Clinical toxicology

Poisoning by over the counter drugs

Part II

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Pseudoephedrine and phenylephrine Toxicity

The FDA issued an advisory in 2008 recommending against the use of cough and cold medicines (which contain decongestants as well as antihistamines and/or dextromethorphan) to children younger than 2 years of age because of reports of serious and life-threatening side effects.

Example on drug containing decongestant: Panadol cold and flu, Panadol sinus, Dolo cold, Actifed, Tusseram syrup, Tussilate syrup, Congestal and Advil sinus

Mechanism of toxicity

All these agents stimulate the adrenergic system, with variable effects on alpha- and beta-adrenergic receptors, depending on the compound.

A. Phenylephrine is direct alpha-adrenergic agonists.

B. Ephedrine and pseudoephedrine have both direct and indirect alpha- and beta-adrenergic activity but clinically produce more beta-adrenergic stimulation than does phenylephrine.

Toxic dose

- If the patient exceed the usual daily adult dose (which is 100-200 mg for ephedrine, 180-360 mg for pseudoephedrine and 40—60 for phenylphrine). However, Patients with autonomic insufficiency and those taking monoamine oxidase (MAO) inhibitors (selegiline and phenelzine) may be extraordinarily sensitive to these and other sympathomimetic drugs, developing severe hypertension after ingestion of even subtherapeutic doses.
- **A.** Phenylephrine, and ephedrine have low toxic-to-therapeutic ratios. Toxicity often occurs after ingestion of just 2–3 times the therapeutic dose.
- **B.** Pseudoephedrine is less toxic, with symptoms occurring after four- to fivefold the usual therapeutic dose.

Clinical presentation

- The major toxic effect of these drugs is hypertension, which may lead to headache, confusion, seizures, and intracranial hemorrhage.
- Bradycardia or atrioventricular (AV) block is common in patients with moderate to severe hypertension associated with phenylephrine owing to the baroreceptor reflex response to hypertension.
- The presence of drugs such as antihistamines and caffeine prevents reflex bradycardia and may enhance the hypertensive effects of phenylephrine. (Explain that??)
- Myocardial infarction and diffuse myocardial necrosis have been associated with ephedra intoxication.

Diagnosis

- ✓ From history
- ✓ Presence of hypertension. Bradycardia or AV block suggests phenylephrine. Severe headache, focal neurologic deficits, or coma should raise the possibility of intracerebral hemorrhage.
- ✓ Measurement of electrolytes, glucose, BUN, creatinine, creatine kinase (CK) with MB isoenzymes (found in myocardium), cardiac troponin, ECG monitoring, and CT head scan if intracranial hemorrhage is suspected.

Treatment

Emergency and supportive measures

1. Treat hypertension aggressively (see below).
2. Treat seizures (Diazepam injection)
3. Treat ventricular tachyarrhythmias (Lidocain, DC shouck) if they occur.
4. . Do not treat AV block or sinus bradycardia associated with hypertension; because increasing the heart rate with atropine may abolish this reflex response that serves to limit hypertension, resulting in worsening elevation of the blood pressure.

Specific drugs and antidotes

1.No specific antidote

2. The Hypertension treated by a vasodilator such as phentolamine or nitroprusside. But if there is CT or obvious clinical evidence of intracranial hemorrhage, lower the diastolic pressure cautiously to no lower than 90 mm Hg and consult a neurosurgeon immediately.

Do not use beta blockers to treat hypertension without first giving a vasodilator; otherwise, paradoxical worsening of the hypertension may result.

3. Arrhythmias: Tachyarrhythmias usually respond to low-dose esmolol or metoprolol.

Decontamination. Administer activated charcoal orally.

Enhanced elimination. Dialysis and hemoperfusion are not effective. Urinary acidification may enhance elimination of ephedrine, and pseudoephedrine but may also aggravate myoglobin deposition in the kidneys if the patient has rhabdomyolysis.

Acetyl salicylic acid (Aspirin) Toxicity

Epidemiology

- There are approximately 18000 aspirin poisoning per year in the United States.
- ASA causes 26 % of all analgesic deaths each year.
- More than 35 deaths per year.
- Increased levels of ASA in ointments, liniments, keratolytics, vaporizer oils which contain methyl salicylate, 1-2 tsp. lethal in children.
- During the latter part of the 20th century, the number of poisonings from salicylates declined, mainly because of the increased popularity of other over-the-counter analgesics such as paracetamol (acetaminophen)

Acetyl salicylic acid (ASA) Toxicity

Pharmacology & Toxicology

- Aspirin and other salicylates are analgesics, anti-inflammatories, and antipyretics, a combination of traits shared by all medications of varying structures known as NSAIDs. Most of the beneficial effects of NSAIDs result from the inhibition of cyclooxygenase (COX). This enzyme enables the synthesis of prostaglandins, which in turn mediate inflammation and fever.
- After ingestion of therapeutic doses of immediate-release salicylate, significant serum concentrations are achieved in 30 minutes, and maximum concentrations are often attained in less than 1 hour.
- Salicylates have substantially longer apparent half-lives at toxic concentrations than at therapeutic concentrations, varying from 2 to 4 hours at therapeutic concentrations to as long as 20 hours at high concentrations.

