# Approaches to Common Clinical Toxicology Problems in Thailand 2015

น.พ. สัมมน โฉมฉาย
ภาควิชาเวชศาสตร์ป้องกันและสังคม
คณะแพทยศาสตร์ศิริราชพยาบาล
มหาวิทยาลัยมหิดล

## The most common cause of death from poisoning

- Respiratory failure
- Circulatory failure
- Tissue hypoxia
- Seizures, hyperthermia and rhabdomyolysis
- Organ damage

## Approach to a poisoned patient

- Stabilization: A,B,C
- Evaluation
- Supportive care
- Decontamination
- Enhancement of elimination
- Antidotes
- Observation and disposition

## Goals of Clinical Toxicology Assessment

- Recognition and assessment of possible morbidity and mortality
- Seek opportunities to exert specific toxicological management

## Approaches of Clinical Toxicology Assessment

- Clinical (manifestation)-based assessment
- Hazard based assessment

## Toxic syndrome (Toxidromes)

| Toxidrome | manifestation | toxicants |
| --- | --- | --- |
| Sympathomimetics | Tachycardia, hypertension, mydriasis, diaphoresis, tremor, delirium, hyperthermia | Amphetamine, cocaine, stimulants, entactogenics, withdrawal syndrome, thyroxine |
| Anticholinergic | Tachycardia, hypertension, mydirasis, dry skin, dry mucosa, urine retention, ileus, delirium, hyperthermia | Atropine, antispasmodic<br>Antihistamines,<br>Tricyclic antidepressants,<br>Antipsychotics |
| Cholinergic | Muscarinic: SLUDGE:<br>Salivation, small pupils, lacrimation, urine incontinence, diarrhea, diaphoresis, GI upset, emesis<br><br>Nicotinic: Muscle fasciculation, paralysis, tachycardia, HT | Organophosphorus, carbamates, muscarinic agents, nicotine, neonicotinoid<br><br>Other mimickers:<br>chlorophenoxyacetic acid |
| Sympatholytic | Bradycardia, bradypnea, miosis, altered mental status | Opiates and opioids,<br>Imidazolines: oxymethazoline, tetrahydrazoline<br>clonidine, methyldopa |

## Primary Considerations for Presenting Chief Complaint in the Poisoned Patient

| CHIEF COMPLAINT | COMMON CAUSES |
|---|---|
| Coma | Alcohol, Antipsychotics/antidepressants, Antileptic medications, Carbon monoxide, Opiates, Sedative/hypnotics |
| Delirium | Anticholinergics/cholinergics/ antidepressant<br>Muscle relaxants<br>Sympathomimetics<br>Withdrawal syndromes |
| Seizure | Isonaizid<br>Anticholinergics/cholinergics<br>Antidepressants<br>Mushrooms (*Gyrometra sp.*)<br>Sympathomimetics<br>Toxic alcohols<br>Withdrawal syndromes |

## Primary Considerations for Presenting Chief Complaint in the Poisoned Patient

| CHIEF COMPLAINT | COMMON CAUSES |
|---|---|
| Hepatic injury | Acetaminophen<br>Carbon tetrachloride<br>Ethanol<br>Mushrooms *(Amanita phalloides, verna, virosa)* |
| Renal injury | Ethylene glycol<br>Heavy metal salts (mercury)<br>Mushrooms (*Cortinarius orellanus)*<br>Rhabdomyolysis (cocaine, amphetamines) |
| | |

## ECG Toxic syndromes

- Sodium channel blockade
- Potassium channel blockade
- Digoxin effect/ Digoxin intoxication
- Calcium channel blocker/ betablocker
- Hydrofluoric acid toxicity

## Sodium channel blockade

- Criteria

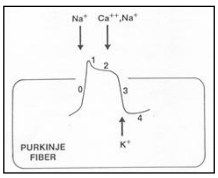
1. Prolonged QRS interval (≥100msec)
2. Prominent R in avR
   1. R > 3 mV
   2. R/Q or R?S > 0.7

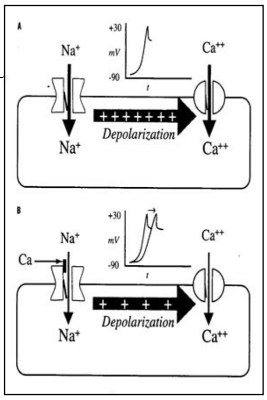
Causes: tricyclic antidepressant, cocaine, diphenhydramine,

Thioridazine, mesoridazine, propoxyphene

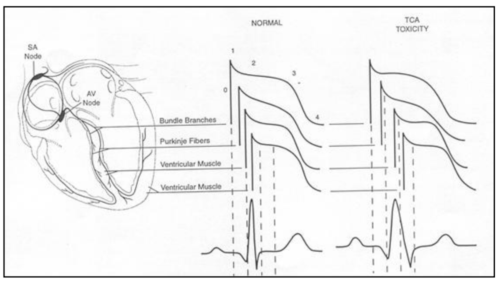
- Treatment: IV $NaHCO_3$, hyperventilation

## Membrane stabilizing effects

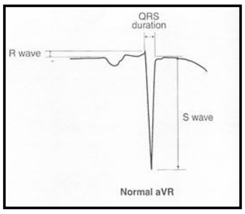


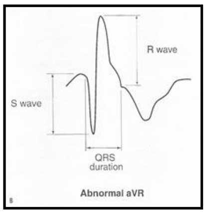




## Membrane-stabilizing effects and the ECG

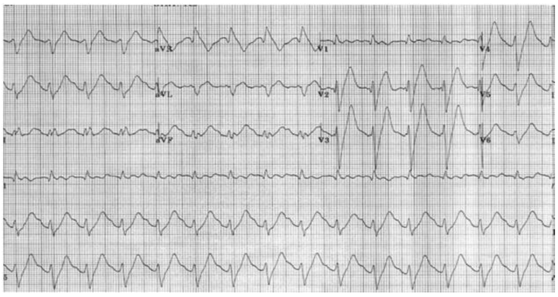


## ECGs as prognostic factors and treatment indicators

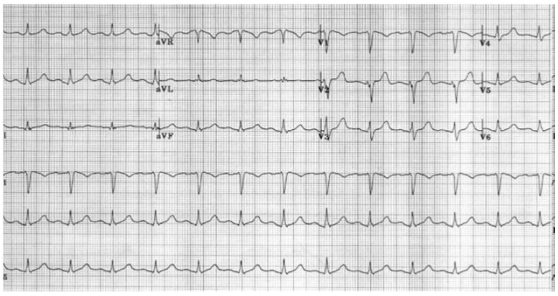



## ECG from a TCA-poisoned patient



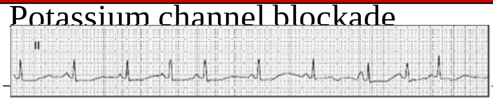
## ECG from a TCA-poisoned patient after NaHCO3 administration

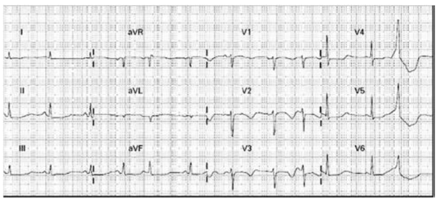


## Potassium channel blockade

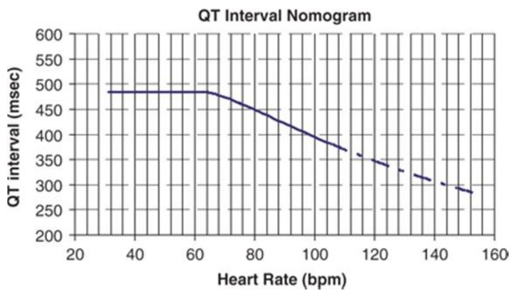
- Sign of potassium channel bloclade: QT prolongation
  - QTc interval > 0.44 seconds in men and 0.46 seconds in women
  - Risk of Torsade des pointes
- Toxicants:
  - Antihistamines (Astemizole Diphenhydramine Loratidine Terfenadine)
  - Antipsychotics
  - Arsenic trioxide
  - Chloroquine, Hydroxychloroquine
  - Cisapride
  - Citalopram
  - Class IA, Ic and III antidysrhythmics
  - Cyclic antidepressants
  - Fluoroquinolones Ciprofloxacin Gatifloxacin Levofloxacin Moxifloxacin Sparfloxacin
  - Macrolides (Clarithromycin Erythromycin)
  - Pentamidine
  - Quinine
  - Tacrolimus
  - Venlafaxine

## Potassium channel blockade





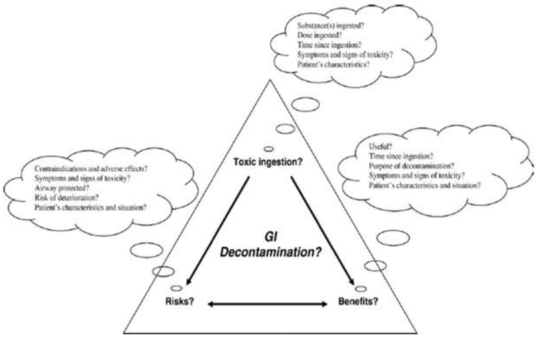
## QT interval nomogram



## GI decontaminations

- **Choices**
  - **Do nothing**
- or
  - Perform gastric lavage
  - Administer activated charcoal
  - Whole bowel irrigation

