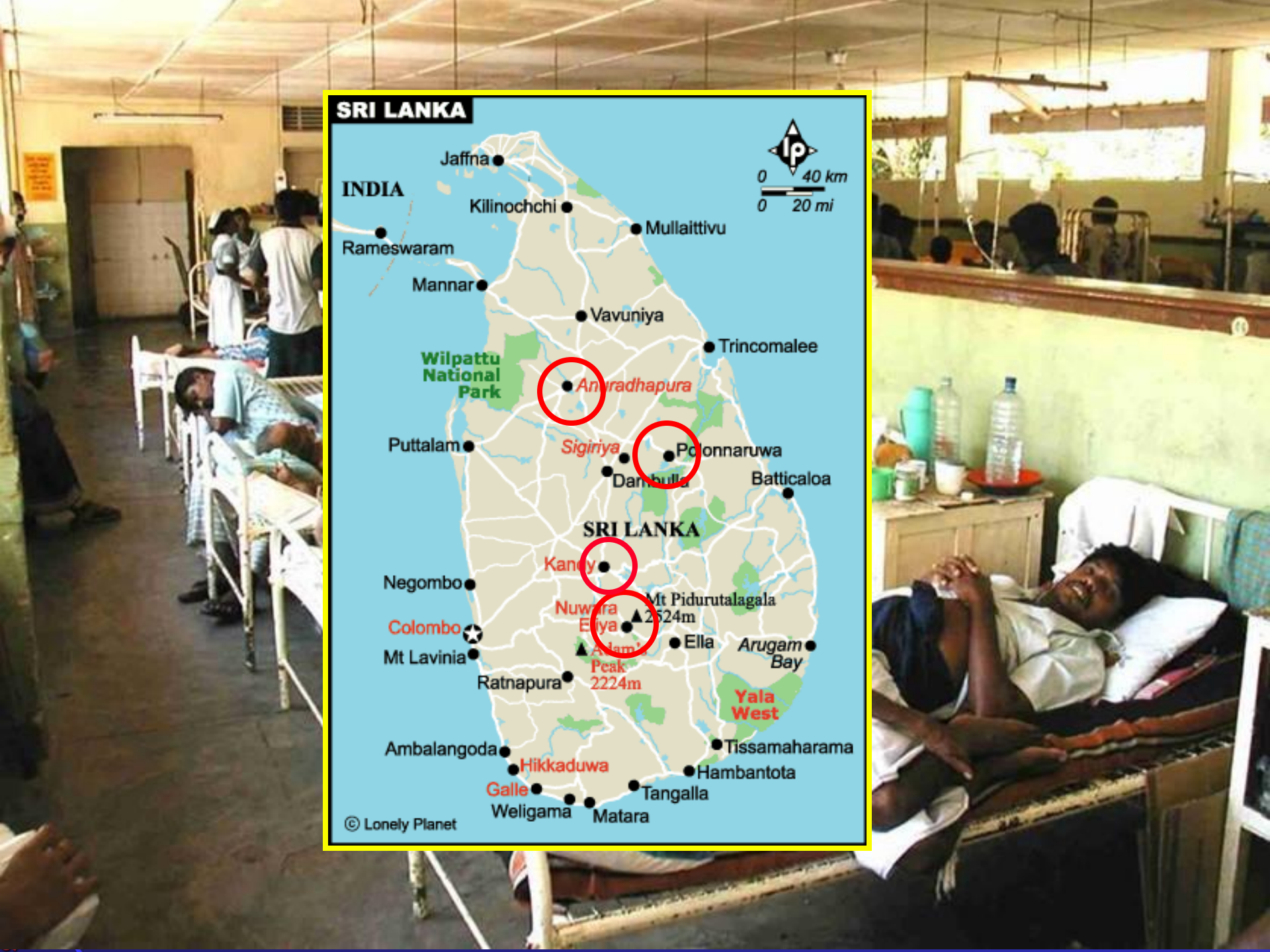
Recent understanding in the treatment of pesticide poisonings

Andrew Dawson

South Asian Clinical Toxicology Research Collaboration


SRI LANKA
INDIA
Jaffna
Kilinochchi
Mullaittivu
Rameswaram
Mannar
Vavuniya
Trincomalee
Wilpattu National Park
Anuradhapura
Puttalam
Sigiriya
Polonnaruwa
Dambulla
Batticaloa
SRI LANKA
Kandy
Negombo
Nuwara Eliya
Mt Pidurutalagala 2524m
Colombo
Ella
Arugam Bay
Mt Lavinia
Adam's Peak 2224m
Ratnapura
Yala West
Ambalangoda
Tissamaharama
Hikkaduwa
Hambantota
Galle
Tangalla
Weligama
Matara
0 40 km
0 20 mi
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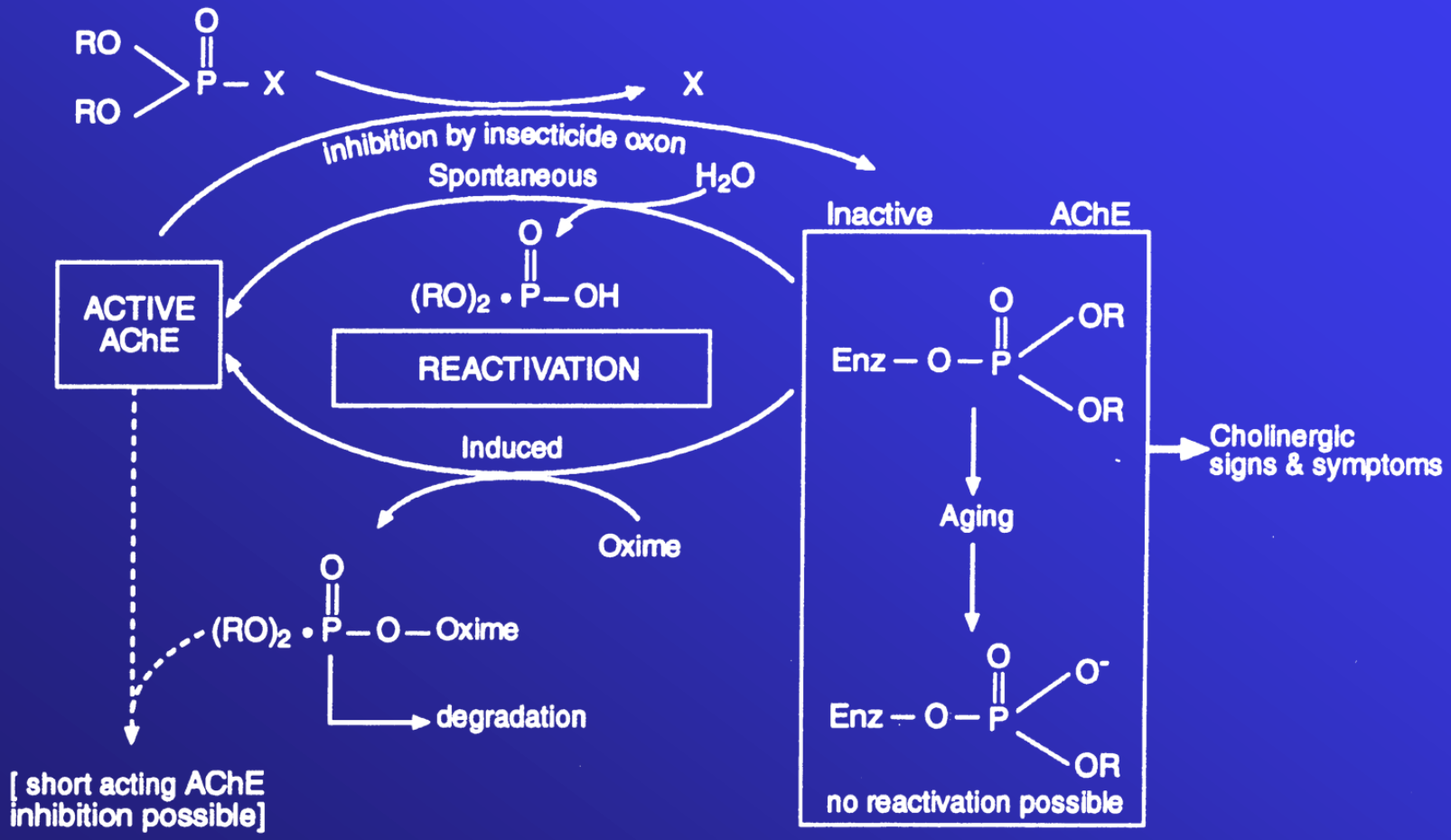
Simplified Acute OP Toxicity