Toxic dose of Aspirin of aspirin poisoning

- **Acute ingestion** of 150–200 mg/kg of aspirin will produce mild intoxication; severe intoxication is likely after acute ingestion of 300–500 mg/kg. Fatalities have been reported in children with ingestion of 5mL or less of oil of wintergreen.
- **Chronic intoxication** with aspirin may occur with ingestion of more than 100 mg/ kg/d for 2 days or more.
- Serum Concentrations higher than 30 mg/dL are associated with signs and symptoms of toxicity.
- When administered chronically, a small increase in dosage or a small decrease in metabolism or renal function may result in substantial increases in serum salicylate concentrations and toxicity.

Pathophysiology of Aspirin

- Centrally stimulates the brainstem respiratory center, causing hyperventilation & respiratory alkalosis.
- Toxic concentrations of salicylate impair renal hemodynamics, leading to the accumulation of inorganic acids.
- Promotes anaerobic metabolism with ketosis, lactic acidosis, & hypoglycemia.
- **Correlation Between Cerebrospinal Fluid and Serum Salicylate Concentrations:** Salicylate concentrations in the cerebrospinal fluid (CSF) directly correlate with death.
- ASA causing neuronal dysfunction and ultimately cerebral edema.
- Salicylates reduce lipogenesis by blocking the incorporation of acetate into free fatty acids and increase peripheral fatty acid metabolism as an energy source, resulting in ketone formation.
- The buildup of fatty acids in the hepatocyte results in microvesicular steatosis, which is characteristic of Reye syndrome.

Pathophysiology of Aspirin poisoning

- ASA increased pulmonary capillary permeability and subsequent exudation of high-protein edema fluid into the interstitial or alveolar spaces.
- Hypoxia results in pulmonary arterial hypertension and a local release of vasoactive substances.
- GI manifestations result from local gastric irritation at lower doses and from stimulation of the medullary chemoreceptor trigger zone at higher doses. Hemorrhagic gastritis, decreased gastric motility, and pylorospasm also result from the direct gastric irritant effects of salicylates

- Salicylates doses above 300 mg/kg may cause acute renal failure, and chronic aspirin poisoning may cause reversible or irreversible acute renal failure.
- The hematologic effects of salicylate poisoning include hypoprothrombinemia and platelet dysfunction.

Clinical presentation

ASA overdose

- Salicylate overdose causes a high anion gap metabolic acidosis in both children and adults. Adults commonly develop a mixed acid-base disorder as a respiratory alkalosis due to direct respiratory centr stimulation occurs as well.

Unique toxic effects include

1-Reye's syndrome
2-Non-cardiogenic pulmonary edema
3-Hypoxia & pulmonary hypertension
4-Hypertension
5-Hypoprothrombinemia & platelet dysfunction
6-Nausea, vomiting, slow GI motility, hemorrhagic gastritis
7-Rhabdomyolysis from hypermetabolism, seizure activity, & increased heat production
8-Tinnitus preceding deafness (> 20-40 mg/dL)

Clinical presentation

Acute ASA poisoning

➢ Early acute

- Nausea, vomiting, fever, diaphoresis, tinnitus & tachypnea.

➢ Late acute

- CNS = tinnitus, deafness, vertigo, high fever, hyperventilation, agitation hyperactivity, seizures, delirium, hallucination & coma.
- Acid-base = respiratory alkalosis & metabolic acidosis.
- Gastrointestinal distress.
- Coagulopathy.
- Metabolic = hypoglycemia, ketonemia & ketonuria.
- Pulmonary = tachypnea, hyperpnea, non-cardiogenic pulmonary edema (NCPE), cardiopulmonary collapse.

Clinical presentation

Chronic ASA poisoning

- Mainly a CNS effects = tinnitus, deafness, dyspnea, hyperventilation, tachycardia, hyperthermia, CNS hyperactivity, agitation, confusion, slurred speech, hallucination, seizures & coma.
- Chronic GI distress.
- Possibility of non-cardiogenic pulmonary edema (NCPE).

