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)
- Guaifensen (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

- H_1 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
- H_2 Antagonists
  - gastric/duodenal ulcers, gastroesophageal reflux disease, stress ulcers, gastrinomas
- H_3 Antagonists
  - no approved agents to date

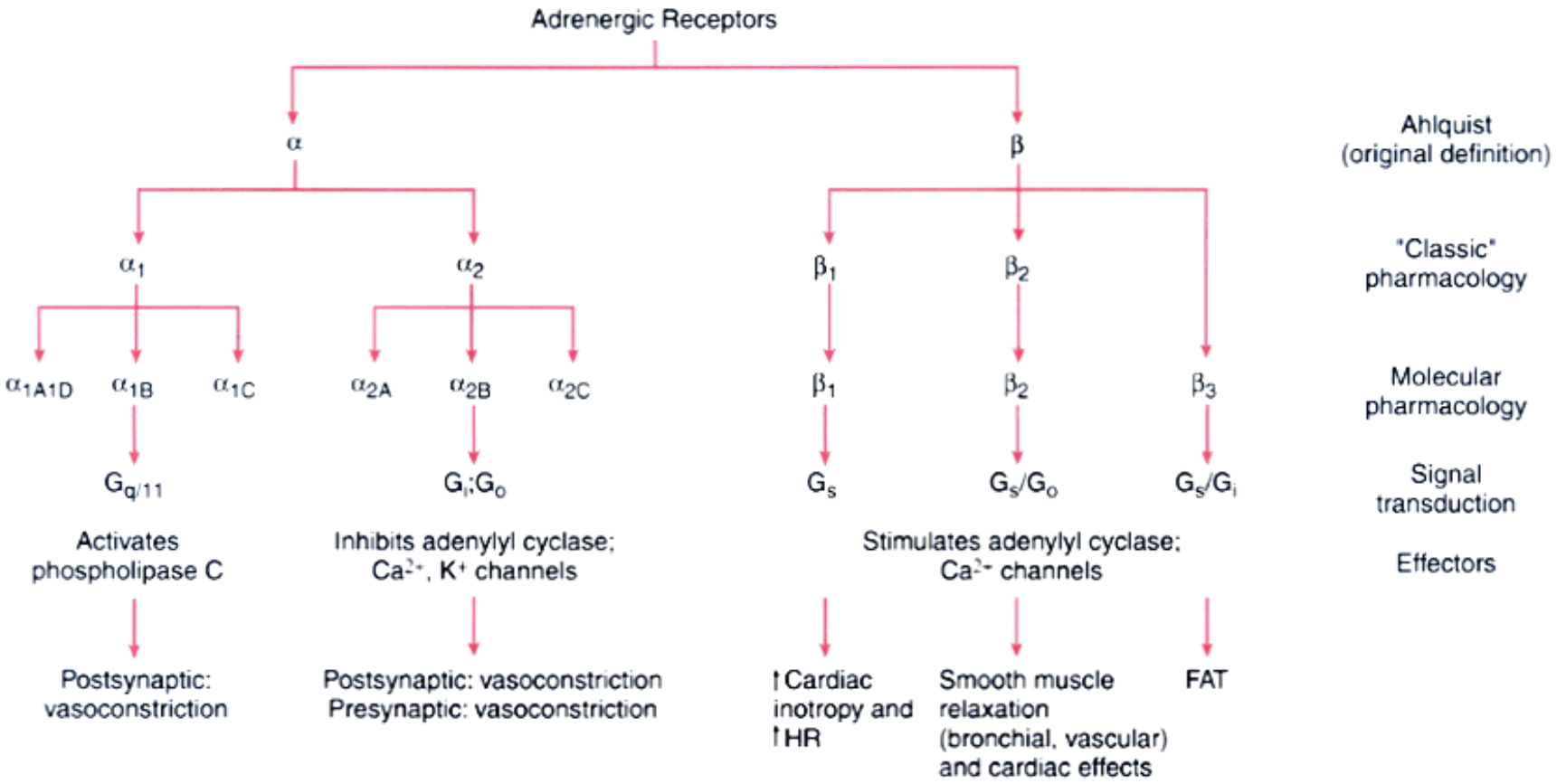
Antihistamine SAR's

TABLE 1. Structural classification of antihistamines

Structural group	Molecular weight (g/mol)	SI conversion	Comments
Alkylamines			Highly potent, significant sedative action. Acrivastine is a nonsedating alkylamine antihistamine.
Brompheniramine maleate	435.3	μg/L × 3.13 = nmol/L	
Dexchlorpheniramine	390.9	mg/L × 3.64 = μmol/L	
Pheniramine	240.4	mg/L × 4.16 = μmol/L	
Triprolidine	278.4	μg/L × 3.59 = nmol/L	
Acrivastine[a]	—	—	
Monoethanolamines			Pronounced sedative and antimuscarinic action.
Clemastine fumarate	460.0	mg/L × 2.91 = μmol/L	
Dimenhydrinate	470.0	mg/L × 2.13 = μmol/L	
Diphenhydramine	255.4	mg/L × 3.92 = μmol/L	
Doxylamine	270.4	mg/L × 3.70 = μmol/L	
Ethylenediamines			Selective H_1 antagonists, moderate sedation, gastrointestinal upset.
Antazoline HCl	301.8	mg/L × 3.77 = μmol/L	
Mepyramine HCl	321.8	mg/L × 3.39 = μmol/L	
Phenothiazines			Significant sedative effects, pronounced antiemetic and antimuscarinic effects, photosensitivity.
Methdilazine	296.4	mg/L × 3.37 = μmol/L	
Promethazine	284.4	mg/L × 3.52 = μmol/L	
Trimeprazine	298.5	mg/L × 3.35 = μmol/L	
Piperazines			Moderate sedation, significant antiemetic action. Cetirizine causes less sedation.
Cetirizine[a]	—	—	
