Pharmacology/Therapeutics II Block I Lectures – 2013-14

54. H2 Blocker, PPIs – Patel
55. Principles of Clinical Toxicology – Kennedy
56. Anti-Parasitic Agents – Johnson (To be posted later)
57. Palliation of Constipation & Nausea/vomiting – Kristopaitis (Lecture in Room 190)

Date: January 9, 2013: 10:30 a.m.
Reading Assignment: Katzung, *Basic and Clinical Pharmacology,* 11th Edition, pp. 1067-1077.

KEY CONCEPTS AND LEARNING OBJECTIVES

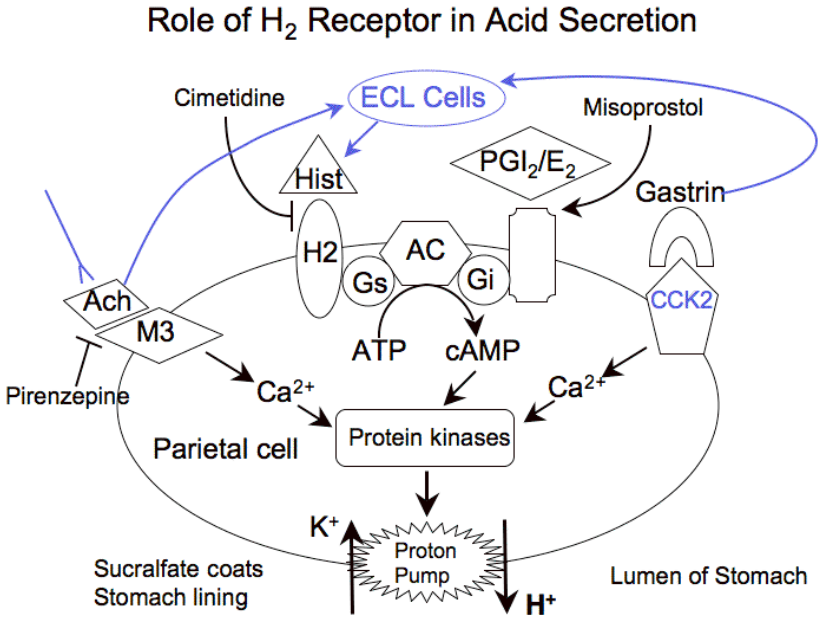
Histamine via its different receptors produces a number of physiological and pathological actions. Therefore, anti-histaminergic drugs may be used to treat different conditions.

1. To know the physiological functions of histamine.
2. To understand which histamine receptors mediate the different effects of histamine in stomach ulcers.
3. To know what stimuli cause the release of histamine and acid in stomach.
4. To know the types of histamine H_2 receptor antagonists that are available clinically.
5. To know the clinical uses of H_2 receptor antagonists.
6. To know the drug interactions associated with the use of H_2 receptor antagonists.
7. To understand the mechanism of action of PPIs
8. To know the adverse effects and drugs interactions with PPIs
9. To know the role of H. pylori in gastric ulceration
10. To know the drugs used to treat H. pylori infection

Drug List: See Summary Table Provided at end of handout.

Histamine H2 receptor antagonists and PPIs in the treatment of GI Ulcers:

The following section covers medicines used to treat ulcer. These medicines include H_2 receptor antagonists, proton pump inhibitors, mucosal protective agents and antibiotics (for treatment of *H. Pylori*).



A. H_2 Receptor Antagonists

These drugs reduce gastric acid secretion, and are used to treat peptic ulcer disease and gastric acid hypersecretion. These are remarkably safe drugs, and are now available over the counter.

The H_2 antagonists are available OTC:

1. Cimetidine (Tagamet®)
2. Famotidine (Pepcid®)
3. Nizatidine (Axid®)
4. Ranitidine (Zantac®)

All of these have different structures and, therefore, different side-effects.

The H_2 antagonists are rapidly and well absorbed after oral administration (bioavailability 50-90%). Peak plasma concentrations are reached in 1-2 hours, and the drugs have a $t_{1/2}$ of 1-3 hours.

H2 antagonists also inhibit stimulated (due to feeding, gastrin, hypoglycemia, vagal) acid secretion and are useful in controlling nocturnal acidity – useful when added to proton pump therapy to control "nocturnal acid breakthrough".

The H_2 receptor antagonists are mostly excreted unchanged by the kidney (renal function!).

However, the H_2 blockers undergo hepatic biotransformation, with cimetidine exhibiting the greatest hepatic metabolism. Because of the hepatic metabolism and renal excretion, H_2 receptor antagonists should be used with care (lower doses) in patients with hepatic and renal impairment. One last point is that a small number of men taking cimetidine (0.2%) develop gynecomastia due to decreased estrogen metabolism (Cyt P450 competition/inhibition) - In women galactorrhea.

B. Proton Pump Inhibitors

Proton Pump Inhibitors (PPI) irreversibly inhibit the gastric parietal cell proton pump H^+/K^+ ATPase.

Prodrugs – activated in acid environment – enter the parietal cells from the blood

The prolonged duration of anti-secretory action of PPI reflects irreversible inactivation by covalent modification, of the parietal cell H^+ ,K^+ -ATPase, rather than a prolonged serum half-life.

A single daily dose can effectively inhibit 95% of gastric acid secretion.

Because the PPI are so effective, they are the drug of choice for treating Zollinger-Ellison syndrome, which is a gastric acid secreting tumor and in Gastric esophageal reflux disease (GERD) when this is not responsive to H2 antagonists.

