Recent understanding in the treatment of pesticide poisonings

Andrew Dawson

South Asian Clinical Toxicology Research Collaboration
Simplified Acute OP Toxicity

- Inactivation of acetylcholinesterase enzyme

Inhibition by insecticide oxon
Spontaneous

Inactive AChE

REACTIVATION

Induced Oxime

Degradation

Short acting AChE inhibition possible

Cholinergic signs & symptoms
Clinical Syndromes

- Acute Cholinergic:
  - Central
  - Peripheral Muscarinic
  - Peripheral Nicotinic
- Intermediate Syndrome
- Delayed peripheral neuropathy
- Neurocognitive dysfunction

Respiratory failure
Other Acute Toxicity

- Oxidative injury
- Catecholamine excess
- Non ACh mediated events
- Medical Complications
  - Poisoning
  - Treatment
The results of observational data on gastric emptying (GE) in pesticide self-poisoning

Case fatality
Anuradhapura Hospital
in and not in RCT

- GCS <14
- GCS <10

No GE (in trial)
GE (NIT)
Antidotes

- Atropine
- Oximes
  - Expensive
- Does treatment affect outcome
  - Intermediate Syndrome?
  - OPIDN?
Atropine Dose in Organophosphates

Ventilated OP patients who survived required

- Mean initial dose of 23.4 mgs.
- Maximum dose of 75 mg

38 texts with 31 different recommendations

- Eddleston et al. Speed of initial atropinisation in significant organophosphorus pesticide poisoning. J Tox Clin Tox 2004, 865-877
Scheme of atropinization
(endpoints to be reached)

<table>
<thead>
<tr>
<th>2</th>
<th>4</th>
<th>8</th>
<th>16</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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</tbody>
</table>

- **Atropine requirement**
- Poor air entry into lungs caused by bronchospasm and bronchorrhoea
- Excessive sweating
- (Hypotension)
- (Bradycardia)
- (Miosis)

- **Atropinization**
- Clear lungs
- Dry axillae
- Systol. BP > 80 mm Hg
- Heart rate > 80/min
- No miosis

*Journal of Toxicology – Clinical Toxicology 2004;6:865-875.*
Variation in organophosphorus pesticide syndromes

<table>
<thead>
<tr>
<th></th>
<th>Chlorpyrifos</th>
<th>Dimethoate</th>
<th>Fenthion</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of cases</strong></td>
<td>440</td>
<td>266</td>
<td>100</td>
</tr>
<tr>
<td><strong>WHO Toxicity</strong></td>
<td>II</td>
<td>II</td>
<td>II</td>
</tr>
<tr>
<td><strong>Formulation</strong></td>
<td>40% EC</td>
<td>40% EC</td>
<td>50% EC</td>
</tr>
<tr>
<td><strong>Chemistry</strong></td>
<td>Diethyl</td>
<td>Dimethyl</td>
<td>Dimethyl</td>
</tr>
<tr>
<td><strong>Rat oral LD50 (mg/kg)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WHO</td>
<td>135</td>
<td>150</td>
<td>Not Given</td>
</tr>
<tr>
<td>OSHA</td>
<td>97</td>
<td>250</td>
<td>215-245</td>
</tr>
</tbody>
</table>
Anti-cholinesterases

dimethoate
quinalphos
profenofos
fenthion
chlorpyrifos
diazinon
phenthoate
malathion
carbosulfan
fenobucarb
carbofuran

Case fatality ratio (95% CI)
Timing of death post-ingestion for 3 OPs

Myocardial Depression
## Median (IQR) Hours to Adm

<table>
<thead>
<tr>
<th></th>
<th>Chlorpyrifos</th>
<th>Dimethoate</th>
<th>Fenthion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hours to Adm</td>
<td>4 (2 to 5)</td>
<td>3 (2 to 5)</td>
<td>4 (2 to 7)</td>
</tr>
</tbody>
</table>

## Admission values

<table>
<thead>
<tr>
<th></th>
<th>Chlorpyrifos</th>
<th>Dimethoate</th>
<th>Fenthion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean [OP] (μM)</td>
<td>1.28</td>
<td><strong>355.5</strong></td>
<td>4.86</td>
</tr>
<tr>
<td>Median BuChE (mU/ml)</td>
<td>33.5</td>
<td>1129</td>
<td>0.0</td>
</tr>
<tr>
<td>Median AChE (mU/μmol Hb)</td>
<td>63.5</td>
<td>69.0</td>
<td>64.2</td>
</tr>
<tr>
<td>Median aged AChE</td>
<td><strong>19.4%</strong></td>
<td>71.9%</td>
<td>70.3%</td>
</tr>
</tbody>
</table>
Chlorpyrifos poisoning

- AChE in vivo
- AChE in vitro

- BChE

Time [h]

mU/µmol Hb

mU/ml Plasma
Dimethoate poisoning

- AChE in vivo
- AChE in vitro

- BChE

Graph showing the enzyme activity over time (h) for AChE in vivo and AChE in vitro, as well as BChE activity in plasma.
OPs are different

- Differing Toxicity
- Different Kinetics
- Different Clinical Syndromes
- Different Response to Antidotes
- ? Need Different Treatment Responses

Complicates Assessment of the Evidence for Oximes
Oximes

- Ineffective in some situations
  - Ageing
  - Variation between organophosphates

- Effective protocols not established
  - Variation in use
    - Zero – 24 grams a day

- Expensive
  - USA $30-600 / gram
  - India $6-9 / gram
  - Sri Lanka 55 cents / gram

- Unlikely to address Non-ACh effects
Are old drugs the new hope?