Cinnarizine	368.5	mg/L × 2.71 = μmol/L	
Cyclizine	266.4	mg/L × 3.75 = μmol/L	
Flunarizine	404.5	mg/L × 2.47 = μmol/L	
Hydroxyzine	374.9	mg/L × 2.67 = μmol/L	
Piperidines			Moderate or low sedation; highly selective for H_1 receptors. Astemizole, loratadine, and terfenadine are nonsedating.
Azatadine[a]	—	—	
Cyproheptadine	287.4	μg/L × 3.48 = nmol/L	
Astemizole[a]	—	—	
Loratadine[a]	—	—	
Terfenadine[a]	—	—	

HCl, hydrochloride.
[a]Low-sedating and nonsedating antihistamines are addressed in Chapter 87.

Decongestant Pharmacology



Pharmacologic Profile of Common Decongestants

TABLE 35–2. Decongestants

Decongestant	Class	Duration of Action	Alpha/Beta Activity
Ephedrine	Sympathomimetic	3–5 h	$\alpha_{1,2}$ and $\beta_{1,2}$
Naphazoline	Imidazoline	8 h	α_2
Oxymetazoline	Imidazoline	6–7 h	α_2
Phenylephrine	Sympathomimetic	1 h	$\alpha_{1,2}$
Phenylpropanolamine	Sympathomimetic	12 h (sustained release)	$\alpha_{1,2}$
Pseudoephedrine	Sympathomimetic	3–4 h	$\alpha_{1,2}$ and $\beta_{1,2}$
Tetrahydrozoline	Imidazoline	4–8 h	α_2
Xylometazoline	Imidazoline	5–6 h	α_2

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 survive
  - May produce drowsiness ir

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

Desloratidine (Clarinex)

- Metabolite of loratidine
- 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, tachyc
  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 did not produce QTc prolongation. Ma drowsiness.

allegra® fexofenadine HCl

Pratt C, Brown AM, Rampe D, Mason J, Russell T, Reynolds R, Ahlbrandt R. Cardiovascular safety of fexofenadine HCl. Clin Exp Allergy. 1999 Jul;29 Suppl 3:212-6

