Serum urea concentration and the risk of hepatotoxicity after paracetamol overdose


From the Scottish Poisons Information Bureau, The Royal Infirmary of Edinburgh, Edinburgh, UK

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Summary

Background: Glutathione depletion increases the incidence of toxicity after paracetamol overdose. Risk factors for toxicity, including chronic ethanol excess and malnutrition, are associated with low serum urea concentrations. Therefore, we hypothesized that low serum urea concentration might itself be predictive of hepatotoxicity in patients that present to hospital after paracetamol overdose.

Methods: The present study prospectively collected data from 1085 patients attending the Emergency Department after paracetamol overdose. Hepatotoxicity was pre-defined by prothrombin time ratio >1.3 or alanine transaminase ≥1000 U/l. Serum urea concentrations were considered in a stepwise multiple regression analysis that included paracetamol dose, co-ingestion of ethanol and other drugs, serum concentration, N-acetylcysteine, interval to treatment, vomiting and serum creatinine.

Results: Median (IQR) serum urea concentrations were 3.3 mmol/l (2.7–4.2 mmol/l) in those without risk factors, compared with 3.0 mmol/l (2.4–3.9 mmol/l) in those with chronic excess ethanol intake (P < 0.001 by Mann Whitney test) and 2.5 mmol/l (1.9–2.8 mmol/l) in patients with other risk factors (P < 0.001). Multivariate analysis found that serum urea concentrations were not independently associated with hepatotoxicity.

Conclusions: Low serum urea concentration is not an independent risk factor for hepatotoxicity after paracetamol overdose.

Introduction

Paracetamol is the most common means of deliberate self-poisoning and, in the United Kingdom alone, paracetamol overdose results in more than 70,000 emergency department attendances every year.1,2 The risk of acute liver injury is highest in patients that present >24 h after overdose, or that have serum paracetamol concentrations higher than the Rumack-Matthew nomogram, the so-called ‘200-line’.3,4 The nomogram describes an exponential decay between 200 mg/dl at 4 h and 30 mg/dl at 15 h, and is often extrapolated to 6.25 mg/dl at 24 h in clinical practice.5,6 A small but significant number of patients with serum paracetamol concentrations below the ‘200-line’ develop hepatotoxicity and require admission to a specialist liver unit.7 Chronic ethanol intake, enzyme-inducing drugs and malnutrition are thought to increase susceptibility to paracetamol toxicity, due to depletion of intracellular glutathione and greater accumulation of toxic metabolites.8 These risk factors are supported by only limited data, and the extent to which they increase toxicity is somewhat controversial. Nonetheless, a lower treatment threshold is generally adopted for patients with any one of these risk factors, for example the ‘100-line’ representing 50% of the standard nomogram concentrations.3 No objective laboratory measure exists to enable early identification of patients that might have increased susceptibility to paracetamol toxicity.

The urea cycle is the key pathway for disposal of excess dietary and endogenous nitrogen in people, and urea is predominantly derived from amino acids
metabolized within hepatocytes. Low serum urea concentrations indicate reduced protein catabolism, and may be due to malnutrition, cachexia or inadequate dietary protein intake. Serum urea concentrations below the normal reference range are found in the setting of chronic ethanol excess, carbohydrate rich and protein poor diet and impaired synthetic function in patients with established liver disease. The conditions that give rise to low serum urea concentrations are the same as those thought to increase susceptibility to paracetamol toxicity. We hypothesized that low serum urea concentrations might allow identification of patients at highest risk of paracetamol toxicity by means of a readily available laboratory test. The present study was designed to prospectively examine whether low serum urea concentrations might enable risk stratification in patients presenting to hospital after paracetamol overdose.

Methods
Study design
This was a prospective, observational study of consecutive patients presenting to the emergency department after paracetamol overdose between March 2005 and July 2006 inclusive. The protocol was reviewed and approved by the local research ethics committee. A standard operating procedure is used to ensure consistency between the emergency department and the toxicology unit, and is in accordance with TOXBASE, the standard resource for poisoning management advice in the United Kingdom. In brief, intravenous N-acetylcysteine is indicated after acute ingestion if serum paracetamol concentration is above the Rumack-Matthew ‘200-line’ nomogram, or above the ‘100-line’ and the patient is considered at high risk due to chronic ethanol excess, enzyme inducing drugs (carbamazepine, phenobarbital, phenytoin, rifampicin, St John’s wort), HIV disease or malnutrition. N-acetylcysteine is also considered after a staggered overdose of >12 g or 150 mg/kg (up to 110 kg body weight) in the previous 24 h, and a lower threshold may be adopted if risk factors are present. Chronic ethanol excess is defined by regular consumption of >21 units (168 g) per week in men or >14 units (112 g) in women. Intravenous N-acetylcysteine 300 mg/kg is administered over 20.25 h, and serum electrolytes, urea, creatinine and liver biochemistry and prothrombin time ratio are measured at baseline and after infusion.

