Poisoning From Cough & Cold Preparations

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Epidemiology

- 7th most common form of poisoning
- 4.5% of all poisonings (about 109K)
- Very common in the winters
- Very common in children
Most Common Ingredients

• Antihistamine (runny nose and itchy eyes)
• Decongestant (stuffy/runny nose)
• Dextromethorphan (cough suppressant)
• Guaifenesin (expectorant)
• Analgesic (aches and pains)
Histamine Pharmacology

- $H_1$
  - smooth muscle contraction, dilation of capillaries, increased capillary permeability

- $H_2$
  - gastric acid secretion

- $H_3$
  - autoregulation of histamine release in CNS; prevents bronchoconstriction and puritis

- $H_4$
  - Differentiation of myeloblasts and promyelocytes

Simons FE. NEJM 2004;351:2203-17
Therapeutic Uses Of Antihistamines

- **H₁ Antagonists**
  - Allergy, motion sickness, vertigo
  - 1st generation (sedating) vs 2nd generation (non-sedating)
    - 2nd Gen: less CNS H1 binding and less α and β receptor binding

- **H₂ Antagonists**
  - gastric/duodenal ulcers, gastroesophageal reflux disease, stress ulcers, gastrinomas

- **H₃ Antagonists**
  - no approved agents to date
# Antihistamine SAR’s

## TABLE 1. Structural classification of antihistamines

<table>
<thead>
<tr>
<th>Structural group</th>
<th>Molecular weight (g/mol)</th>
<th>SI conversion</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alkylamines</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brompheniramine maleate</td>
<td>435.3</td>
<td>µg/L × 3.13 = nmol/L</td>
<td>Highly potent, significant sedative action. Acrivastine is a nonsedating alkylamine antihistamine.</td>
</tr>
<tr>
<td>Dextrophanine</td>
<td>390.9</td>
<td>mg/L × 2.56 = µmol/L</td>
<td></td>
</tr>
<tr>
<td>Pheniramine</td>
<td>240.4</td>
<td>mg/L × 4.16 = µmol/L</td>
<td></td>
</tr>
<tr>
<td>Triprolidine</td>
<td>278.4</td>
<td>µg/L × 3.59 = nmol/L</td>
<td></td>
</tr>
<tr>
<td>Acrivastine&lt;sup&gt;a&lt;/sup&gt;</td>
<td>—</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Monoethanolamines</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clemastine fumarate</td>
<td>460.0</td>
<td>mg/L × 2.91 = µmol/L</td>
<td>Pronounced sedative and antimuscarinic action.</td>
</tr>
<tr>
<td>Dimenhydrinate</td>
<td>470.0</td>
<td>mg/L × 2.13 = µmol/L</td>
<td></td>
</tr>
<tr>
<td>Diphenhydramine</td>
<td>255.4</td>
<td>mg/L × 3.92 = µmol/L</td>
<td></td>
</tr>
<tr>
<td>Doxylamine</td>
<td>270.4</td>
<td>mg/L × 3.70 = µmol/L</td>
<td></td>
</tr>
<tr>
<td>Ethylenediamines</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antazoline HCl</td>
<td>301.8</td>
<td>mg/L × 3.77 = µmol/L</td>
<td>Selective H&lt;sub&gt;1&lt;/sub&gt; antagonists, moderate sedation, gastrointestinal upset.</td>
</tr>
<tr>
<td>Mepyramine HCl</td>
<td>321.8</td>
<td>mg/L × 3.39 = µmol/L</td>
<td></td>
</tr>
<tr>
<td>Phenothiazines</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methdilazine</td>
<td>296.4</td>
<td>mg/L × 3.37 = µmol/L</td>
<td>Significant sedative effects, pronounced antiemetic and antimuscarinic effects, photosensitivity.</td>
</tr>
<tr>
<td>Promethazine</td>
<td>284.4</td>
<td>mg/L × 3.52 = µmol/L</td>
<td></td>
</tr>
<tr>
<td>Trimetazine</td>
<td>298.5</td>
<td>mg/L × 3.35 = µmol/L</td>
<td></td>
</tr>
<tr>
<td>Piperazines</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cetirizine&lt;sup&gt;a&lt;/sup&gt;</td>
<td>—</td>
<td>—</td>
<td>Moderate sedation, significant antiemetic action. Cetirizine causes less sedation.</td>
</tr>
<tr>
<td>Cinnarizine</td>
<td>368.5</td>
<td>mg/L × 2.71 = µmol/L</td>
<td></td>
</tr>
<tr>
<td>Cyclizine</td>
<td>266.4</td>
<td>mg/L × 3.75 = µmol/L</td>
<td></td>
</tr>
<tr>
<td>Flunarizine</td>
<td>404.5</td>
<td>mg/L × 2.47 = µmol/L</td>
<td></td>
</tr>
<tr>
<td>Hydroxyzine</td>
<td>374.9</td>
<td>mg/L × 2.67 = µmol/L</td>
<td></td>
</tr>
<tr>
<td>Piperidines</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Azetadine&lt;sup&gt;a&lt;/sup&gt;</td>
<td>—</td>
<td>—</td>
<td>Moderate or low sedation; highly selective for H&lt;sub&gt;1&lt;/sub&gt; receptors. Astemizole, loratadine, and terfenadine are nonsedating.</td>
</tr>
<tr>
<td>Cyproheptadine</td>
<td>287.4</td>
<td>µg/L × 3.48 = nmol/L</td>
<td></td>
</tr>
<tr>
<td>Astemizole&lt;sup&gt;a&lt;/sup&gt;</td>
<td>—</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Loratadine&lt;sup&gt;a&lt;/sup&gt;</td>
<td>—</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Terfenadine&lt;sup&gt;a&lt;/sup&gt;</td>
<td>—</td>
<td>—</td>
<td></td>
</tr>
</tbody>
</table>