- Inactivation of acetylcholinesterase enzyme



Clinical Syndromes

- Acute Cholinergic:
  - Central
  - Peripheral Muscarinic
  - Peripheral Nicotinic
- Intermediate Syndrome

Respiratory failure

- Delayed peripheral neuropathy
- Neurocognitive dysfunction

Other Acute Toxicity

- Oxidative injury
- Catecholamine excess
- Non ACh mediated events
- Medical Complications
  - Poisoning
  - Treatment

SACTRC

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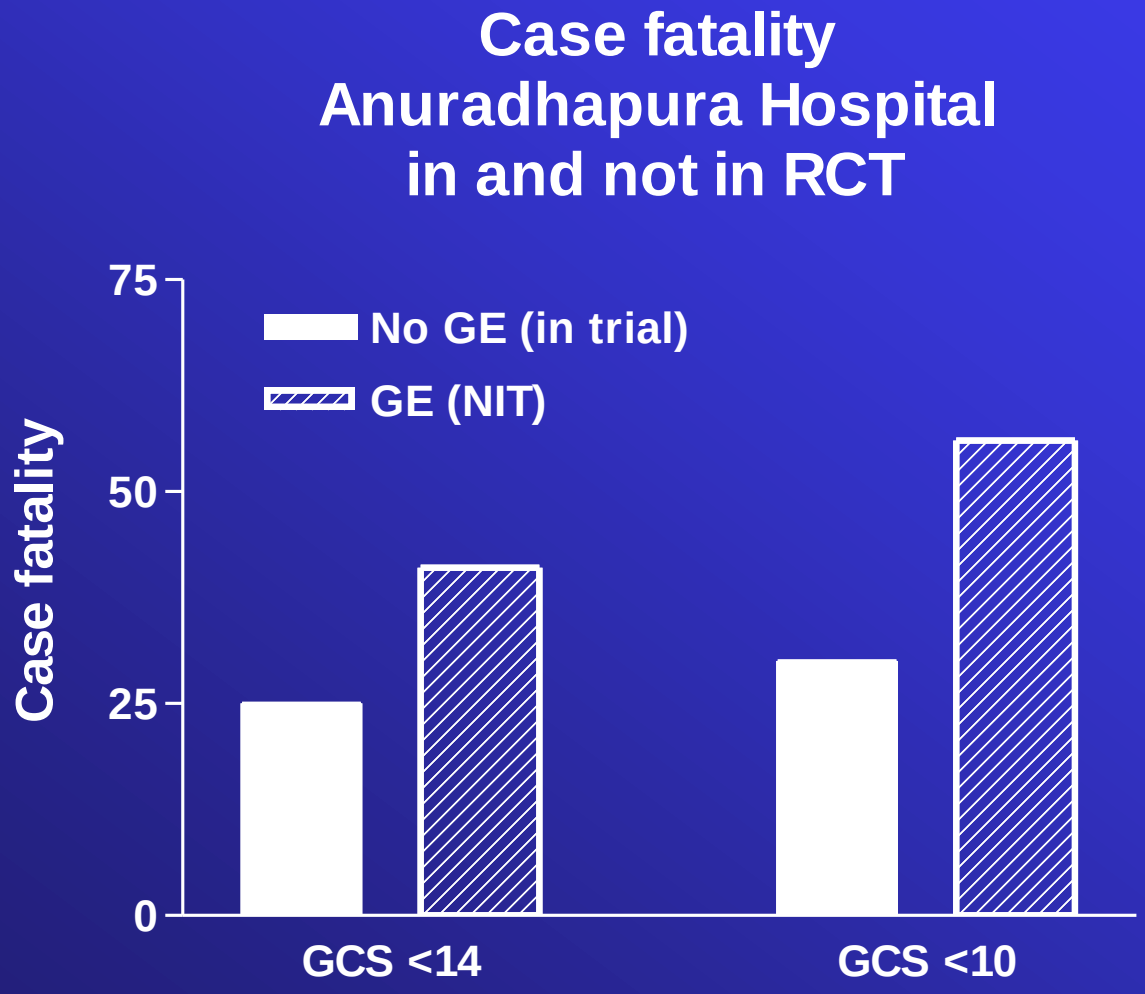
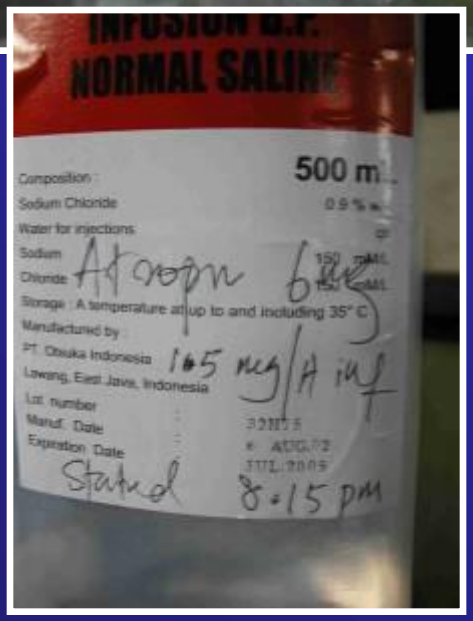
The results of observational data on gastric emptying (GE) in pesticide self-poisoning





