects (67.7% vs 43.8%; respectively, p = .002; Figure 1).

The most common clinical diagnosis among medically treated suicide attempters was adjustment disorder (45.7%) followed by impulsive behavior (24.3%), major depression (10.7%), and anxiety (2.1%). Hypokalemia was significantly associated with the presence of major depression (p = .04), adjustment disorder (p < .001), anxiety (p = .01), and suicidal attempts (p = .04). However, normokalemia was significantly associated with impulsive behavior (p < .001), the absence of psychiatric illness (p = .002), and the presence of accidental overdose (p = .04; Table 1).

One hundred and twelve patients with adjustment disorder and six patients with anxiety were found to have hypokalemia, and the prevalence of hypokalemia among these patients was higher than that in the overall study population and in patients with other psychiatric disorders (100% and 87.5%, respectively). Similarly, their mean potassium level was lower than that of the overall study population (3.16 ± 0.41 and 3.2 ± 0.21 mmol/L, respectively) (Table 2).

Eight hypokalemic patients (4.5%) were supplemented with oral potassium medication, and 85 hypokalemic patients (47.8%) were treated with intravenous potassium chloride, and their potassium levels were normalized in the next blood test. Additionally, most of the treated patients (59) were in mild-stage hypokalemia and 32 patients were in moderate-stage hypokalemia. Few patients (2) were in severe-stage hypokalemia.

Discussion

This study is the first of its kind in Malaysia and has been carried out to determine the prevalence of hypokalemia in patients presenting to hospital after acute acetaminophen overdose, and to investigate the clinical correlates in acute psychiatric illness among hypokalemic and normokalemic patients after acetaminophen overdose in 280 patients with acute acetaminophen overdose collected retrospectively from a records registry.

In this study, hypokalemia was identified in 178 patients, and the prevalence of hypokalemia among hospitalized patients with acetaminophen overdose was 63.6%. A previous study found that hypokalemia was common in medical inpatient settings.
About 20% of stroke, 10% of myocardial infarction patients, 21.2% of psychiatric disorders, and about one third of acute acetaminophen overdose patients suffered from hypokalemia. The high prevalence of hypokalemia after acetaminophen overdose might be due to multiple risk factors. The etiology of hypokalemia is complex. The level of serum potassium depends on the balance between oral intake, renal and gastrointestinal losses as well as the balance and movement between extra and intracellular compartments. A previous study found that 7.6% of psychiatric patients had nutritional problems; inadequate dietary potassium intake was relatively rare unless daily potassium intake was less than 25 mmol.

This study found that it was the psychiatrically ill patients, rather than those patients with no psychiatric illness, who were more likely to develop hypokalemia. This finding is consistent with other published studies that showed that hypokalemia was common among acute psychiatric inpatients. Adjustment disorders are often precipitated by stress reactions. For most people, stress is associated with higher cortisol levels. Previous studies have suggested that high cortisol levels may be the principal cause of hypokalemia.

In this study, patients with anxiety were suffering from a low mean potassium concentration and a high prevalence of hypokalemia. The explanation of this finding is that anxiety increases the circulating epinephrine, which induces a β₂-receptor-mediated influx of potassium into skeletal muscle.

In the present study, patients with major depression were suffering from a high prevalence of hypokalemia. This finding is similar to a previous work that has shown small decreases in serum potassium among 200 pre-operative patients who had an increase in anxiety. The explanation of this finding is that anxiety increases the circulating epinephrine, which induces a β₂-receptor-mediated influx of potassium into skeletal muscle.

Expected findings in our study were the low incidence of hypokalemia in the patients with impulsive behavior. These patients differed significantly from the other types of psychiatric illness and considered as a part of the normal behavior.

### Table 1. Demographics and spectrums of psychiatric illness and hypokalemia (n = 280)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total; N = 280</th>
<th>Hypokalemic patients; K⁺ level &lt;3.5; N = 178</th>
<th>Normokalemic patients; K⁺ level ≥ 3.5; N = 102</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>23.4 ± 7.1</td>
<td>24 ± 7.1</td>
<td>22.3 ± 7</td>
<td>.06</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>45 (16.1)</td>
<td>33 (18.5)</td>
<td>12 (11.8)</td>
<td>.21</td>
</tr>
<tr>
<td>Female</td>
<td>235 (83.9)</td>
<td>145 (81.5)</td>
<td>91 (88.2)</td>
<td>.12</td>
</tr>
<tr>
<td>Psychiatric illness</td>
<td>232 (82.9)</td>
<td>157 (88.2)</td>
<td>75 (73.5)</td>
<td>.002</td>
</tr>
<tr>
<td>Major depression</td>
<td>30 (10.7)</td>
<td>24 (13.5)</td>
<td>6 (5.9)</td>
<td>.04</td>
</tr>
<tr>
<td>Adjustment disorder</td>
<td>128 (45.7)</td>
<td>112 (62.9)</td>
<td>16 (15.7)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Anxiety disorder</td>
<td>6 (2.1)</td>
<td>6 (3.4)</td>
<td>0 (0.0)</td>
<td>.01</td>
</tr>
<tr>
<td>Impulsive behavior</td>
<td>68 (24.3)</td>
<td>15 (8.4)</td>
<td>53 (52)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>No psychiatric illness</td>
<td>48 (17.1)</td>
<td>21 (11.8)</td>
<td>27 (26.5)</td>
<td>.002</td>
</tr>
<tr>
<td>Suicide attempt</td>
<td>239 (85.4)</td>
<td>157 (88.2)</td>
<td>82 (80.4)</td>
<td>.04</td>
</tr>
<tr>
<td>Accidental overdose</td>
<td>41 (14.6)</td>
<td>21 (11.8)</td>
<td>20 (19.6)</td>
<td>.04</td>
</tr>
</tbody>
</table>

