Paracetamol overdose - A hepatology perspective

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Outline

Paracetamol induced acute liver failure

• Why does it happen?
• How to recognise it
• How it kills
• What to do and when to refer
• What happens in the transplant unit
• Aftermath…
Why does it happen?
Why does it happen?
Why does it happen?

N-Hydroxylation and rearrangement (CYP-mediated)

Glutathione
Why does it happen?
Why does it happen?

[Diagram showing the metabolism of paracetamol including N-hydroxylation, sulfation, glucuronidation, and GSH conjugation]

Toxic reactions with proteins and nucleic acids
Why does it still happen?

- Legislation was passed (UK) in 1998 to limit the number of tablets to 16 tablets (up to 32 tablets in pharmacies).
- Blister packs; may make take the actual tablets take longer.

**BMJ** 2013 Feb 7. Hawton K et al

- ‘estimated reduction of 17 deaths per ¼ in involving paracetamol alone… 61% reduction in registrations for liver transplantation…’

Suicide and open verdict deaths involving paracetamol in England and Wales, 1993-2009
Paracetamol related liver transplantations, 1995-2009

Legislation introduced (3rd quarter, 1998)
Fatal Accident Inquiry into the death of Danielle Welsh (2008)

“...a foundation year one doctor, was asked to prescribe pain relief and anti-emetic drugs. She did not know her weight. She proceeded to prescribe on the basis that Danielle was an adult. In the event, the dosage prescribed, 1g four times daily, was in excess of the appropriate dosage for someone of Danielle’s weight (35kg). She should have received 525mg per dosage.”

“Danielle was seen by 11 nurses and 12 different doctors and received 20 doses of paracetamol. The doctors were at all levels and not one of them noted the overdose.”
Simplified nomogram
# How to recognise it – 1] 3 phases

<table>
<thead>
<tr>
<th>0-24 hrs</th>
<th>24-48 hrs</th>
<th>72 hrs +</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea, vomiting, anorexia, sweating</td>
<td>May feel better, RUQ pain, blood tests deranged</td>
<td>Liver failure, somnolence, jaundice, multi-organ failure</td>
</tr>
</tbody>
</table>
How to recognise it - 2] features

• Transaminase elevation
  – ‘hepatocellular necrosis’…many 1000’s

• The cardinal features of ALF
  – Encephalopathy, Coagulopathy…NOT jaundice

• Liver specific features
  – Hypoglycaemia, lactic acidosis, rising bilirubin, unrecordable INR
How it kills - 1] Cerebral oedema

- Young patients (less cranial ‘space’)
- ‘Hyperacute’ ALF cases.
- Predicted by high grade encephalopathy (grade III/IV)
- Arterial ammonia > 100 mmol/L
Signs of cerebral oedema

Grade I – Euphoria, fluctuating confusion, slurred speech
Grade II – Drowsiness with ability to converse
Grade III – Rousable sleep but unable to hold conversation
Grade IV – Unrousable and comatose

90% of grade 3 will progress to grade 4.

- Early: bradycardia, sluggish pupils
- Late: hypertonicity, clonus, Cushings response (high BP, low pulse), fixed pupils, abnormal temperature, false localising signs
How it kills - 2] Shock

- Vasodilatory (looks like septic shock)
- Often fluid unresponsive but vasopressor responsive
- Need to maintain cerebral perfusion

NB: *Adrenocorticoid insufficiency* found in 62% of ALF
Vasopressor sparing effect of steroids recognised
  - (300mg hydrocortisone over 24 hours)
How it kills - 3] Sepsis

• ALF is highly immunosuppressing
  – 80% of ALF develop positive bacterial cultures
  – 30% fungal infection reported
  – If fulfilling ‘poor prognostic’ criteria:
    • Tazocin 4.5g TDS IV
    • Fluconazole 50mg OD PO/IV
How it kills - 4] Renal failure

• Renal replacement therapy may be required to manage acidosis (continuous veno-venous haemofiltration)
How it kills - 5] others…

- Unrecognised hypoglycaemia
- Lung injury/ARDS (9/24 ≈ 37% in one study)
- Pancreatitis

...but very rarely bleeding despite high INR
What to do…
What to do...

Left brain
I am the left brain.
I am a scientist. A mathematician.
I love the familiar. I categorize. I am accurate. Linear.
Analytical. Strategic. I am practical.
Always in control. A master of words and language.
Realistic. I calculate equations and play with numbers.
I am order. I am logic.
I know exactly who I am.