Ordinarily, H_2 antagonists should not be given simultaneously with PPI, because the antagonists reduce the efficacy of the PPI, and produce a less favorable outcome – but useful for nocturnal acidity control – see above.

The current proton pump inhibitors that are available are:

1. Omeprazole (Prilosec®)
2. Lansoprazole (Prevacid®)
3. Rabeprazole (Aciphex®)
4. Pantoprazole (Protonix®)
5. Esomeprazole (Nexium®)

Important Drug Interactions of PPIs:

PPIs are metabolized by Cyt P450 and, therefore, can decrease the metabolism and clearance of benzodiazepines (Diazepam), warfarin, phenytoin, etc.

PPIs reduce absorption of ketoconazole but increase absorption of digoxin.

New (12/10/13): Long term use of PPIs may cause Vit B12 deficiency – acidic

environment required for B12 absorption!

Adverse Reactions of PPIs:

Few (<3% of patients) and generally mild

Include diarreah, headache, drowsiness, muscle pain, and constipation.

C. Mucosal Protective Agents

Sucralfate (Carafate ®) is aluminum sucrose sulfate.

It is thought to polymerize and bind selectively to necrotic tissue, thereby creating a barrier between the gastric contents and the gastric mucosa.

Sucralfate is very effective for treating duodenal ulcers, and also suppresses H. Pylori (see below). For your information (but not required for memorization), Sucralfate is given 1g per dose QID on an empty stomach (1 hr before meals).

It is important to note that citric acid, such as that present in grapefruits, promotes absorption of the aluminum in sucralfate. This poses a problem for patients with renal failure who have an impaired ability to eliminate the aluminum.

Do not give with cimetidine/ranitidine but can be given 2h prior.

Colloidal Bismuth (Pepto-Bismol) also acts like sucralfate to bind necrotic tissue and creates a barrier.

D. Helicobacter Pylori

H. Pylori is present in only 0.3-0.5 % of the normal healthy population. H. Pylori is present in drinking water, although the mode of transmission has not been definitively proven. The presence of H. Pylori dramatically increases the risk that a patient will have a recurrent ulcer. Recurrence rates during the follow-up period range from 60% to 85% for patients with persisting *H. pylori* infection; in contrast, in most studies only 5% to 10% of patients without *H. pylori* show recurrence. Patients who had *H. Pylori* but were cured, have only a 5 – 10% rate of recurrence.

H. Pylori is treated by a combination therapy consisting of a PPI plus two of three antibiotics (clarithromycin, metronidazole, or amoxicillin). A 1 week treatment with this regimen produces a 90% cure rate for H. Pylori. If a PPI is used with a single antibiotic (typically clarithromycin), the patient must be treated for two weeks, and the cure rate is 10-20% lower.

Generic Name	Trade Name	Mechanism	T½ hrs	Elimination	Benefit
Cimetidine	Tagamet	H2 antagonist	1-3	Hepato-renal	Safe/OTC

Famotidine	Pepcid	H2 antagonist	1-3	Mainly Renal	Safe/OTC
Nizatidine	Axid	H2 antagonist	1-3	Mainly Renal	Safe/OTC
Ranitidine	Zantac	H2 antagonist	1-3	Mainly Renal	Safe/OTC
Omeprazole	Prilosec	Proton Pump Inhibitor	24	hepatic	+Effective
Lansoprazole	Prevacid	Proton Pump Inhibitor	24	hepatic	+Effective
Rabeprazole	Aciphex	Proton Pump Inhibitor	24	hepatic	+Effective
Carafate	Sulcralfate	Mucosal Protective Agent	6		

OTC = over the counter medication

BBB = reduced transfer across the blood brain barrier

+Effective = more effective than the H2 antagonists (which are already quite effective!!).

SUMMARY REVIEW TABLE FOR LECTURE

Drug	Classification	Biochemical mechanism of anti-asthmatic action	Routes of administration	Type of therapeutic use	Contraindications	Major side effects	Comments
Cimetidine (Tagamet®)	Histamine **H2 receptor** antagonist	Blocks histamine H2 receptors and decreases gastric acid secretion	1. Oral 2. i.v. 3. injection	1. duodenal ulcers 2. gastric ulcers 3. erosive gastroesophageal reflux disease (GERD) 4. Prevention of upper GI bleeding 5. hypersecretory conditions (Zollinger-Ellison Syndrome)		Gynecomastia with long-term use and in some incidences impotence	1. i.v. bolus reported to cause cardiac arrythmias and hypotension (although rare). 2. H2 antagonists can be added to PPIs to stop nocturnal acid breakthrough - BUT may decrease efficacy of PPIs
Ranitidine (Zantac®)	Histamine **H2 receptor** antagonist	Blocks histamine H2 receptors and decreases gastric acid secretion	1. Oral 2. i.v.	Same as Cimetidine		Rare but include agitation, anemia, confusion and depression	1. May increase risk of developing pneumonia 2. H2 antagonists can be added to PPIs to stop nocturnal acid breakthrough. – BUT may decrease efficacy of PPIs
Omeprazole	**PPI**	1. Inhibits H^+/K^+ pump (proton pump) in the gastric parietal cells	1. Oral	1. Zollinger-Ellison Syndrome 2. GERD 3. short term treatment of duodenal ulcers. 4. Rx of H. Pylori in combination with Antibiotics	1. Can increase concentrations of **diazepam, warfarin, and phenytoin** by decreasing their clearance by the liver. 2. PPIs can reduce absorption of **ketoconazole** and increase absorption of **digoxin.**	Diarrhea, nausea, skin rash, dizziness	Not normally used with H2 antagonists – reduced efficacy of PPIs. **NEW:** long term use may cause Vit B12 deficiency
Rabeprazole	**PPI**	1. Inhibits H^+/K^+ pump (proton pump) in the gastric parietal cells	1. Oral	Same as Omeprazole	Same as for Omeprazole	Headache	Not normally used with H2 antagonists – reduced efficacy of PPIs. **NEW:** long term use may cause Vit B12 deficiency
Sucralfate (Carafate®)	**Mucosal Protective agent**	1. binds selectively to necrotic tissue to form a barrier against gastric acid.	1. Oral	1. Duodenal Ulcers 2. suppresses H. pylori infection	1. Can decrease absorption of cimetidine, ciprofloxacin, digoxin, ofloxacin, ranitidine if given simultaneously with Sucralfate. 2. Grapefruit promotes absorption of Al in sucralfate – problem in patients with renal insufficiency/failure.	Minor: Constipation, flatulence, dry mouth, diarhhea, nausea	Colloidal Bismuth works in same manner as Sucralfate.