Chronic salicylism

- Most common in the elderly-unintentional
- May include any sign consistent with acute toxicity
- May also present as:
  - Delirium
  - Dementia
  - Encephalopathy of unknown origin
  - Congestive heart failure

Acetyl salicylic acid (ASA) Toxicity

Acute vs. Chronic ASA Poisoning

	Acute	Chronic
Age	Young	Old
Etiology	Overdose	Iatrogenic
Diagnosis	Classic	Unrecognized
Associated diseases	None	Chronic pain
Suicidal ideation	Yes	No
Mortality	Rare	25%
Serum levels	High	Intermediate

Diagnosis of Aspirin poisoning

- Arterial blood gas assessments will typically find respiratory alkalosis early in the course of the overdose due to hyperstimulation of the respiratory center, and may be the only finding in a mild overdose.
- An anion-gap metabolic acidosis occurs later in the course of the overdose especially if it is a moderate to severe overdose, due to the increase in protons (acidic contents) in the blood.
- The diagnosis of poisoning usually involves measurement of plasma salicylate, the active metabolite of aspirin, by automated spectrophotometric methods.

Diagnosis of Aspirin poisoning

- Plasma salicylate levels generally range from 30–100 mg/L (3–10 mg/dL) after usual therapeutic doses, 50–300 mg/L in patients taking high doses and 700–1400 mg/L following acute overdose.
- Patients may undergo repeated testing until their peak plasma salicylate level can be estimated.
- Optimally, plasma levels should be assessed four hours after ingestion and then every two hours after that to allow calculation of the maximum level, which can then be used as a guide to the degree of toxicity expected.
- Monitoring of biochemical parameters such as electrolytes and solutes, liver and kidney function, urine analysis, and complete blood count is undertaken along with frequent check in of salicylate and blood sugar levels.

Treatment of Aspirin poisoning

- Resuscitation
- Gastric cleansing by administering activated charcoal, which adsorbs the aspirin in the gastrointestinal tract.
- Inducing vomiting with syrup of ipecac is not recommended.
- Intravenous fluids containing dextrose such as D5W are recommended to keep a urinary output between 2 and 3 ml/kg/h.
- Alkalinization of the urine by sodium bicarbonate in a significant aspirin overdose (salicylate level greater than 35 mg/dl 6 hours after ingestion) regardless of the serum pH, as it enhances elimination of aspirin in the urine. It is given until a urine pH between 7.5 and 8.0 is achieved.

Treatment of Aspirin poisoning

- **Alkalinization of the urine**
- Sodium bicarbonate is given in a significant aspirin overdose (salicylate level greater than 35 mg/dl 6 hours after ingestion) regardless of the serum pH, as it enhances elimination of aspirin in the urine. It is given until a urine pH between 7.5 and 8.0 is achieved.

Treatment of Aspirin poisoning

- **Hemodialysis**: can be used to enhance the removal of salicylate from the blood. Hemodialysis is usually used in those who are severely poisoned.
- Example of severe poisoning include people with high salicylate blood levels: 100 mg/dL in acute ingestions or 40 mg/dL in chronic ingestions, significant neurotoxicity (agitation, coma, convulsions), kidney failure, pulmonary edema, or cardiovascular instability.
- Hemodialysis also has the advantage of restoring electrolyte and acid-base abnormalities while removing salicylate.

6- Acetaminophen Toxicity
N-acetyl para-aminophenol (APAP)

- Acetaminophen has been approved for OTC use since 1960
- Although the drug is remarkably safe, toxicity can occur even with therapeutic doses.
- Alcoholics are particularly susceptible to hepatotoxicity
- Therapeutic dose of acetaminophen is 10-15 mg/kg/dose in children and 325-1000 mg/dose every 4-6 hours in adults, with a maximum of 4g/day.

Biochemical Basis of Acetaminophen Toxicity

- At therapeutic doses, 90% of APAP is metabolized in the liver to sulfate and glucuronide conjugates that are then excreted in the urine
- The remaining 10% is metabolized via the cytochrome CYP2E1 (P450 2E1) to a toxic, reactive, N-acetylimidoquinone (NAPQI)
- NAPQI binds covalently with hepatocyte macromolecules, producing hepatic cell lysis.
- With normal doses, NAPQI is rapidly conjugated with hepatic glutathione, forming a nontoxic compound which is excreted in the urine.
- With toxic doses, however, the sulfate and glucuronide pathways become saturated, resulting in an increased fraction of acetaminophen being metabolized by CYP2E1.
- NAPQI begins to accumulate once glutathione stores are depleted by about 70%