>>200 ‘proof of concept’ publications
1962-2004
Alternate Sites for Antidotes

- Protect AChE
- Supply AChE
- Reduce ACh
- Protect ACh Receptor
- Reduce OP Load
- Multiple Mechanisms
? Other Cholinesterase inhibitors: Protecting the enzyme
Magnesium

- Reduces acetylcholine release
  - Blockage pre-synaptic calcium channels
  - Central and Peripheral Nervous System

- ? Non neuromuscular effects – cardiac

- Decrease toxicity in animal models

- Limited human studies
  - in 4 OP patients improved neuromuscular response to repetitive nerve stimulation
Magnesium sulfate in acute human OP poisoning
Pajoumand et al Hum Exp Toxicol. 2004
23(12):565-9

- 16 gram continuous infusion \( \text{MgSO}_4 \) for 24 hours

- Normal care (oximes and atropine) in both groups
  - Death
    - 0/11 patients died with magnesium
    - 5/34 control patients
  - Methodological issues
    - pseudorandomisation
Clonidine

- Decrease the presynaptic synthesis and release of acetylcholine.
  - Central nervous system > peripheral cholinergic synapses

- Animal Work: Soman models
  - 1/7 deaths vs 14/16 in controls (Soman)
  - Ineffective against echothiopate (a peripheral acting OP)
    - Centrally Mediated

Diazepam

- Diazepam reduces
  - cognitive deficit (primates)
  - respiratory failure (rats)

- Postulate “uncoordinated stimulation of the respiratory centres decreases phrenic nerve output”.
Diazepam

TABLE 1. Survival after Dichlorvos Exposure

<table>
<thead>
<tr>
<th>Group</th>
<th>10 Minutes</th>
<th>24 Hours</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Survival</td>
<td>p</td>
</tr>
<tr>
<td>Saline (n = 16)</td>
<td>0%</td>
<td>NA</td>
</tr>
<tr>
<td>Atropine (n = 8)</td>
<td>100%</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Diazepam (n = 16)</td>
<td>44%</td>
<td>0.007*</td>
</tr>
<tr>
<td>Nebulized IB (n = 8)</td>
<td>0%</td>
<td>1</td>
</tr>
<tr>
<td>Nebulized IB + diazepam (n = 8)</td>
<td>88%</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>GLYC (n = 8)</td>
<td>0%</td>
<td>1</td>
</tr>
<tr>
<td>GLYC + diazepam (n = 8)</td>
<td>88%</td>
<td>&lt;0.001*</td>
</tr>
</tbody>
</table>

*p < 0.05 vs. controls by the Fisher exact test with Bonferroni correction for multiple comparisons applied (Bonferroni).

**Synergistic response with anticholinergics**

pH manipulation?

- Organophosphate Hydrolase is pH sensitive.
- Binding of pralidoxime is pH sensitive.
- Acetylcholinesterase
- Aging of OP-AChe complex and reactivation.
Organophosphate: pH sensitive

85% survival pH 7.3 → 7.53

COMPARATIVE EFFICACY OF I.V. PRALIDOXIME vs. NaHCO₃ IN RATS LETHALLY POISONED WITH O-P INSECTICIDE. Dr. Anthony Wong Brazil

N= 10 rats in each group

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>D.D.V.P.</td>
<td>0</td>
</tr>
<tr>
<td>Atropine</td>
<td>309.43</td>
</tr>
<tr>
<td>Atrop. + Oxime</td>
<td>462.17</td>
</tr>
<tr>
<td>Atrop. + Bicarb.</td>
<td>7012.12</td>
</tr>
<tr>
<td>Atrop. + NaCl</td>
<td>2611.17</td>
</tr>
</tbody>
</table>

p<0.001 D~B and D~C
p<0.01    D~E
Effect of High Doses of Sodium Bicarbonate in Acute Organophosphorous Pesticide Poisoning. Mahdi BalaliMood Clinical Toxicology, 43:571-574, 2005

- RCT N=30
- NaHCO$_3$ pH 7.45-7.55
  - 5 mEq/Kg over 60 minutes
  - 5-6 mEq/Kg over 24 hours
- Length of hospital stay
  - Controls $5.59 \pm 1.97$
  - Treatment $4.33 \pm 1.99$
Conclusion

- There is clinically important diversity in organophosphate poisoning
- Oximes have a number of limitations
- There are a number of drugs “old friends” deserving clinical trial
- The answers will be found in Asia through collaborative research
Acknowledgments

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Contact:
– adawson@sactrc.org
5th APAMT Congress

Sunday 6th to Tuesday 8th August 2006
Colombo Sri Lanka.

www.asiatox.com