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Antidotes

- Atropine
- Oximes
  - Expensive

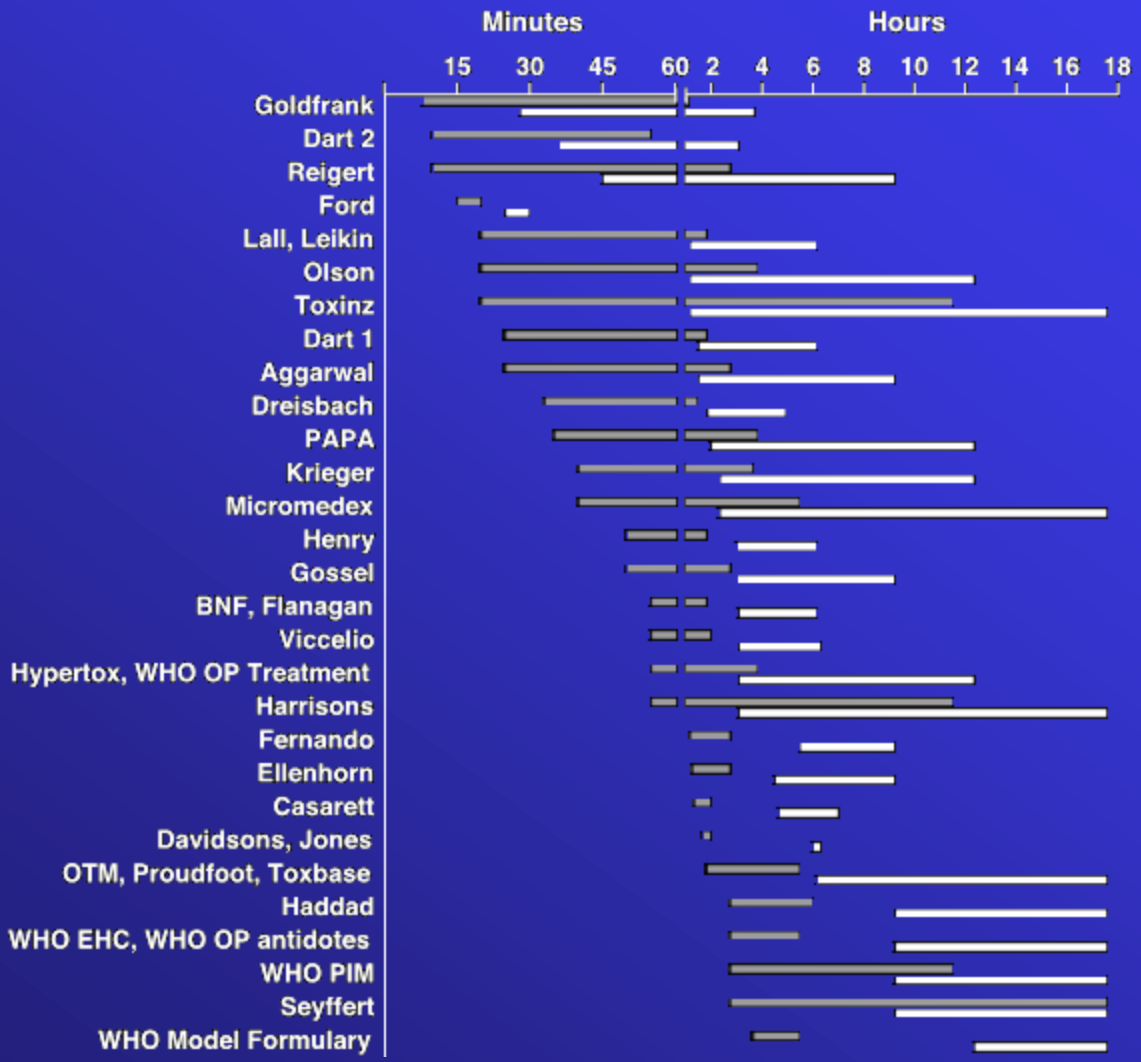
? Dose
? Duration
? Effectiveness

- Does treatment affect outcome
  - Intermediate Syndrome?
  - OPIDN?

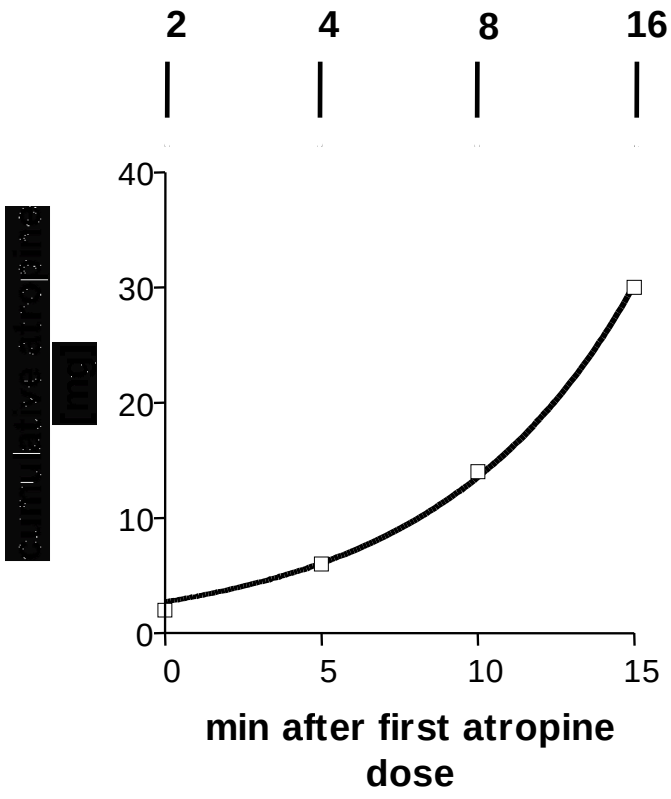
Atropine Dose in Organophosphates

- 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


Minutes
Hours
15
30
45
60
2
4
6
8
10
12
14
16
18
Goldfrank
Dart 2
Reigert
Ford
Lall, Leikin
Olson
Toxinz
Dart 1
Aggarwal
Dreisbach
PAPA
Krieger
Micromedex
Henry
Gossel
BNF, Flanagan
Viccelio
Hypertox, WHO OP Treatment
Harrisons
Fernando
Ellenhorn
Casarett
Davidsons, Jones
OTM, Proudfoot, Toxbase
Haddad
WHO EHC, WHO OP antidotes
WHO PIM
Seyffert
WHO Model Formulary

