Title

- Text
Depolarize This!

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Objectives

- Physiology review
  - Sympathetic and Parasympathetic
  - Neurotransmitters

- Discussed mechanism of selected toxins
  - Anticholinergic, cholinergic toxicity
  - Medications, iatrogenic, others?

- Discuss treatment options
Tox 101

- Identify the patient
- Decontamination
- Antidote
- Enhanced elimination
Emesis

Vomiting induced immediately except when contraindicated (in comatose patient or after ingestion of corrosives, atropine, and petroleum distillates).

Syrup of ipecac administered, followed by 1 or 2 glasses of water.

Child bounced up and down to hasten emetic effect of syrup of ipecac.
Physiology

- Autonomic vs. somatic
- We will focus on the autonomic nervous system

- ALL preganglionic neurons of the ANS release ACh
- Postganglionic neurons release either ACh, NE, or neuropeptides
Autonomic nervous system

- Sympathetic – thoracolumbar
- Parasympathetic – brain stem and sacral spinal cord

Costanzo. Physiology. 2005
Sympathetic

- Also known as fight or flight
Sympathetic

- Preganglionic neurons always release ACh
  - Specifically act on nicotinic receptors

- Postganglionic neurons of the sympathetic NS are adrenergic with one exception
Special sympathetic pathway

- Adrenal medulla

- Preganglionic neuron to adrenal medulla (chromaffin cells) which then release epinephrine (80%) and norepinephrine (20%)

- Tumor of the adrenal medulla
Parasympathetic

- Rest and digest
Parasympathetic

- Preganglionic neurons always release ACh
  - Specifically act on nicotinic receptors

- Most postganglionic neurons are cholinergic
  - Specifically act on muscarinic receptors
Let’s review

- Preganglionic neurons always release ACh
- Sympathetic NT are usually adrenergic
- Parasympathetic NT are usually ACh
<table>
<thead>
<tr>
<th></th>
<th>Sympathetic</th>
<th>Parasympathetic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart Rate</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>Bronchioles</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>GI tract (digestion)</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>Eye</td>
<td>Dilate pupil</td>
<td>Constricts pupil</td>
</tr>
<tr>
<td>Skin</td>
<td>Sweat</td>
<td>N/a</td>
</tr>
</tbody>
</table>
Example

- Rural area
- Patient with increased secretions, weakness, blurry vision
Cholinergic toxicity

- Organophosphates are absorbed through:
  - Lungs
  - GI
  - Mucous membranes
  - Topical/dermal (if potent OP)
Cholinergic toxicity

- Organic phosphorus compounds and carbamates

- Pesticides
  - Common source of suicide in Asia
  - Tighter control of potent pesticides in industrialized countries

- Concerned about rural exposures and…
Pathophysiology

- What’s the problem here?
- Leading to cholinergic EXCESS
  - Unable to break down ACh
Organophosphates and carbamates

Goldfrank’s Toxicologic Emergencies. 2015

Goldfrank’s Toxicologic Emergencies. 2015
Pathophysiology

- OPs bind to a hydroxyl group at the active site of the AChE.
- As the leaving group of the OP insecticide is split off by AChE, a stable but reversible bond results between the remaining substituted phosphate of the OP and AChE, effectively inactivating the enzyme.
Pathophysiology
Pathophysiology

- How long does the OP compound-enzyme last?
Carbamates – “organophosphate light”

- Carbamate insecticide
- Also carbamate pharmaceuticals
  - Physostigmine, pyridostigmine, neostigmine
- What’s the difference? Why “light”
Clinical Presentation

- Mneumonic?
  - What’s the real problem there?

- In reality?
  - Most patients become symptomatic shortly after ingestion
  - May have mild symptoms
Activates both sides of the ANS

- May get activation of sympathetic and parasympathetic NS

- May also get fasciculations mimicking seizures
Activates both sides of the ANS.
Acute threat in cholinergic toxicity

- What is the real problem?

- Respiratory
  - Bronchorrhea
  - Diaphragm weakness
  - Both lead to hypoxia and respiratory arrest
Treatment

- ABCs
  - With particular attention to airway

- Standard treatment (what’s in your drug box?)
  - Atropine
Why atropine?

- Competitively antagonize ACh at receptors

- How much?
  - No standard dosing strategy
  - 1-5mg every 2-20 minutes or double the dose every 5 minutes until a response occurs
Anything else?

- **Pralidoxime (2-PAM)**
  - Regenerates AChE – lowering ACh concentration
  - However – if the agent becomes “aged” – oxime administration will not have an effect
What about benzodiazepines?