## Decontamination triangle




## Gastric lavage

- Indication:
  - Potentially life-threatening poisoning and presentation within 1 hour
- Contraindications
  - Compromised, unprotected airway
  - Corrosive ingestion
  - Hydrocarbon ingestion
- Complications
  - Aspiration of gastric contents
  - Esophageal rupture

## Activated charcoal

- Charcoal provides a very large surface area for the adsorbance of toxins
- Inications: Drug ingested is **adsorbed by charcoal** and has **significant potential for toxicity And t**ime since ingestion is less than 1 hours
- Toxicants not adsorbed by charcoal: **Acids & Alkalis, salts, hydrocarbons, metals, alcohol**
- Contraindications
  - Compromised, unprotected airway
  - Corrosive ingestion
  - Hydrocarbon ingestion
- Complications: aspiration of charcoal, bowel obstruction

## Whole bowel irrigation

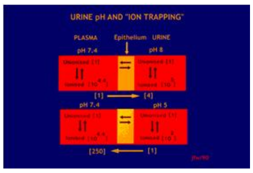
- Polyethylene glycol in a balanced electrolyte solution
  - No net gain or loss of fluids or electrolytes
- Rate (2 L./hr; 30mL/kg/hr)
- Endpoint: clear effluent, clear content
- Indication:
  - Large ingestion of iron, lithium or poisons poorly absorbed by activated charcoal
  - Large ingestion of sustained-release or enteric coated tablets
  - Ingestion of drug-filled packets [Body packers]
- Contraindications
  - Ileus or intestinal obstruction
  - Unprotected airway
- Adverse effects: nausea, aspiration

## Enhancement of elimination

- 3 Methods
  - **Intracorporeal**
    - 1. Ion trapping: Urinary alkalinization(ion-trapping)
    - 2. Repeated dose activated charcoal
  - 3. **extracorporeal** such as hemodialysis.
- Indications:
  - Critically ill despite supportive care
  - Known lethal dose or blood level
  - Usual route of elimination impaired
  - Risk of prolonged coma/ intoxication
- Considerations: volume of distribution, clearance

## Urine alkalinization

- IV $NaHCO_3$
- Enhance ionization of weak acid in alkaline urine
- Trap the ions [prevent diffusion/ reabsorption]
- **useful for salicylates, phenobarbital, chlorpropamide**
- Risk of fluid overload

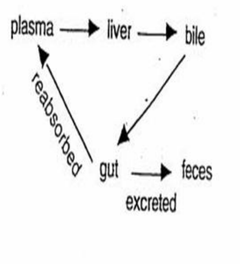



## Hemodialysis

- Best if drug is:
  - Small Vd ~ 0.7 L/kg, (<1 L/kg)
  - water-soluble
  - small (MW <500)
  - not highly protein bound
- Aspirin, valproic acid, theophylline, toxic alcohols (ethanol, methanol, ethylene glycol, isopropanol), lithium, metofrmin

## Multiple dose oral charcoal - "gut dialysis"

- Repeated charcoal administration along the entire intestinal tract
- Large surface area for adsorption of drug diffusing across intestinal epithelium from capillaries
- Useful if drug are well adsorbed by charcoal, small Vd, low protein binding
  - **Phenytoin**, aspirin, theophylline, phenobarbital, **carbamazepine, dapsone**




## Antidote

- Not necessary in many cases
- Supportive care is still the mainstay
- Absolutely necessary in some cases
- May cause adverse effects (even fatal effects)

## Available antidotes in Thailand

| Antidote | Use |
|---|---|
| N-acetylcysteine | Acetaminophen, p* |
| Antivenom | Snake |
| Atropine | Organophosphorus, carbamate p* |
| Pralodoxime (2-PAM) | Organophosphorusp* |
| Diazepam | Organophosphorus, carbamate p* |
| Benztropine | Acute dystonia |

| Antidote | Use |
|---|---|
| Sodium bicarbonate | Tricyclic antidepressant, salicylate p* |
| Botulinim antitoxin | Botulism |
| Calcium | Calcium blocker, Beta blocker, Hydrofluoric acid p* |
| Bromocriptine | Neuroleptic malignant syndrome |
| Cyproheptadine | Serotonin syndrome |

**p*= poisoning**

## Available antidotes in Thailand(2)

| Antidote | Use |
|---|---|
| Calcium disodium EDTA | Lead, zinc, manganese and cadmium p* |
| *Succimer (DMSA)* | Lead, mercury, arsenic |
| *Dimercaprol* | Arsenic, mercury, lead p* |
| DMPS, Unithiol | Arsenic, mercury, lead p* |
| D-penicillamine | Lead, mercury and copper p* |
| Deferoxaime | Iron p* |

| Antidote | Use |
|---|---|
| Ethanol | Methanol, ethylene glycol poisoning |
| Fomepizole (4-methylpyrazole, 4-MP) | Methanol, ethylene glycol poisoning |
| Folic acid, folinic acid | Methanol, methotraxate poisoning |
| Flumazenil | Benzodiazepine |
| Digoxin Fab | Digoxin |

**p*= poisoning**

## Available antidotes in Thailand(3)

| Antidote | Use |
|---|---|
| Methylene blue | Methemoglobinemia |
| Sodium nitrite | Cyanide p*, hydrogen sulfide |
| Sodium thiosulfate | Cyanide p* |
| Hydroxycobalamine | Cyanide p* |
| Oxygen hyperbaric oxygen | Carbon monoxide p* |

| Antidote | Use |
|---|---|
| Pyridoxine (Vitamin B6) | Isoniazid, gyromitra mushroom p* |
| Vitamin K1 | Warfarin and superwarfarin poisoning |
| Glucagon | Calcium blocker, Beta blocker, p* |
| Insulin | Calcium blocker, Beta blocker, p* |
| Octreotide | Sulfonylurea-induced hypoglycemia |
| 20% Lipid emulsion | Local anesthetic poisoning |

**p*= poisoning**

## Observation

- An appropriate period of observation is needed in most patient with potentially toxic exposure
- Some toxic substances are associated with 'delayed toxidrome':

## Examples of toxicants with delayed toxic syndrome

| Toxicants | Delay | Syndrome |
|---|---|---|
| Acetonitrile | 24 hours | Cyanide poisoning |
| Organophosphorus | 18 hours | Cholinergic syndrome |
| Hydrofluoric acid | 24 hours | Hypocalcemia, skin burns |
| Zinc phosphide | 24-72 hours | Pulmonary edema |
| Methanol intoxication | 12-24 hours | Metabolic acidosis, visual loss |

## Poisoning in Thailand

| Categories | No. of Cases | (%) | No. of Death | Death rate(%) |
|---|---|---|---|---|
| Pesticides | 6,229 | 41.5 | 622 | 10.0 |
| Household products | 2,932 | 19.5 | 29 | 1.0 |
| Pharmaceutical products | 2,815 | 18.7 | 49 | 1.7 |
| Technical and occupational products | 1,372 | 9.1 | 32 | 2.4 |
| Plant toxins/poisonous plants | 562 | 3.7 | 23 | 4.1 |
| Poisonous animals | 409 | 2.7 | 24 | 5.9 |
| Thai/Chinese herbs | 109 | 0.7 | 2 | 1.8 |
| Recreational and abused agents | 81 | 0.5 | 7 | 8.6 |
| Food toxins and contaminants | 21 | 0.1 | 1 | 4.8 |
| Health food/cosmetics | 14 | 0.1 | 0 | 0.0 |
| Food additives | 12 | 0.1 | 0 | 0.0 |
| Chemical weapons | 9 | 0.1 | 0 | 0.0 |
| Combined chemicals | 287 | 1.9 | 8 | 2.8 |
| Others | 21 | 0.1 | 0 | 0.0 |
| Unknown | 143 | 1.0 | 22 | 15.4 |
| **Total** | **15,016** | | **820** | **5.5** |

## Categories of pesticides involved

| Type of pesticide | No. of cases | (%) |
|---|---|---|
| Insecticides | 3,217 | 50.0 |
| Herbicides | 1,588 | 24.7 |
| Rodenticides | 911 | 14.2 |
| Miticides | 297 | 4.6 |
| Plant hormone & growth regulators | 145 | 2.3 |
| Others | 262 | 4.0 |
| Unknown pesticides | 17 | 0.3 |
| **Total** | **6,437*** | |

## Pharmaceutical products involved

| Major/subgroup classification | No. of cases | (%) |
|---|---|---|
| Tranquillizers | 645 | 16.5 |
| Analgesic & antipyretics | 631 | 16.1 |
| Antidepressants | 264 | 6.7 |
| Respiratory system | 241 | 6.2 |
| Anti-infectives | 211 | 5.4 |
| Hypnotics & sedatives | 195 | 5.0 |

## Pesticides

| Insecticides | Herbicides | Rodenticides |
|---|---|---|
| Organophosphorus/ carbamates | Paraquat | Anticoagulants |
| Pyrethroids & pyrethrin | Glyphosate | Zinc phosphides |
| Organochlorine | Phenoxychloroacetic (2,4-D), (2,4,5-T) | Strychnine |
| Abamectin | Propanil | |

## Case 1

- A previously healthy 31-year-old male farmer was found unconscious at home with some stains in the perioral area and chest wall. An empty container of "pesticide" is found at the scene

At the ED:

- P110/min, BP 130/90 mmHg, RR 28/min, T 38.5 C, SaO2 93% @ room air
- Comatose, profuse sweating, pinpointed pupils
- Chest: Marked bronchospasm
- CVS and abdomen: WNL
- NS: no lateralization, areflexia, muscle fasciculation in the extremeties

## Case 2

- A 35-year-old Thai male is brought into the emergency department after he was found unconscious at home.
- At the emergency department, he was unconscious, unresponsive to deep pain
- His vital signs were BP 80/50 mmHg, heart rate 50/min, respiration 22/min, O2Sat 97 % room air

## Case 2

- His skin appeared to be wet and cold, pupils size 1 mm and he was dyspnic, solvent-like breath odor, spilled liquid on the chest and arms
- Respiratory system: generalized rales and bilateral wheeze
- Cardiovascular: unremarkable
- Abdomen: flat, soft, increased bowel sounds
- Nervous system: Comatose, areflexia, muscle fasciculations on extremities

## Case 3

- A 46-year-old man ngested one mouthful of paraquat 30 minutes before presentation.
- The patient had no previous medical illnesses
- He complains of burning sensation in his oral cavity.
- PE: P 84/min, BP 130/80 mmHg, R 20/min
- Greenish stain on around his mouth and body

## Challenge questions

Q1: Pralidoxime has **no** role in management of organophosphate poisoning, since it offers no clinical improvement and may increase mortality.

