General Principles of Pharmacology and Toxicology

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Management of a poisoned patient

Please take a look at your reference book if you like
(e.g. chapter 58 of Katzung 11th version or relevant chapters in other books)
It is only around 12 pages!
Poisoning is important!

- > 2 million poison exposures per year
- ½ of exposures in children 1-6 years-old
- Children account for 10% of admissions
- Adults account for 90% of admissions
- Approximately 11,000 deaths per year
What is a poison?

- In common usage: poisons are chemicals or chemical products that are distinctly harmful to human

- More precisely: a poison is a foreign chemical (xenobiotic) that is capable of producing a harmful effect on a biologic system

“In wise hands, poison is medicine. In foolish hands, medicine is poison.”

Hippocrates
Poison / Toxin? Make it clear Doc!

A poison is any substance that is harmful or deadly to living cells even in small quantities.

A toxin, strictly speaking, is a poison that is produced naturally by living things.

A toxicant is the currently preferred scientific term for all poisons.
A case!

29 year old man
- found “down”
- EMS transports
- Reports from scene: “he took something”
- No pill bottles on scene
- No family with him
- Roommates that found him are long gone

EMS: Emergency Service Transport
What do I do with him?

- What do I order?
- How do I treat him?
- How do I decontaminate him?
- Do I give him an antidote?
You may...

- Start with the basics (ABCs)
  - Airway, Breathing, Circulation

- Get a better history
  - Get EMS to get pill bottles, tell you what they do know (found outside, inside, garage...)
  - Call friends, family, neighbors
  - Call psych or primary MD to see what he is on regularly

- Get him to tell you
  - Always remember that suicidal patients (just like everyone else) can lie so be skeptical of their history

- Establish a pattern to his symptoms
  - Toxic syndrome
  - Also known as a: TOXIDROME
What is a Toxidrome?

- It is the association of several clinically recognizable features, signs, symptoms, phenomena or characteristics which often occur together, so that the presence of one feature alerts the physician to the presence of the others.
5 Basic Toxidromes

1. Sympathomimetic
2. Opiate
3. Anticholinergic
4. Cholinergic
5. Seditive Hypnotic

And remember Withdrawal Toxidrome
1) Toxidrome - Sympathomimetics

- Cocaine
- Methamphetamine/Amphetamines
  - Ecstasy (MDMA = 3,4-Methylenedioxymethamphetamine)
  - ADHD medicines like Methylphenidate (ritalin)
- Ephedrine
- Caffeine

Excessive SYMPATHETIC stimulation involving epinephrine, norepinephrine and dopamine

Excessive stimulation of alpha and beta adrenergic system

Tachycardia +/- arrythmias
Hypertension +/- ICH (intracranial hemorrhage)
Confusion with agitation
Seizures
Rhabdomyolysis (damage to skeletal muscle cells and their toxic effect on kidney)
  - Renal failure can result

ADHD: Attention-deficit hyperactivity disorder
What do you do about it?

Supportive care
• Monitor airway, diagnose ICH, Rhabdomyolysis
• Intravenous fluids (IVF) for insensible loses and volume repletion

Benzodiazepines

NEVER GIVE BETA BLOCKERS!
2) Toxidrome - Opiate

**Opiate**: derived directly from the opium poppy
- morphine and codeine

**Opioids**: much broader class of agents that are capable of producing opium-like effects or of binding to opioid receptors
- Heroin
- Methadone
- Meperidine
- Hydrocodone
- Oxycodone

Primarily bind to the mu, kappa or delta opioid receptor
- There are others but these play the biggest role
Toxidrome - Opiate

- Coma
- Miosis
- Respiratory depression

- Peripheral vasodilation
- Orthostatic hypotension
- Flushing (histamine)
- Bronchospasm
- Pulmonary edema
- Seizures (meperidine, propoxyphene)
What do you do about it?

Competitive opioid antagonist: **Naloxone**

- Goal of return of spontaneous respirations sufficient to ventilate the patient appropriately
  - May have to re-dose as opiates may act longer than antagonist

There are other longer acting opioid antagonists such as nalmefene and naltrexone but these are not often used
3) Toxidrome - Anticholinergic

- By definition these agents ANTAGONIZE the effects of endogenous Acetylcholine
- Ach receptors are either nicotinic or muscarinic
- The “anti-cholinergic” drugs just block the muscarinic receptors
- Some have argued that the “anticholinergic” poisoning syndrome should be called the “antimuscarinic poisoning syndrome” because you do not see anti-nicotinic symptoms
- Poisoning caused by overdosing with an Antimuscarinic (atropine, scopolamine, and ipratropium bromide) or by ingesting of plants such as *Amanita muscaria*, *Atropa belladonna* and *Datura stramonium* plants
What goes wrong?