- Tend to have lower incidence of seizures
Practical application?

Figure: http://www.atsdr.cdc.gov/csem/csem.asp?csem=11&po=22
Switching gears

- 20 yo male presents with tachycardia and altered mental status after taking "Tylenol PM"
Anticholinergic toxicity

- Mnemonic

- Hot as a hare, red as a beet, blind as a bat, dry as a bone, mad as a hatter
Anticholinergic toxicity

- Everywhere!
Anticholinergic toxicity
Clinical presentation

- How do these typically present?

- What does this look like?
  - More importantly, how does this differ?

- Consider non-tox diagnoses
  - Sepsis, hypoxia, etc…
Treatment

- Initial treatment?

- Is there an antidote?
  - Physostigmine – AChE inhibitor
Disposition/Duration

- Anticholinergic symptoms may last for days!
Next case

- 25 yo female presents with altered mental status after recent break up with her significant other. Slight tremor noted on lower extremities > upper extremities
Famous case

http://blog.targethealth.com/?p=13063

Serotonergic agents

- **SSRI**
  - Citalopram
  - Escitalopram
  - Fluoxetine
  - Paroxetine
  - Sertraline
  - Mirtazapine

- **SNRI**
  - Desvenlafaxine
  - Duloxetine
  - Milnacipran
  - Venlafaxine
More serotonergic drugs

- Trazodone
- Buspirone
- Phenelzine
- Valproate
- Meperidine
- Tramadol
- Ondansetron
- Metoclopramide
- Linezolid
- Dextromethorphan
- MDMA
- …and many more
Spectrum of disease

Boyer. NEJM 2005
Hunter Serotonin Toxicity Criteria Decision Rules

In the presence of a serotonergic agent

1. IF (spontaneous clonus = yes) THEN serotonin toxicity = YES
2. ELSE IF (inducible clonus = yes) AND (agitation = yes) OR (diaphoresis = yes) THEN serotonin toxicity = YES
3. ELSE IF (ocular clonus = yes) AND (agitation = yes) OR (diaphoresis = yes) THEN serotonin toxicity = YES
4. ELSE IF (tremor = yes) AND (hyperreflexia = yes) THEN serotonin toxicity = YES
5. ELSE IF (hypertonic = yes) AND (temperature >38 C) AND (ocular clonus = YES) OR (inducible clonus = yes) THEN serotonin toxicity = YES
6. ELSE serotonin toxicity = NO
Clinical presentation

- Symptoms vary but a reasonable to consider when:
  - Serotonergic agent
  - Neuromuscular abnormality - clonus (spontaneous or inducible), hyperreflexia or tremor (LE>UE)
  - AMS (usually mild agitation or confusion)
  - Autonomic instability
Treatment

- **ABCs**
- Consider decontamination
- Other therapies for serious symptoms
  - Cooling
  - Cyproheptadine
  - Benzodiazepines
  - IVF
  - Rhabdomyolysis
  - RSI
# One slide on Neuroleptic malignant syndrome

<table>
<thead>
<tr>
<th></th>
<th>NMS</th>
<th>Serotonin Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>History</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inciting drug</td>
<td>Dopamine antagonist (or sudden withdrawal of dopamine agonist)</td>
<td>Serotonin agonist</td>
</tr>
<tr>
<td>Time course of symptom onset</td>
<td>Days to weeks</td>
<td>Hours</td>
</tr>
<tr>
<td>Duration of symptoms</td>
<td>Days to 2 weeks</td>
<td>Usually 24 hours</td>
</tr>
<tr>
<td><strong>Symptoms</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mental status</td>
<td>Confusion, mutism</td>
<td>Agitated, confused</td>
</tr>
<tr>
<td>Temperature</td>
<td>Markedly elevated in 90% of cases</td>
<td>Elevated in severe cases</td>
</tr>
<tr>
<td>Creatinine kinase</td>
<td>Markedly elevated in 90% of cases</td>
<td>Normal or mildly elevated</td>
</tr>
<tr>
<td>Neuromuscular manifestations</td>
<td>“Lead-pipe” rigidity</td>
<td>Hyperreflexia, clonus</td>
</tr>
</tbody>
</table>
Neurotoxic?
Neurotoxic?
Neurotoxic?

- Yes
How do these drugs work?

- Succinylcholine
- Rocuronium
- Vecuronium
References

- Costanzo, L Physiology, Third edition. 2005
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