- T ____
- F ____

Q2: In organophosphate and carbamate poisoning, atropine should be given as 1-3 vials (0.6 mg/vial) every 5-15 minutes until pupils are dilated.

- T ____
- F ____

## Challenge questions

- Q3: There is no specific treatment for paraquat poisoning.

- T ____
- F ____

- Q4: An adult patient who ingests 20-30 mL of paraquat are likely to die and only supportive treatment should be given.

- T ____
- F ____

## Cases 1 and 2: What toxic syndrome are they manifesting?

**Cholinergic toxidrome**

- SLUD: salivation, small pupils, lacrimation, urine incontinence, diarrhea, diaphoresis
- 3B: Bradycardia, bronchorrhea, bronchospasm
- Nicotinic symptoms: tachycardia, hypertension, muscle fasciculation and paralysis
- CNS

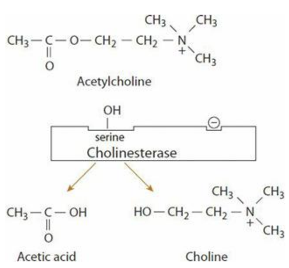
**Other toxic syndrome**

- ????

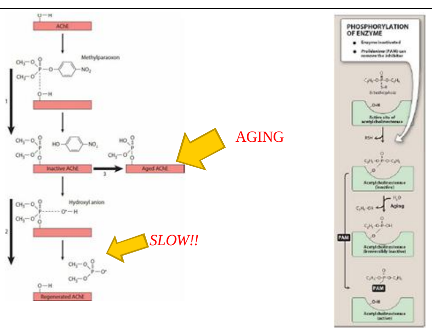
## Organophosphorus and carbamates poisoning

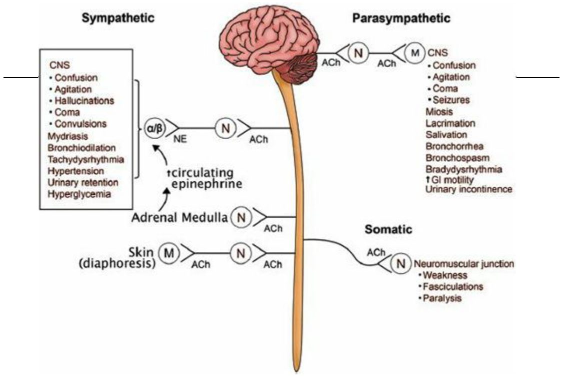
- Inhibitor of acetylcholine esterase (AchE)
- Bind to AchE and form a stable compound
- Inactivate AchE molecule inactive
- Once AchE molecules are unavailable, continued stimulation
  - cholinergic overstimulation
  - paralysis

## Acetylcholinesterase




## AChE inactivation and reactivation by organophosphorus






# Organophosphorus and Carbamate Insecticides

Signs and Symptoms

- I. Muscarinic or parasympathetic symptoms
  - **SLUD + 3 KILLER Bs**
  - **Salivation, small pupils, lacrimation, urine incontinene, diarrhea, diaphoresis**
  - **Bradycardia, bronchorrhea (bronchial secretion), bronchospasm**
- II. Nicotinic/ganglionic/NM symptoms
  - Muscle fasciculation, progressive paralysis and respiratory failure.
  - Hypertension, tachycardia, pupillary dilatation and pallor
- III. CNS symptoms
  - Restlessness, tremor, confusion, ataxia, slurred speech and seizure.

# Laboratory Diagnosis

Clinical diagnosis

“Therapeutic trial” atropine

Cholinesterase level

- Suppression of level by at least 50% in symptomatic cases

- Wide normal range
- RBC cholinesterase
  - Specific
  - Hardly available
- Plasma cholinesterase
  - More available
  - Non-specific

# Diagnostic aids for cholinergic toxidrome and the mimics

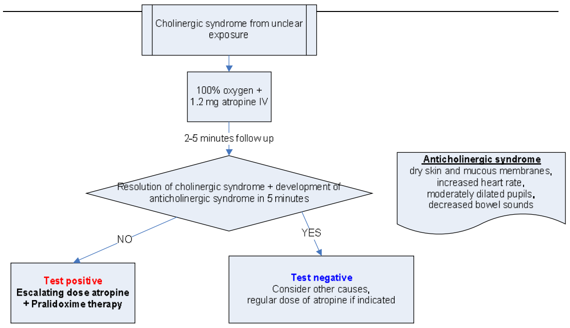
**“Therapeutic trial” atropine**

- **1.2 mg IV atropine**, check response within **5 minutes**
  - **Test positive: <u>no change</u> in P, BP, pulmonary secretion, miosis → cholinesterase inhibition→ <u>OP/CB</u>**
  - **Test negative: tachycardia, HT, dry secretion, decreased rhonchi, mydriasis, <u>“towards anticholinergic”</u> → <u>other</u> mimicking toxicants: neonicotinoids, chlorophenoxyacetic acids**

**Cholinesterase acitivity**

- Less useful in clinical care
- Confirm exposure
  - Decreased cholinesterase activity
- Confirm adequacy of 2-PAM (pralidoxime)therapy (cholinesterase reactivatability)

# “Atropine therapeutic trial” in suspected cholinergic syndrome




# Treatment of OP poisoning

- Antagonizing muscarinic effects ***
- Reactivating blocked cholinesterase
- Treatment of muscle hyperstimulation/ seizures

Lancet. 2008 Feb 16;371(9612):597-607.

Therapeutic decisions for organophosphoruses:
**Therapeutic trial atropine makes no changes**

**Atropine**

- Escalating dose regimen
- Indications:
  - Bradycardia
  - Bronchorrhea
  - Bronchospasm

**2-PAM**

- Loading dose 1 g
- Continuous infusion of 700-1g/hour
- Indications: organophosphoruses
- Duration: as long as the patient needs 2-PAM

## Clinical parameters to be monitored

- Pupils
- Sweating
- Lung sounds: air entry, bronchospasm, secretion
- Heart rate
- Blood pressure

Lancet. 2008 Feb 16;371(9612):597-607.

## Atropine dosing: escalating dose regimen

- Atropine 1.8–3 mg (three to five 0.6 mg vials)
- 3-5 minutes after giving atropine, check the five markers of cholinergic poisoning
- The most important parameters are
  - Air entry on chest auscultation
  - Heart rate
  - Blood pressure

Lancet. 2008 Feb 16;371(9612):597-607.

## Endpoint for adequate atropine

**Indicators**

- Clear chest on auscultation with no wheeze
- Heart rate >80 beats/min
- Pupils no longer pinpoint
- Dry axillae
- Systolic blood pressure >80 mmHg

**Pitfalls**

- Pupils
- Lung sounds (crepitations)

*Critical Care* 2004, 8:R391-R397

- With no improvement in 3-5 minutes: double dose the atropine until the goal is achieved
- **Continue doubling the dose each time that there is no response**
- From a review of 22 surviving patients with OP-poisoning and respiratory failure dose of atropine 1-75 mg(mean23.4 mg, 22.0 sd) to clear the lungs, raise the pulse above 80bpm, and restore systolic blood pressure to more than 80 mmHg
- **Standard textbook therapy will take**
  - Up to 1380 mins to mean dose
  - Up to 4440 mins to 75 mg dose

- J Toxicol Clin Toxicol. 2004;42(6):865-75.
- Crit Care. 2004 Dec;8(6):R391-7.

## Maintenance atropine therapy

- Infusion of atropine
- Rate per hour = 10-20% loading dose
- Atropine intoxication: agitation, confusion, urinary retention, hyperthermia, bowel ileus and tachycardia
- With intoxication: stop the atropine infusion and check every 30 minutes
- Once the atropine intoxication subsides restart the infusion at the rate 70-80% of the previous rate

Lancet. 2008 Feb 16;371(9612):597-607.

## Use of pralidoxime (2-PAM)

- Oximes reactivate acetylcholinesterase inhibited by organophosphorus
- Despite the beneficial effects of pralidoxime, its effectiveness (and safety) has been much debated
  - Resistance to 2-PAM effect may result from solvents in the formulation.
    - Toxicol Sci. 2013 Dec;136(2):274-83.

