Long Live the King!
Comparing prognostic markers in acetaminophen poisoning fatalities

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Disclosure

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• None of the authors have any conflicts of interest to disclose with respect to this presentation.
Introduction

• Acetaminophen (APAP) is the most common etiology of acute liver failure (ALF) in many countries
• Most APAP-poisoned patients recover uneventfully
• Decision on whom to consider for transplant remains challenging
APAP poisoning: prognostic markers

- Imperfect sensitivity
- Time from ingestion to marker becoming ‘positive’ not well described
- Some tests not readily available
- Applicability to patients not in specialized liver failure units unclear
Objective

• To compare several different prognostic markers in a large national cohort of patients who died or were referred for liver transplant secondary to acetaminophen poisoning
Methods

- Structured retrospective medical record review of patients between 1980-2010
  - Primary or secondary discharge diagnosis of APAP poisoning
  - ICD 9 (965.4) or 10 (T39.1) codes
  - 34 hospitals in 8 Canadian cities (Calgary, Vancouver, Kingston, Halifax, Ottawa, Montréal, Toronto, Edmonton)
- Explicit *a priori* definitions
- Trained data abstractors, standardized forms
- Inter-rater reliability > 0.8 achieved in all cases

Inclusion criteria

• Acute (≤ 8 hours) or chronic (> 8 hours) APAP overdose with known time of ingestion

• During hospitalization:
  – Coagulopathy (peak INR>1.5 or PT>16 seconds)
  – Encephalopathy grade ≥ 1
  – Death or referral for liver transplant
Prognostic markers

- King’s College Criteria (KCC)
- MELD > 33
  - Age < 12 excluded
- Phosphate > 1.2 mmol/L
- Lactate > 3.5 mmol/L
- KCC or Phosphate > 1.2 mmol/L
- KCC or Lactate > 3.5 mmol/L
Outcome measures

• Primary:
  – Sensitivity of each prognostic marker

• Secondary:
  – Time interval from ingestion and hospital admission until each prognostic marker became ‘positive’
Results

11,987 charts identified from 1980-2005

173 fatalities + 22 referrals for liver transplant

11,792 patients recovered

34 fatalities from 2006-2010

207 fatalities + 22 referrals for liver transplant

161 excluded
  • chart not available = 56
  • inclusion criteria not met = 105

68 patients met inclusion criteria
### Patient characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Result (n=68)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, y (IQR)</td>
<td>39.5 (22.7)</td>
</tr>
<tr>
<td>Gender, female, no. (%)</td>
<td>40 (58.8)</td>
</tr>
<tr>
<td>Acute APAP ingestion (≤ 8 hour period), no. (%)</td>
<td>6 (8.8)</td>
</tr>
<tr>
<td>Acute ethanol ingestion, no. (%)</td>
<td>27 (39.7)</td>
</tr>
<tr>
<td>Chronic ethanol ingestion, no. (%)</td>
<td>37 (54.4)</td>
</tr>
<tr>
<td>N-acetylcysteine (NAC) given, no. (%)</td>
<td>60 (88.2)</td>
</tr>
<tr>
<td>Median time from ingestion to start of NAC (assuming known time of ingestion), hours (IQR)</td>
<td>58.8 (76.6)</td>
</tr>
<tr>
<td>Median duration of treatment with NAC, hours (IQR)</td>
<td>29.5 (41.5)</td>
</tr>
<tr>
<td>Death, no. (%)</td>
<td>61 (89.7)</td>
</tr>
<tr>
<td>Received liver transplant, no. (%)</td>
<td>3 (4.4)</td>
</tr>
</tbody>
</table>
## Patient characteristics

