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
  - http://www.epa.gov/oppfead1/safety/healthcare/handbook/handbook.htm
- 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"

Schenk M, et al. *Acad Med* 1996; 71:499-501
Roberts JR, Gitterman B. *Amb Peds* 2003;3:57-59

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

Balbus JM, et al. J Agromedicine 2006;11:27-38.

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)

Roberts JR, et al. Ambulatory *Pediatrics* 2009;9:129-30

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

Zwiener RJ, Ginsburg CM. Pediatrics 1988;81:121-6
Sofer S, et al. Pediatric Emerg Care 1989;5:222-5

Poison Control Center Data

Pesticide	1997-1999	2001-2003
	Total/ mod to severe morb/ death	
• Pyrethroids	25,569/ 2,388/ 1	52,767/ 2333/ 4
• Organophos-phates	40,090/ 1,994/ 21	28,503/ 1700/ 23
• Carbamates	12,051/ 523/ 1	11,249/ 502/ 3
• Strychnine	563/ 72/ 5	401/ 50/ 4
• Paraquat	453/ 56/ 4	232/ 35/ 8

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

Pesticide	2006[1] Total/ mod-severe morb/ death	2009[2] Total/ mod-severe morb/ death
• Pyrethroids	26,083/ 889/ 3	23,060/ 768/ 4
• Organophos-phates	5,411/ 242/ 3	4,223/ 187/ 3
• Carbamates	3,175/ 119/ 2	2,611/ 102/ 3
• Strychnine	104/ 6/ 0	84/ 7/ 0
• Paraquat	61/ 8/ 1	111/ 7/ 2
• Boric Acid	4,216/ 11/ 0	4,821/ 11/ 1

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

Biomarkers in NHANES

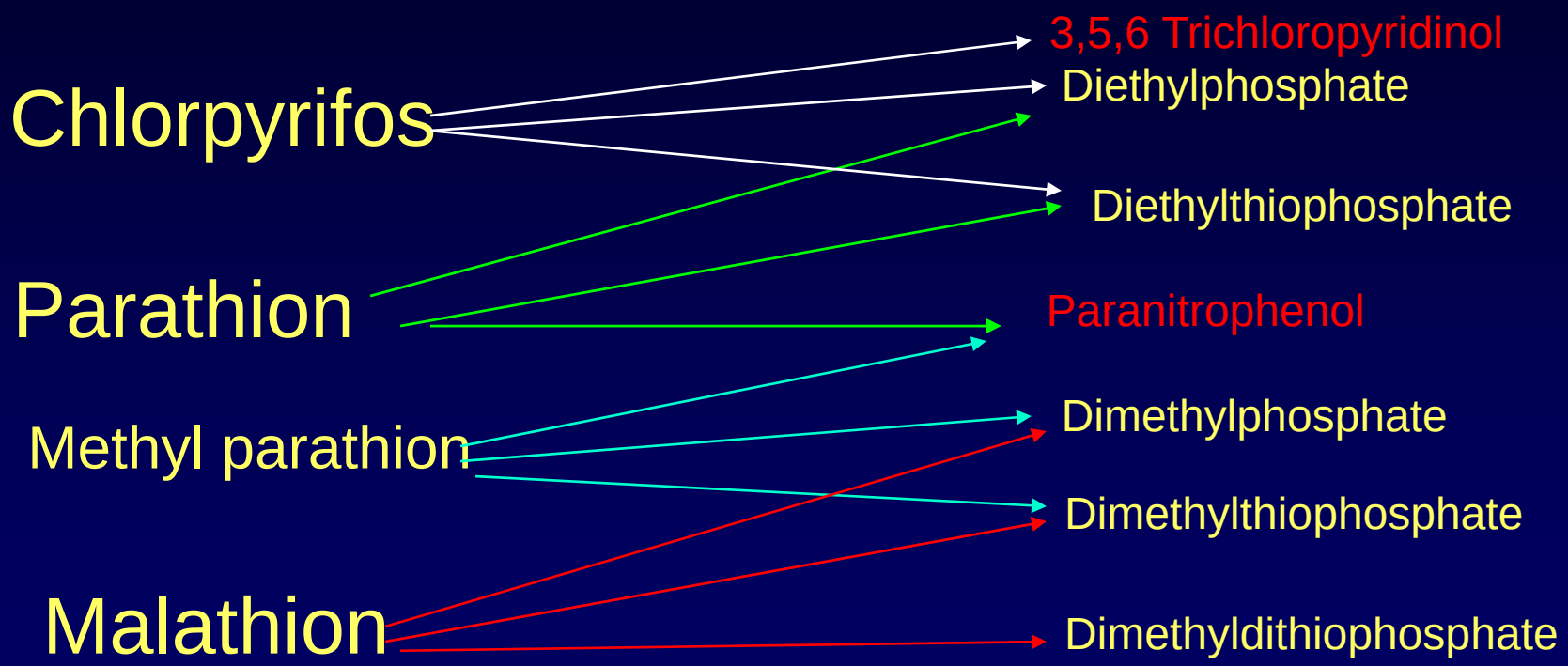
- Organophosphates
- Carbamate
- Pyrethroid Insecticides
- Organochlorine Insecticides
- DEET metabolite
- Chlorophenoxy herbicides (2,4 D, etc)
- Atrazine
- *ortho*-Phenylphenol
- *para*-Dichlorobenzene (2,5-Dichlorophenol)