CNS muscarinic blockade:
- Confusion
- Agitation
- Myoclonus
- Tremor
- Picking movements
- Abnormal speech
- Hallucinations
- Coma

Peripheral muscarinic effects:
- Mydriasis
- Anhidrosis
- Tachycardia
- Urinary retention
- Ileus
A better way to remember it!

Hot as Hades – Fever
Fast as a Hare – Tachycardia
Dry as a Bone – Lack of diaphoresis
Red as a Beet – Flushed skin
Mad as a Hatter – Delirium
Full as a Tick – Urinary retention
Blind as a Bat – Mydriasis
What do you do about it?

Supportive care
  - IVF to replace insensible losses from agitation, hyperthermia

Benzodiazepines to stop agitation

Physostigmine
  - Induces cholinergic effects
  - Short acting
  - May help with uncontrollable delirium
  - Do not use if ingestion not known
    - Danger with TCAs
4) Toxidrome - Cholinergic

- Block acetylcholinesterase from working (acetylcholinesterase inhibitors)
- Organophosphate poisoning
- End up with excess of acetylcholine in synapses
- Leads to excess stimulation of the muscarinic and nicotinic systems

D - Diarrhea
U - Urination
M - Miosis
BBB – Bradycardia, Bronchorrhea, Bronchospasm
E - Emesis
L - Lacrimation
S - Salivation
What goes wrong?

S - Salivation
L - Lacrimation
U - Urination
D - Diaphoresis
G - Gasterointestinal upset
  • vomiting, diarrhea
E - Eye
  • Miosis

What to do?

• Antagonize muscarinic symptoms
  • Atropine
• Stop aging of enzyme blockade
  • 2-PAM (Pralidoxime)
• Prevent and terminate seizures
  • Diazepam
• Supportive care
5) Toxidrome - Sedative-Hypnotic

- Sedative-hypnotics are a group of drugs that cause CNS depression. Benzodiazepines and barbiturates are the most commonly used agents in this class.
- Different agents have different mechanisms
- Many interfere in the GABA system

What goes wrong?

- CNS depression, lethargy
- Can induce respiratory depression
- Can produce bradycardia or hypotension

What to do?

- Supportive care
- Flumazinil? / Meprobamate / Methaqualone /
Remember me?? Withdrawal Toxidrome

Tachycardia
Dilated pupils
Diarrhea
Abdominal cramps
Piloerection (Erection of the hair of the skin)
<table>
<thead>
<tr>
<th>Toxidrome</th>
<th>Pulse</th>
<th>BP</th>
<th>RR</th>
<th>Tem p</th>
<th>Mental Status</th>
<th>Pupils</th>
<th>Skin</th>
<th>Bowel Sounds</th>
<th>Bladder</th>
</tr>
</thead>
<tbody>
<tr>
<td>Opiate</td>
<td>Low</td>
<td>Low/Normal</td>
<td>Low</td>
<td>Normal/Low</td>
<td>AMS, sedated, coma</td>
<td>Small</td>
<td>Normal</td>
<td>None</td>
<td>Normal</td>
</tr>
<tr>
<td>Cholinergic</td>
<td>Low/High</td>
<td>Low</td>
<td>Low/High</td>
<td>Normal/Low</td>
<td>Variable, AMS, agitation, confusion</td>
<td>Small</td>
<td>Wet</td>
<td>Hyperactive</td>
<td>Empty</td>
</tr>
<tr>
<td>Anti-cholinergic</td>
<td>High</td>
<td>High</td>
<td>Normal/High</td>
<td>High</td>
<td>AMS, delirious</td>
<td>Large</td>
<td>Dry, Flush Red</td>
<td>None</td>
<td>Distended</td>
</tr>
<tr>
<td>Adrenergic</td>
<td>High</td>
<td>High</td>
<td>High</td>
<td>High</td>
<td>AMS, delirious</td>
<td>Large</td>
<td>Wet</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Sed-Hypn</td>
<td>Normal/Low</td>
<td>Normal/Low</td>
<td>Normal/Low</td>
<td>Normal/Low</td>
<td>AMS, sedated</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Withdrawal</td>
<td>High</td>
<td>High</td>
<td>High</td>
<td>High</td>
<td>AMS, delirious</td>
<td>Large</td>
<td>Wet</td>
<td>Normal</td>
<td>Normal</td>
</tr>
</tbody>
</table>

