Inorganic pharmaceutical chemistry

Protectives-adsorbents & Cathartics

Lecture six

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Protectives and Adsorbents

- This group of gastrointestinal agents is commonly used for the treatment of mild diarrhea.
- Diarrhea may be acute or chronic.
- Acute diarrhea can be caused by bacterial toxins, chemical poisons, drugs, allergy and disease.
- Chronic diarrhea can result from gastrointestinal surgery, carcinomas, chronic inflammatory conditions and various absorptive defects.

- The antidiarrheal agents will only treat the symptoms and occasionally the cause, but they will not treat the complications.
- Most products for the treatment of diarrhea will consist of an **adsorbent-protective**, an **anti spasmodic**, and possibly an **antibacterial agent**.
- The adsorbent-protectives adsorb toxins, bacteria, and viruses along with providing a protective coating of the intestinal mucosa. They include **bismuth salts**, **special clays**, and **activated charcoal**.

Bismuth-Containing Products:

- Although the bismuth salts used as anti diarrheals are considered to be water insoluble, a small amount does go into solution.
- The soluble bismuth cation exerts a mild astringent and antiseptic action but it is doubtful whether this is clinically significant.
- Intestinal hydrogen sulfide acts upon the bismuth salts to form bismuth sulfide; hence, the black stools resulting from the oral administration of bismuth-containing preparations.

Bismuth Subnitrate:

- It is practically insoluble in water and in a1cohol but is readily dissolved by hydrochloric or nitric acid.
- It is assayed in terms of bismutth trioxide (Bi_2O_3).
- Bismuth subnitrate apparently can inhibit pepsin, However, its main use is as a component of Milk of Bismuth, where it probably functions as a mild astringent-protective.

Milk of Bismuth:

- It contains bismuth hydroxide and bismuth sub-carbonate as suspension in water.

- It is made by converting bismuth sub-nitrate to bismuth nitrate [$Bi(NO_3)_3$] by the addition of nitric acid, then, by treatment with ammonium carbonate and ammonia solution, bismuth nitrate is converted to bismuth hydroxide and bismuth sub-carbonate.

Bismuth Sub-carbonate$[(BiO)_2CO_3]_2.H_2O$

- It is practically insoluble in water and in alcohol but dissolves completely in nitric acid and in hydrochloric acid.

- Found in milk of bismuth.

Non official Bismuth Compounds

- Bismuth Subgallate.
- Bismuth Subsalicylate.
- Bismuth Ammonium Citrate.

Activated Clays and Other Adsorbents

1. Kaolin

- It is usually found together with the vegetable carbohydrate & pectin and used as an adsorbent.
- Kaolin-containing products have been reported to interfere with the intestinal absorption of lincomycin.

2. Activated Charcoal.

- It has been used as an adsorbent in the treatment of diarrhea.
- It is now a recommended antidote in certain types of poisoning.

Saline Cathartics

- They are agents that increase evacuation from the bowels, while laxatives are mild cathartics.
- Laxatives should only be used for short term therapy, as prolonged use may lead to loss of spontaneous bowel rhythm upon which normal evacuation depends, causing the patient to become dependent on laxatives, the so-called "laxative habit"

Drug evaluations states that cathartics are properly used :

(1) To ease defecation in patients with painful hemorrhoids or other rectal disorders.

(2) To avoid potentially hazardous rises in blood pressure during defecation in patients with hypertension, cerebral, coronary, or other arterial diseases.

(3) To relieve acute constipation.

(4) To remove solid material from the intestinal tract.

Basically there are four types of laxatives:

(1) stimulant.

(2) bulk-forming.

(3) emollient.

(4) saline.

The stimulant laxatives

- They act by local irritation of the intestinal tract, which increases peristaltic activity.
- Examples of this group are, cascara extract, castor oil and bisacodyl, etc.

The bulk-forming laxatives

- They are made from cellulose and other non digestible polysaccharides.
- They swell when wet, with the increased bulk they'll stimulating peristalsis.
- Examples of this group are methyl cellulose, and sodium carboxy methyl cellulose, psyllium seed, etc.

The emollient laxatives

- They act either as lubricants facilitating the passage of compacted fecal material or they act as stool softeners.
- Mineral oil is the main lubricant laxative used.