PRINCIPLES OF CLINICAL TOXICOLOGY

Date: January 16, 2014 – 10:30 AM
Reading Assignment: none

KEY CONCEPTS AND LEARNING OBJECTIVES

At the end of this lecture the learner will be able to:

1. Define toxicology and the dose-response relationships which describe toxicological effects;

2. Describe the types of toxic agents and routes of exposure;

3. Describe the organ systems commonly affected by toxic agents;

4. List the ratings for teratogenicity;

5. Describe the general diagnostic and treatment strategies for acutely poisoned patients; and

6. Describe common toxic syndromes.

PRINCIPLES OF CLINICAL TOXICOLOGY

I. Definition: Toxicology is the study of the adverse effects of chemicals on living organisms.

II. Introduction

A. Major toxic endpoints
1. Organ toxicity (hepatotoxicity, neurotoxicity)
2. Carcinogenesis and mutagenesis
3. Developmental toxicology or teratogenicity

B. Types of toxic substances
1. Drugs
2. Food additives
3. Industrial chemicals (benzene)
4. Environmental pollutants (dioxin)
5. Natural toxins (aflatoxin)
6. Household poisons (insecticides)
7. Nerve gases (soman)
8. Bioterroristic (select) agents (anthrax)

C. Major routes of exposure
1. Oral
2. Inhalation (solvents, gases)
3. Dermal (pesticides)

D. Types of exposures
1. Intentional ingestion/suicide ("sleeping pills")
2. Occupational exposure (farmers, industrial hazards)
3. Environmental exposure (ozone, food contaminants)
4. Accidental poisoning (drugs, pesticides, household products)
5. Terrorism

E. Length of exposure
1. Acute - single dose, usually large
2. Chronic - long term

III. Dose-response relationship - All substances are poisons at a high enough dose

A. Dose-response – Within a population, the relationship defining the proportion of individuals responding to a given dose. For example, the number of mortalities increases as a function of dose. This may be affected by:
1. Route of exposure
2. Biotransformation
3. Health and nutritional state of the individual
4. Age (childhood, senescent)

5. Genetics

B. LD_{50} – The dose of a substance that kills 50% of subjects (animals)

C. Comparison of LD_{50} values for various toxic compounds in experimental animals.

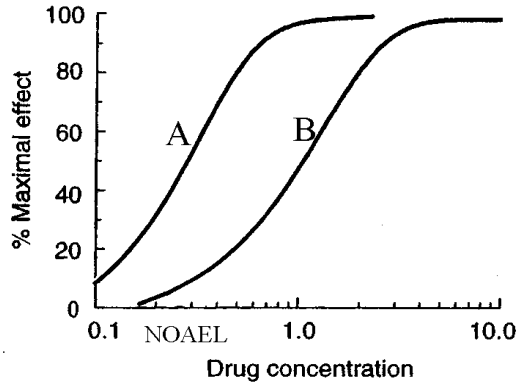
Compound	LD_{50} (mg/kg)
Ethanol	10,000
DDT	100
Nicotine	1
Tetrodotoxin	0.1
Botulinus toxin	0.00001

D. For drugs, ED_{50} is the dose required to achieve a half-maximal effect. TD_{50} is the dose required to achieve 50% toxicity (e.g. liver toxicity). Toxic actions may or may not be extensions of the therapeutic action of drugs.

D. The Therapeutic Index (margin of safety) is calculated by dividing $LD_{50,}$ or $TD_{50,}$ by ED_{50}. For acetaminophen the margin of safety is about 10; for digitalis it can be as low as 2.

E. Threshold Dose - the dose below which some compounds are considered to be non-toxic. This is also called the No Observed Adverse Effect Level (NOAEL) and is determined in animals using the most sensitive species.

F. Dose-response curves illustrating NOAEL:



In the figure above, Compound A produces a toxic response at all doses; compound B shows a NOAEL below which the compound is safe. Most carcinogenic chemicals are believed to be similar to A. Most clinically available drugs have a dose-response similar to B. The therapeutic dose is considered safe, but an overdose dose may be toxic.

