Medical Management of Pesticide Poisoning: Why We Need Diagnostic Tools

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Who I Am

• General Pediatrician & Academician
  – MPH from Univ Alabama at Birmingham

• Focus area of Pediatric Environmental Health (PEH)
  – Lead poisoning and GIS
    Pesticide poisoning and exposure
  – Environmental contributors to asthma

• Actively see patients in teaching setting
EPA’s Recognition and Management of Pesticide Poisonings

• Co-Editor of 5th Edition – 1999
  – Acute Care Manual
  – New Chapters, References
  – English and Spanish
• Wide Distribution in US and Latin America
• Available On-line
• Chapter revisions for the 6th edition are currently underway

Finished!!
New for the 6th Edition

- Revisions of all chapters
- Pyrethroids as a stand alone chapter
- New content in acute poisoning
  - Neonicotinoids and N-Phenylpyrazole insecticides
  - Glyphosate
- Chronic Effects
  - Neurological/neurodevelopmental
  - Cancer
  - Endocrine
  - Asthma
Medical School and Residency Training

• In medical school, ~ 7 hours on environmental health (EH) related topics (over all 4 years)\(^1\)

• US pediatric residency spends an average of two hours on EH related material\(^2\)
  – Highly dependent on presence of faculty with expertise

• RRC requirement to include environmental influences on health
  – “effects on child health of common environmental toxins, such as lead, and also of potential agents used in bioterrorism”

What most Physicians Know about Diagnosis

• Rely on clinician’s ability to recognize pesticide by clues in the history and PE
• My experience with students/ residents
  – They often equate “Pesticide” with “Insecticide”
    • (and “Insecticides” with “Organophosphates”)
  – Most can recall generalities of OP poisoning
    • Not differences between kids and adults
    • A differential diagnosis of pesticides?!
  – Rat poison equates “look for bleeding”
    • No institutional memory of convulsants
Home Use of Pesticides

- Insecticides are applied as a spray or powder in 66% of homes
  - 19% once a month
  - 14% two times a month or more often
- 12% said their doctor discussed pesticides
- Information sources for parents?
  - Pediatricians—52%
  - (next closest, Internet at 30%)
What most Physicians Know about Diagnosis

- 160 Washington DC area physicians\(^1\)
  - 69% did not diagnose pesticide toxicity
  - 53% had ever considered the diagnosis
  - 64% felt poorly prepared to answer patients’ questions about pesticides
  - 40% needed more information on pesticides

- Need for clinically relevant CME
- Greater discomfort with chronic or subacute toxicity

What most Physicians Know about Diagnosis

- Survey of teachers of pediatric environmental health (PEH)
- Asked about abilities to teach specific subjects
  - >80% confident teaching about lead poisoning, asthma, and tobacco smoke exposure
  - 72% for carbon monoxide
  - 64% for mercury and neurodevelopment
  - 40% said they felt confident in teaching about pesticides (3rd lowest)

What some Physicians Have Missed about Diagnosis

• OP poisoning may be different in kids than adults
  – Seizures (22-25% in kids)\(^1,2\) (2-3% in adults)
  – Mental status changes (lethargy/ coma: 54-96\%)\(^1,2\)
  – 80% transferred with wrong diagnosis\(^1\)

• Lack of diagnostic tests for many pesticides
  – Cholinesterase testing
  – Anything other than organophosphates are often not on their radar

• Pesticide levels/ metabolites
  – Public health biomarkers
  – Research tool

Poison Control Center Data

<table>
<thead>
<tr>
<th></th>
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<tbody>
<tr>
<td></td>
<td>Total/ mod to severe morb/ death</td>
<td></td>
</tr>
<tr>
<td>Pyrethroids</td>
<td>25,569/ 2,388/ 1</td>
<td>52,767/ 2333/ 4</td>
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<tr>
<td>Organophosphates</td>
<td>40,090/ 1,994/ 21</td>
<td>28,503/ 1700/ 23</td>
</tr>
<tr>
<td>Carbamates</td>
<td>12,051/ 523/ 1</td>
<td>11,249/ 502/ 3</td>
</tr>
<tr>
<td>Strychnine</td>
<td>563/ 72/ 5</td>
<td>401/ 50/ 4</td>
</tr>
<tr>
<td>Paraquat</td>
<td>453/ 56/ 4</td>
<td>232/ 35/ 8</td>
</tr>
</tbody>
</table>