Scheme of atropinization (endpoints to be reached)



Atropine requirement	Atropinization
Poor air entry into lungs caused by bronchospasm and bronchorrhoea	Clear lungs
Excessive sweating	Dry axillae
(Hypotension)	Systol. BP > 80 mm Hg
(Bradycardia)	Heart rate > 80/min
(Miosis)	No miosis

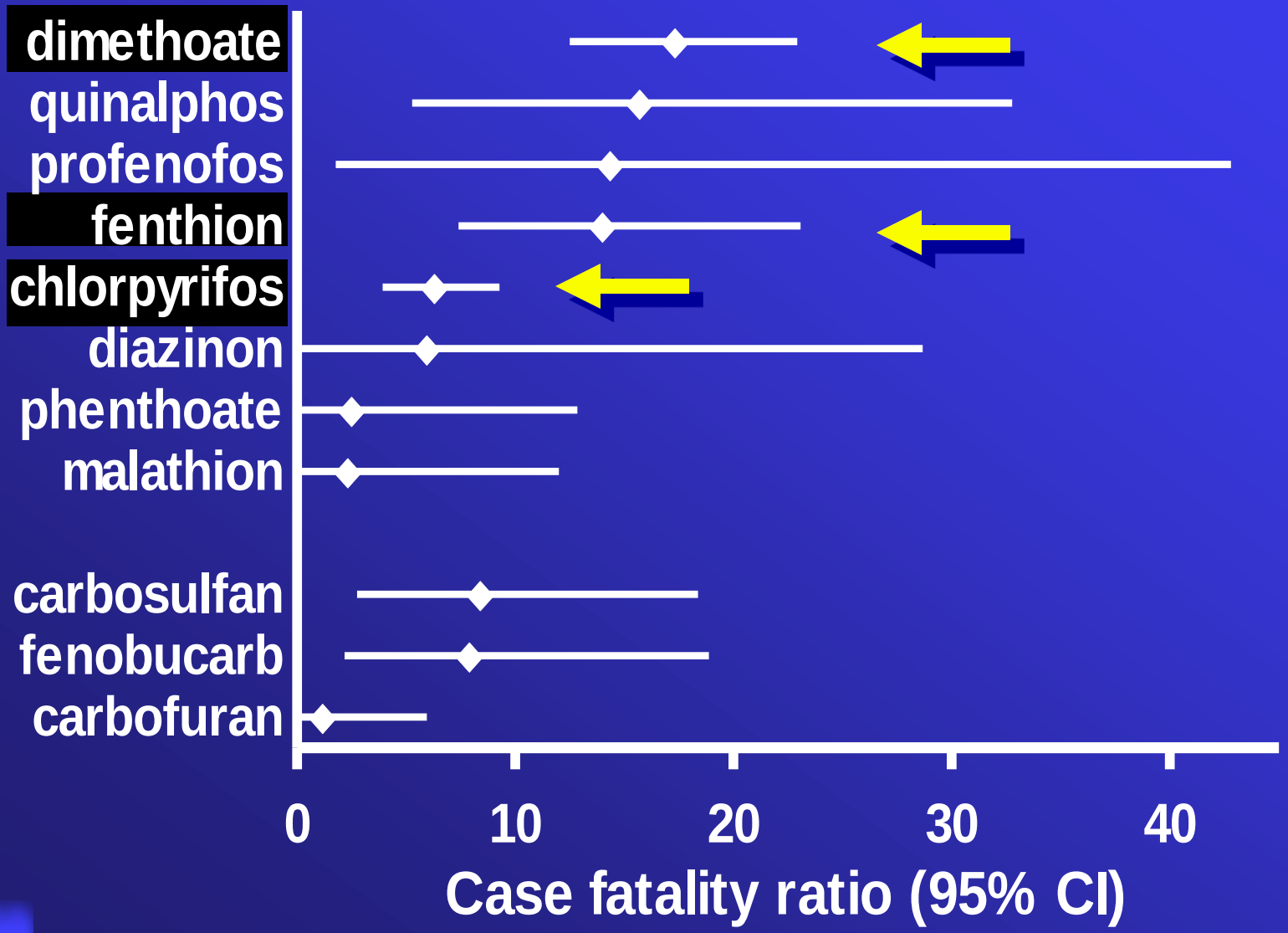
📖 Journal of Toxicology – Clinical Toxicology 2004;6:865-875.

Variation in organophosphorus pesticide syndromes

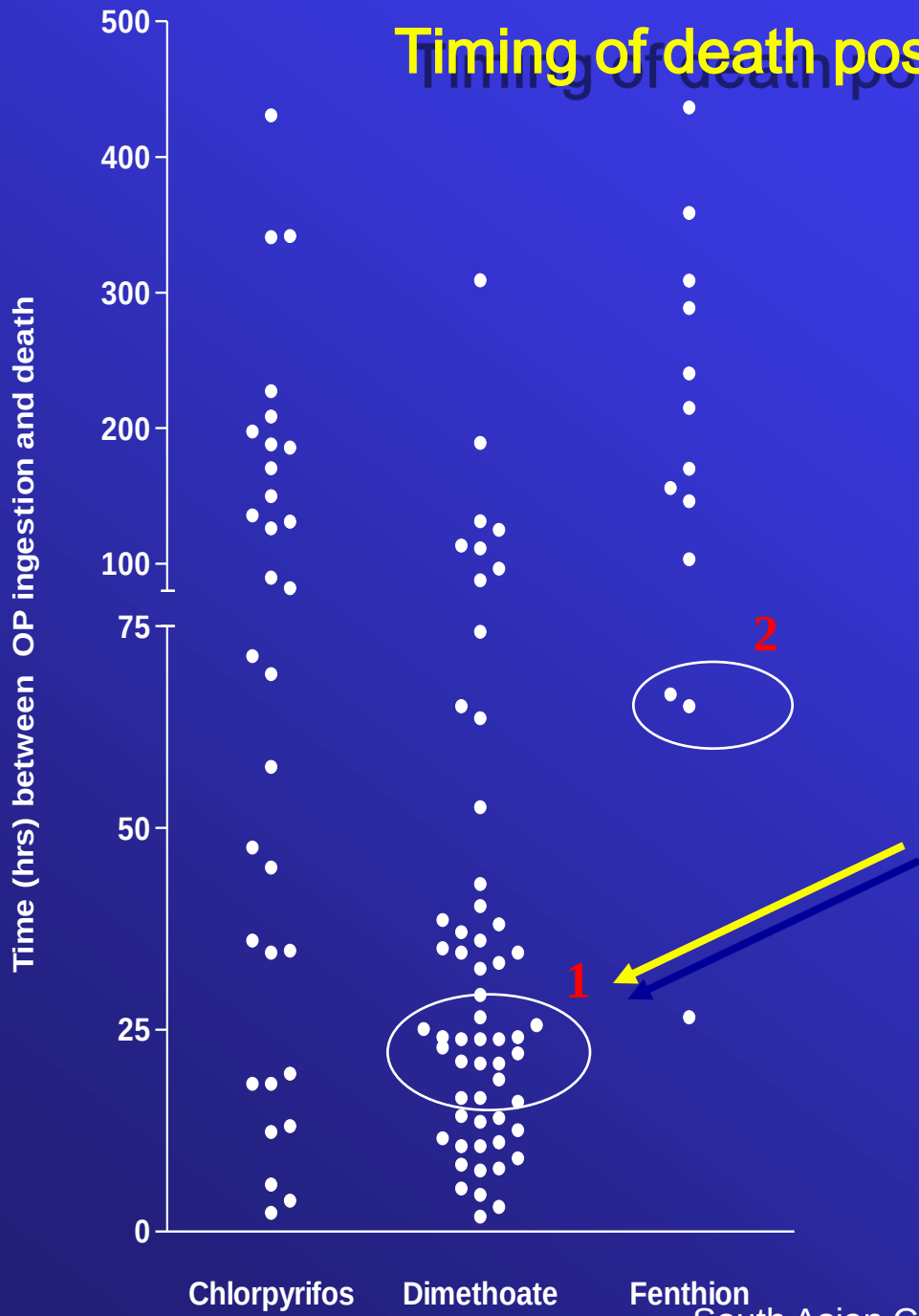
- Eddleston M et al Differences between organophosphorus insecticides in human self-poisoning: a prospective cohort study. Lancet. 2005 Oct 22-28;366(9495):1452-9

