Controversies in Toxicology

Dr Angela Chiew
Clinical Toxicologist and Emergency Physician
Prince of Wales Hospital
NSW PIC
• Activated Charcoal
• Acetylcysteine Dose
• Intravenous Lipid Emulsion (ILE)
• Digoxin-Specific Antibodies
Activated Charcoal

• “No indication for charcoal anymore”

• “Do we still use activated charcoal?”

• “The patients won’t drink it, so I don’t offer it”

• “But the ingestion was over 1 h ago.”
Activated Charcoal

• Significant decrease in the use of activated charcoal in recent years:
  – A position statement published in 1997 questioned the use of single-dose activated charcoal (SDAC) more than an hour after ingestion.
  – based on little new evidence
  – possibly because the overall mortality in overdose patients is low.
• Charcoal isn’t for every patient HOWEVER
A 22 year old, 55 kg woman presents 1 h post-ingestion of 30 tablets of 500 mg paracetamol (15 g).

She denies any other co-ingestion.

She is awake and alert and denies any symptoms.

DO YOU ADMINISTER
Results: Who gave charcoal?

– Clinical Toxicologist: 16 (89%) (n= 18)
– Emergency Consultants : 96 (50%) (n= 192)
– Emergency Registrars: 101 (53%) (n=189)

• Reasons not to give:
  – Toxicity (25%)
  – Time (56%)

• Many commented - acetylcysteine was a superior and safer treatment strategy
The average reduction in systemic drug absorption was
- 47.3% at 30 min,
- 40.1% at 60 min and
- 16.5% at 120 min
Volunteer Studies

• Different drugs are affected by charcoal in different ways:
  – Decrease absorption
  – Increase clearance
  – Or both

• ??? whether decrease in drug concn leads to a clinical benefit
RCT’s

**Cooper et al**
- 327 pts randomised - 50g AC vs no AC
- Found no difference in the length of hospital stay
- Large number of patients included unlikely to develop toxicity – would have had a good outcome irrespective of SDAC
- Patient’s with severe toxicity excluded

**Eddleston et al**
- Rural Sri Lanka
- 4632 pts randomised 50g AC every 4h for 6 doses vs no AC
- No mortality difference
- Limitations:
  - Mainly included pesticides and oleander
  - Median time to treatment > 4h


Paracetamol

- **Buckley et al:**
  - January 1987 and September 1996: HATS
  - AC within 2 hrs vs no AC - 15% vs 41% required acetylcysteine

- **Duffull et al:**
  - 1997-2011: HATS

SDAC reduces the probability of NAC by:
- up to 14% at 28g
- < 10% at either doses lower than 19 g or doses greater than 37 g

2. Duffull SB, Isbister GK. Predicting the requirement for N-acetylcysteine in paracetamol poisoning from reported dose. Clinical Toxicology (Phila) 2013; 51: 772-776.
Specific Poisoning

- **Citalopram:**
  - SDAC almost doubled the clearance and reduced the fraction absorbed by 22%
  - SDAC reduced the chance of high-risk QT-RR combinations by approximately 60%

• Low risk procedure in awake and alert patient
• ?? Distasteful - AC RCT: adults allocated to treatment with AC consumed 83% of their first dose.
Vomiting

• AC is frequently blamed for causing an increased risk of vomiting but this is not the case.

• Cooper et al

<table>
<thead>
<tr>
<th></th>
<th>No decontamination ((n = 161))</th>
<th>Charcoal ((n = 166))</th>
<th>(P) value (Fisher’s exact)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vomited in hospital</td>
<td>23 (14%)</td>
<td>25 (15%)</td>
<td>0.88</td>
</tr>
<tr>
<td>Ventilated</td>
<td>3 (2%)</td>
<td>8 (5%)</td>
<td>0.22</td>
</tr>
<tr>
<td>Aspiration</td>
<td>1</td>
<td>1</td>
<td>NA</td>
</tr>
<tr>
<td>Death</td>
<td>1</td>
<td>0</td>
<td>NA</td>
</tr>
</tbody>
</table>
Severe complications

- Aspiration pneumonia:
  - Cohort study of more than 4500 overdose patients
  - 71 (1.6%) developed aspiration pneumonitis.
  - Emesis, seizure and altered mental status were among the independent predictors of aspiration but NOT the administration of activated charcoal.