## Pralidoxime (2-PAM) Current recommendations

- Pralidoxime be given to all symptomatic patients who need atropine or manifesting neuromuscular manifestations
- Pralidoxime chloride
  - Adults: 1 g loading dose followed by 700-**1000** mg/h.
- Continue until
  - Recovery (12 hours after stopping administration of atropine
  - Butyrylcholinesterase increase

Lancet. 2006 Dec 16;368(9553):2136-41.
Lancet. 2008 Feb 16;371(9612):597-607.

## Benzodiazepine

- Overall effects of benzodiazepine: reducing anxiety and restlessness, reducing muscle fasciculation and seizures, controlling agitation
- Indications: patients poisoned with OP whenever convulsions, agitation or pronounced muscle fasciculation are present
- Doses:
  - Diazepam 5-10 mg (0.05-0.3 mg/kg/dose)
  - Midazolam 5-10 mg (0.15-0.2 mg/kg/dose)
    - Lancet. 2008 Feb 16;371(9612):597-607.

## Insecticide poisoning in Thailand

| Chemical group | Clinical manifestations | Management |
|---|---|---|
| Organophosphorus/ carbamate | Typical cholinergic syndrome | • **Atropine (escalting dose regimen)**<br>• **Pralidoxime** |
| Pyrethroids '-thrin' e.g. permethrin | Tremor, myoclonus, seizure | Supportive symptomatic care |
| Abamectin | Coma, flaccid tone, seizure, hypotension, pulmonary edema | Supportive symptomatic care |
| Neonicotinoids e.g. Imidacloprid | Miosis, sweating, hypersecretion, increase bowel sound, bracycardia | Atropine, regular doses |

## Paraquat

- A bipyridium herbicide
- Toxicokinetics
  - Rapid absorption: peak plasma level within 1-2 hours
  - Incomplete absorption: 10-30%
  - Distribute to tissues: Lung, Kidney
  - Elimination: 90% eliminated within 12 -24 hours via kidney (half-life 10-12 hours)

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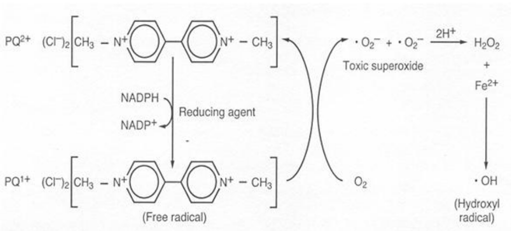
- Ingestion of paraquat leads to
  - Generation of free oxygen radicals
  - Lipid peroxidation
  - Damaging cell membranes and leading to cell death.
- Paraquat is actively taken up into type II pneumocytes and renal tubular cells.




## Paraquat toxicity

| Severity | Dose (mg/kg) | Dose (mL of 27.6% PQ) | GI | Renal | Systemic | Urine dithionite | Plasma dithionite |
|---|---|---|---|---|---|---|---|
| Mild | <20 | <5 | Mild | normal | - | - in first 24 hrs | - |
| Mod-sev | ≥20 | ≥5 | Severe | Creatinine↑ | Hepatitis Interstitial pneumonitis | + | - |
| Fulminant | ≥ 40 | ≥10-15 | Very Severe | Creatinine ↑↑ | ARDS, Shock, Encephalopathy, Severe Hepatitis | + | + |

## Plasma paraquat level

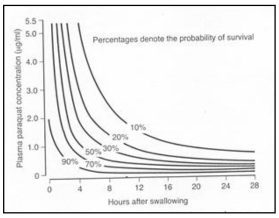
*Hart's Nomogram*

Plasma paraquat level drawn within 28 hours

Those with level 3 mg/L at anytime: 100% mortality

No fulminant poisoning:

- 2.0 mg/L at 4 hr
- 0.3 mg/L at 10 hr
- 0.1 mg/L at 24 hr




Eddleston M, Wilks MF, Buckley NA. *Qjm* 2003;96(11):809-24.

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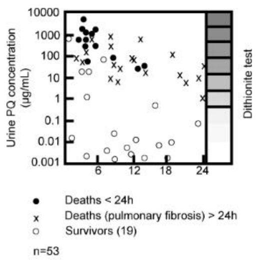
## Urine paraquat

## Urine dithionite test → Semiquantitative test

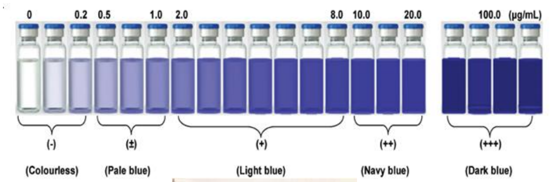
- In a study with 53 cases of paraquat poisoning
- *All patients with urinary paraquat concentrations less than 1 µg/ml(no color change-pale blue), within 24 h of ingestion, survived*
- Cases with results more than ++ (navy blue; >10 µg/ml) within 24 h following ingestion have a high probability of death
  - Hum Toxicol1987 Jan;6(1):91-3.

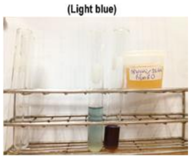
## A study of urine paraquat test as a prognostic predictor

Hum Toxicol1987 Jan;6(1):91-3.




## Urine dithionite test for paraquat



## Plasma dithionite test

- A study using sodium dithionite test for plasma paraquat as a qualitative test in 233 paraquat poisoning patients
- Blood samples were drawn within 12 hours
- Detection limits: concentration ≥ 2 mg/L
  - Levels above 2 mg/L are associated with high mortality in many studies
  - Patients with a plasma paraquat level < 2.0 mg/L have the potential for recovery with vigorous treatment
- Sensitivity 0.67
- Specificity 1.0
- Positive predictive value 1.0
  - Am J Med Sci2009 Nov;338(5):373-7.

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- Urine should be tested serially for 24 h after ingestion
- An early urinary semiquantitative testing may underestimate the amount of paraquat systemically absorbed
  - Crit Rev Toxicol. 2008;38(1):13-71.

---

- Although quantitative plasma paraquat concentrations have a greater predictive value, qualitative urine and plasma may contribute to a more rapid evaluation of prognosis with more availability

**Am J Med Sci2009 Nov;338(5):373-7.**

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## GI decontamination

Activated charcoal/ Fuller's earth/ bentonite

Improve survival in animal studies

Equivocal efficacy in animal studies

Adsorbent therapy alone has never shown increase survival in human

Meredith TJ, Vale JA. *Hum Toxicol* 1987;6(1):49-55.

76

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## Enhancement of elimination: Charcoal hemoperfusion/ hemodialysis

- Significant clearance and improved survival shown in canine models loaded with LD50 and LD100 dose.
- No systematic study showing that hemodialysis or hemoperfusion is efficacious in human
- Possible cause of failure:
  - Relatively small amount cleared
  - While renal function is still intact, external clearance is smaller than renal clearance
  - When renal failure develops, pulmonary uptake has already occurred.
- Recommendation: perform charcoal hemoperfusion only if it can be started within 4 hours.

***Med J Aust* 1991;154(9):617-22.**

77

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## Specific therapy

- Immunosuppressive therapy: the regimens consisting of
  - Cyclophosphamide
  - Corticosteroids
- Concepts: Reduction of pulmonary inflammation and fibrosis using anti-inflammatory and immunosuppressive therapy
- Current clinical findings: Immunosuppressive therapy significantly reduce mortality rate in patients with significant paraquat exposure
  - Cochrane Database Syst Rev. 2014 Aug 7;8:

- Regimen: cyclophosphamide 5 mg/kg/day and dexamethasone 24 mg/day for 14 days
- Total cases = 72
- Mortality: treated 20/72(27.8)% vs. historical control 42/61(68.9%)
  - Lancet. 1986 May 17;1(8490):1117-20.
- Another study
- Survival: treated 20/31(64.5%) vs. historical control 9/14(64.3%)
  - Hum Exp Toxicol. 1992 Mar;11(2):129-34.

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- A single-blinded randomized clinical trial in 142 paraquat-poisoned patients, pulse therapy reduced mortality in moderate to severe poisoning from 53/65(81.5%) to 38/56(67.9%)
- Pulse therapy included

1. 15 g/kg/day of cyclophosphamide for 2 days
2. 1 g/day of methylprednisolone for 3 days

- All patients also received dexamethasone 30mg/day for 14 days
  - Am J Respir Crit Care Med. 1999 Feb;159(2):357-60.

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## A repeated pulse regimen

- Inclusion criteria:
- cases of paraquat poisoned patients with predictive mortality > 50% but < 90% by plasma level
- Control N = 52
  - Initial pulse therapy:
  
  cyclophosphamide (15 mg/kg/day, i.v., 2 days) and methylprednisolone (1 g/day i.v., 3 days)
  
  Followed by dexamethasone 5 mg, i.v., every 6 h until PaO2 > 80 mmHg
- 59cases for initial pulse therapy ***PLUS*** repeated pulse therapy if PaO2 was < 60 mmHg: 3 days of methylprednisolone and 1 day of cyclophosphamide
- Mortality rate:
  - control 48/52 = 92%
  - Study 39/59 = 66% (p=0.003)
    - Intensive Care Med (2011) 37:1006–1013

---

## Anti-inflammatory effect and survival

- A retrospective study in 54 cases
- Significantly higher survival with suppression of leucocyte or neutrophil counts by at least 10% after the initiation of immunosuppressive
  - Journal Of the Chinese Medical Association2009;72(9 supplement):S20-1.