	Chlorpyrifos	Dimethoate	Fenthion
Number of cases	440	266	100
WHO Toxicity	II	II	II
Formulation	40% EC	40% EC	50% EC
Chemistry	Diethyl	Dimethyl	Dimethyl
Rat oral LD50 (mg/kg)			
WHO	135	150	*Not Given*
OSHA	97	250	215-245

Anti-cholinesterases



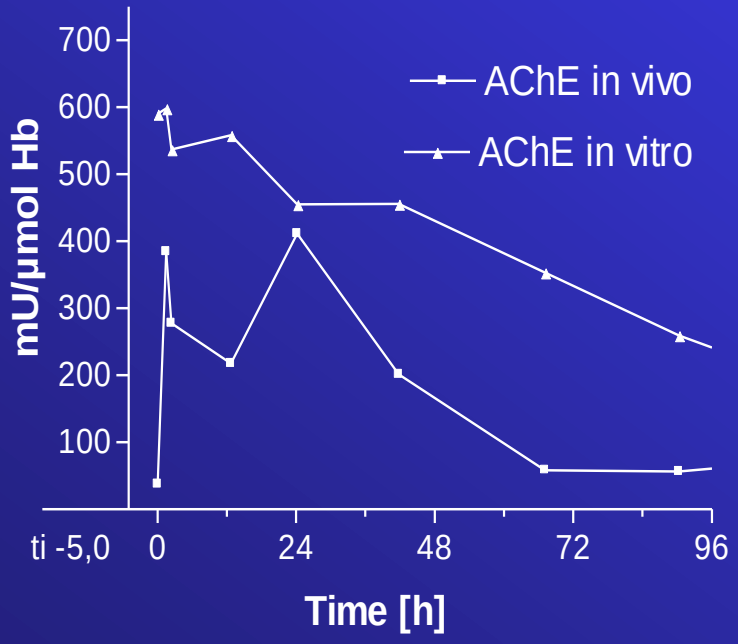
Timing of death post-ingestion for 3 OPs

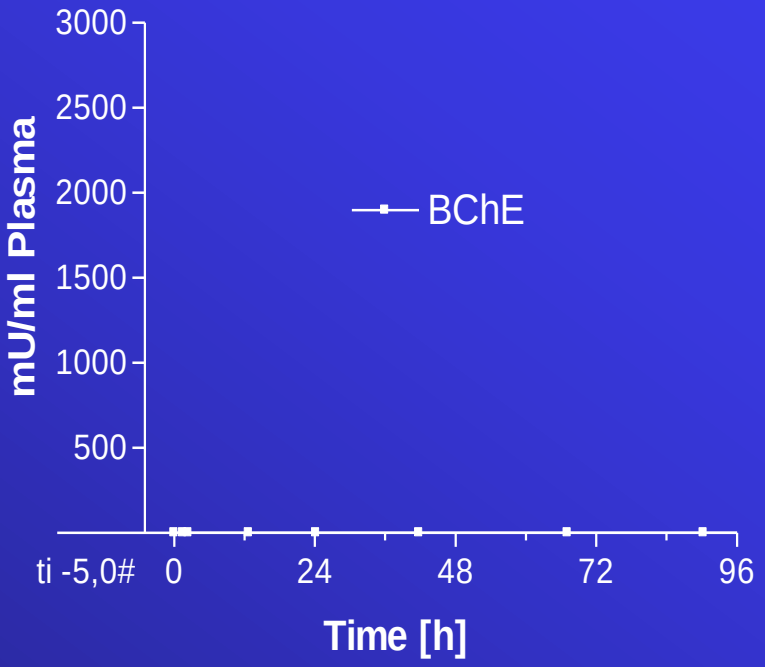


Myocardial Depression

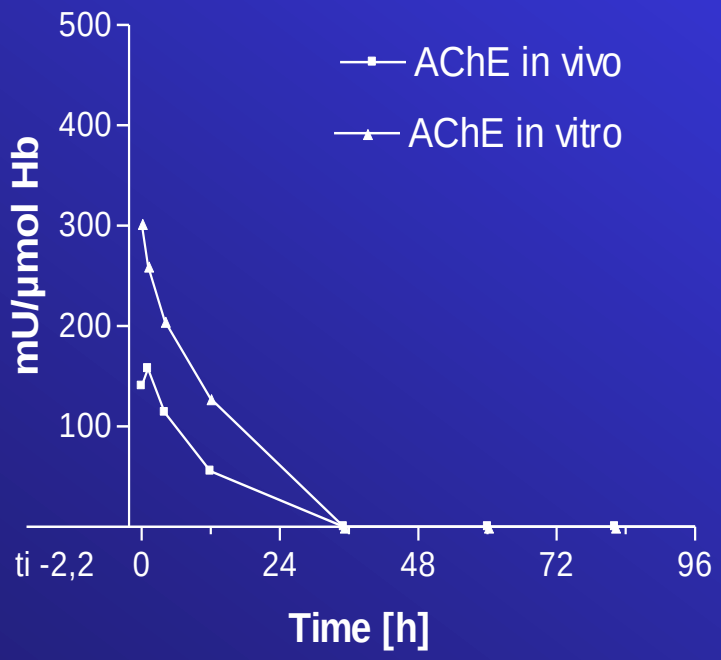
	Chlorpyrifos	Dimethoate	Fenthion
Median (IQR) Hours to Adm	4 (2 to 5)	3 (2 to 5)	4 (2 to 7)
Admission values			
Mean [OP] (uM)	1.28	355.5	4.86
Median BuChE (mU/ml)	33.5	1129	0.0
Median AChE (mU/μmol Hb)	63.5	69.0	64.2
Median aged AChE	19.4%	71.9%	70.3%