The saline cathartics

- They act by increasing the osmotic load of the gastrointestinal tract.
- They are salts of poorly absorbable anions and sometimes cations.
- The body relieves the hypertonicity of the gut by secreting additional fluids into the intestinal tract, the resulting increased bulk stimulates peristalsis.

- Poorly absorbed anions that are used as saline cathartics are biphosphate, phosphate, sulfate, and tartrate.
- Soluble magnesium salts are cathartic due to the poorly absorbed magnesium cation.
- The saline cathartics are water soluble and are taken with large amounts of water, this prevents excessive loss of body fluids and reduces nausea and vomiting.

- The saline cathartics, when taken for brief periods, are relatively free of side effects while over a longer term, patients on low sodium diets should not use the sodium containing saline cathartics (sodium biphosphate, sodium phosphate, sodium sulfate, and potassium sodium tartrate).
- For those with impaired renal function the magnesium salts should be restricted, since some magnesium cation is absorbed.

Official Saline Cathartics

- Sodium Biphosphate.
- Sodium Phosphate.
- Dried Sodium Phosphate.
- Potassium Sodium Tartrate.
- Magnesium Hydroxide.
- Magnesium citrate solution.
- Magnesium sulfate.

Non Official Saline Cathartics

- Sodium sulfate.
- Potassium phosphate.
- Potassium bitartrate.
- Calomel.

Topical agents

Definition

- Chemical agents applied to the skin and mucous membranes for localized effects within the skin or membrane are topical drugs.

- These include antibiotics, antiseptic, corticosteroids, antineoplastics, local anesthetics etc.

- Locally acting topical agents have limited chemical and pharmacological activity generally have a physical basis of action.

Classification

Topical agents can be broadly classified into three categories based on their usual action or use:

1. Protectives.
2. Antimicrobial.
3. Astringent compounds.

It may also be noted that there is a tremendous amount of overlapping between categories.

The particular use will depend on:

1) The area of application.
2) The concentration of the agents.
3) The presence of other compounds in the preparation.
4) The solubility (e.g. insoluble zinc oxide is a protective and soluble zinc sulfate is an astringent).

Protectives

A protective is any agent that isolates the exposed surface (skin or other membranes) from harmful or annoying stimuli.

Substances that protect by mechanical or other physical means are considered to be protectives.

Compounds most appropriate for this purpose are:

1. Insoluble.
2. Chemically inert.

Insolubility is a desirable property for protectives because:

1. This limits the absorption of the compounds through the skin.

2.Makes it difficult to wash them off and diminishes metallic properties on tissue.

- Chemical inertness prevents interaction between the protective substance and the tissue.

- Adsorbent action is also an important property of protectives by which they adsorb moisture from the surface of the skin.

Removing moisture tends to:

1. Lessen mechanical friction and irritation.
2. Discourages certain bacterial growth.
3. The adsorptive capacity is important to the GI protective action of chemically inert powders taken internally.

Applications

- Protectives are generally applied as:

1. Dusting powders.
2. Suspensions containing the insoluble protective substance.
3. Ointments and creams.

- Usually they are applied to:

1. The areas of skin which are subject to constant irritation due to moisture or friction.
2. Areas which have already become irritated or inflamed due to friction, allergy, etc.

- If the area to which protective is to be applied is abraded and exuding fluid, adsorbent type protectives should not be used, these substance will mix with the exudate and dry to a crust which adheres to the open tissue.

Purified Talc ($3MgO.4SiO_2.H_2O$)

It is a purified magnesium silicate containing a small portion of aluminum silicate.

Used as lubricant, protective and dusting powder, it protect the skin from irritation due to friction because of its inert and unctuous nature

Uses:

1. Lubricant.
2. Cosmetic purpose.
3. Filtering aid.
4. Protective on broken skin of wounds and surgical incision.
5. Used as dusting powder on surgical gloves.

Calamine($ZnO.xFe_2O_3$)

Calamine is a ZnO with small amount of Fe_2O_3 and on ignition yield not less that 98% of ZnO.

Uses:

1.Due to its soothing, adsorbent and protective properties calamine is used in dusting powder, ointments and lotions.