### Table 2. The mean serum potassium value, SD, and prevalence of hypokalemia among patients in the different diagnostic groups (n = 280)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean serum K⁺ level</th>
<th>Prevalence of hypokalemia; %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psychiatric illness</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major depression</td>
<td>3.34 ± 0.38</td>
<td>80</td>
</tr>
<tr>
<td>Adjustment disorder</td>
<td>3.16 ± 0.41</td>
<td>87.5</td>
</tr>
<tr>
<td>Anxiety disorder</td>
<td>3.2 ± 0.21</td>
<td>100</td>
</tr>
<tr>
<td>Impulsive behavior</td>
<td>3.62 ± 0.35</td>
<td>23.1</td>
</tr>
<tr>
<td>No psychiatric illness</td>
<td>3.5 ± 0.06</td>
<td>43.8</td>
</tr>
<tr>
<td>Suicide attempt</td>
<td>3.34 ± 0.44</td>
<td>65.7</td>
</tr>
<tr>
<td>Accidental overdose</td>
<td>3.37 ± 0.4</td>
<td>51.2</td>
</tr>
</tbody>
</table>

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concluded in previous study that the decreased peripheral epinephrine levels may be involved in pathophysiology of impulsive and hyperactive behaviors. This mechanism results in a decreased uptake of potassium by cells. In addition, this study found that it was the suicidal patients, rather than those with accidental overdose, who were more likely to develop hypokalemia. Attempted suicide is assumed to be a hyperadrenergic state. A retrospective study carried out on patients with psychiatric disorders concluded that significant differences existed among the attempted suicide group with regard to hypokalemia. β-adrenergic receptor stimulation causes hypokalemia in experimental animals and humans. There is little doubt that one of the mechanisms of hypokalemia is a beta 2-receptor-mediated influx of potassium into skeletal muscle, induced by circulating epinephrine. It has been demonstrated that epinephrine causes excessive activation of the sodium/potassium-ATPase pump as a result of β2-adrenergic receptor stimulation. This mechanism results in an increased uptake of potassium by cells, leading to a decrease in serum potassium levels. As the influence of the adrenergic system on serum potassium is found in many psychiatric situations, it may explain why a high prevalence of the patients included in our study were presented with hypokalemia.

A high percentage of patients (47.7%) were still not being treated for low potassium levels, putting their health in jeopardy. The common occurrence of hypokalemia in patients with acute acetaminophen overdose should alert all clinicians to the importance of correcting potassium loss, since most of the patients with an acetaminophen overdose might have received intravenous fluids or N-acetylcysteine in serum dextrose 5%. However, this may have altered serum potassium concentrations through endogenous insulin production induced by 5% dextrose, resulting in movement of potassium into the intracellular compartment. Nonetheless, the extensive use of dextrose may expose the patients to higher risks.

This study is the first one of its type in Malaysia to investigate the clinical correlates in acute psychiatric illness among hypokalemic and normokalemic patients after acetaminophen overdose. It is also the first study suggested that hypokalemia is related to psychiatric status after acetaminophen overdose rather than the previous studies that showed a dose-dependent relationship between fall in serum potassium and serum acetaminophen at presentation. Our study suffers from a few limitations. First, further risk factors for hypokalemia were not taken into account in the analysis. A second limitation is its retrospective nature and the lack of structured interview assessment of the subjects. Third, we can only suggest, rather than prove, that the psychiatric state is responsible for the high occurrence of hypokalemia diagnosed in our population.

**Conclusions and recommendations**

In conclusion, hypokalemia is highly prevalent among psychiatrically ill patients and after acute acetaminophen overdose. Therefore, monitoring of serum potassium concentration may be clinically important on emergency admission for all cases of acute acetaminophen overdoses to prevent the consequences of hypokalemia. Supplemental potassium administration should be commenced as soon as possible.

**Acknowledgements**

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**Conflict of interests**

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

**References**