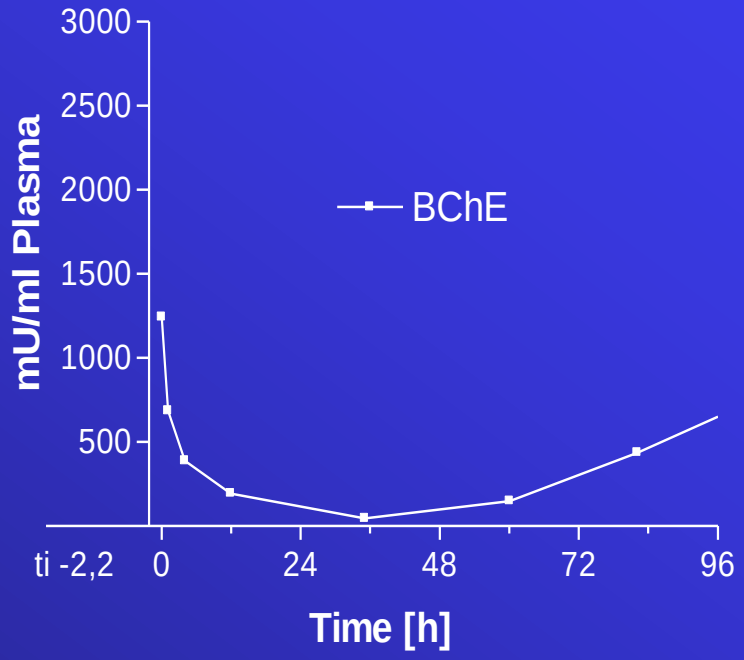
Chlorpyrifos poisoning





Dimethoate poisoning





OPs are different

- Differing Toxici
- Different Kineti
- Different Clinica dromes
- Different Respo Antidotes
- ? Need Differe ent Responses

Complicates Assessment of the Evidence for Oximes

Oximes

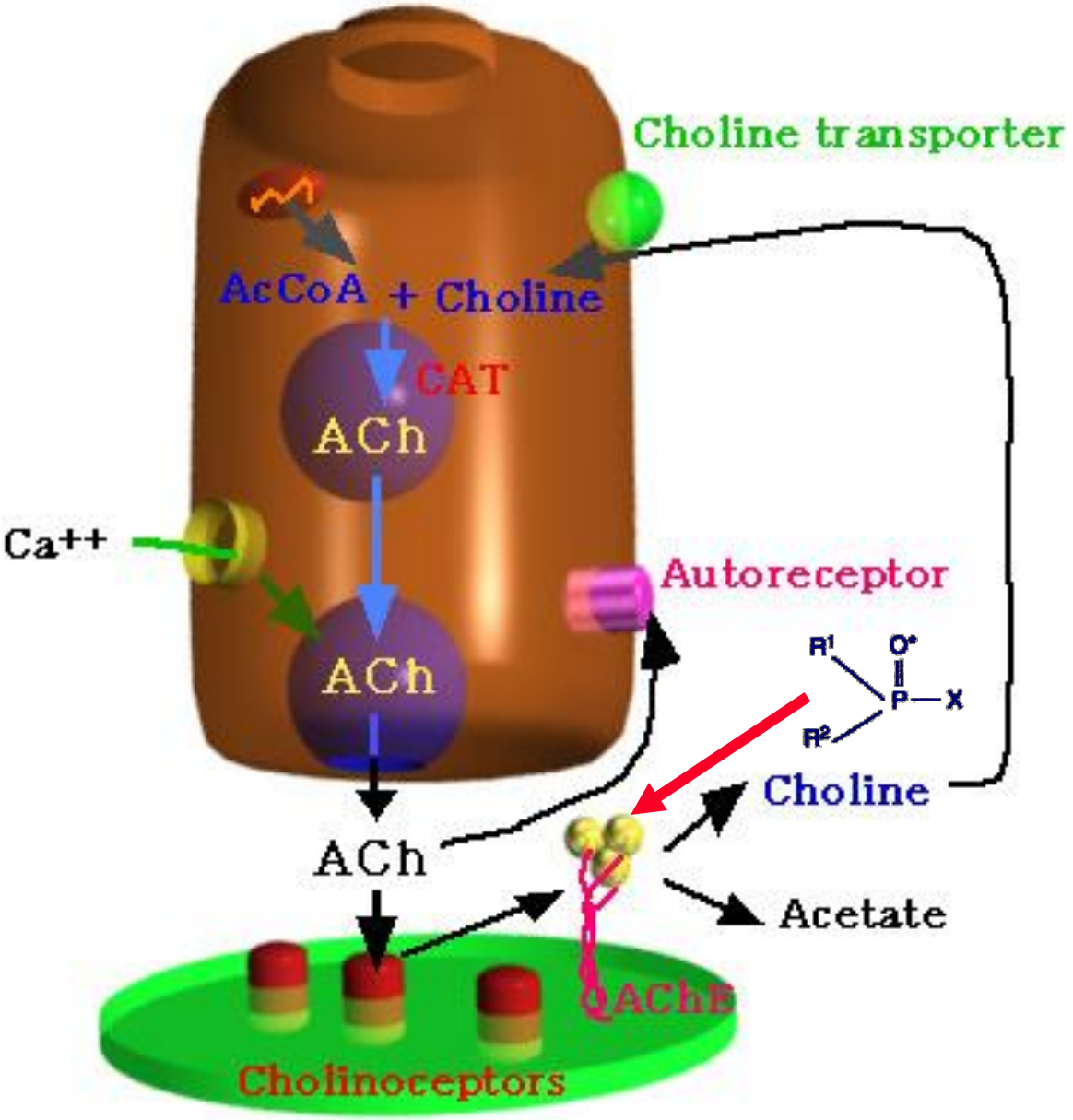
- Ineffective in some situations
  - Ageing
  - Variation between organophosphates
- Effective protocols not established
  - Variation in use
    - Zero – 24 grams a day
- Expensive
    - USA $30-600 / gram
    - India $6- 9 / gram
    - Sri Lanka 55 cents / gram
- Unlikely to address Non-ACh effects

Are old drugs the new hope?