Biochemical Basis of Acetaminophen Toxicity

Liver damage due to excess NAPQI can occur in four circumstances:

- Excessive intake of acetaminophen
- Excessive CYP2E1 activity due to induction by other drugs or chronic alcohol use
- Competition for conjugation enzymes
- Depletion of glutathione stores due to malnutrition or chronic alcohol ingestion

Factors influencing toxicity

- Chronic alcoholics are at increased risk of developing severe hepatic disease even at therapeutic doses
- In contrast, acute alcohol ingestion is not a risk factor for hepatotoxicity and may even be protective by competing for CYP2E1
- Alcohol acts at least in part by induction of CYP2E1, which results in enhanced generation of NAPQI
- Other drugs which induce CYP2E1 enzymes include Phenobarbital and antituberculosis drugs such as isoniazid and rifampin

4 Stages of Acetaminophen Poisoning

Phase I (30 minutes to 4 hours)

- Within a few hours after ingestion, patients experience anorexia, nausea, pallor, vomiting, and diaphoresis. Malaise may be present.

  Patient may appear normal

4 Stages of Acetaminophen Poisoning

Phase II (24 to 48 hours)

- Symptoms of Phase II are less severe. May seem like a period of recovery. Right upper quadrant pain may be present due to hepatic damage. Blood chemistry becomes abnormal with elevations of liver enzymes.
- Prothrombin times may be prolonged.
- Renal function may begin to deteriorate.

4 Stages of Acetaminophen Poisoning

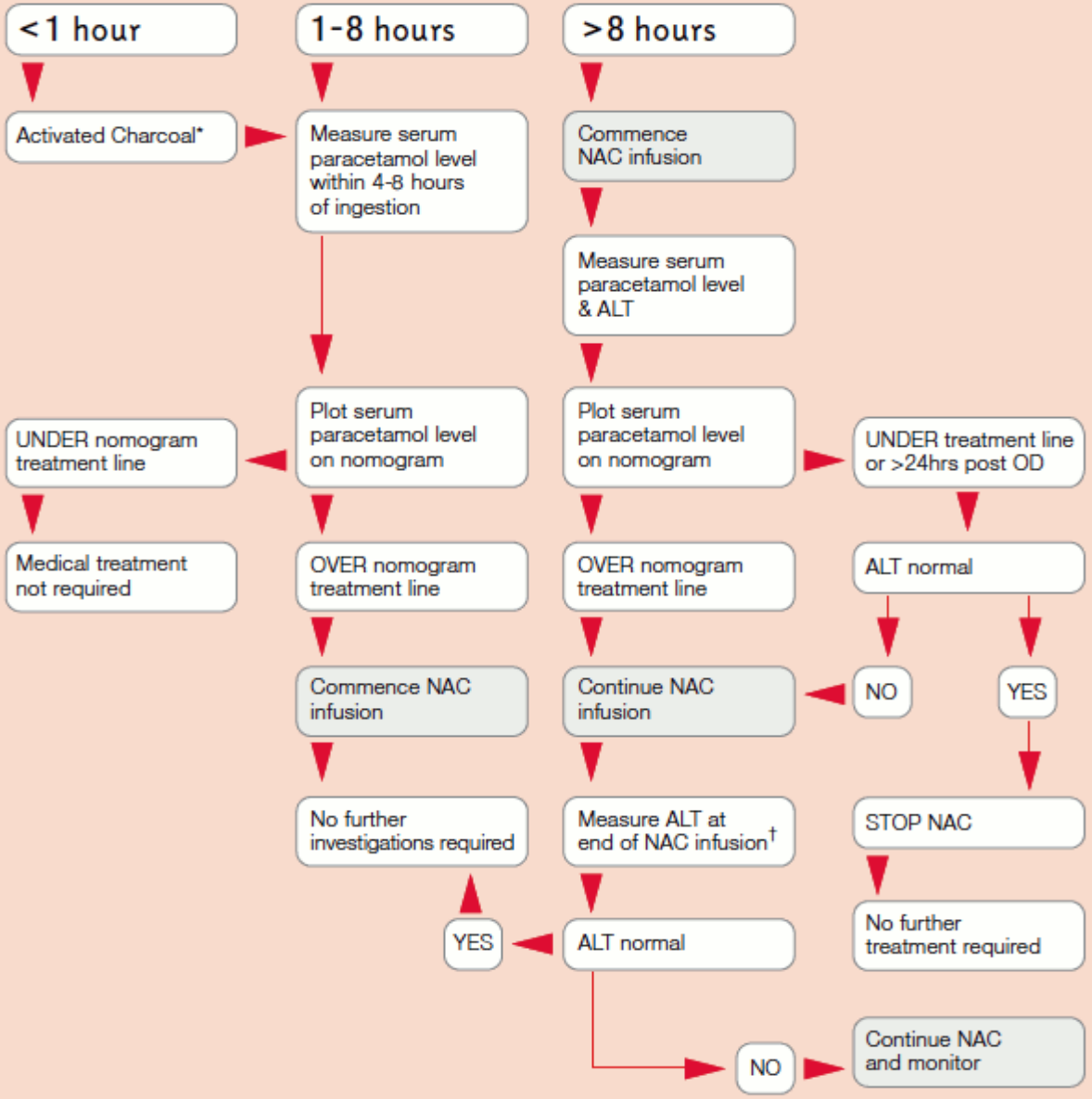
Phase III (3 to 5 days)