<table>
<thead>
<tr>
<th>Characteristic (first measurement)</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aminotransferase level, IU/L, median (IQR)</td>
<td>2203 (4780)</td>
</tr>
<tr>
<td>INR, median (IQR)</td>
<td>3.8 (4.9)</td>
</tr>
<tr>
<td>Creatinine, umol/L, median (IQR)</td>
<td>170 (203)</td>
</tr>
<tr>
<td>Serum pH, median (IQR)</td>
<td>7.27 (0.29)</td>
</tr>
<tr>
<td>Phosphate, mmol/L, median (IQR)</td>
<td>1.6 (1.6)</td>
</tr>
<tr>
<td>Lactate, mmol/L, median (IQR)</td>
<td>9.2 (10.4)</td>
</tr>
<tr>
<td>Ammonia, mmol/L, median (IQR)</td>
<td>108.8 (102.0)</td>
</tr>
<tr>
<td>Grade of encephalopathy, no. (%)</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>9 (13.2)</td>
</tr>
<tr>
<td>1</td>
<td>1 (1.5)</td>
</tr>
<tr>
<td>2</td>
<td>12 (17.6)</td>
</tr>
<tr>
<td>3</td>
<td>17 (25)</td>
</tr>
<tr>
<td>4</td>
<td>29 (42.7)</td>
</tr>
</tbody>
</table>
## Prognostic markers

<table>
<thead>
<tr>
<th>Prognostic marker (for death)</th>
<th>Number of patients with data (%)</th>
<th>Sensitivity, % (95% CI)</th>
<th>Median time from ingestion to marker fulfillment, hours [IQR]</th>
<th>Median time from hospital admission to marker fulfillment, hours [IQR]</th>
</tr>
</thead>
<tbody>
<tr>
<td>KCC</td>
<td>68 (100)</td>
<td>80.3 (68.2, 89.4)</td>
<td>90.8 [109.7]</td>
<td>17.8 [25.3]</td>
</tr>
<tr>
<td>MELD &gt; 33</td>
<td>59 (87)</td>
<td>47.1 (33.3, 61.3)</td>
<td>88.3 [66.7]</td>
<td>14.8 [18.5]</td>
</tr>
<tr>
<td>Lactate &gt; 3.5 mmol/L</td>
<td>55 (81)</td>
<td>65.3 (50.4, 78.3)</td>
<td>108.3 [98.3]</td>
<td>19.9 [15.8]</td>
</tr>
<tr>
<td>Phosphate &gt; 1.2 mmol/L</td>
<td>31 (46)</td>
<td>79.3 (60.3, 92.0)</td>
<td>112.4 [123.3]</td>
<td>17.6 [17.8]</td>
</tr>
<tr>
<td>KCC or phosphate &gt; 1.2 mmol/L</td>
<td>68 (100)</td>
<td>83.6 (71.9, 91.9)</td>
<td>90.9 [103.6]</td>
<td>16.3 [10.6]</td>
</tr>
<tr>
<td>KCC or lactate &gt; 3.5 mmol/L</td>
<td>68 (100)</td>
<td>90.2 (79.8, 96.3)</td>
<td>69.8 [97.8]</td>
<td>16.3 [12.4]</td>
</tr>
</tbody>
</table>
Discussion

• Addition of lactate improved sensitivity
• Prognostic markers became positive:
  – 3-5 days after ingestion
  – during the first 24 hours after hospital admission

Craig et al. Alim Pharm Ther 2010;31:1064-1076
Discussion

• ICU scoring systems (e.g. SOFA, APACHE II) may provide better assessment of overall organ status at ICU admission*

• Early-identification prognostic markers (e.g. Psi, MALD) require prospective validation**

Strengths

- Adult, pediatric, tertiary, community, transplant hospitals represented
- Markers studied throughout hospitalization
- Adherence to generally accepted criteria for medical record reviews
Limitations

- Retrospective, small numbers
- Fatalities only
- Intentional vs. unintentional overdose not clarified
- Lactate arterial or venous
- Fluid resuscitation and FFP use not assessed
- Inclusion of liver transplant recipients
- Other scoring systems not studied
Conclusions

• In this cohort of Canadian patients hospitalized for acetaminophen poisoning:
  – Addition of lactate > 3.5 mmol/L to KCC provided the highest sensitivity and the shortest time interval from ingestion to criteria fulfillment
  – Markers became positive during the first day of hospital admission

• Ongoing efforts at earlier detection of those unlikely to survive is required
  – Early listing of those likely to require transplant
  – Avoid transplantation of those likely to survive
CAOS Death Analysis
Investigators

David Johnson, Marco Sivilotti, Alberto Nettel-Aguirre, Charlemaigne Victorino, Chris DeWitt, Sophie Gosselin, Nancy Murphy, Benoit Bailey, Kathryn Dong, Elizabeth Haney, Roy Purssell, Randall Berlin, Margaret Thompson, Rob Myers, Jason Lord, Daniel Spyker, Barry Rumack
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