- Bowel obstruction

SDAC MAY BE OF BENEFIT TO DECREASE LOS, NEED FOR INVASIVE TREATMENTS OR ANTIDOTES

LIFE THREATENING WITH SEVERE COMPLICATIONS

“Do I believe that the overdose is likely to cause life threatening toxicity, that can not be treated with good supportive care and or specific antidotes, that I am willing to intubate this patient against there will to administer charcoal?”
Activated Charcoal

• Severe Toxicity:
  – Verapamil
  – Colchicine
  – “Massive” ingestions – dose that makes the poison !!!

• SDAC may be of benefit
  – Paracetamol
  – Aspirin
  – MR preparations – metformin, paracetamol
  – Citalopram
  – Venlafaxine MR
  – Digoxin
Paracetamol Case

Benefits:
• Decreased need for acetylcysteine.
• Decrease LOS
• Acetylcysteine up to 48% reaction rate

Risks of charcoal minimal in an awake alert pt
Massive Paracetamol Overdose
Case: Massive paracetamol overdose

• A 15 year old 55 kg female
• Background of depression and previous self harm
• 1 hour earlier ingested:
  – 100 x 500mg paracetamol = 50g
  – X 2 Sudafed
• Only symptom was nausea
Case

- Patient offered activated charcoal but refuses
- Paracetamol level = 260mg/L (1739µmol/L) (45mins)
- AST = 25  ALT = 17, INR = 1.2
- NAC started 2.5 hours post overdose
- 7 hour paracetamol level was 513mg/L (3426µmol/L)
- NAC was temporarily ceased during the third bag for 2 hours as the patient removed her cannula
• At the completion of the standard 20 hour IV acetylcysteine treatment (24 hours post overdose), NAC is ceased.
• Paracetamol level = 1779µmol/L (267mg/L)
• LFTs were now mildly elevated:
  – ALT: 191 U/L,
  – INR = 1.3
• IV NAC restarted (2 hours later) at 100mg/kg over 16 hours and was continued at this dose
Progress

- 30 hours post overdose she became confused with worsening LFT’s.
- 48 hours post overdose:
  - hypoglycaemia,
  - pH= 7.25, lactate = 14.5
  - INR 3.5
  - Intubated for grade III encephalopathy.
- Transferred to the liver unit
- 50 hours post overdose INR = 6.4
- Requires liver transplant 5 days post overdose.
Patients with high initial paracetamol levels have an increased risk of hepatotoxicity despite time to treatment.
Do we need more acetylcysteine in large overdoses?

• Acetylcysteine dosing is based on body weight and not paracetamol body burden.

• The original acetylcysteine dosing was conceived to detoxify the paracetamol toxic metabolite NAPQI, based on a 4% conversion rate.

• Theoretically, the standard IV acetylcysteine dose has been estimated to be sufficient to treat a paracetamol overdose of around 16 g.

• Severely poisoned patients have a higher proportion of the dose undergoes conversion to NAPQI
• Length of IV protocol based on 5 x 4hr T1/2
• DO WE NEED MORE ACETYLCYSTEINE AND FOR LONGER?
• When do we increase the dose and by how much ??
Australian Paracetamol Study (APP)

• Observational Study – prospectively and retrospectively cases (toxicology unit databases)

• **Inclusion:**
  – Paracetamol ≥40g
  – Ingested over ≤8h
  – Immediate release preparation
“Massive” (> 40g) Paracetamol Ingestion
### Table: Hepatotoxicity Outcome