Compiled from Annual Reports from Poison Control Center Data; reported every fall in *Am J Emer Med* (at least until recently, now in *Clinical Toxicology*)
## 2006 Report of Poison Control Centers’ National Poison Data System

<table>
<thead>
<tr>
<th>Pesticide</th>
<th>2006¹</th>
<th>2009²</th>
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<tbody>
<tr>
<td></td>
<td>Total/ mod-severe morb/ death</td>
<td>Total/ mod-severe morb/ death</td>
</tr>
<tr>
<td>Pyrethroids</td>
<td>26,083/ 889/ 3</td>
<td>23,060/ 768/ 4</td>
</tr>
<tr>
<td>Organophosphates</td>
<td>5,411/ 242/ 3</td>
<td>4,223/ 187/ 3</td>
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<tr>
<td>Carbamates</td>
<td>3,175/ 119/ 2</td>
<td>2,611/ 102/ 3</td>
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<tr>
<td>Strychnine</td>
<td>104/ 6/ 0</td>
<td>84/ 7/ 0</td>
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<tr>
<td>Paraquat</td>
<td>61/ 8/ 1</td>
<td>111/ 7/ 2</td>
</tr>
<tr>
<td>Boric Acid</td>
<td>4,216/ 11/ 0</td>
<td>4,821/ 11/ 1</td>
</tr>
</tbody>
</table>

¹Bronstein AC, Spyker DA, et al. *Clinical Toxicology* 2007;45(8):815-917
²Bronstein AC, Spyker DA, et al. *Clinical Toxicology* 2010;48(10):979-1178
Biomarkers in NHANES

- Organophosphates
- Carbamate
- Pyrethroid Insecticides
- Organochlorine Insecticides
- DEET metabolite
- Chlorophenoxy herbicides (2,4 D, etc)
- Atrazine
- *ortho*-Phenylphenol
- *para*-Dichlorobenzene (2,5-Dichlorophenol)
  Moth balls, room deodorizer

NHANES= National Health and Nutrition Examination Survey
Organophosphate Metabolites
(Found in children’s urine)

- Chlorpyrifos
  - 3,5,6 Trichloropyridinol
  - Diethylphosphate
  - Diethylthiophosphate

- Parathion
  - Paranitrophenol
  - Dimethylphosphate
  - Dimethylthiophosphate

- Methyl parathion
  - Dimethylphosphate
  - Dimethylthiophosphate

- Malathion
  - Dimethylthiophosphate
Pyrethroid Metabolites
(Found in children’s urine)

- Cypermethrin
- Deltamethrin
- Permethrin
- 3-Phenoxybenzoic acid
Pesticide Biomarkers

Pros

• Allows population based data
• Helpful for research
• Tracking exposure in populations and comparing to national average

Cons

• Exposure does not equate to disease
• Not immediately accessible
  – No help to the clinician trying to manage a case
  – Not considered diagnostic
Pesticides with Diagnostics
(Some only of limited availability)

- OPs and Carbamates
- Paraquat and Diquat
- Arsenic
- Hydrogen Cyanide
- Brodifacoum (and other warfarins)
- AI and Zn phosphide
- Thallium sulfate
- Cholinesterase level*
- Dithionite test (colorimetric)#
- 24 hour urine*
- Cyanide ion (CN⁻)
- Prothrombin Time (PT)
- Hyperphosphatemia (non sp)
- 24 hour urine, also serum*

*Though available, still sent out to reference lab
#Questionable availability
Pesticides without available tests:
Or: Limited to Gov’t or University Lab
(Partial Listing)

- Pyrethroids/pyrethrins
- Chloropicrin
- Chlorophenoxy herbicides
- Neonicotinoids
- N-phenylpyrazones (Fipronil)
- Carbon disulfide
- Organochlorines
- Strychnine
- Tetramethylenedi-sulfotetramine (TETS)
- Hexachlorobenzene
Neonicotinoids