HCl, hydrochloride.

<sup>a</sup>Low-sedating and nonsedating antihistamines are addressed in Chapter 87.
Decongestant Pharmacology

Adrenergic Receptors

\[ \alpha \]

- \( \alpha_1 \)
  - \( \alpha_{1A} \)
  - \( \alpha_{1B} \)
  - \( \alpha_{1C} \)
  - \( G_q/G_1 \)
    - Activates phospholipase C
      - Postsynaptic: vasoconstriction
  - \( \alpha_{1A} \)
  - \( \alpha_{1B} \)
  - \( \alpha_{1C} \)
  - \( G_q/G_1 \)
    - Inhibits adenylyl cyclase; Ca\(^{2+}\), K\(^{+}\) channels
      - Postsynaptic: vasoconstriction
        - Presynaptic: vasoconstriction

- \( \alpha_2 \)
  - \( \alpha_{2A} \)
  - \( \alpha_{2B} \)
  - \( \alpha_{2C} \)
  - \( G_\alpha/G_0 \)
    - Stimulates adenylyl cyclase; Ca\(^{2+}\) channels
      - ↑Cardiac inotropy and ↑HR
      - Smooth muscle relaxation (bronchial, vascular) and cardiac effects
        - FAT

- \( \beta \)
  - \( \beta_1 \)
  - \( \beta_2 \)
  - \( \beta_3 \)
  - \( G_\beta/G_0 \)
    - Ahlquist (original definition)
      - "Classic" pharmacology
    - Molecular pharmacology
      - Signal transduction
    - Effectors

From Miller: Miller’s Anesthesia, 6th ed., Copyright ̊ 2005 Churchill Livingstone, An Imprint of Elsevier
### TABLE 35–2. Decongestants