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## The latest systematic review

- Systematic review
- 3 RCT
- Total cases : 164 moderate to severe cases
- Inclusion criteria: Urine navy blue or dark blue and/ or plasma level in the range of mortality 50-90%
- Interventions: IV cyclophosphamide and dexamethasone
- Main outcomes: mortality at the end of follow up (at least 30 days post ingestion)
- Results: RR 0.72 (95% CI 0.59 to 0.89)
  - Cochrane Database Syst Rev. 2014 Aug 7;8:

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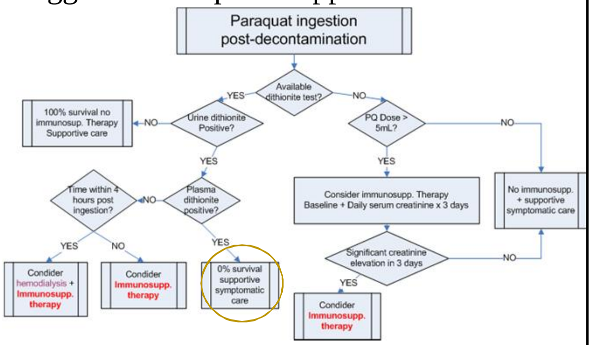
## Suggested therapeutic approach



## Herbicide poisoning in Thailand

| Chemical group | Clinical manifestations | Management |
|---|---|---|
| Paraquat | GI corrosive, acute kidney injury, interstitial pneumonitis | Immunosuppressive therapy |
| Glyphosate | GI corrosive, hypotension, pulmonary edema | Supportive symptomatic care |
| Chlorophenoxy-acetic acid | Coma, seizure, miosis, muscle fasciculation, fever, bronchospasm | Supportive symptomatic care |
| Propanil | Loss of consciousness, methemoglobinemia | Methylene blue |

## Chlorphenoxy herbicides

- Plant growth regulators :
  - 2,4 dichlorophenoxyacetic acid (2,4-D)
  - 2,4,5,trichlorophenoxyacetic acid (2,4,5-T)

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## Chlorphenoxy herbicides : Mechanism of poisoning

- Direct irritant effects in gastrointestinal tract
- Severe toxicity and death is often preceded by multi-system effects
  - Cellular dysfunction
  - Uncoupling of oxidative phosphorylation

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## Chlorphenoxy herbicides: Toxicokinetics

- **Absorption**
- Chlorophenoxy herbicides are well absorbed from the gastrointestinal tract, with peak plasma concentrations around 2-6h post-ingestion.
- There is minimal absorption across the skin
- **Distribution**
- Protein binding is saturated with moderate exposures to chlorophenoxy herbicides which increases the volume of distribution.
- Acidosis may also increase the distribution of chlorophenoxy herbicides
- **Metabolism - Elimination**
- Renal clearance is the main route of elimination, although there is some hepatic processing.
- Renal elimination may become saturated with high exposures, prolonging the elimination half life.
- The plasma elimination half-life in humans is typically in the range of 15-45h, but may be prolonged up to 180 hours.

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## Clinical manifestations

- The most common: vomiting and mouth burning, abdominal pain and diarrhea
- Pre-renal renal failiure due to volume loss

Bradberry SM. *J Toxicol Clin Toxicol* 2000;38(2):111-22.
Brahmi N. *Vet Hum Toxicol* 2003;45(6):321-2.

89

- Severe cases:
  - Diagnosis by clinical syndrome
  - Coma preceded by confusion and agitation
  - Neuromuscular manifestations : hypertonia, fasciculation, weakness, miosis, nystagmus, ataxia, hallucination, seizures
  - Hypermetabolism: tachycardia, tachypnea, hyperthermia
  - Metabolic complications: acidosis and rhabdomyolysis
  - Pulmonary edema
  - Hyperventilation with respiratory alkalosis may be an early sign of severe poisoning.

Bradberry SM. *J Toxicol Clin Toxicol* 2000;38(2):111-22.
Brahmi N. *Vet Hum Toxicol* 2003;45(6):321-2.

90

## Management

- Typical GI decon
- Supportive care
  - Urine output should be monitored, and maintenance of a good output (>1 mL/kg body weight) is a priority in patients with moderate to severe poisoning. This may prevent the onset of renal dysfunction and increase clearance of the chlorophenoxy herbicide
  - Hypotension
  - Acidosis
  - Respiratory support

Bradberry SM. *J Toxicol Clin Toxicol* 2000;38(2):111-22.
Brahmi N. *Vet Hum Toxicol* 2003;45(6):321-2.

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- Enhancement of elimination: no evidence of benefits
  - Urine alkalinization: may be beneficial in severe cases
  - Hemodialysis
    - Acidosis unresponsive to sodium bicarbonate
    - Renal failure

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## Observation

- The correlation between dose ingested and severity of toxicity is not well defined.
  - Large exposures (reports of up to 100 mL) have been associated with mild or moderate toxicity only.
  - However, ingestion of volumes less than 100 mL has been associated with severe toxicity and death.
- Patients who remain asymptomatic for 6h post-ingestion are unlikely to progress to severe toxicity.
- Patients who develop symptoms should be monitored until asymptomatic.
  - Severe toxicity may not develop in some patients until 24-48h post-exposure.

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## Glyphosate

- Yellow or brown color
- Generally consist of an aqueous mixture of
  - Glyphosate salts
  - Surfactants
  - Various minor components: anti-foaming and colour agents, biocides and inorganic ions to produce pH adjustment
- Human poisoning with this herbicide is not with the active ingredient alone but with complex and variable mixtures

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- Majority: mild, transient, gastrointestinal features
  - Gastrointestinal corrosive effects, with mouth, throat and epigastric pain and dysphagia
- Renal failure
- Rare but serious complications
  - Respiratory distress, pulmonary edema
  - Shock, arrythmias
  - Alteration of consciousness: confusion, seizure

  - Talbot AR. *Hum Exp Toxicol* 1991;10(1):1-8.

95

## DETERMINATION OF SEVERITY

- **Ingested dose**
  - The ingestions of 5-50 mL may result in no symptoms or minor gastrointestinal symptoms only.
  - Moderate symptoms occur with 50-100 mL of the concentrate
  - Severe symptoms are likely when 100 mL or more of the concentrate are ingested

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- **Asymptomatic** No physical or laboratory abnormalities
- **Mild**
  - Predominantly gastrointestinal symptoms
  - stable vital signs and no other organ involvement
- **Moderate**
  - Gastrointestinal symptoms lasting longer than 24 hours
  - Hypotension, responsive to intravenous fluids
  - Pulmonary dysfunction not requiring intubation
  - Acid base disturbance
  - Evidence of transient hepatic renal damage or temporary oliguria
- **Severe**
  - Pulmonary dysfunction requiring intubation
  - Renal failure requiring dialysis
  - Hypotension requiring pressor amines
  - Cardiac arrest
  - Coma, Repeated seizures

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- Death
  - Within first 2 days
  - Pulmonary edema and shock

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# Management

- Typical GI decontamination
- Supportive care
- Enhancement of elimination
  - Hemodialysis may significantly remove glyphosate
  - No proven benefit
  - Reserve for renal faliure

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# Propanil

- Propanil (3,4-dichloropropioanilide) is a selective acylanilide herbicide
- Commercial products contain 36-48% propanil.
- Methemoglobinemia: the most important manifestation with acute poisoning
- Propanil (3,4-dichloropropioanilide) is hydrolysed *in vivo* to 3,4-dichloroaniline which is then metabolized to other compounds, including 3,4-dichlorophenylhydroxylamine, the major cause of toxicity

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- The major apparent biochemical effect is the production of metHb by oxidation of the ferrous heme (Fe2+) in erythrocytes to the ferric state (Fe3+).
- MetHb is unable to bind and transport oxygen in the vascular system, inducing a relative hypoxia at the tissue level, despite adequate inhaled oxygen and ventilation.
- Clinically the *cardiovascular, central nervous and respiratory systems* are the main organs affected, although any organ with a high metabolic activity is likely to be susceptible

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# Clinical manifestations: propanil toxicity

- Clinical effects are generally noted within six hours of ingestion of propanil, the principle effect being metHb
- Skin discoloration
- Nausea, vomiting and diarrhea
- Dyspnea
- Hyperventilation secondary to metabolic acidosis may be noted initially, which is followed by hypoventilation and hypoxemia with severe poisoning
- Tachycardia, hypotension and cardiac ischemia
- Headache, dizziness, syncope, confusion, sedation, coma and seizures
- Metabolic acidosis with an elevated lactate
- The high case fatality ratio in humans (approaching 12%) suggests that all oral ingestions should be treated as potentially severe.

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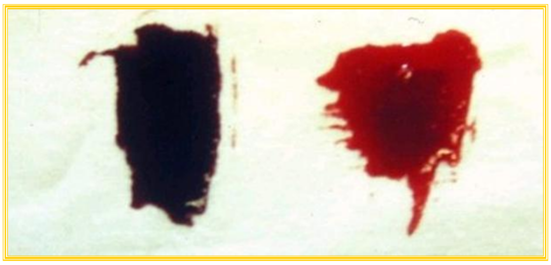
## Picture quiz

## Picture quiz



## Laboratory diagnosis

- Co-oximeter
- The diagnosis is suspected when low saturations are noted on pulse oximetry despite a normal or elevated pO2 on arterial blood gas measurements.
- Elevations in metHb are noted within a few hours of poisoning and may continue to rise beyond 6h.
- Once metHb is diagnosed, serial venous lactate measurements may be useful to monitor the course of poisoning (including response to antidotes).