- Insecticide; Marketed in US early 1990s
  - Quickly expanding market share– 11-15%
- Acts on nicotinic ACh receptors (nAChR)
- Selective for insect nAChRs
  - Human toxicity has been reported
  - Have some other metabolic responses
    - Activation of protein kinase cascade which may decrease neurologic functions

Neonicotinoids

- Human data limited to several case reports and one series of 68 patients
  - 2 deaths of autopsy-confirmed imidacloprid poisoning
- Excess nicotinic stimulation
  - Disorientation, agitation, drowsiness, loss of consciousness, tachycardia
  - Rhabdomyolysis, V tach/V Fib in severe cases
- Case series primarily GI complaints (N/V, diarrhea)
  - 1 patient with respiratory failure
- Diagnostics not available
- On the other hand, is less acutely toxic than OPs, and it would be helpful to distinguish the two
N-Phenylpyrazole Insecticides
Fipronil

- First registered in 1996
  - Agricultural crops, Lawns, Pets for fleas and ticks
- Inhibit GABA receptor and blocks gated chloride channels
  - Produces hyper excitability of cell
  - Same mechanism as organochlorines, but only affects some channels and high affinity for insects
- Some reports of human toxicity
  - GI symptoms predominate (n/v diarrhea)
  - Neurologic symptoms may occur
    - Loss of consciousness and seizures

• How do physicians typically use diagnostic testing in the clinical setting?
Infectious Disease Example

- Sore throat, feels hot
- Headache, fatigue
- Red throat, 103.8° F
- Swollen lymph nodes
- Half of his class was out last week with swine flu
- Mom is panicked
How do I know what it is?

- Differential Diagnosis
  - Gp A strep, Influenza,
  - (including H1N1)
  - Adenovirus, Mono
  - “other virus”

- Rapid Test!
  - Available for Strep throat and Influenza
  - Monospot for mononucleosis
Treat Strep Throat: Happy Outcome
Clinical Medicine is not Always that Clear…

- 4 year old child is brought in because he “doesn’t look right”
- Child is not responsive to voice
- Shortly after arrival you notice some twitching of the side of his face, and eyes deviate
- Progresses to generalized
- 2-3 minute seizure, but within 15 minutes they start up again, last longer, harder to stop
Managing the Seizure

- Rectal diazepam (Valium®) initially until an IV can be placed
- Subsequent doses of lorazepam (Ativan®) and maybe a second medication
  - Breathing often stops by this time
- On exam, he is now sedated, on the ventilator
- Afebrile, crackles in his lungs
- What do we have at our disposal to figure out why he is seizing?
Medical History

• In this case, often not so helpful
• Typically, a sound from the bedroom or toddler found lying on the ground
• Previous hx of seizures? Family Hx?
• Often initially a negative hx of any exposure
  – True in pesticide exposures
  – True in other cases (cocaine, stimulants, PCP)
  – Medications, sometimes more forthcoming
• Febrile illness preceded seizure?
Evaluating A Patient with Seizures

- Head CT/Brain MRI—“Always” done
  Often negative
- EEG—may be helpful or even diagnostic
  – often normal
- Spinal fluid culture—No Meningitis (48°)
- Rapid tests W. Nile v. and Herpes neg. (12-48°)
- Blood sugar and serum NA & Ca normal
- Lead level—typically 1 week, but can be STAT
- Urine drug screen (positive for benzodiazepines)
- Cholinesterase testing (still a send out)
  – Normal, but reported 2 days later
Summary

• Pesticides were among the least of all PEH related topics that faculty felt comfortable teaching about

• Having a way of testing would likely increase physician’s ability to consider and diagnose
  – Lead level, chelation therapy
  – Cotinine, anti-smoking aids
  – Asthma, skin allergy testing; multiple options
Summary
A Clinician’s Wish List

• Rapidly available diagnostic testing
  – Could be part of registration process
• Provide greater support for effective clinical education, particularly front line personnel
• Helps diagnose and begin appropriate Rx
  – We have atropine and pralidoxime
    • Or even tell us atropine would be inappropriate to give
    • Supportive care
  – Allows provider to reassure a patient/family if we can definitely rule it out