<table>
<thead>
<tr>
<th>Decongestant</th>
<th>Class</th>
<th>Duration of Action</th>
<th>Alpha/Beta Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ephedrine</td>
<td>Sympathomimetic</td>
<td>3–5 h</td>
<td>$\alpha_{1,2}$ and $\beta_{1,2}$</td>
</tr>
<tr>
<td>Naphazoline</td>
<td>Imidazoline</td>
<td>8 h</td>
<td>$\alpha_2$</td>
</tr>
<tr>
<td>Oxymetazoline</td>
<td>Imidazoline</td>
<td>6–7 h</td>
<td>$\alpha_2$</td>
</tr>
<tr>
<td>Phenylephrine</td>
<td>Sympathomimetic</td>
<td>1 h</td>
<td>$\alpha_{1,2}$</td>
</tr>
<tr>
<td>Phenylpropanolamine</td>
<td>Sympathomimetic</td>
<td>12 h (sustained release)</td>
<td>$\alpha_{1,2}$</td>
</tr>
<tr>
<td>Pseudoephedrine</td>
<td>Sympathomimetic</td>
<td>3–4 h</td>
<td>$\alpha_{1,2}$ and $\beta_{1,2}$</td>
</tr>
<tr>
<td>Tetrahydrozoline</td>
<td>Imidazoline</td>
<td>4–8 h</td>
<td>$\alpha_2$</td>
</tr>
<tr>
<td>Xylometazoline</td>
<td>Imidazoline</td>
<td>5–6 h</td>
<td>$\alpha_2$</td>
</tr>
</tbody>
</table>
H1 Antihistamine Pharmacokinetics

- Absorption
  - Peak blood level: 2-3 hours

- Metabolism
  - Hepatic

- Elimination/Duration
  - 3-24 hours
H2 Antihistamine Pharmacokinetics

- **Absorption**
  - Onset: 1-2 hours

- **Distribution**
  - VD: 1-2 L/kg
  - Protein binding: 6-43%

- **Elimination**
  - Most are metabolized then renally cleared
  - Half-life: 2-4 hours
  - Duration: 4-12 hours
Acrivistine (Semprex-D)

- Structural analogue of triprolidine
- Dose: 8 mg Q 4-6 hours
- Pharmacokinetics
  - Abs: onset in 1 hr; Peak in 4 hrs
  - Dist: 0.82 L/kg; PB 50%
  - Elim: t1/2 1.9 hr
- Overdose: 322 mg survived uneventfully
  - May produce drowsiness in OD
Cetirizine (Zyrtec)

- Metabolite of hydroxyzine
- Dose: 5 - 10 mg daily
- Pharmacokinetics
  - Abs: onset in 1 hr; Peak in 1 hrs
  - Dist: 24 L/kg; PB 93%
  - Elim: t1/2 8.3 hr
- Overdose: No reports
  - May produce drowsiness at therapeutic dose and in OD
  - No QTc prolongation @ 6X MDD
Desloratadine (Clarinex)

- Metabolite of loratadine
- Dose: 5 mg daily
- Pharmacokinetics
  - Abs: onset in 1 hr; Peak in 4 hrs
  - Dist: 24 L/kg; PB 82%-87%
  - Elim: t1/2 28 hr
- Overdose: No reports
  - Somnolence at 10 mg/day and 20 mg/day
Loratidine (Claritin)

- Piperadine antihistamine; least sedating of all antihistamines on US market
- Dose: 10 mg daily
- Pharmacokinetics
  - Abs: onset in 1-3 hr; Peak in 1-2 hrs
  - Dist: PB 97%
  - Elim: t1/2 8.4 hr
- Overdose: Somnolence, tachycardia, headache
Fexofenadine (Allegra)

- Metabolite of terfenadine (Seldane)
- Dose: 60 mg BID daily
- Pharmacokinetics
  - Abs: onset in 2-3 hr; Peak in 2-3 hrs
  - Dist: Vd: 12 L/kg; PB 60%-70%
  - Elim: t1/2 14.4 hr
- Overdose: Doses up to 690 mg BID for a month did not produce QTc prolongation. May produce drowsiness.

