Clinical Outcomes and Predictive Factors in “Massive” Paracetamol Overdose

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Background

- Paracetamol overdose common
- Readily treatable with N-acetylcysteine (NAC)
- NAC dose determined only by weight
- Unclear whether NAC dose should vary for larger paracetamol overdoses
Aim

To evaluate determinants of outcome in “massive” paracetamol overdose
Methods

- Retrospective observational study
  - Two UK tertiary care hospitals
  - All presentations from 2005-2013
  - Prospective data entry on toxicology database

- Inclusion criteria
  - Single acute timed overdoses
  - Reported ingestion ≥30g paracetamol
  or
  - Plasma paracetamol concentration 2* >150mg/L treatment line
Demographics and Case Features

- 127 cases identified:
  - 88 (69.2%) female
  - Age: median 32 (IQR 23-42) years

- Ingested dose: 24 (16-36) g
- Plasma concentration: 182 (79-256) mg/L
- Time to presentation: 5.5 (3.5-13.3) h
  - Presentation >8h: 41.7%
Liver Injury

- Serum transaminase rise:
  - >3x ULN: 32 (25.6%)
  - >5x ULN: 28 (22.0%)
  - >1,000iu/L: 17 (13.4%)
  - >10,000iu/L: 4 (3.1%)

- INR rise:
  - >2: 12 (9.4%)
  - >6.5: 2 (1.6%)
Time to Presentation and NAC

- $r=0.2096$, $p=0.02$
- $r=0.1179$, $p=0.2$
- $r=0.2964$, $p=0.008$
- $r=0.2740$, $p=0.02$
No Association with Dose or Unadjusted Plasma Paracetamol Concentration

- Serum Aminotransferase vs. Ingested Dose: $r=0.1442$, $p=0.12$
- INR vs. Ingested Dose: $r=0.093$, $p=0.3$
- Serum Aminotransferase vs. [APAP]$_{pl}$: $r=-0.063$, $p=0.5$
- INR vs. [APAP]$_{pl}$: $r=-0.091$, $p=0.3$
\[ [\text{APAP}]_{pl} : [\text{APAP}]_t \]
$[\text{APAP}]_{pl}: [\text{APAP}]_t$ Predicts Adverse Outcome

$r = 0.3279$

$p = 0.0002$
Patients Receiving NAC Within 8h

\[
\frac{[\text{APAP}]_{\text{pi}}}{[\text{APAP}]_t}
\]

- No Liver Injury: \(n=25\)
- Liver Injury: \(n=4\)

\(p=0.03\)
Limitations

- Reliance on patient history and contemporaneous medical documentation
- Blood tests during routine clinical care and so not completely systematic
- No repeated $[APAP]_{pl}$ to allow calculation of $t^{1/2}$
## Plasma paracetamol concentration at hospital presentation has a dose-dependent relationship with liver injury despite prompt treatment with intravenous acetylcysteine

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<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>Edinburgh 301–500</th>
<th>Edinburgh 501+</th>
<th>London 300+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases</td>
<td>82</td>
<td>45</td>
<td>127</td>
</tr>
<tr>
<td>Sex (%male)</td>
<td>32</td>
<td>43</td>
<td>31</td>
</tr>
<tr>
<td>Median age (years)</td>
<td>33</td>
<td>39</td>
<td>32</td>
</tr>
<tr>
<td>Median admission APAP level (IQR)(mg/L)</td>
<td>279 (179–349)</td>
<td>101 (49–236)</td>
<td>182 (79–256)</td>
</tr>
<tr>
<td>Number with ALT &gt;150 U/L</td>
<td>11 (13%)</td>
<td>12 (27%)</td>
<td>32 (26%)</td>
</tr>
<tr>
<td>Number with ALT &gt;1000U/L (% group)</td>
<td>5 (6%)</td>
<td>8 (18%)</td>
<td>17 (1%)</td>
</tr>
</tbody>
</table>
Conclusions

- Massive paracetamol overdose associated with significant hepatotoxicity, even with early NAC

- Optimal management will depend on whether this relates to plasma AUC or disturbed absorption/elimination

- Implications for use of early biomarkers and abbreviated treatment regimens