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

Decongestant	Peak (hrs)	Vd (L/Kg)	Half-life (hrs)	Duration (hrs)
Ephedrine	1		3-4	3-5
Phenylephrine			2-3	1
Phenylpropanolamine	1-3	2.5-5	3-7	6-12
Pseudoephedrine	3	2.5-3	5-8	3-4
Naphazoline				2-6
Oxymetazoline			5-8	6-7
Tetrahydrozoline			1.2-4	4-8
Xylometazoline				5-6

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

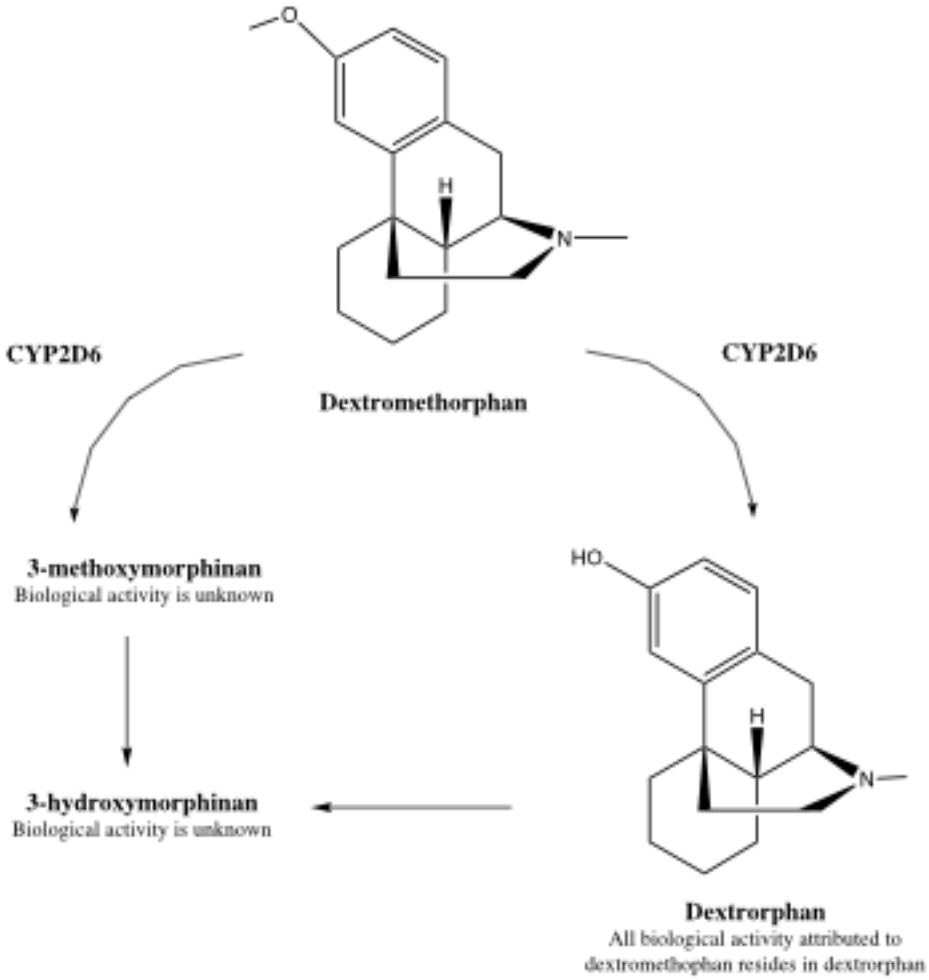
Dextromethorphan

- 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 κ_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



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 intoxication: 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

Versie et al. Ann Med Leg 1962; 42:561-565.

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

Maximum Daily Doses For Common Decongestants

Agent	< 2 yr	2-6 years	6-12	Adult*
Phenylpropanolamine	2.5 mg/kg	37.5 mg	75 mg	75 mg
Ephedrine	2 mg/kg	30 mg	50 mg	75 mg
Phenylephrine	1 mg/kg	15 mg	30 mg	50 mg
Pseudoephedrine	4 mg/kg	60 mg	120 mg	120 mg

Decongestant Clinical Manifestations

- Sympathomimetic
  - Most common: tachycardia, hypertension, reflex bradycardia, CNS stimulation
  - Serious toxicity: Headache, central nervous system depression,bradycardia, ventricular dysthythmias, 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