G. Acceptable Daily Limit (ADL) is used to determine the safe level of additives and contaminants (pesticides, veterinary drugs) in food. The ADL is usually some factor such as 1/100 to 1/1000 of the NOAEL.

H. Threshold Limit Value (TLV) and Permissible Exposure Limit (PEL), also determined from NOAEL, are important in regulating industrial exposure to toxic chemicals.

IV. Toxicological End Points

A. Organ System Toxicity

1. Blood
   a. Chemical-induced hypoxia (CO)
   b. Aplastic anemia (chloramphenicol)

2. Immune System Toxicity
   a. Immunosuppression (cyclophosphamide, cigarette smoke)
   b. Hypersensitivity reactions (penicillin)

3. Liver Toxicity
   a. Hepatocyte death (acetaminophen, carbon tetrachloride)
   b. Cirrhosis (ethanol)

4. Kidney Toxicity
   a. Tubular necrosis (heavy metals, cisplatin)
   b. Papillary necrosis (NSAIDs)

5. Respiratory Toxicity
   a. Fibrosis (chronic) – ozone, asbestos
   b. Emphysema (chronic) – tobacco smoking

6. Neurotoxicity
   a. Neuropathies (methylmercury, trimethyltin)
   b. Myelinopathies (hexachlorophene, lead)

7. Skin Toxicity
   a. Contact dermatitis (phenols)
   b. Phototoxicity/photosensitivity (tetracyclines, sulfonamides)

8. Other sites of toxicities
   a. Heart (doxorubicin)
   b. Male reproductive system (high dose androgens)
   c. Female reproductive system (endocrine disrupters)
   d. Eye (organophosphates cause cataracts)

B. Chemical Carcinogenesis – A major cause of cancer. Basic tenet - the chemical becomes adducted to DNA covalently → misreading of DNA in daughter cells → a mutagenic event that initiates a series of changes leading to cancer. Alkylating agents may directly modify DNA by covalent interaction; most chemical carcinogens are metabolically activated to

reactive metabolites. Some chemicals may modify DNA by formation of reactive oxygen species that modify DNA by oxidization.

1. Examples of chemicals that cause cancer and are metabolized to DNA adducts
    a. Aromatic amines (amino acid pyrolysis products from cooking meat; 4-aminobiphenyl from cigarette smoke)
    b. Nitrosamines (N-nitrosonicotine from cigarette smoke; nitrosamines formed from sodium nitrite in preserved meat)
    c. Polycyclic aromatic hydrocarbons (in burned meat, cigarette smoke)
    d. Aflatoxin (from *Aspergillus flavus* mold growing on grains)

2. Alkylating agents
    a. Cyclophosphamide
    b. Melphalan
    c. Nitrogen mustard (mechlorethamine)

C. Tetratogenicity – the study of congenital defects

1. The FDA has assigned risk factors to drugs based on the level of risk they pose to the fetus.
    a. Category A – Studies in women during the first trimester are negative.
    b. Category B – Either animal studies have not demonstrated a risk and studies in women are not available; or an adverse effect seen in animals was not confirmed in a human trial in the first trimester.
    c. Category C – Either animal studies revealed adverse fetal effects with no verification from human studies; or studies in women and animals are not available. Drugs should be given only if the potential benefit justifies the potential risk to the fetus.
    d. Category D – There is positive evidence of human risk, but the benefits to the woman may be acceptable in a life threatening or serious disorder for which safer drugs are not available.
    e. Category X – Animal and human data reveal fetal impacts or there is evidence of fetal risk based on human experience or both, and the risk of the drug clearly outweighs any possible benefit. The drug is contraindicated in women who are or who may become pregnant.

2. Examples of drugs and chemicals known to be teratogenic – thalidomide, tetracycline, cyclophosphamide, phenytoin, cocaine, ethanol

V. Acute Treatment of the Poisoned Patient

A. Introduction

1. Acute poisonings are common in the emergency department.
2. Patients most often present with signs and symptoms, not firm diagnoses.

3. It is important to determine if intoxication represents a suicide attempt, an accident or a failed homicide as psychiatric care or police intervention may be required.
4. A patient may be unwilling or unable to relate the quantity, identity, exposure route, or dosing time of the agent. Thus, supportive care is often the mainstay of management unless a toxicological syndrome that has an antidote is present.
5. There are far more potential poisons than anyone can appreciate, much less manage. Familiarize yourself with regional poison control and drug information centers.
6. Emergency management takes first priority; may proceed simultaneously with H&P, laboratory testing, decontamination, antidote administration and toxicant removal.

B. Emergency Management (ABCD's – airway, breathing, circulation, dextrose)

1. Most common causes of death due to acute poisoning – airway obstruction, aspiration, respiratory arrest, hypotension (circulating volume, cardiac contractility/rhythm, or vasodilation), cellular hypoxia, hyperthermia, and seizures.
2. Initial considerations include ensuring adequate airway, cervical spine protection, ventilation and circulation/perfusion.
3. In any compromised patient, it is appropriate to administer oxygen, monitor cardiac rhythm and establish IV access. Before beginning infusion, baseline blood work should be drawn along with extra tubes for additional testing.
4. In some ER's patients with altered mental status immediately receive thiamine (Wernicke's syndrome) and glucose. When a patient with a depressed sensorium does not respond to glucose, it may be followed by IV naloxone. It is unnecessary to administer glucose if blood levels are within an acceptable range.