- Characterized by symptoms of hepatic necrosis.
- Coagulation defects, jaundice, and renal failure have all been noted.
- Encephalopathy has been noted.
- Hepatic biopsy at this time would indicate centrilobular necrosis.
- Nausea and vomiting may reappear.
- Death is due to hepatic failure

Phase IV (4 days to 2 weeks)

- Complete resolution or death

Acute Ingestion Management Flow-Chart



* Cooperative adult patients who have potentially ingested greater than 10g or 200mg/kg, whichever is less

† Please refer to the section "What to do when the nomogram does not apply; unknown time of paracetamol ingestion."

Diagnosis

- In the patient with a history of APAP overdose, a serum APAP level should be measured between 4 and 24 hours after ingestion.
- The value obtained should be evaluated according to the Rumack-Matthew nomogram for determining the risk of hepatotoxicity and the need for NAC therapy.
- Recognition of acetaminophen intoxication is often more difficult in the chronic alcoholic.
- Several factors contribute to this problem including the onset of symptoms and failure to ask specifically about APAP use.

Diagnosis

- Characteristic laboratory findings of APAP hepatotoxicity include:
- marked elevation in plasma hepatic enzyme levels (>5000 IU/L)
- rising prothrombin time
- These abnormalities distinguish this syndrome from alcoholic liver disease where transaminase values almost never exceed 500 IU/L.
- Aspartate aminotransferase (AST) level typically exceeds that of alanine transaminase (ALT), in both conditions.

- The combination of acute renal failure and liver disease with markedly increased transaminases in a chronic alcoholic should suggest the diagnosis of acetaminophen toxicity.

Treatment

- *1- N-acetylcysteine (NAC)*
- The mainstays of the therapy of APAP intoxication include gastric decontamination with activated charcoal and the administration of N-acetylcysteine (NAC)
- Activated charcoal avidly adsorbs APAP, reducing its absorption by 50 to 90%
- However, activated charcoal also adsorbs NAC and, by causing nausea and vomiting, may interfere with the administration of NAC
- NAC should optimally be given within 8 to 10 hours after ingestion
- More delayed therapy is associated with a progressive increase in hepatic toxicity although some benefit may still be seen 24 hours or later after ingestion

Treatment

- ***N-Acetylcysteine therapy***
- Prevents toxicity by limiting N-acetylimidoquinone (NAPQI) formation
- Increases capacity to detoxify formed NAPQI
- Improved oxygen delivery and utilization in extrahepatic organs
- Helps preserve cerebral blood flow, possibly due to mediation of microvascular tone

Treatment

NAC is indicated in:

- All patients with a serum APAP concentration above the possible hepatic toxicity line on the Rumack-Matthew nomogram
- Patients with an estimated ingestion of greater than 140 mg/kg
- Patients with an unknown time of ingestion
- Patients with a presentation more than 24 hours after ingestion with elevated transaminases

Treatment

- **NAC regimen is used in the United States**
  - A loading dose of 140 mg/kg in a 5 % solution is given either orally or via nasogastric tube
  - This is followed by 70 mg/kg every four hours for 17 doses; any doses vomited should be repeated

❑ **NAC complication**

- Orally : nausea, vomiting & diarrhea
- I.V : possibility of anaphylactic reaction

Treatment

2-GI decontamination

- Syrup of Ipecac
  - return usually 30-40% at best
  - best if used early (first 1-2 hours)

3-Gastric lavage

- Effectiveness diminishes with time

- *4-Activated charcoal*
  - Dose 50-100 Grams
- *5-Cathartic*
  - Utilized to speed transit time
- *6-Hemodialysis*
  - Limited benefit
  - Damage occurs quickly
- *7-Hemoperfusion*
  - No benefit
- *8-Peritoneal dialysis*
  - No benefit


THANK
YOU!