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## Treatment

- **Supportive**
- Hypotension: intravenous fluids.
- Reversal of significant metHb levels remains a priority and cardiac monitoring should be available.
- Normoglycemia should be ensured since adequate glucose concentrations are required by the reducing enzymes present in erythrocytes and the antidote methylene blue
- Supplemental oxygen should be given to all symptomatic patients.
- Intubation and assisted ventilation should be performed on patients with significant CNS depression or hypercarbia

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- **Methylene blue**
  - Moderate poisoning: 1mg/kg methylene blue as a bolus injection over 1 minute. MetHb should be reassessed after one hour, and the methylene blue can be repeated if toxicity persists.
  - Severe poisoning: 2mg/kg methylene blue as a bolus injection over 1 minute followed by an infusion of 10 mg/hour for 10 hours
  - The maximum recommended daily dose of methylene blue is 7mg/kg
  - Adverse effects from methylene blue include nausea, vomiting, diaphoresis, burning sensation of the mouth and fingers and abdominal pain, hypotension, exacerbation of MetHb and haemolysis
  - Methylene blue should not be administered to patients with G6PD deficiency

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- Other treatment
  - N-acetylcysteine
  - Ascorbic acid
  - Blood exchange

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## Herbicides

- Try to identify or exclude paraquat
- Propanil: specific clinical syndrome
- Otherwise, supportive care is the mainstay

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## Other toxicologic causes of methemoglobinemia

- Local anesthetics: benzocaine, lidocaine, prilocaine
- Antimicrobials: Chloroquine, dapsone, primaquine, sulfonamides, trimethoprim
- Analgesics: phenazopyridine, phenacetin
- Nitrite and nitrates
- Others: Aniline, bromate, chlorate, nitrobenzene, nitrogen oxides, nitroglycerin, propanyl

## Cases and Challenge questions

Case 1: 2,4 D herbicide: the symptoms responded towards anticholinergic after 1.2 mg of atropine.

Case 2: Organophosphorus poisoning

Case 3: Significant paraquat ingestion, immunosuppressive regimen should be started

- Q1: F
- Q2: F
- Q3: F
- Q4: F

## Challenge questions

Q1: Pralidoxime has **no** role in management of organophosphate poisoning, since it offers no clinical improvement and may increase mortality.

- T ____
- F ____

Q2: In organophosphate and carbamate poisoning, atropine should be given as 1-3 vials (0.6 mg/vial) every 5-15 minutes until pupils are dilated.

- T ____
- F ____

## Challenge questions

- Q3: There is no specific treatment for paraquat poisoning.

- T ____
- F ____

- Q4: An adult patient who ingests 20-30 mL of paraquat are likely to die and only supportive treatment should be given.

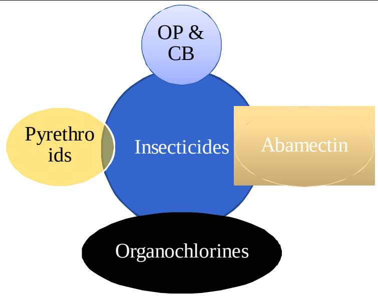
- T ____
- F ____

## Case 4

- A 18 y/o woman was brought in because of alteration of consciousness with a container of abamectin 1.8% W/V beside her
- BP 102/60 mmHg, P 64/min, R 26/min, O2sat 90% @ room air
- E1V1M2, pupils 3mm not reactive to light, normal skin and mucosa
- CVS & Chest: WNL
- Abdomen: Soft normal bowel sound
- NS: Flaccid tone, reflexes: 1+ upper extremities, absent: lower extremities

## Questions for case 4

- What is abamectin?
- What are the expected signs, symptoms and clinical course?




## Abamectin

- Abamectin is a potent antihelmintic, insecticide, and miticide
- Derived from *Streptomyces avermitilis* (species of Actinomyces)
- Abamectin: a mixture of avermectins containing >80% avermectin B1a and <20% avermectin B1b
  - Similar biological and toxicological properties

## Abamectin toxicity

- Toxic effects of abamectin are usually seen after oral ingestions
- May be absorbed dermally
- Following their absorption, maximum
- Serum concentrations peak 2.7 to 5 hours after oral dosing
- Elimination half-life was 2.8 to10 hours among healthy volunteers
  - Largely excreted into the bile and feces
    - Clin Toxicol (Phila). 2007;45(3):299-300.

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- CNS symptoms such as incoordination, tremor, lethargy, excitation, and mydriasis via GABA agonistic effect
- Deaths related to Abamectin ingestion are commonly a result of respiratory failure
- From Thai experiences: shock and status epilepticus

  - Clin Toxicol (Phila). 2007;45(3):299-300.

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- Only one study in the literature by Chung et al
- a significant correlation between the ingested abamectin dose and clinical severity
  - For asymptomatic and mild poisoning, the average ingested dose was 23.0 mg/kg
  - Average dose for severely poisoned patients was 100.7 mg/kg ~ 280 mL
  - CNS and gastrointestinal effects:diarrhea, nausea, vomiting, AMS, dizziness and weakness
    - Ann Emerg Med. 1999 Jul;34(1):51-7.

## Treatment

- Airway protection
- Hypotension: intravenous fluid and vasopressor
    - Clin Toxicol (Phila). 2007;45(3):299-300.

## Pyrethrins and pyrethroids

- A common household insecticide
- “-thrin” (permethrin, allethrin)
- Pyrethrins: compounds extracted from chrysanthemums
- Pyrethroids: synthetic derivatives of pyrethrins
    - More stable
    - More toxicity

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## Toxicokinetics

- Rapid absorption through GI tract and rapid metabolism at liver
- Minimal dermal absorption

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## Clinical manifestation

- Ingestion: Abdominal pain, nausea, vomiting within 10 minutes to 1 hours
- Allergic and hypersensitivity: Pyrethrin
    - Allergic rhinitis
    - Contact dermatitis
    - Asthma
    - Anaphylactoid
- Systemic manifestations:
    - Clinical diagnosis
    - Increase sodium influx into neurons
    - Increase neurotransmitter release
    - Toxic potency type II > type I (classified by chemical structures)
    - Paresthesia, numbness: onset hours, duration: less than 24 hours
    - Seizure
    - In cases of ingestion, beware of hydrocarbon pneumonitis

    - Proudfoot AT. *Toxicol Rev* 2005;24(2):107-13.
    - Ray DE, Forshaw PJ. *J Toxicol Clin Toxicol* 2000;38(2):95-101.

124

## Treatment

- Typical GI decontamination
- Be careful in case of hydrocarbon media
- Treat allergic symptoms with antihistamine
- Symptomatic

- Proudfoot AT. *Toxicol Rev* 2005;24(2):107-13.
- Ray DE, Forshaw PJ. *J Toxicol Clin Toxicol* 2000;38(2):95-101.

125

## Case 5

- A 20-year-old pregnant woman 20 hours after acetaminophen overdose
- A 20 y/o woman with 6 week pregnancy presented 20 hours after ingesting twenty 500-mg tablets of acetaminophen. She vomited twice and then came to the emergency department. She denies any other ingestions or complaints.

- *Physical Examination:*

Temperature 36.5°C, pulse *93/min,* respirations *16/min,* blood pressure 116/71 mmHg.

- General: well-developed, well-nourished, no acute distress.
- HEENT: pupils equally round and reactive; sclera anicteric; oropharynx clear.
- Chest: normal. Cardiovascular: normal.
- Abdomen: soft, non-distended, normal bowel sounds; right upper quadrant tenderness to palpation, especially at liver edge; no hepatomegaly.
- Extremities: normal capillary refill. Skin: normal.
- Neuromuscular: awake, alert, oriented; no motor weakness, normal coordination and gait.

*Laboratory Findings:*

- CBC: WBC *7300/microL*, hemoglobin 12 g/dL, platelets *325,000/microL.*
- Serum chemistries: sodium 138 mEq/L, potassium 3.9 mEq/L, chloride 101 mEq/L, CO2 22 mEq/L, BUN 8 mg/dL, creatinine 0.7 mg/dL, total bilirubin 0.8 mg/dL, alanine aminotransferase 32 U/L, aspartate aminotransferase 20 U/L, alkaline phosphatase 61 U/L.
- Acetaminophen level: 17.1 mcg/mL
- Urine pregnancy test: positive

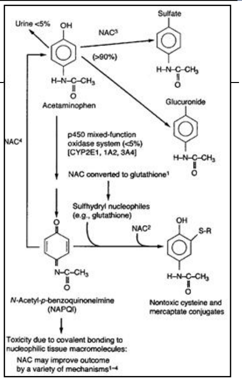
*Questions:* If the time of ingestion was 20 hours ago, how should the "therapeutic" acetaminophen level of 17.1 mcg/mL be interpreted?

- How should she be treated?
- How should the fetus be managed?