C. History and Physical Examination

1. History
   a. If possible after stabilization, identify the poison, and question the patient, paramedics and family for exposure details/past medical history.
   b. After industrial accidents or fires, determine what the patient was doing immediately prior to becoming ill (e.g. was he/she trapped in a smoke-filled room?)
2. Physical Examination
   a. Physical examination is important, particularly in the absence of reliable history; it may provide the only clues for substance identification. Occasionally, injury patterns or toxic syndromes are identified that are characteristic of particular categories of poisons, thus permitting specific as opposed to supportive therapy.
   b. Especially important
      i. Vital signs –blood pressure, heart rate, respiration, and temperature.
      ii. Eyes – pupil size, nystagmus, ophthalmoplegia.
      iii. Mouth – corrosive burns, odors, dry mouth.
      iv. Skin – flushed, hot, dry, sweating, cyanotic.
      v. Abdomen – ileus, hyperactive bowel sounds.
      vi. Nervous system – seizures, ataxia, twitching.

c. *Cholinergic or Anticholinesterase Syndrome* – organophosphate and carbamate insecticides.
   i. Peripheral effects arise from muscarinic and nicotinic receptor stimulation. Muscarinic - sweating, pupillary constriction, lacrimation, sialorrhea, wheezing, abdominal cramps, vomiting, diarrhea, bradycardia, hypotension, blurred vision and urinary incontinence. Nicotinic - fasiculations, cramps, weakness, paralysis, and respiratory compromise.
   ii. Central effects such as anxiety, restlessness, seizures, coma, areflexia and altered respiratory patterns are less specific than peripheral signs.

c. *Anticholinergic Syndrome* - atropine, scopolamine, tricyclic antidepressants, antihistamines, jimson weed
   i. Peripheral effects – dry mouth, dysphagia, blurred vision, pupillary dilation, tachycardia, hyperthermia, dry skin, flushing, abdominal distention, urinary retention.
   ii. Central effects - lethargy, excitement, seizures, confusion, delirium, hallucinations, coma, ataxia, respiratory failure (again nonspecific).

d. *Hemoglobinopathy syndromes* - can cause hypoxia, headache, disorientation, coma, nausea, vomiting, cardiac dysfunction, acidosis and death.
   i. Carboxyhemoglobinemia is more common – from inhalation of excessive CO or follows absorption of methylene chloride, a solvent metabolized to CO; does not cause <u>early</u> cyanosis despite the production of severe hypoxia.
   ii. Methemoglobinemia - when ferrous (+2) iron of hemoglobin is oxidized to the ferric (+3) state; usually does not require treatment until present in excess of 30%. Cyanosis observed.

e. *Narcotic Overdose* - classically presents with pinpoint pupils, respiratory depression and hypotension; rarely, CNS excitation occurs as well as pupillary dilatation. Heroin, oxycodone, morphine and meperidine are common offenders. IV naloxone often produces prompt improvement; may precipitate withdrawal.

f. *Sympathomimetic Excess* - manifested as nervousness, agitation, tremor, diaphoresis/dehydration with time, CNS excitation, hypertension, tachycardia, and seizures.

g. *Withdrawal Syndrome* - suspected in anxious individuals displaying drug-seeking behavior.
   i. Physical signs of opiate withdrawal - mydriasis, piloerection, rhinorrhea and lacrimation. Excluding neonates, opiate withdrawal is not associated with seizures.
   ii. Withdrawal of many kinds of non-opiate CNS depressants may lead to hallucinations, tachycardia, hyperpyrexia and seizures.

D. Common Signs - certain major toxic signs frequently appear that are sometimes valuable in narrowing the spectrum of causative agents. They are managed as they are identified and may or may not be part of a toxic syndrome. Examples:

1. Cardiac conduction and rhythm problems - should be evaluated in any poisoned patient; mandatory for all but trivial ingestions. Although there are no pathognomonic patterns, some are suggestive. A few examples follow:

a. AV block - digitalis glycosides
b. Sinus bradycardia - digitalis, beta-blockers, calcium channel blockers and cholinergic toxicants.
c. Sinus tachycardia - many types of poisoning and non-toxicological conditions; nonspecific.

2. Metabolic acidosis - an important and moderately specific sign; often seen in overdoses with aspirin, methanol and ethylene glycol. Many metabolic abnormalities can accompany or simulate intoxication such as diabetic ketoacidosis, lactic acidosis, or uremia.
3. Gastrointestinal dysfunction - ranges in severity from abdominal cramping, nausea and vomiting in mild cholinergic syndrome to bloody diarrhea after iron poisoning; minimally specific.
4. Seizures - complicate many intoxications, withdrawals, structural lesions and CNS infections. Supportive care, anticonvulsants, and correction of underlying abnormalities are the mainstays of treatment. Diazepam and lorazepam are useful to achieve acute control; phenobarbital for longer term management. Phenytoin is not a good choice for seizures secondary to intoxications.

E. Laboratory Studies

1. Baseline tests in non-trivial cases should usually include electrolytes (with anion gap), BUN and creatinine, glucose, arterial blood gases, liver function tests, EKG and occasionally specific X-rays.
2. Toxicology screens may be of value in management, but delays in obtaining results limit their utility. "Screening for everything" is impossible, and it is impractical to screen for substances that are likely irrelevant. May be useful when selecting treatment options, antidotes, etc.
3. Serum levels are important in ethanol, lithium, theophylline, digoxin, acetaminophen and aspirin overdoses as well as in methanol and ethylene glycol ingestions. However, other levels such as tricyclic antidepressant concentrations are of lesser value; they rarely alter acute management.
4. X-rays may reveal features such as pulmonary edema, aspiration pneumonia, radiopaque agents and intra-intestinal drug packages. CT with head trauma.