Decongestant Pharmacokinetics

- **Absorption**
  - Rapid, with peak effects occurring in 1-3 hours

- **Distribution**
  - Large (2-5 L/Kg)

- **Elimination**
  - Duration: 1-8 hours
## Specific Decongestant Pharmacokinetics

<table>
<thead>
<tr>
<th>Decongestant</th>
<th>Peak (hrs)</th>
<th>Vd (L/Kg)</th>
<th>Half-life (hrs)</th>
<th>Duration (hrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ephedrine</td>
<td>1</td>
<td></td>
<td>3-4</td>
<td>3-5</td>
</tr>
<tr>
<td>Phenylephrine</td>
<td></td>
<td></td>
<td>2-3</td>
<td>1</td>
</tr>
<tr>
<td>Phenylpropanolamine</td>
<td>1-3</td>
<td>2.5-5</td>
<td>3-7</td>
<td>6-12</td>
</tr>
<tr>
<td>Pseudoephedrine</td>
<td>3</td>
<td>2.5-3</td>
<td>5-8</td>
<td>3-4</td>
</tr>
<tr>
<td>Naphazoline</td>
<td></td>
<td></td>
<td></td>
<td>2-6</td>
</tr>
<tr>
<td>Oxymetazoline</td>
<td></td>
<td>5-8</td>
<td></td>
<td>6-7</td>
</tr>
<tr>
<td>Tetrahydrozoline</td>
<td></td>
<td>1.2-4</td>
<td></td>
<td>4-8</td>
</tr>
<tr>
<td>Xylometazoline</td>
<td></td>
<td></td>
<td></td>
<td>5-6</td>
</tr>
</tbody>
</table>
H1 Antihistamine Dose-Response

- Diphenhydramine
  - MDD for children (<6 yrs): 5 mg/kg/day
  - The lowest dose reported to cause severe toxicity (seizures, respiratory arrest, arrhythmias) is 10–15 mg/kg (Hestand HE, Teske DW. Diphenhydramine hydrochloride intoxication. J Pediatr 1977; 90:1017–1018.)
  - HCF Triage point: 7.5 mg/kg (AAPCC Guideline, 2006)
- The rest
  - 4 MDD
1st Generation H1 Clinical Manifestations

- CNS: Sedation, seizures, agitation
- Anticholinergic manifestations (next slide)
- Diphenhydramine blocks sodium channels (QRS prolongation; QT prolongation also reported)
- Hypotension (α blockade)
- Rhabdomyolysis
Anticholinergic Signs/Symptoms

- Central
  - Agitation
  - Hallucinations
  - Confusion
  - Sedation
  - Coma
  - Seizures

- Peripheral
  - Hypertension
  - Tachycardia
  - Hyperthermia
  - Mydriasis
  - Dry flushed skin
  - Decreased GI motility
  - Urinary retention
2nd Generation H1 Clinical Manifestations

- Expect only drowsiness
- Unlikely that there will be QTc prolongation, but look for it nonetheless
Dextromethorphan

- **Pharmacology**
  - Most of the activity is due to dextrorphan
  - Binds to phencyclidine site of NMDA receptor → blocks receptor → sedation, dissociative state
  - Blocks uptake of catecholamines → adrenergic response
  - Blocks pre-synaptic uptake of serotonin → serotonin syndrome
  - Binds to \( \kappa_2 \) receptor → dysphoria
  - High dose: binds to opioid receptors→ classic triad
Dextromethorphan Kinetics

• Absorption
  - Peak in 2.5 hours; metabolite peaks at 1.6-1.7 hours after parent compound

• Distribution
  - Vd: 5-6.7 L/kg

• Elimination
  - Metabolized by CYP2D6 to active metabolite, dextrorphan, which is then demethylated to 3-methoxymorphinan and eliminated renally.
  - T1/2: 2-4 hours
Dextromethorphan Metabolism

CYP2D6 → Dextromethorphan → 3-methoxymorphinan → 3-hydroxymorphinan → Dextrorphan

- Biological activity is unknown
- All biological activity attributed to dextromethorphan resides in dextrorphan
Dextromethorphan Manifestations

• Minimally intoxicated: tachycardia, hypertension, vomiting, mydriasis, diaphoresis, nystagmus, euphoria, loss of motor coordination, and giggling or laughing.