<table>
<thead>
<tr>
<th>Variable</th>
<th>Unadjusted Odds Ratio (95%CI)</th>
<th>Adjusted Odds Ratio (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (10 year increments)</td>
<td>1.27 (0.88 – 1.82)</td>
<td>0.27 (0.07 – 0.98)</td>
</tr>
<tr>
<td>Paracetamol Ratio (continuous)</td>
<td>1.13 (0.95 - 1.34)</td>
<td>0.23 (0.06 - 0.86)</td>
</tr>
<tr>
<td>Time to IV acetylcysteine (hours)</td>
<td>1.2 (1.00 - 1.42)</td>
<td></td>
</tr>
<tr>
<td>Receipt of increased acetylcysteine dose#</td>
<td>0.27 (0.08 – 0.94)</td>
<td></td>
</tr>
</tbody>
</table>

*Note: The adjusted odds ratios were calculated after adjusting for the indicated variables.*

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**Graph A:** Standard acetylcysteine

- **Nomogram Line:** Displays the expected paracetamol concentration over time.
- **Hepatotoxicity Indicator:** Represents the incidence of hepatotoxicity over time.

**Graph B:** Increased dose acetylcysteine

- **Nomogram Line:** Same as Graph A, indicating the expected paracetamol concentration with increased dose.
- **Hepatotoxicity Indicator:** Maintains the same hepatoxicity trend as Graph A, showing the effect of increased dose on hepatotoxicity.
Activated Charcoal in “Massive” Overdose

[Graph showing paracetamol concentration over time post ingestion, with nomogram lines and adjusted odds ratio for hepatotoxicity]
“Massive” Paracetamol Ingestion

• > 30g paracetamol ingested offer activated charcoal until 4 hours post ingestion if co-operative.
• IV acetylcysteine adjustment:
  – Patients who have a paracetamol concentration more than double the nomogram line
  – Consider increasing the dose of NAC in the 100mg/kg over 16 hours infusion (3rd bag) -that is double dose to 200mg/kg IV NAC over 16 hours
• Near the completion of IV acetylcysteine:
  – check ALT and paracetamol concn
  – Acetylcysteine should be continued if they have an ALT >50U/L or a paracetamol greater than 10mg/L (66µmol/L).
There are controversies with the dose and effectiveness of digoxin Fab in chronic digoxin poisoning.

The recommended Digoxin Fab dose vary from half to full neutralisation.

Digoxin Fab (US$750 per vial) is expensive & has a short shelf life.

A prospective observational study of patients recruited through the New South Wales (NSW) Poisons Information Centre (PIC) from Sept 2013 to Feb 2015.
<table>
<thead>
<tr>
<th>Total number of patients</th>
<th>36</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Age</td>
<td>78 years (IQR: 70-85, Rang: 58-92)</td>
</tr>
<tr>
<td>Female (%)</td>
<td>22 (61%)</td>
</tr>
<tr>
<td>Median Creatinine concentration</td>
<td>228 umol/L (IQR: 128 – 277; CI: 194-291)</td>
</tr>
<tr>
<td><strong>Median initial heart rate</strong></td>
<td>45 (IQR: 35-65; CI 43-60)</td>
</tr>
<tr>
<td>Gastrointestinal symptoms</td>
<td>22 patients (61%)</td>
</tr>
<tr>
<td><strong>Initial median total digoxin concentration</strong></td>
<td>4.7 nmol/L (IQR: 3.3 – 6.4; CI: 4.4-5.8)</td>
</tr>
<tr>
<td>Median initial potassium concentration</td>
<td>5.4 mmol/L (IQR: 4.5 – 6.4; CI: 5.1-6.1)</td>
</tr>
<tr>
<td>No. patients taking beta-blockers or calcium antagonists (%)</td>
<td>24 patients (67%)</td>
</tr>
<tr>
<td>No. patients taking Angiotensin converting enzyme inhibitors, angiotensin receptor blockers or spironolactone (%)</td>
<td>24 patient (67%)</td>
</tr>
<tr>
<td>Initial ECG Rhythm</td>
<td>Numbers</td>
</tr>
<tr>
<td>---------------------------------</td>
<td>---------</td>
</tr>
<tr>
<td>AF</td>
<td>20</td>
</tr>
<tr>
<td>Junctional</td>
<td>6</td>
</tr>
<tr>
<td>Paced</td>
<td>5</td>
</tr>
<tr>
<td>Sinus bradycardia</td>
<td>3</td>
</tr>
<tr>
<td>Sinus rhythm</td>
<td>2</td>
</tr>
<tr>
<td>Non sustained VT</td>
<td>2</td>
</tr>
</tbody>
</table>
Median change in HR:
1 vial: 4.5 beats/min
2 vials: 10 beats/min
3 vials or more: 17.3 beats/min