A standardized data collection sheet was used to record patient age, gender, date and time of overdose, stated quantity ingested, risk factors for hepatotoxicity and serum paracetamol concentration. The primary outcome variables was the incidence of hepatotoxicity predefined by prothrombin time ratio >1.3 or alanine transaminase ≥1000 U/l.

Data analyses
Data are presented as median and interquartile range and, where appropriate, proportions and 95% CI constructed by the modified Wald method. Categories were defined by baseline serum urea concentrations lower or higher than the normal reference range (2.5–6.6 mmol/l), and three geometric subgroups were formed within this range (2.5–3.8 mmol/l, 3.9–5.2 mmol/l and 5.3–6.6 mmol/l). Between-group comparisons were made using Mann Whitney tests and Yate’s corrected Chi square proportional tests.

Factors that might influence the risk of hepatotoxicity or alter serum urea concentration were considered using Spearman’s coefficient of correlation, and independently by stepwise multiple regression analysis. The regression model included variables if P-values were <0.05, and the coefficient of determination (R²) was used to examine the goodness of fit of the regression model. Study variables were age, gender, weight, acute ethanol co-ingestion, other drug co-ingestion, the stated paracetamol dose, serum paracetamol concentration, interval between ingestion and N-acetylcysteine, the estimated 4 h paracetamol level, above ‘normal’ treatment line, between treatment lines, below ‘high risk’ treatment line, staggered overdose, chronic excess ethanol intake, other risk factors for hepatotoxicity, N-acetylcysteine administration, vomiting and serum creatinine concentration. Tests were performed using MedCalc statistical software v.9.1.0.1 (Medcalc, Mariakerke, Belgium). P-values <0.05 were accepted as statistically significant in all cases.

Results
During the study period, 1191 patients presented to hospital after paracetamol overdose. Baseline urea concentrations were not measured in 106 patients and, therefore, the study population consisted of 1085 patients (714 women) with median age 33 years (interquartile range 21–43 years). This included 36 who presented >24 h after overdose, 92 who had taken a staggered overdose (>2 h) and 957 who presented within 24 h of acute overdose. The stated quantity of ingested paracetamol was 11.0 g (6.5–17.5 g), and interval between ingestion and presentation was 4.5 h (4.0–6.7 h). N-acetylcysteine was administered to 390 patients.
(35.9%), and the overall incidence of hepatotoxicity was 5.4%. There were 394 patients (36.3%) considered to be at high risk due to chronic alcohol excess (340), malnutrition (40) and use of enzyme inducing drugs (14).

Baseline urea concentrations were normal in 874 (80.6%), whereas 161 (14.8%) had concentrations <2.5 mmol/l and 50 (4.6%) had concentrations >6.6 mmol/l. Median (interquartile range) serum urea concentration was 3.3 mmol/l (2.7–4.2 mmol/l) in those without risk factors, compared with 3.0 mmol/l (2.4–3.9 mmol/l) in those with chronic excess ethanol intake (P<0.001) and 2.5 mmol/l (1.9–2.8 mmol/l) in patients with other risk factors for hepatotoxicity (P<0.001). Correlation between clinical and laboratory variables and the risk of hepatotoxicity is shown in Table 1. There was a tendency for increasing urea concentrations to be associated with a higher risk of hepatotoxicity, and the highest risk was observed in those with concentrations >6.6 mmol/l (Figure 1). Stepwise multiple regression analysis found that serum urea concentrations did not predict hepatotoxicity; explanatory variables were acute ethanol co-ingestion (inverse), above ‘normal’ treatment line, interval, serum paracetamol concentration, equivalent 4 h concentration, male and vomiting (R² = 0.173). The same explanatory variables and similar coefficient of determination were found when multiple regression analysis considered a lower alanine transaminase value (≥500 U/l).

![Figure 1. Baseline serum urea concentration and risk of hepatotoxicity after paracetamol overdose, not corrected for confounding by other variables. Data are shown as proportion and 95% CI for each group, normal reference range 2.5–6.6 mmol/l. *P=0.0246 compared with 2.5–3.8 mmol/l group by Yate’s corrected Chi square proportional test.](image)

### Discussion

Low serum urea concentrations were encountered in a high proportion of patients after paracetamol overdose. This is likely to be explained by a high prevalence of risk factors for hepatotoxicity. Chronic ethanol excess is associated with low serum urea

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**Table 1** Spearman’s rank correlation coefficient (ρ) and 95% CI for univariate analyses between clinical variables and risk of hepatotoxicity defined by prothrombin time ratio >1.3 or alanine transaminase >1000 U/l