• Moderate intoxication: hallucinations and a distinctive, plodding ataxic gait that has been compared with "zombie-like" walking.

• Severely intoxicated: dissociated state, agitated or somnolent; Extremely agitated patients may develop hyperthermia and metabolic acidosis.
Dextromethorphan Dose-Response (Abuse)

- 1st Plateau (100-200 mg): mild stimulant effect
- 2nd Plateau (200-400 mg): euphoria similar to ethanol and marijuana
- 3rd Plateau (300-600 mg): out-of-body experience
- 4th Plateau (600-1500 mg): full-blown dissociative state

Boyer E. Ped Em Care 2004;20(12):585-563
Dextromethorphan Dose-Response (Acute OD)

- As little as 12.9 mg/kg produced seizures in a 4 year-old 30 minutes after ingestion
- NMPDIC Triage Point: 7.5 mg/kg

Decongestant Toxicity

- Depends on type
  - Sympathomimetics
    - Toxicity expected at 4X maximum daily dose (Ekins et al. Vet Hum Tox 1983;25:81-85.)
  - Imidazolines
    - 2-4 mls of nasal or eye products
# Table of MDD’s

<table>
<thead>
<tr>
<th>Agent</th>
<th>&lt; 2 yr</th>
<th>2-6 years</th>
<th>6-12</th>
<th>Adult*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenylpropanolamine</td>
<td>2.5 mg/kg</td>
<td>37.5 mg</td>
<td>75 mg</td>
<td>75 mg</td>
</tr>
<tr>
<td>Ephedrine</td>
<td>2 mg/kg</td>
<td>30 mg</td>
<td>50 mg</td>
<td>75 mg</td>
</tr>
<tr>
<td>Phenylephrine</td>
<td>1 mg/kg</td>
<td>15 mg</td>
<td>30 mg</td>
<td>50 mg</td>
</tr>
<tr>
<td>Pseudoephedrine</td>
<td>4 mg/kg</td>
<td>60 mg</td>
<td>120 mg</td>
<td>120 mg</td>
</tr>
</tbody>
</table>
Decongestant Clinical Manifestations

- **Sympathomimetic**
  - Most common: tachycardia, hypertension, reflex bradycardia, CNS stimulation
  - Serious toxicity: Headache, central nervous system depression, bradycardia, ventricular dysthytthmias, myocardial infarction, and cerebral hemorrhage

- **Imidazoline**
  - Bradycardia, apnea, hypotension, and coma
Laboratory Assessment

- APAP/ASA level if product is unknown
- CT and lumbar puncture for patients with an abnormal neuropsychiatric exam
Cough & Cold Treatment

- Preventing absorption
  - Consider AC and/or lavage; MDAC for antihistamine

- Enhancing elimination
  - Not applicable

- Antidote
  - Consider physostigmine for anticholinergic syndrome (next slide)
Physostigmine (Antilirium)

• Pharmacology
   Acetylcholinesterase inhibitor
   Tertiary amine

• Indications
   Pronounced agitation/hallucinations
   Narrow complex supraventricular arrhythmias resulting in hemodynamic instability and not responding to conventional treatments
   Intractable seizures

• Side effects
   Seizures
   Cholinergic crisis
   Arrhythmias

• Contraindications
   Asthma, gangrene, ischemic disease, peripheral vascular disease, mechanical obstruction of GI/GU tract

• Dose
   Child: 0.02 mg/kg
   Adult: 1-2 mg slowly

• Dosage forms
   1 mg/ml; 2 ml vial
Cough & Cold Supportive Care Measures

- Agitation/hallucinations: benzodiazepines => physostigmine
- Fever: External cooling
- Hypotension: Fluids => dopamine => NE
- Hypertension: phentolamine or nitroprusside
- QRS prolongation: Na bicarbonate
- Ventricular dysrhythmia: lidocaine