RR: interval between heart beats known as RR intervals, AMS: Altered Mental Status
Recognition of poisoning

- May be difficult because of non-specific symptoms
- High index of suspicion
  - history may be unreliable
  - look for corroborative history - missing pills, empty container
- Course that a poison runs (toxicidromes) - may help!
- Toxicology screening - helpful only in a few
- Clinical manifestations:
  - Very diverse and varied - depends on the poison
  - Clinical examination should be focused on the possible manifestations of common poisons in the geographical area
Clinical manifestation

Skin and mucosal damage
Neurotoxic manifestations
Cardiovascular manifestations
Metabolic consequences
Eye manifestations
Hepatic dysfunction
Clinical assessments (ABCs)

**Airway** - ensure clear airway, clear secretions, check for cough/gag

**Breathing** - check oxygenation, supplemental $O_2$, breathing pattern & adequacy

**Circulation** - heart rate, rhythm, blood pressure
Laboratory Assessments

- Of limited value
- Paracetamol levels, salicylate levels, alcohol, Red cell/pseudocholinesterase, anti-epileptic drug levels
- Urinary drug screen - opiates, barbiturates, benzodiazepines, amphetamines, cocaine
- **Anion gap & Osmolal gap** (please read about it!)
  - Increased anion gap (Normal 12 ± 4 mEq/L)
    - Ethylene glycol
    - Methanol
    - Salicylate poisoning
  - Increased osmolal gap (Normal 5 ± 7 m osmol/kg)
    - Ethylene glycol
    - Methanol
    - Acetone, ethanol, isopropyl alcohol, propylene glycol
Laboratory Assessments

- Electrolytes
  - **Hypokalemia**
    - Oduvanthalai poisoning (Clistanthis collinis)
    - Diuretics, Methyl xanthine, Toluene
  - **Hyperkalemia**
    - Digoxin
    - Beta-blocker

- Liver function tests
  - Acetaminophen, Ethanol, Carbon tetrachloride

- Renal function tests
  - Ethylene glycol, NSAIDs

*crushed leaves of Cleistanthus collinus (Family: Euphorbiaceae) in an attempt to commit suicide, common for self-harm in India*
Laboratory Assessments

- ECG
  - Digoxin toxicity
  - TCA overdose - sinus tachycardia, QT prolongation, increased QRS
  - Beta-blockers - conduction abnormalities

- Imaging
  - Limited value
Treatment Goals

• Reduce absorption of the toxin (xenobiotic)
• Enhance elimination
• Neutralise toxin

“How do I get the poison out of your body?”
1) Reduce Absorption of the Toxin

- Removal from surface skin, eye
- Emesis induction (Induce vomiting – Ipecac)
- Gastric lavage (Take out e.g. pills from the stomach)
- Activated charcoal administration (Adsorb the toxins in the gut)
- Dilution - milk/other drinks for corrosives
- Whole bowel irrigation (Flush out the system)
- Endoscopic or surgical removal of ingested chemical

"Adsorb" refers to a situation where something gets stuck onto (to?) the surface of a medium.
Ipecac Syrup

- The extract of ipecac root, or ipecacuanha contains alkaloids, **Emetine**, **Cephaeline** and others.

- No longer it is not recommended as a first-line treatment for most ingested poisons, because:
  
  - no evidence that syrup of Ipecac actually helps improve the outcome in cases of poisoning.
  
  - accidental overdose of Ipecac can occur
  
  - Ipecac’s potential side effects, such as lethargy, can be confused with the poison’s effects, complicating diagnosis.
  
  - Ipecac may also delay the administration or reduce the effectiveness of other treatments such as activated charcoal, whole bowel irrigation, or oral antidotes
Gastric Lavage

- Can be a brutal procedure
- Indication: life threatening ingestions that occurred within one hour
- Airway protection is key
- Limited indications
- Lots of complications
Charcoal

- Basically, everybody gets a dose
- Works to adsorb substances to its matrix
  - Not for metals
- Generally safe, few contraindications
  - Aspiration, bowel obstruction
Whole Bowel

• Isotonic polyethylene glycol electrolyte solutions (GoLytely)

• Large volumes ingested “wash” the substances through the bowel
  • Especially useful for metals or other things not well adsorbed by charcoal