  Moth balls, room deodorizer

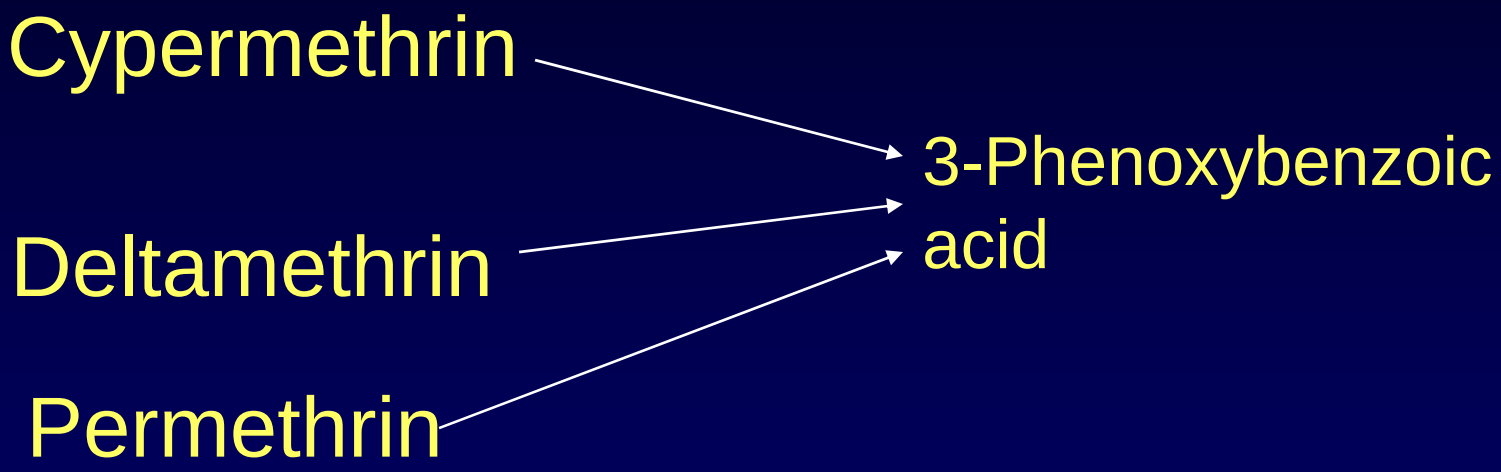
NHANES= National Health and Nutrition Examination Survey

Organophosphate Metabolites

(Found in children's urine)



Pyrethroid Metabolites
(Found in children's urine)



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)
- Al 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

Tomizawa M, Casida JE. Neonicotinoid insecticide toxicology: mechanisms of selective action. *Annu Rev Pharmacol Toxicol.* 2005;45:247-268

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

Fung HT, et al J Tox Clin Tox 2003;41:245-8
Chowdowski Z, et al. J Tox Clin Tox 2004;42:189-90
Lee S, et al. Clin Tox 2010;48:737-44

- 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

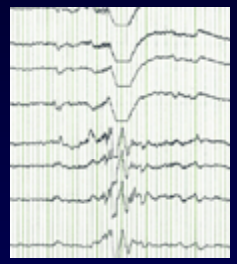
Managing the Seizure

- 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