F. Removal and Deactivation of Absorbed Agents - removal of unabsorbed agents from the eyes, skin and gut should proceed as soon as possible after initial stabilization.

1. Decontamination
   a. Eyes - immediate irrigation is the best initial move, especially with caustic agents.
   b. Skin - a shower works well for most exposures. Bag clothing.
   c. Gut - the best technique for GI decontamination remains a matter of debate. “Reflex” use of syrup of ipecac, charcoal, lavage or whole bowel irrigation may complicate the situation. The decision to decontaminate the gut and the technique selected are individualized for each patient; most ingested materials will likely be out of the stomach within approximately one hour.

i. Vomiting induced by syrup of ipecac has many limitations. An alert patient who has not ingested a caustic material, sharps, a petroleum distillate or an agent that produces seizures may be a candidate for this technique; best suited for use in the home under the direction of a poison center.
ii. Gastric lavage may help empty the stomach even in a comatose patient unless ingested particles are too large; may be difficult in children due to size and cooperation. If there is any question about the adequacy of the gag reflex, tracheal intubation must precede lavage. Lavage is generally contraindicated in caustic ingestions.
iii. Activated charcoal is often used to treat ingestions of adsorbable material. As charcoal is constipating and may cause bowel obstruction, most clinicians administer with sorbitol or a saline cathartic. Castor oil or mineral oil is not used because of risk of aspiration. Cathartics are not used with corrosive agents; they may increase the injury.
iiii. Whole bowel irrigation with solutions such as Go Lytely may be used in stable, cooperative patients who have ingested sustained release preparations, etc.

2. Deactivation/Dilution
   a. A few toxicants may be neutralized by other agents – e.g. ingested iodine can be complexed by starch lavage.
   a. Dilution is fine for cutaneous and ocular exposures. Its use in ingestions of anything aside from caustics may be contraindicated; it may enhance both aspiration risk and absorption. If required for oral poison, water is usually the best choice in limited quantities (distention may cause gastric emptying)

G. Antidotes – specific antidotes exist for a few poisons. Several important examples follow:

1. Deferoxamine for iron
2. Acetylcysteine for acetaminophen
3. 2-PAM chloride and atropine for organophosphates
4. Amyl nitrite, sodium nitrite and sodium thiosulfate for cyanide
5. Naloxone for opiates
6. Atropine for carbamates
7. Physostigmine for anticholinergic poisoning
8. Ethanol for methanol and ethylene glycol
9. Oxygen for carbon monoxide
10. Digitalis antibodies
11. Flumazenil for benzodiazepines

H. Elimination of Absorbed Substances - always desirable in theory but not always practical or possible. Some available modalities include repeated doses of charcoal, forced diuresis (mannitol or furosemide; questioned by some), ion trapping in urine, hemodialysis (peritoneal dialysis), and hemoperfusion. There are at least five indications for these methods.

1. Severe poisoning syndromes that do not respond to supportive therapy – e.g. refractory hypotension, seizures or arrhythmias.
2. Deterioration despite full supportive care.
3. Overwhelming dose of a chemical that the body cannot handle estimated on the basis of history or levels (methanol ingestion)
4. Impairment of normal excretory routes (aspirin overdose in an individual with chronic renal failure)
5. Severe disease that precludes tolerance of supportive care (congestive heart failure suggests an individual can not handle the fluid load associated the alkaline diuresis used to treat aspirin overdose)

Pharmacologic Palliation of Constipation & Nausea/Vomiting

I. A goal of palliative care is to relieve the suffering of patients.
Control of pain and other physical symptoms, as well as psychological, social and spiritual problems is paramount.

II. The most common symptoms experienced by patients with serious and advanced diseases include
- A. Asthenia
- B. Anorexia
- C. Pain
- **D. Nausea**
- **E. Constipation**
- F. Sedation/Confusion
- G. Dyspnea

III. Pharmacologic Palliation of Constipation

A. BULKING AGENTS

Agents
- Dietary fiber (bran)
- Psyllium (Metamucil)

Mechanisms of Action
- Bulk-forming laxatives cause retention of fluid and an increase in fecal mass, resulting in stimulation of peristalsis.
- They usually have an effect within 12 to 24 hours and reach a maximum after several days

Side Effects
Flatulence

Contraindications
In debilitated patients who cannot drink adequate fluid (1.5 – 2 liters/day) could result in fecal impaction, intestinal obstruction

B. OSMOTIC LAXATIVES

These are soluble but nonabsorbable compounds that result in increased stool liquidity due to an obligate increase in fecal fluid**.**

- **Nonabsorbable sugars**

Agents
- Lactulose
- Sorbitol

Mechanism of Action
Lactulose is a synthetic disaccharide. Bacteria in the colon degrade lactulose into lactic acid, acetic acid and formic acid resulting in an increase in osmotic pressure and acidification of intestinal contents which in turn, softens the stool by promoting stool water content

Side Effects
- Bloating, cramps, flatulence
- Very sweet – may be difficult for patients to tolerate
- Can worsen dehydration by drawing body water into the bowel lumen

Saline and magnesium salt laxatives

Agents
- Magnesium citrate
- Magnesium hydroxide (Milk of Magnesia)
- Sodium Phosphate (Fleets Phospho-Soda)

Mechanism of Action
- Saline laxatives have an osmotic effect causing increased intraluminal volume that acts as a stimulus for intestinal motility.
- Laxatives that contain magnesium have been shown to release cholecystokinin that causes intraluminal accumulation of fluid and electrolytes and promotes small bowel and possibly even colonic transit.
- Rapid movement of water into distal small bowel and colon leads to high volume of liquid stool.
- High doses produce bowel evacuation in 1-3 hours.