• Avoid in patients with bowel obstruction or ileus

• Do it in volume sufficient to create clear rectal effluent
2) Enhanced Elimination

Increased elimination is possible only if

- the drug is distributed predominantly in the ECF
- has a low protein binding
- the induced rate of elimination is faster than the normal rate
- hazards of having a longer time of exposure to the drug are potentially fatal

Methods

- Keep a good urine output 150-200 ml/hr
- Alkalisation of urine - clinical efficacy accepted for salicylate & phenobarbital poisoning
- Hemodialysis - Barbiturates, Salicylates, Acetaminophen, Valproate, Alcohols, Glycols
- Hemoperfusion - theophylline, digitalis, lipid soluble drugs
### 3) Neutralise Toxin - Antidotes

<table>
<thead>
<tr>
<th>Toxin Type</th>
<th>Antidote</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetaminophen</td>
<td>N-acetyl cysteine</td>
</tr>
<tr>
<td>Anti-cholinergics</td>
<td>Physostigmine</td>
</tr>
<tr>
<td>Benzodiazepenes</td>
<td>Flumazenil</td>
</tr>
<tr>
<td>Ca channel blockers</td>
<td>Glucagon, Insulin + dextrose, Calcium</td>
</tr>
<tr>
<td>Carbamate</td>
<td>Atropine</td>
</tr>
<tr>
<td>Cyanide</td>
<td>Thiosulphate, nitrate</td>
</tr>
<tr>
<td>Digoxin</td>
<td>Digoxin antibodies</td>
</tr>
<tr>
<td>INAH</td>
<td>Pyridoxine</td>
</tr>
<tr>
<td>Methanol</td>
<td>Ethanol, Fomepizole</td>
</tr>
<tr>
<td>Glycol</td>
<td>Ethanol, Fomepizole</td>
</tr>
<tr>
<td>Opioid</td>
<td>Naloxone</td>
</tr>
<tr>
<td>Oral hypoglycaemics</td>
<td>Glucose</td>
</tr>
<tr>
<td>Organophosphate</td>
<td>Atropine, P2AM</td>
</tr>
<tr>
<td>Warfarin</td>
<td>Vitamin K</td>
</tr>
</tbody>
</table>
Who’s At Risk for drug overdose?

Anyone who uses drugs has the potential to overdose

Any period of abstinence

Completion of residential treatment

Release from prison or jail

Anticipation or occurrence of, any major life transition
Major disappointment

Reuniting with family with history of conflicts

Holidays
Bio-Psycho-Social Risk Factors

Physical health
Weight
Mental health
Self-esteem
Social Isolation
Unstable housing and living conditions
Drinking problems
Symptoms of Drug Overdose

Awake, but unable to talk
Body is very limp
Face is very pale
Pulse (heartbeat) is slow, erratic or not there at all
Throwing-up
Passing out
Choking sounds, or a gurgling noise
Breathing is very slow and shallow, erratic or has stopped
What drugs are responsible for rise in Fatal overdoses?

Drugs of Potential Abuse

CNS Depressants:
- Opioid analgesics (narcotics*) - pain medications & heroin
  - Most associated with overdoses nationally & in Ohio –
    - Methadone
    - Fentanyl – often used as a patch (transdermal application)
    - Oxycodone
    - Hydrocodone
- Benzodiazepines – anxiety/sleep - Diazepam
- Other Sedatives, sleeping medications (Ambien®)
- Solvents/inhalants – Alcohol

Stimulants – Cocaine, amphetamine, methamphetamine

Anti-depressants
Risk Groups for Opioid Overdose

1. Pain patients:
   • Taking high doses of medication.
   • Taking medications incorrectly.
2. Nonmedical pain medication users and those with a history of substance abuse
3. Persons who have already experienced a drug overdose.
4. Persons taking multiple medications, especially multiple CNS depressants, simultaneously
Risk Groups for Opioid Overdose

5. **Persons with chronic health problems such as:** COPD, emphysema, respiratory illness, heart problems, renal dysfunction or hepatic disease.

6. **Using after a period of abstinence** (e.g., after SA treatment or *recently released prisoner population*)

7. **Patients newly starting methadone for pain control and patients who have switched to methadone** after treatment with other strong opioid pain relievers
Pharmacokinetic Considerations in Clinical Toxicology
Clinical Applications

Darren M. Roberts and Nick A. Buckley

South Asian Clinical Toxicology Research Collaboration, Medical School, Australian National University, Canberra, Australia
Questions?

Next time, we will explore heavy metals together!