## Paracetamol Poisoning

- *Types of Paracetamol overdose*
- Acute paracetamol overdose:
  - Ingestion of 7.5 grams (150 mg/kg) or more of paracetamol within 4 hours
- Chronic paracetamol overdose:
  - Ingestion of 4 grams or more of paracetamol per 24 hours
  - Bizovi KE, Smilkstein MJ. Acetaminophen. In: Goldfrank LR, Flomenbaum NE, Lewin NA, Howland MA, Hoffman RS, Nelson LS, eds. Goldfrank's Toxicologic Emergencies. 7 ed. New York: McGraw-Hill, 2002: 480-501

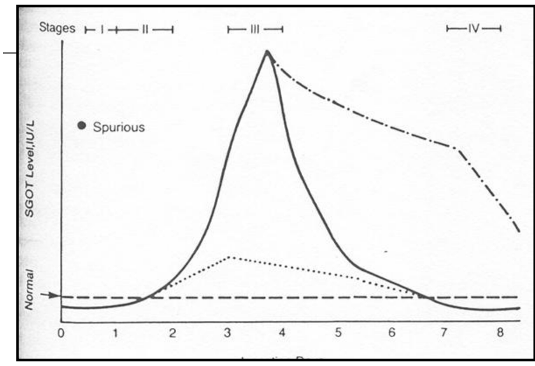
## Mechanism of Toxicity

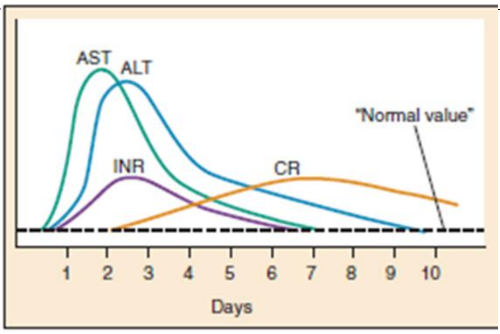



## Mechanism of Toxicity

- Generation of toxic metabolite: *N-acetyl-p-benzoquinoneimine* (NAPQI)
- Glutathione detoxifies NAPQI.
- Liver injury occurs when glutathione storage is depleted.
- From calculations based on average value from healthy people, the storage lasts for 8 hours after an acute paracetamol overdose.
- Renal toxicity is believed to occur by similar mechanisms.

- Phase 1: 0.5-24 hours: Normal, nausea, malaise, vomiting
- Phase 2: 24-72 hours 'Onset of Toxicity': Less pronounce phase 1 manifestations, RUQ pain, elevation of liver enzymes, bilirubin, INR
- Phase 3: 72-96 hours 'Time of Maximal Toxicity':
  - Sequelae of hepatic necrosis, coagulopathy, hepatic encephalopathy
  - Renal failure, nausea, vomiting, RUQ reappear
- Phase 4: 96 hours - 2 weeks: If the damage reversible, complete resolution




## Diagnosis

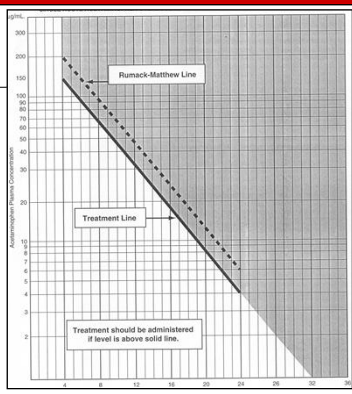
- History of ingestion
  - Acute (≤4 hours: ≥ 150 mg/kg)
  - Staggered ((≤4 hours: ≥ 4 g/day)
- Serum paracetamol level
  - Acute: Rumack-Matthew Nomogram
  - Staggered: paracetamol level > 10 mg/L or elevated liver enzyme

## Risk Assessment in Acute Overdose

- Serum paracetamol level at or after 4 hours after the ingestion
- Interpret the level using Rumack-Matthew Nomogram
- Use the *'Treatment Line': the line with level 150 mg/L at 4 hours*

## Rumack-Matthew Nomogram

Our patient: 20 mg/L at 20 hours



- At any level above the 'Treatment Line':
  - N-acetylcysteine therapy should be started
  - AST (SGOT) should be checked

## NAC therapy: Mechanisms of action

1. **"Prophylactic Effects"** : Replenish glutathione supply: as long as paracetamol level > 10 mg/dL
   - Protection against severe hepatitis in cases with toxic paracetamol levels

- 2. **"Restorative Effects"** : In cases with paracetamol-induced fulminant hepatic failure
  - Decrease mortality, Cerebral Edema, Hemodynamic instability, Multi-organ failure, Hepatic encephalopathy
    - Harrison PM, Keays R, Bray GP, Alexander GJ, Williams R. Improved outcome of paracetamol-induced fulminant hepatic failure by late administration of acetylcysteine. *Lancet* 1990;**335**(8705):1572-3.
    - Harrison PM, Wendon JA, Gimson AE, Alexander GJ, Williams R. Improvement by acetylcysteine of hemodynamics and oxygen transport in fulminant hepatic failure. *N Engl J Med* 1991;**324**(26):1852-7.
    - Keays R, Harrison PM, Wendon JA, et al. Intravenous acetylcysteine in paracetamol induced fulminant hepatic failure: a prospective controlled trial. *Bmj* 1991;**303**(6809):1026-9.

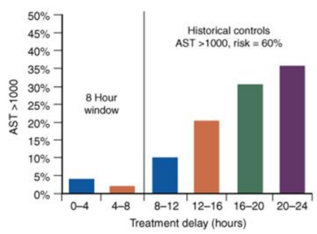
## NAC therapy :Routes of administration

- Oral: 18 doses over ~70 hours
  - 140 mg/kg for loading
  - 70 mg/kg for maintenance every 4 hours x 17 doses
  - Low risk of anaphylactoid
  - Vomiting
- Intravenous: ~ 21 hours
  - 150 mg/kg in in 15 minutes (45-60 minutes)
  - 50 mg/kg in 4 hours
  - 100 mg/kg in 16 hours
  - Anaphylactoid reaction

## Oral vs. IV: Which is more efficacious?

- Outcome: Prevention of hepatotoxicity
- No side- by-side study
- A couple of meta-analyses
- Not enough evidence to prove the difference in efficacy between the two routes
- Choice depends on clinical situation
  - Buckley NA, Whyte IM, O'Connell DL, Dawson AH. Oral or intravenous N-acetylcysteine: which is the treatment of choice for acetaminophen (paracetamol) poisoning? *J Toxicol Clin Toxicol* 1999;37(6):759-67.
  - Brok J, Buckley N, Gluud C. Interventions for paracetamol (acetaminophen) overdoses. *Cochrane Database Syst Rev* 2002(3):CD003328.

## Time to N-acetylcysteine (hours) and hepatotoxicity (%)




*N Engl J Med* 1988; 319:1557-1562

## How early should NAC therapy be started?

- NAC therapy should be started within 8 hours after the ingestion
- The is no difference in outcome for treatments started at 0-4 and 4-8 hours after ingestion
- Progressive, significant increase in hepatotoxicity for delays after 8 hours
  - Smilkstein MJ, Knap GL, Kulig KW, Rumack BH. Acetaminophen overdose: how critial is the delay to N-acetylcysteine? Vet Hum Toxicol;29(6):486.

## How should the follow up be done?

- AST, INR should be followed at least every 24 hours
- Renal function should be checked when AST > 1,000.
- The patient should be followed to at least 36 hours after the ingestion.

## Management of Anaphylactoid reactions from IV NAC

- Flushing: continue treatment
- Urticaria:
  - Diphenhydramine 50 mg IV
  - Continue treatment
- Angioedema
  - Stop NAC
  - Diphenhydramine 50 mg IV
  - Restart if no symptoms after 1 hour

Bailey B, McGuigan MA. Management of anaphylactoid reactions to intravenous N-acetylcysteine. *Ann Emerg Med* 1998;31(6):710-5.

## Short course of NAC therapy:

- NAC therapy can be discontinue, if at 36 hours (or more) after the ingestion:
  - AST, PT and INR is normal or have returned to normal
  - Serum paracetamol level < 10 mg/L
  - Woo OF, Mueller PD, Olson KR, Anderson IB, Kim SY. Shorter duration of oral N-acetylcysteine therapy for acute acetaminophen overdose. *Ann Emerg Med* 2000;35(4):363-8.

## Prolonged course of NAC therapy

- If the AST > 1,000 u/L or INR > 2 or hepatic encephalopathy develops, intravenous NAC should be given.
- Endpoint:
  - AST < 1,000 and
  - INR < 2 and
  - Hepatic encephalopathy resolve

## Case 6

- A 37-year-old female patient was brought into the ED by emergency medical services.
- She was last seen approximately 4 hours before presentation; she was found unresponsive in her bed.
- On arrival in the ED, the patient was lethargic.

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- Physical examination:
- Unresponsive to any verbal and tactile command
- Intubated for airway protection.
- BP100/60 mm Hg, pulse 110 /minute, respiratory rate 26 /minute.
- Dilated fixed pupils
- Dry skin
- Absent bowel sounds

- What toxic syndrome is she manifesting?
- What is your differential diagnosis?
- What further test are you ordering?