Side Effects/Contraindications
- Contraindicated in any form of bowel obstruction
- Can produce dehydration without adequate fluid replacement
- Because the ions can be partially absorbed, laxatives containing magnesium and phosphorous are contraindicated in patients with impaired renal function
- Avoid sodium phosphate-containing formulations in patients with congestive heart failure, liver failure – severe electrolyte abnormalities can occur.
- Rare reports of ischemic colits with magnesium citrate and sodium phosphate thought secondary to a rapid fluid shift from the intravascular compartment to the gut lumen resulting in transient colonic hypoperfusion and ischemia

Clinical Indications
- Magnesium citrate and sodium phosphate indicated for bowel cleansing in preparing patients for surgery or the colon for x-ray or endoscopy
- Magnesium hydroxide is indicated for relief of constipation

- **Polyethylene Glycol**

Trade names
Constipation - Miralax, GlycoLax
Bowel Cleanser - Colyte, Golytely

Mechanism of Action:
- Polyethylene glycol is an osmotic agent that causes retention of water in the stool resulting in a softer stool and more frequent bowel movements.
- It appears to have no effect on active absorption or secretion of glucose or electrolytes
- No significant intravascular fluid or electrolyte shifts occur

Side Effects
Minimal

Clinical Indications
- Large volume (ie 4 liters) ingested rapidly causes rapid evacuation for bowel cleansing before endoscopy
- Smaller daily doses can be used for constipation.

C. STIMULANT LAXATIVES

Agents:
- Senna
- Bisacodyl (Dulcolax)

Mechanism of Action:
- Bisacodyl is a contact laxative that acts on the large intestine to produce strong but brief peristaltic movements. This agent stimulates sensory nerve endings to produce parasympathetic reflexes that results in peristalsis of the colon. Local axon reflexes and segmental reflexes are stimulated, which produces widespread peristalsis of the colon.
- Senna undergoes conversion to active metabolites in the colon that stimulate the myenteric plexus and induce net fluid secretion.
- Response in 6-12 up to 24 hours.

Side Effects
- Electrolyte abnormalities depending on volume of stool
- Melanosis coli – brown pigmentation of the colon

Clinical Indication
Relief of constipation

D. DETERGENT LAXATIVES

Agent

Docusate (Colace)

Mechanism of Action

- Docusate is an anionic surfactant that is believed to stimulate intestinal secretion and increase the penetration of fluid into the stool by emulsifying feces, water, and fat
- Soft feces = easier passage
- Minimal effect on peristalsis
- Initial response in 1-3 days

Clinical Indications

Docusate is used to soften or prevent the formation of hard stools.

E. LUBRICANTS

Agents

- Glycerin suppository/enema
- Mineral oil enema

Mechanism of Action

- Due to its osmotic effect, glycerin softens, lubricates, and facilitates the elimination of inspissated feces. By serving as a bowel irritant it may also stimulate rectal contractions.
- Mineral oil helps soften (by coating fecal material with mineral oil) and lubricate hard stools, easing their passage without irritating the mucosa.
- Lubricants may stimulate a response within 30 minutes.

Side effects/contraindications

Mineral oil should **never be administered orally**, particularly to debilitated patients - inhalation/aspiration of the oil can lead to lipoid pneumonitis**.**

Clinical Indications

Usually reserved for treatment of fecal impaction

F. LARGE VOLUME ENEMAS

Agents

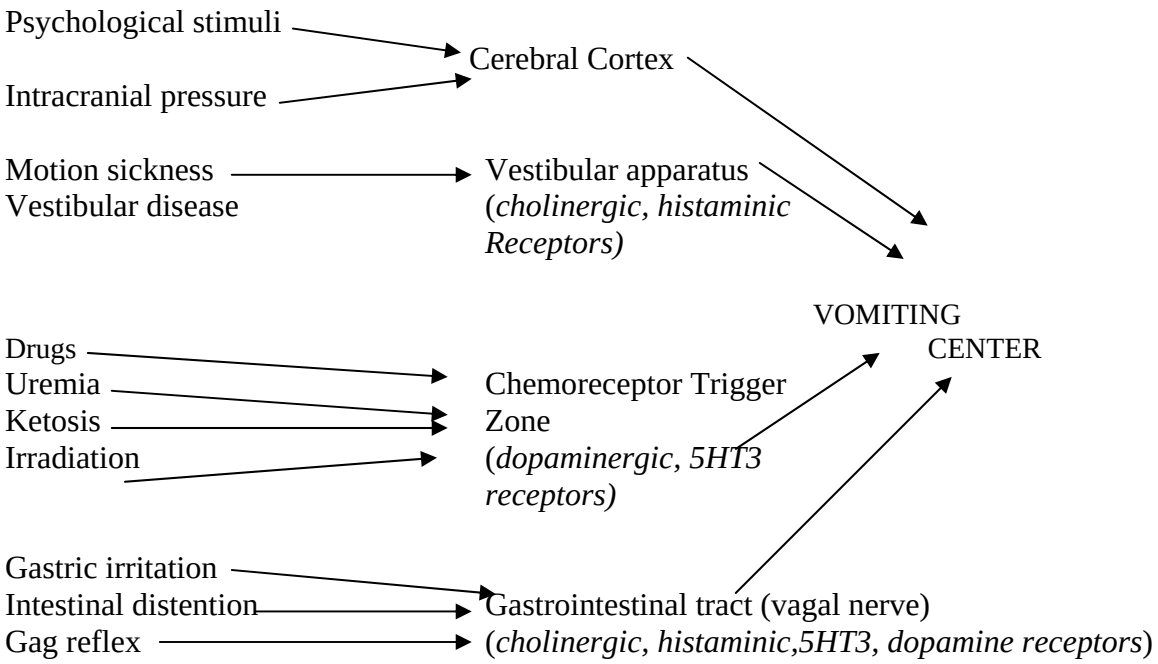
Sodium phosphate enema (Fleet's enema)

