Serum Phosphate is an Early Predictor of Outcome in Severe Acetaminophen-Induced Hepatotoxicity

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Overview

- Acetaminophen overdose can result in fatal fulminant hepatic failure
- The Decision to Transplant Difficult
  - Psychosocial issues
  - Potentially survivable
  - Rapid progression of the illness
  - Multisystem organ dysfunction
Transplant Criteria

- King’s College Criteria
  - Ph < 7.30 @ 24 hrs after fluid correction
  - Prothrombin time > 100 sec (INR 6.5)
  - Encephalopathy = grade 3/4
  - Creatinine > 300 µmol/l (3.4 mg/dl)
Kings Performance

- Sensitivity 69% (55 – 100%)
- Specificity 92% (43 – 100%)
- +LR 12.33 and –LR 0.29

PO$_4$ and Liver Failure

- Hypophosphatemia reported in cases of acute liver from Acetaminophen
- The degree of hypophosphatemia correlated with severity

Jones et al. The Lancet, 2:8663, 1989
Mean minimum serum PO4 conc (mmol/l) in with acetaminophen ingestions

Adapted from Jones et al. The Lancet, 2:8663, 1989
Serum Phosphate Is an Early Predictor of Outcome in Severe Acetaminophen-Induced Hepatotoxicity

Lars E. Schmidt and Kim Dalhoff

Hypophosphatemia is frequently observed in acetaminophen-induced hepatotoxicity and may be involved in the pathogenesis of hepatic failure. The aim of the study was to evaluate the prognostic value of serial measurements of serum phosphate in patients with severe acetaminophen poisoning. Prospectively, serial measurements of serum phosphate were performed in 125 patients with severe acetaminophen poisoning. The optimum threshold value of serum phosphate to discriminate nonsurvivors was identified. Prognostic value and speed of identification were compared with those of the King’s College Hospital (KCH) criteria. Phosphate concentrations were significantly higher in nonsurvivors than in survivors at 48 to 72 hours after overdose (mean 2.65 ± 1.16 mmol/L vs. 0.68 ± 0.22 mmol/L, P < .001) as well as 72 to 96 hours after overdose (2.12 ± 0.22 mmol/L vs. 0.59 ± 0.23 mmol/L, P < .001). A threshold phosphate concentration of 1.2 mmol/L at 48 to 96 hours after overdose had sensitivity 89%, specificity 100%, accuracy 98%, positive predictive value 100%, and negative predictive value 98%. The phosphate criteria had higher sensitivity, accuracy, and positive and negative predictive values than the KCH criteria, and it identified patients significantly earlier after transfer (median 1 hour vs. 12 hours (2-192 hours), P < .05, respectively). In nonsurvivors, the degree of hypophosphatemia correlated with renal dysfunction (R = .55; P = .02). In conclusion, hypophosphatemia after acetaminophen overdose is seen exclusively in nonsurvivors, which makes it a highly specific as well as sensitive predictor of nonsurvival. We propose that hypophosphatemia is caused by renal dysfunction in the absence of hepatic regeneration, as the latter appears to be associated with lowering of serum phosphate. (HEMATOLOGY 2002;36:659-665.)
Study Design

- Prospective Observational Study
  - 1999 - 2000
- Patients transferred to Liver center with concern for APAP-induced hepatoxicity
- All patients given NAC
- Daily phosphate levels
- Daily metabolic panel
- Daily INR
# Results

<table>
<thead>
<tr>
<th>Baseline Demographics (n=125)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age</td>
<td>35 (range 13 – 79)</td>
</tr>
<tr>
<td>Female</td>
<td>84 (67%)</td>
</tr>
<tr>
<td>Median quantity APAP ingested</td>
<td>35 g (interquartile range 22-50g)</td>
</tr>
<tr>
<td>Time to NAC</td>
<td>23 hrs (Interquartile range 14-42 hr)</td>
</tr>
</tbody>
</table>
Outcomes

- Severe hepatoxicity
  - ALT > 1000
- Encephalopathy
  - Grade II or III
- Liver Transplant
- Death
Fig. 1. Phosphate concentrations on days 2 and 3 for patients without severe hepatotoxicity (NoTox), with severe hepatotoxicity without hepatic encephalopathy (HepTox), with hepatic encephalopathy and spontaneous survival (HE), and without spontaneous survival (Death/OLT). Dotted lines depict normal range.