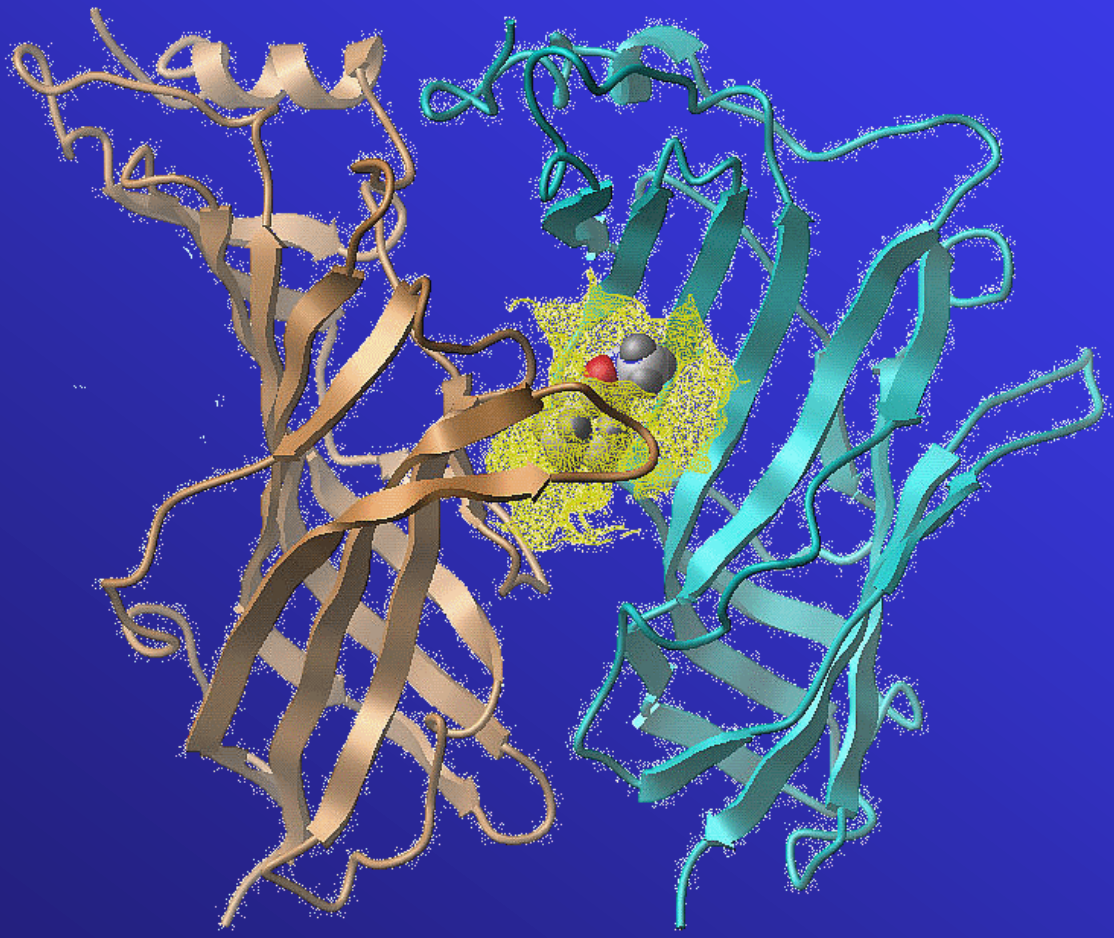
>>200 ‘proof of concept’ publications 1962-2004

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
    - Singh G. Electroencephalogr.Clin.Neurophysiol. 1998;107(2):140-8.

Magnesium sulfate in acute human OP poisoning Pajoumand et al Hum Exp Toxicol. 2004 23(12):565-9

- 16 gram continuous infusion $MgSO_4$ 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

  - Aronstam RS, Smith MD, Buccafusco JJ. Clonidine protection from soman and echothiophate toxicity in mice. Life Sci. 1986;39(22):2097-102.

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

Group	10 Minutes		24 Hours		95% CI 10-minute Survival
	Survival	p	Survival	p	
Saline ($n = 16$)	0%	NA	0%	NA	0.00% to 0.18%
Atropine ($n = 8$)	100%	<0.001*	100%*	<0.001	0.72% to 1.0%
Diazepam ($n = 16$)	44%	0.007*	0%	1	0.29% to 0.59%
Nebulized IB ($n = 8$)	0%	1	0%	1	0.00% to 0.28%
Nebulized IB + diazepam ($n = 8$)	88%	<0.001*	88%*	<0.001	0.55% to 0.98%
GLYC ($n = 8$)	0%	1	0%	1	0.00% to 0.28%
GLYC + diazepam ($n = 8$)	88%	<0.001*	88%*	<0.001	0.55% to 0.98%

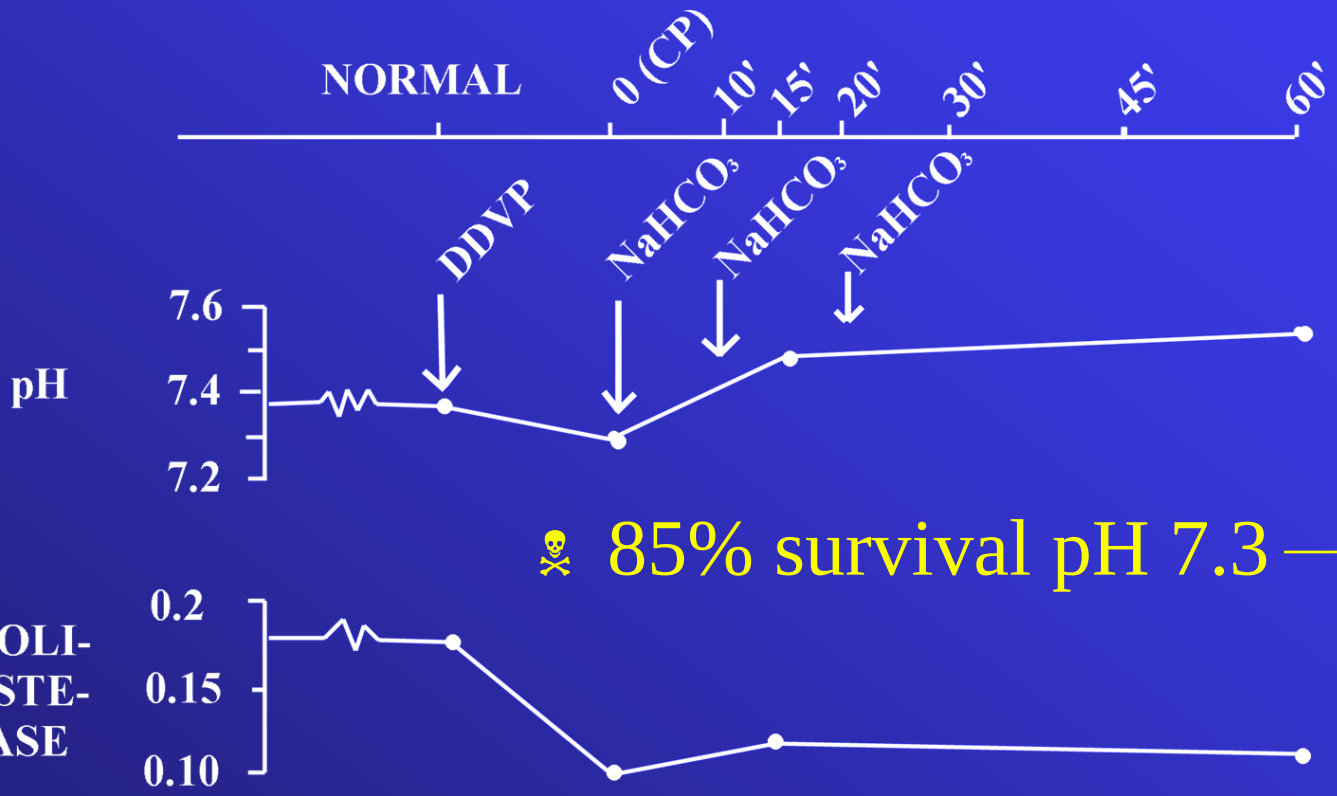
*$p < 0.05$ vs. controls by the Fisher exact test with Bonferroni correction for multiple comparisons applied (Bonferroni).
IB = ipratropium bromide; GLYC = glycopyrrolate.