Mechanism of Action
Soften stool by increasing water content
Distend distal colon inducing peristalsis

Clinical Indications
Usually reserved for treatment of fecal impaction

IV. Pharmacologic Palliation of Nausea and Vomiting

A. Pathophysiology of nausea and vomiting



Chemoreceptor trigger zone is located in the area postrema outside the blood brain barrier
Vomiting Center is located in the lateral reticular formation of the medulla and coordinates the motor mechanisms of vomiting

B. Antiemetic Drugs
Dopamine receptor antagonists
Phenothiazines - **Prochlorperazine (Compazine)**
Butyrophenones - Haloperidol (Haldol)
Benzamides – Metoclopramide (Reglan)

Serotonin (5HT3) antagonists
Ondansetron (Zofran)
Granisetron (Kytril)

Antihistamines
Promethazine (Phergan)
Diphenhydramine

Anticholinergics
Scopolamine

Corticosteroids
Dexamethasone

Benzodiazepenes
Lorazepam
Alprazolam

C. Select Antiemetics

- **Agent -** Metoclopramide (Reglan)

Mechanism of Action

- Antiemetic properties are due to central and peripheral dopamine receptor inhibition
- Within the gastrointestinal tract activation of dopamine receptors inhibits cholinergic smooth muscle stimulation; blockade of this effect is believed to be the primary prokinetic mechanism of action of metoclopramide. Metoclopramide increases esophageal peristaltic amplitude, increase lower esophageal sphincter pressure, and enhance gastric emptying but has no effect on small intestine or colonic motility

Adverse Effects

- Extrapyramidal effects, such as dystonia, akathisia, parkinsonism, may develop due to central dopamine receptor blockade.
- Acute dystonic reactions, such as trismus, torticollis, facial spasms, can be treated with an anticholinergic agent (benztropine or diphenhydramine).
- Cautious use in patients with Parkinson's Disease

Clinical Indications

- Vomiting due to dysmotility of the upper GI tract - gastric stasis and diabetic gastroparesis
- Chemotherapy induced nausea and vomiting

- **Agent -** Prochlorperazine (Compazine)

  Mechanisms of Action
  - Prochlorperazine acts centrally by inhibiting the dopamine receptors in the medullary chemoreceptor trigger zone
  - It peripherally blocks the vagus nerve in the gastrointestinal tract

  Adverse Effects
  Extrapyramidal effects, dystonic reactions

  Clinical Indications
  - Opioid related nausea and vomiting
  - Moderately effective for nausea caused by various GI disorders (ie gastroenteritis)

- **Agent -** Promethazine (Phenergan)

  Mechanism of Action
  Antiemetic effects come from its H(1) receptor blocking properties.

  Adverse Effects
  Sedation

  Clinical Indications
  Promethazine is effective in the active and prophylactic treatment of motion sickness

- **Agent -** Ondansetron (Zofran); Granisetron (Kytril)

  Mechanism of Action

  - Ondansetron is a competitive, highly selective antagonist of 5-hydroxytryptamine (serotonin) subtype 3 (5-HT 3) receptors. 5-HT 3 receptors are present peripherally on vagal nerve terminals and centrally in the area postrema of the brain. It is not certain whether ondansetron's action is mediated peripherally, centrally, or both. Cytotoxic drugs and radiation appear to damage gastrointestinal mucosa, causing the release of serotonin from the enterochromaffin cells of the gastrointestinal tract. Stimulation of 5-HT 3 receptors causes transmission of sensory signals to the vomiting center via vagal afferent fibers to induce vomiting. By binding to 5-HT 3 receptors, ondansetron blocks vomiting mediated by serotonin release.

Side Effects
Most common side effect is headache
Small but statistically significant prolongation of the QT interval.

Clinical Indications
- Chemotherapy induced nausea and vomiting and its prophylaxis
- Radiation induced nausea and vomiting and its prophylaxis

- **Agent** Scopolamine

Mechanism of Action
Pure anticholinergic agent

Adverse Effects
- *Dry mouth (xerostomia)
- Acute narrow angle glaucoma (contraindicated in patients with known glaucoma)
- Urinary retention
- Confusion

Clinical Indications
- Treatment of motion sickness
- *In patients who are hours to days from death and who can an no longer swallow their own secretions, it is used to decrease production of saliva