From Schmidt and Dalhoff, Hepatology, 36:3, 2002.
Table 1. Levels of Serum Phosphate, INR, Creatinine, and pH for Different Groupings of Patients With Severe Acetaminophen-Induced Hepatotoxicity

<table>
<thead>
<tr>
<th></th>
<th>Patients With Hepatotoxicity</th>
<th>Patients With HE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Non-HE</td>
<td>HE</td>
</tr>
<tr>
<td><strong>Day 2</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum phosphate</td>
<td>0.67 ± 0.21</td>
<td>1.78 ± 1.33*</td>
</tr>
<tr>
<td>(mmol/L)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>INR</td>
<td>3.10 ± 1.29</td>
<td>5.20 ± 1.96†</td>
</tr>
<tr>
<td>Creatinine</td>
<td>97 ± 61</td>
<td>196 ± 92†</td>
</tr>
<tr>
<td>(μmol/L)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Day 3</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum phosphate</td>
<td>0.67 ± 0.22</td>
<td>1.61 ± 1.07†</td>
</tr>
<tr>
<td>(mmol/L)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>INR</td>
<td>2.23 ± 0.96</td>
<td>4.49 ± 1.80†</td>
</tr>
<tr>
<td>Creatinine</td>
<td>114 ± 87</td>
<td>246 ± 126†</td>
</tr>
<tr>
<td>(μmol/L)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>After fluid</td>
<td></td>
<td></td>
</tr>
<tr>
<td>resuscitation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>pH</td>
<td>7.44 ± 0.08</td>
<td>7.27 ± 0.18†</td>
</tr>
</tbody>
</table>

**NOTE.** Values are given as mean ± SD.
Abbreviations: HE, hepatic encephalopathy; INR, international normalized ratio; OLT, orthotopic liver transplantation.

*P < .05.
†P < .001 (Mann-Whitney).
Phosphate as a predictor of outcome

- ROC curves Day 2 and 3 for Phosphate and nonsurvival
- Serum PO4 level = 1.2 mmol/L

Table 2. Assessment of Serum Phosphate Measurement and King’s College Hospital (KCH) Criteria as Prognostic Indicators in 106 Patients With Severe Acetaminophen-Induced Hepatotoxicity

<table>
<thead>
<tr>
<th>Indicator</th>
<th>n</th>
<th>Died</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
<th>Accuracy</th>
<th>Time (h)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phosphate criteria</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;1.2 mmol/L on day 2 (n = 83)</td>
<td>9</td>
<td>9</td>
<td>90</td>
<td>100</td>
<td>100</td>
<td>99</td>
<td>99</td>
<td>6 (1-38)</td>
</tr>
<tr>
<td>&gt;1.2 mmol/L on day 3 (n = 101)</td>
<td>16</td>
<td>16</td>
<td>89</td>
<td>100</td>
<td>100</td>
<td>98</td>
<td>98</td>
<td>10 (1-62)</td>
</tr>
<tr>
<td>Either phosphate criterion</td>
<td>16</td>
<td>16</td>
<td>89</td>
<td>100</td>
<td>100</td>
<td>98</td>
<td>98</td>
<td>1 (1-38)†</td>
</tr>
<tr>
<td>KCH criteria</td>
<td>15</td>
<td>12</td>
<td>67</td>
<td>97</td>
<td>80</td>
<td>93</td>
<td>92</td>
<td>12 (2-192)</td>
</tr>
<tr>
<td>KCH or either phosphate criterion</td>
<td>20</td>
<td>17</td>
<td>94</td>
<td>97</td>
<td>85</td>
<td>99</td>
<td>96</td>
<td>4 (1-79)†</td>
</tr>
</tbody>
</table>

Abbreviations: PPV, positive predictive value; NPV, negative predictive value.

*Median (range) time from transferal to the department of hepatology to the criteria being fulfilled.
†P < .05 in comparison with KCH criteria (Mann-Whitney).

From Schmidt and Dalhoff, Hepatology, 36:3, 2002.
Authors Conclusions

- Hyperphosphatemia after APAP overdose seen only in non-survivors
- Serum PO4 level > 1.2 mmol/l better predictor of survival than KCH
- Hypophosphatemia associated with survival
- Hyperphosphatemia caused by renal failure
Letters to the Editor and further work

  - Provide data showing PO4 not better than KCH

- Go et al. Hepatology, 38:2, 2003
  - Provides data showing PO4 worse performance than KCH

- Ng and Bathgate, Liver Transplantation, 10:1, 2004
  - Provide data showing PO4 not reliable indicator of survival
Conclusion

- For LLSA
  - Serum PO4 > 1.2 mmol/l on day 2 or 3 after APAP overdose associated with non-survival
  - PO4 better predictor than KCH
  - Hyperphosphatemia secondary to Renal failure
  - Hypophosphatemia associated with Liver toxicity recovery

- For the Real world
  - An elevated PO4 is associated with poor outcome but does not add anything to already established predictor models.