<table>
<thead>
<tr>
<th>Variable</th>
<th>ρ</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.045</td>
<td>−0.014 to 0.105</td>
<td>0.136</td>
</tr>
<tr>
<td>Male</td>
<td>0.079</td>
<td>0.020 to 0.138</td>
<td>0.009</td>
</tr>
<tr>
<td>Patient weight</td>
<td>−0.036</td>
<td>−0.141 to 0.070</td>
<td>0.503</td>
</tr>
<tr>
<td>Acute ethanol co-ingestion</td>
<td>−0.096</td>
<td>−0.155 to −0.037</td>
<td>0.002</td>
</tr>
<tr>
<td>Other co-ingested drugs</td>
<td>−0.074</td>
<td>−0.133 to −0.015</td>
<td>0.015</td>
</tr>
<tr>
<td>Stated paracetamol dose</td>
<td>0.195</td>
<td>0.131 to 0.257</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Serum paracetamol concentration</td>
<td>0.084</td>
<td>0.025 to 0.143</td>
<td>0.006</td>
</tr>
<tr>
<td>Interval after ingestion</td>
<td>0.138</td>
<td>0.077 to 0.199</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Estimated 4 h paracetamol level</td>
<td>0.169</td>
<td>0.110 to 0.226</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Above ‘normal’ treatment line</td>
<td>0.224</td>
<td>0.187 to 0.299</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Between treatment lines</td>
<td>−0.011</td>
<td>−0.070 to 0.049</td>
<td>0.723</td>
</tr>
<tr>
<td>Below ‘high risk’ treatment line</td>
<td>−0.171</td>
<td>−0.228 to −0.112</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Staggered overdose</td>
<td>0.060</td>
<td>0.001 to 0.119</td>
<td>0.484</td>
</tr>
<tr>
<td>Chronic excess ethanol intake</td>
<td>0.007</td>
<td>−0.052 to 0.067</td>
<td>0.810</td>
</tr>
<tr>
<td>Other risk factors for hepatotoxicity</td>
<td>0.036</td>
<td>−0.024 to 0.095</td>
<td>0.238</td>
</tr>
<tr>
<td>N-acetylcysteine administered</td>
<td>0.249</td>
<td>0.192 to 0.304</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Vomiting</td>
<td>0.181</td>
<td>0.123 to 0.238</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Serum creatinine concentration</td>
<td>0.094</td>
<td>0.034 to 0.152</td>
<td>0.002</td>
</tr>
<tr>
<td>Serum urea concentration</td>
<td>−0.043</td>
<td>−0.103 to 0.016</td>
<td>0.153</td>
</tr>
</tbody>
</table>
regardless of whether there is any established liver disease. In the present series, high risk patients had lower serum urea concentrations, although the numerical difference was small and clinically insignificant. In contrast to our hypothesis, low serum urea concentrations did not independently predict an increased risk of hepatotoxicity.

Increased risk of hepatotoxicity in patients with high serum urea concentrations might be explained by association with other variables, for example vomiting, dehydration, renal impairment and delay to N-acetylcysteine administration. There might also be a discrepancy between the mechanisms determining the extent of urea production and hepatic glutathione concentrations. Chronic ethanol consumption is associated with reduced skeletal muscle protein synthesis, increased muscle and hepatic protein breakdown and an increased circulating amino acid pool. In conditions where the uptake of cysteine into glutathione is impaired, the increased circulating cysteine concentrations then become available for incorporation in urea synthesis. However, the rate at which cysteine is metabolized by the liver into sulphate and protons depends on its circulating concentrations. Extensive cysteine catabolism results in proton-mediated inhibition of carbamoyl phosphate, the rate limiting step in urea synthesis, thereby favouring formation of glutamine rather than urea. Whereas both low serum urea concentrations and diminished glutathione stores are recognized findings in patients with malnutrition, these different aspects of cysteine metabolism do not necessarily change in parallel.

Administration of sublethal paracetamol dosages causes up-regulation of certain enzymes involved in the urea cycle, but does not independently alter urea production. In contrast, hypoglycaemia is a characteristic finding and of prognostic value after paracetamol overdose. Insulin-facilitated glucose transport mechanisms are essential for maintaining adequate intracellular glutathione concentrations, at least in part due to activation of gamma-glutamylcysteine synthetase. This transporter system is impaired by regular ethanol consumption, and ethanol is capable of inhibiting hepatic gluconeogenesis in a dose dependent manner. Therefore, diminished glucose availability and transport might contribute to glutathione depletion independent of effects on urea synthesis. If glutathione depletion is the mechanism responsible for increased susceptibility to toxicity, then biomarkers of this specific aspect of nutrition might allow better risk stratification than serum urea concentrations.

A limitation is that the data were derived from a single centre, and a fairly conservative approach is adopted in the guidelines for N-acetylcysteine administration. The study population had a high prevalence of risk factors for paracetamol toxicity, and the present findings might not be generalizable to populations with lesser ethanol consumption, or different policies regarding N-acetylcysteine administration. A small number of patients developed hepatotoxicity despite paracetamol concentrations below the ‘100-line’, as reported elsewhere. The study design does not address the prognostic value of serum urea concentrations in an untreated population. For example, low serum urea concentrations might serve as a marker of risk in patients lacking conventional risk factors, and the possible merit of N-acetylcysteine treatment in such patients requires further consideration.

In conclusion, low serum urea concentrations do not independently predict an increased risk of hepatotoxicity after paracetamol overdose, in the setting of treatment practices at this particular emergency department. Further work is required to explore whether specific measures of glutathione depletion might provide a more useful means of initial risk stratification.

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**Conflict of interest:** None declared.

**References**