- Synergystic response with anticholinergics
  - Dickson EW et al Diazepam inhibits organophosphate-induced central respiratory depression. Acad.Emerg.Med. 2003;10(12):1303-

pH manipulation?

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

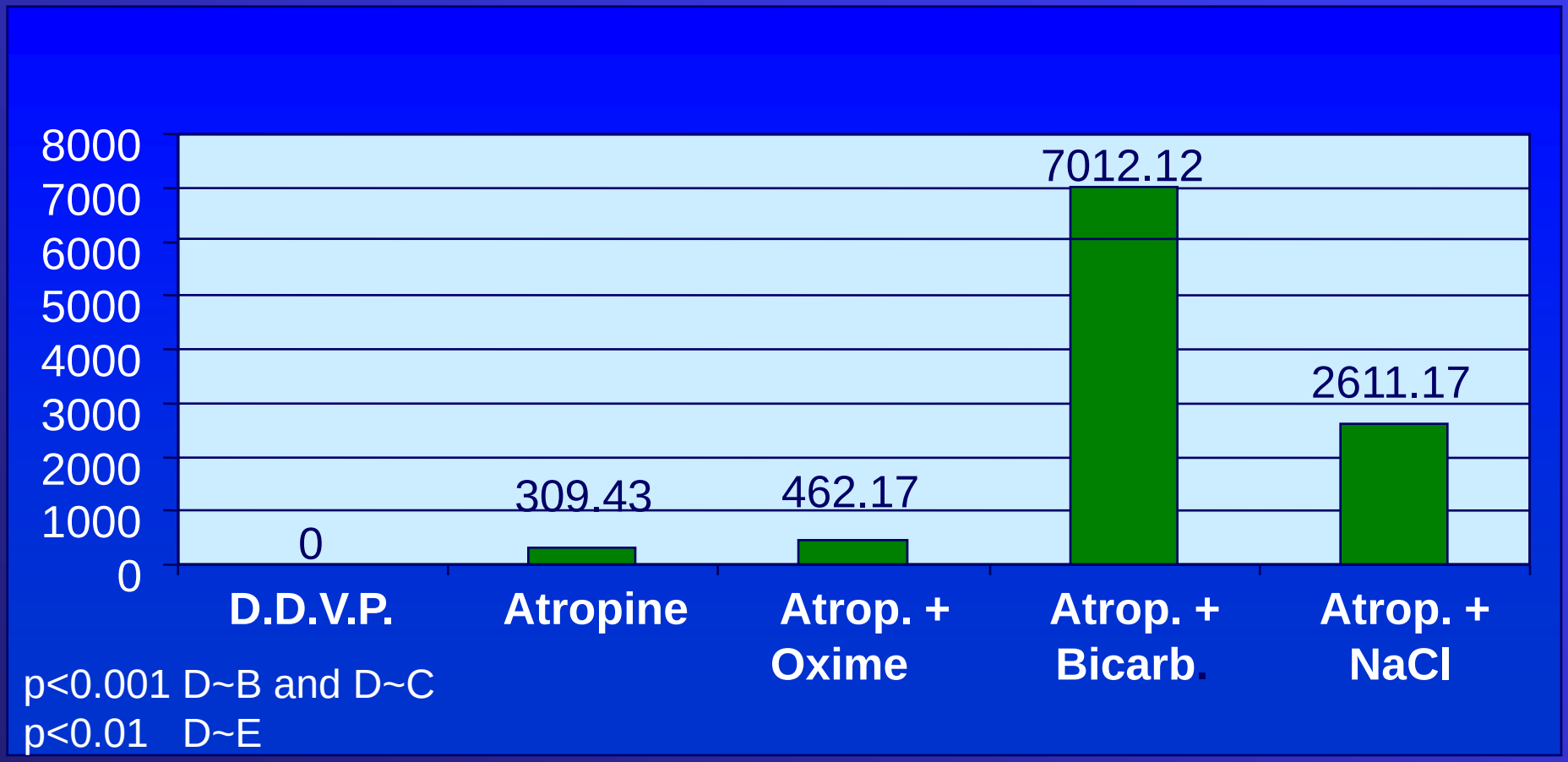
Organophosphate:? pH sensitive



☠ 85% survival pH 7.3 → 7.53

📖 Cordoba D. Cadavid S. Angulo D. Ramos I. Organophosphate poisoning: modifications in acid base equilibrium and use of sodium bicarbonate as an aid in the treatment of toxicity in dogs. *Veterinary & Human Toxicology. Vol 25(1) (pp 1-3), 1983*. 0145-6296

COMPARATIVE EFFICACY OF I.V. PRALIDOXIME vs. $NaHCO_3$ IN RATS LETHALLY POISONED WITH O-P INSECTICIDE. Dr. Anthony Wong Brazil



N= 10 rats in each group

Effect of High Doses of Sodium Bicarbonate in Acute Organophosphorous Pesticide Poisoning. Mahdi BalaliMood Clinical Toxicology, 43:571574, 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 ± 1.97
  - Treatment 4.33 ± 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

- Wellcome Trust & NHMRC
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- Mahdi BalaliMood, Tony Wong
- Ravindra Fernanado, Nimal Senanayake, Rezvi Sheriff, Nick Buckley, David Henry, Darren Roberts & other members of SACTRC

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