No change in systolic BP

Decrease in potassium was 0.3 mmol/L (IQR: 0–0.8)
Free digoxin concentrations decreased to almost zero following the administration of anti-digoxin Fab regardless of the antibody dose used.

Patients who received >2 vials anti-digoxin Fab had excess free antibodies.
<table>
<thead>
<tr>
<th>Sex/Age</th>
<th>Initial free digoxin conc (nmol/L)</th>
<th>Free Digoxin conc following Dig Fab (nmol/L)</th>
<th>Dig Fab (mg)</th>
<th>HR before Dig Fab</th>
<th>HR after Dig Fab</th>
<th>K conc before Dig Fab</th>
<th>Cr before Dig Fab</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>F69</td>
<td>4</td>
<td>0</td>
<td>40</td>
<td>120</td>
<td>120</td>
<td>6.1</td>
<td>196</td>
<td>Respiratory &amp; cardiac failure</td>
</tr>
<tr>
<td>F72</td>
<td>4.7</td>
<td>0</td>
<td>80</td>
<td>73</td>
<td>73</td>
<td>6.6</td>
<td>167</td>
<td>Severe CCF.</td>
</tr>
<tr>
<td>F87</td>
<td>2.0</td>
<td>0</td>
<td>80</td>
<td>65</td>
<td>71</td>
<td>7.5</td>
<td>237</td>
<td>Respiratory failure</td>
</tr>
<tr>
<td>F90</td>
<td>3.9</td>
<td>0</td>
<td>80</td>
<td>64</td>
<td>62</td>
<td>7.2</td>
<td>429</td>
<td>UTI sepsis</td>
</tr>
<tr>
<td>F83</td>
<td>2.9</td>
<td>0.8</td>
<td>40</td>
<td>52</td>
<td>60</td>
<td>4.7</td>
<td>100</td>
<td>Respiratory failure</td>
</tr>
</tbody>
</table>
Case 1

1 vials DigiFab

Rebound in the free digoxin concentrations was seen in 25 BUT NOT associated with worsening clinical effects.
Conclusion

- One or two vials Digoxin-Fab was efficacious in reducing free digoxin concentration to zero.
- This was associated with only a moderate improvement in HR and potassium, suggesting bradyarrhythmia and hyperkalaemia may be from other co-morbidities.
- Digoxin-Fab may play a role in patients with significant haemodynamic compromise but one to two vials of Digoxin-Fab are adequate.
Conclusion/ Questions

- Decision to use AC is not well suited to an algorithmic approach but rather requires clinical judgement involving a global assessment of several patient-specific factors.
- In massive paracetamol overdose – don’t forget charcoal and increased acetylcysteine
- Digoxin-Fab may play a role in patients with significant haemodynamic compromise but one to two vials of Digoxin-Fab are adequate.
SAVE THE DATE
TAPNA Scientific Meeting
27 – 29 APRIL 2017
Novotel Melbourne on Collins
www.tapna.net