## Anticholinergic syndrome

- Tachycardia, hypertension, hyperthermia
- Delirium
- Mydriasis
- Dry mucosa, dry skin
- Ileus, urine retentio n

## DDX anticholinergic syndrome

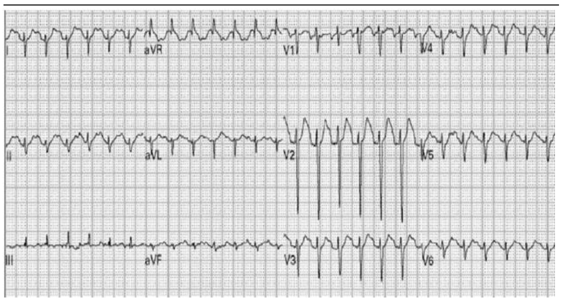
**Pure anticholinergic**

- Antihistamine: Chlorpheniramine
- Atropine
- Hyoscine, hyoscyamine

**Anticholinergic plus cardiotoxicity**

- Tricyclic antidepressant
- Antipsychotics (thioridazine, mesoridazine)
- Antihistamine (diphenhydramine)

## Case 6: ECG




- The presentation of significant TCA ingestion is often nonspecific
- Altered mental status as the primary initial finding
- ECG change typically precedes the development of clinically apparent neurologic and cardiac toxicity

## Tricyclic antidepressant: Mechanism of toxicity

- Inhibition of synaptic reuptake of norepinephrine and serotonin
- Anticholinergic: 'Anti-muscarinic': CNS, viscera, exorcine glands, pupils
- Alpha-adrenergic blockade:
  - Peripheral vasodilation
  - Pupil constriction

Tricyclic antidepressant: Mechanism of toxicity
Membrane stabilizing effects

- Also called: membrane-depressant effects, quinidine-like effects
- The most important contribution to death
- Inhibition of fast sodium channel
  - Cardiac conduction defect
  - Decrease myocardial contractility
- pH dependent sodium channel

---

- Anticholinergic effect
- Cardiovascular: impaired conduction, arrhythmias, hypotension
  - Impaired conduction:
    - Prolongation of PR, QRS, QT intervals, AV blocks
    - Rightward shift of terminal 40 msec of frontal plane QRS complex (normal<90)(Abnormal 130-270)
  - Arrhythmias: Sinus tachycardia, SVT, VT, VF
  - Hypotension: mainly from cardiogenic causes
- Seizure: recurrent, persistent seizure
  - Hyperthermia, rhabdomyolysis, lactic acidosis
  - Worsens conduction & arrhythmias
- Natural history: Death due to arrhythmias, intractable shock
  - Severe complications usually occur within 12 hours

---

ECGs as prognostic factors and treatment indicators

- QRS interval prolongation reflects severity
- QRS = or > 100 msec
  - 33% seizures
  - 14% VT, VF
- QRS = or > 160 msec
  - 50% VT, VF
- Boehnert MT, Lovejoy FH, Jr. Value of the QRS duration versus the serum drug level in predicting seizures and ventricular arrhythmias after an acute overdose of tricyclic antidepressants. *N Engl J Med* 1985;313(8):474-9.

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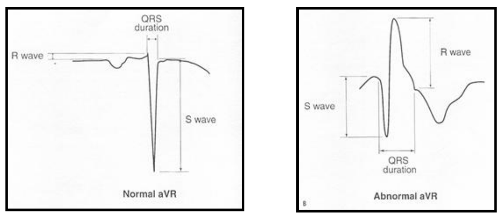
ECGs as prognostic factors and treatment indicators

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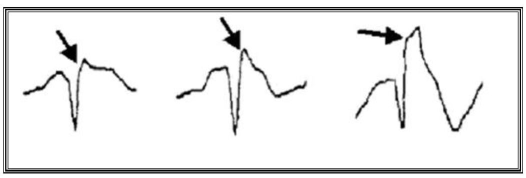
# Prominent R waves



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- *Cardiac monitoring:*
  - Ideally, Asymptomatic patients should have continuous cardiac monitoring for at least six hours.
  - Patients with signs of toxicity should be monitored until these disappear and the ECG has been normal for 12 hours.
- *Gut decontamination:*
  - GI decontamination reduces systemic drug absorption
- *Hypotension*
  - Hypotension may respond to simple measures such as raising the foot of the bed and intravenous plasma expanders
  - Inotropic support may be needed for protracted hypotension
- *Convulsions*
  - Intravenous benzodiazepine and phenobarbital should be used to control

- *Arrhythmias.*
  - Administration of NaHCO3 and correction of acidosis, hypoxia and electrolyte abnormalities are the mainstay of treatment.
  - Antiarrhythmic agents may worsen arrhythmias by further blocking sodium channels (class I) or delaying cardiac repolarisation (class III)
- Following cardiac arrest, recovery has been reported after several hours of cardiopulmonary resuscitation.

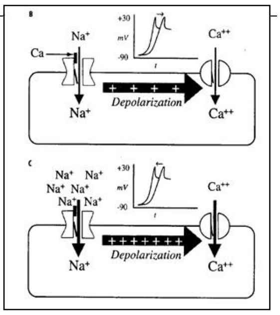
## Tricyclic antidepressant poisoning: Specific Management

- 7.5% Sodium bicarbonate solution
- 2 modes of treatment:
  - IV bolus
  - IV infusion

Liebelt EL. Targeted management strategies for cardiovascular toxicity from tricyclic antidepressant overdose: the pivotal role for alkalinization and sodium loading. *Pediatr Emerg Care* 1998;14(4):293-8.

## Tricyclic antidepressant poisoning: 7.5% Sodium bicarbonate solution IV bolus

- Mechanism:
  - Na gradient across channel
  - Serum pH for channel function
  - Drug-plasma protein binding




## Tricyclic antidepressant poisoning: 7.5% Sodium bicarbonate solution IV bolus

- 1-2 mEq/ kg in 1-2 minutes
- Monitor and document changes
- Indications:
  1. Severe conduction defects
     - QRS > 100-120 msec
     - R in aVR > 3 mm
     - R/S in aVR > 0.7
  2. Cardiac arrhythmias
     - VF
     - VT or wide complex tachycardia
- Endpoints:
  - Cleared of indications
  - Serum pH $\geq 7.55$

## Tricyclic antidepressant poisoning: 7.5% Sodium bicarbonate solution IV infusion

- Mechanism: pH effects on sodium channel
- Indication: serum pH < 7.40
- Goal: Serum pH 7.50-7.55
- Hyperventilation in combination with $NaHCO_3$ infusion may also be useful

## Observation and monitoring for patients with TCA poisoning

- Case 1: Completely Asymptomatic patient except sinus tachycardia
  - Ensure 1 dose of activated charcoal is given
  - Medically cleared after 6 hours of asymptomatic observation
- Case 2: Symptomatic or abnormal ECG other than sinus tachycardia
  - Ensure 1 dose of activated charcoal is given
  - Observe until the abnormality is cleared for at least 24 hours

## Serotonin syndrome:

- Hunter Criteria
  - Pt must have taken a serotonin agent and had one of the following
    - Spontaneous clonus
    - Inducible clonus plus agitation or diaphoresis
    - Tremor and hyperreflexia
    - Hypertonia
    - Temp >38 plus ocular or inducible clonus
- Management: Discontinuation of causative agent, suportive care, fluid, electrolyte, hyperthermia
  - Cyproheptadine(anecdotal report)

10/05/58

**Table 1.** Drugs and Drug Interactions Associated with the Serotonin Syndrome.

**Drugs associated with the serotonin syndrome**

Selective serotonin-reuptake inhibitors: sertraline, fluoxetine, fluvoxamine, paroxetine, and citalopram
Antidepressant drugs: trazodone, nefazodone, buspirone, clomipramine, and venlafaxine
Monoamine oxidase inhibitors: phenelzine, moclobemide, clorgiline, and isocarboxazid
Anticonvulsants: valproate
Analgesics: meperidine, fentanyl, tramadol, and pentazocine
Antiemetic agents: ondansetron, granisetron, and metoclopramide
Antimigraine drugs: sumatriptan
Bariatric medications: sibutramine
Antibiotics: linezolide (a monoamine oxidase inhibitor) and ritonavir (through inhibition of cytochrome P-450 enzyme isoform 3A4)
Over-the-counter cough and cold remedies: dextromethorphan
Drugs of abuse: methylenedioxymethamphetamine (MDMA, or "ecstasy"), lysergic acid diethylamide (LSD), 5-methoxydiisopropyltryptamine ("foxy methoxy"), Syrian rue (contains harmine and harmaline, both monoamine oxidase inhibitors)
Dietary supplements and herbal products: tryptophan, *Hypericum perforatum* (St. John's wort), Panax ginseng (ginseng)
Other: lithium

**Drug interactions associated with severe serotonin syndrome**

Zoloft, Prozac, Sarafem, Luvox, Paxil, Celexa, Desyrel, Serzone, Buspar, Anafranil, Effexor, Nardil, Manerix, Marplan, Depakote, Demerol, Duragesic, Sublimaze, Ultram, Talwin, Zofran, Kytril, Reglan, Imitrex, Meridia, Redux, Pondimin, Zyvox, Norvir, Parnate, Tofranil, Remeron
Phenelzine and meperidine
Tranylcypromine and imipramine
Phenelzine and selective serotonin-reuptake inhibitors
Paroxetine and buspirone
Linezolide and citalopram
Moclobemide and selective serotonin-reuptake inhibitors
Tramadol, venlafaxine, and mirtazapine

## Neuroleptic malignant syndrome

- A potentially life-threatening emergency. Although
- Clinical settings: Treatment with a D2-receptor antagonist or withdrawal of dopamine agonists
- Risk factors for the young age, male gender, extracellular fluid volume contraction, use of high-potency antipsychotics, depot prep, cotreatment with lithium, multiple agents in combination, rapid dose escalation. but appears to involve abrupt reductions in central dopaminergic
- 1. Altered mental status 2. Motor Symptoms "Lead pipe" rigidity, cogwheeling, dysarthria or mutism, parkinsonian syndrome, akinesia, tremor, dystonia, dysphagia, dysphonia, choreiform movements 3. hyperthermia 4. Autonomic instability tachycardia, diaphoresis, sialorrhea, incontinence, respiratory irregularities, cardiac dysrhythmias, hypertension, or hypotension 5. Increase cpk, leucocytosis
- Supportive care: fluid electrolyte, hyperthermia, rhabdomyolysis
- Antidote: diazepam, bromocriptine, dantrolene

Questions are welcomed

# Thank you for your attention

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