Right brain
I am the right brain.
I am creativity. A free spirit. I am passion.
Yearning. Sensuality. I am the sound of roaring laughter.
I am taste. The feeling of sand beneath bare feet.
I am movement. Vivid colors.
I am the urge to paint on an empty canvas.
I am everything I wanted to be.

PROTECT THE BRAIN
What to do…

- Maintain oxygenation
- Escalate level of care
- Review frequently
- Avoid hypoglycaemia
- Avoid cerebral oedema precipitants

PROTECT THE BRAIN
What to do – 2] the clotting question!

• ‘Don’t give FFP, they’ll go mad…’
  – True, to an extent
  – INR is a key prognostic marker
  – Unless bleeding, doesn’t need correcting
  – Can wait until they get to liver unit for most lines
  – Art line can be placed safely with high INR
  – CVC with USS guidance also reasonably safe
What to do – 3] N-acetylcysteine (NAC)

- Give NAC if paracetamol poisoning a possibility regardless of time scale
- Consider staggered overdose
- Don’t stop it
- Some evidence in non-paracetamol poisoning:
  - Reduction in onset of encephalopathy
  - Survival benefit
  - Anti-oxidant, may reduce endothelial dysfunction and inflammation
When to refer…

• Transplant criteria: ideally the transplant unit will receive the patient before these are hit.

**King’s College Criteria**

*Paracetamol related cases only*

► pH < 7.3 following volume resuscitation and >24 hours post ingestion

*or*

► PT > 100 (INR > 6.5) *plus* creatinine > 300 mcmol/l *plus* grade III/IV encephalopathy within a 24 h time frame

*Strongly consider transplantation in paracetamol related cases if arterial lactate > 3.5 mmol/l after early fluid resuscitation.*
<table>
<thead>
<tr>
<th>Day 2</th>
<th>Day 3</th>
<th>Day 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH &lt;7.30</td>
<td>pH &lt;7.30</td>
<td>-</td>
</tr>
<tr>
<td>INR &gt;3</td>
<td>INR &gt;4.5</td>
<td>Any rise in INR</td>
</tr>
<tr>
<td>Encephalopathy</td>
<td>Encephalopathy</td>
<td>Encephalopathy</td>
</tr>
<tr>
<td>Creatinine &gt; 200µmol/L</td>
<td>Creatinine &gt; 200µmol/L</td>
<td>Creatinine &gt; 250µmol/L</td>
</tr>
<tr>
<td>Hypoglycaemia</td>
<td></td>
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</table>
Management in liver unit - 1] General

- ‘Line up’ – CVC, IABP, PiCCO, Vascath
- Optimise filling/ITBV, vasopressors
- Glucose
- Antimicrobial prophylaxis
- Gut protection
- Platelet supplementation
- Medical background
- Social background
  - support, treated psychiatric condition?
Management in liver unit - 2] Brain

- Maintain cerebral perfusion pressure
  \[ \text{CPP} = \text{MAP} - \text{ICP} \] (autoregulation cannot cope)
- Avoidance of hyponatraemia, evidence for hypertonic saline
- Cooling, 45% degree, minimal stimulation
- Reverse IJ line +/- Intracranial ‘bolt’
- Mannitol, Indomethacin, Thiopentone

- Render ‘anhepatic’…
Brain - Intra-cranial ‘bolts’
The decision to transplant

• ‘Yes’
  – Activate on national super-urgent waiting list
  – ‘next available blood group matched liver’

• Surgery
  – May consider ‘auxiliary’ transplant
  – Native liver left in-situ; can recover and take over function from the transplant (no meds for life)
Aftermath: ALF vs cirrhosis survival

Patient survival according to the first indication for liver transplantation in Europe, January 1988 to December 2001. (Source: European Liver Transplant Registry) [Bernal 2004]
Aftermath: mental health

Medical and psychiatric outcomes for patients transplanted for acetaminophen-induced acute liver failure: a case-control study. *Carvellas et al, 2010 Liver Int*

36 paracetamol ALF patients, 1999-2005
Outcomes compared to 35 non-paracetamol ALF patients

| 20 (56%) | had formal psychiatric diagnosis |
| 9 (25%)  | had previous suicide attempt |

During follow (median 5 years):
- No significant differences in rejection, graft failure or survival between the groups
- Two paracetamol ALF patients reattempted suicide post-LT (one died 8 years post-LT)

‘Multidisciplinary approaches with long-term psychiatric follow-up may contribute to low post-transplant suicide rates seen and low rates of graft loss because of non-compliance.’