2. It has mild astringent and antiseptic action on the skin.
3. It has better cosmetic acceptability.
4. It is also used as a cream, ointment or lotion is various skin disorders.
5. Calamine lotion with 1% phenol provides a local anesthetic and antipruritic (anti-itching) action in small or chicken pox infection.

Titanium Dioxide(TiO_2)

It contains not less than 98% of TiO_2 calculated with reference to dry substance.

Uses:

1. Due to its high refractive index, it absorbs ultraviolet light and primarily used as sun screen and topical protectives as creams, paste etc.
2. It is used as a white pigment in lotions and cosmetic preparations such as face powder.
3. It is used for relief of pruritus and exudative dermatoses.

Antimicrobials and astringents

- Antimicrobial:

This term is generally applied to any agent which either kills or inhibits the growth of microorganisms e.g. bacteria, fungi, protozoa etc.

Antiseptic: the term is reserved for those agents used against microorganism growing on man specifically or living tissue in general.

- Germicide:

The term germicide refers to a more specific action in that it describes agents which kills microorganisms. The '–cide' ending on the word means 'to kill'. Hence, this ending can be applied to the names of various classes of microorganisms to provide terms for more specific agents, e.g. bactericide, fungicide, amibicide,etc.

- Those agents which don't kill microorganism, but function primarily by inhibiting their growth, can be described by terms using the suffix ‘–stat’ meaning ‘standing still’. Therefore, the terms, bacteriostat, fungistat, etc are employed with compounds having this aspect of activity against the indicated microorganisms.

Disinfectant:

- This term refers to the same type of activity as the term germicide. Its uses differs in that it is applied to those agents most appropriately used on inanimate objects, e.g. instruments, equipment, rooms etc.

Sterilization: this refers to the use of a disinfectant or other procedure to render an object completely free of microorganisms. This frequently involves the use of chemicals or mechanical process (e.g. heat) which are much too stringent for use on animal or human tissue.

Antimicrobials

- The terms antiseptic and germicide may be further modified according to their area and type of use:

1) Topical.
2) Internal.

- Internal agents may be further subdivided into:

1. Absorbed (systemic; distributed through the circulation & used to treat infections in various organs and tissues).
2. Not-absorbed (non systemic; remain and function in the area where they are applied).

- Antiseptics and disinfectants are extensively used in hospitals and other health care settings for a variety of topical and hard-surface applications.
- In particular, they are an essential part of infection control practices and aid in the prevention of nosocomial infections.
- A wide variety of active chemical agents (biocides) are found in these products, many of which have been used for hundreds of years for antisepsis, disinfection , germicides and preservation, including alcohols, phenols, iodine, chlorine etc.
- Most of these active agents demonstrate broad-spectrum antimicrobial activity.

Common antiseptics include:

1. Alcohol.
2. Boric acid.
3. Hydrogen peroxide.
4. Iodine.
5. Carbolic acid and other phenol compounds.
6. Chlorhexidine as hand wash and mouth wash.
7. Sodium chloride.
8. Sodium hypochlorite and calcium hypochlorite.
9. Essential oils - eucalyptus, methyl salicylate, menthol, thymol (Listerine).
10. Silver compounds.
11. Triclosan (a diphenyl ether derivative having bacteriostatic and fungistatic action).

Mechanism of action M/A

The mechanism of action of inorganic antimicrobial agents can be divided into three general categories:

1) Oxidation.
2) Halogenation.
3) Protein precipitation.

Iodine

- Iodine is rapidly bactericidal, fungicidal, tuberculocidal, virucidal, and sporicidal.
- Although aqueous or alcoholic (tincture) solutions of iodine have been used for 150 years as antiseptics, they are associated with irritation and excessive staining.

- In addition, aqueous solutions are generally unstable; in solution, at least seven iodine species are present in a complex equilibrium, with molecular iodine (I_2) being primarily responsible for antimicrobial efficacy.
- Iodine rapidly penetrates into microorganisms and attacks key groups of proteins (in particular the free-sulfur amino acids cysteine and methionine), nucleotides, and fatty acids, which ends in cell death.

Hydrogen peroxide (Peroxygens)

- Hydrogen peroxide (H_2O_2) is a widely used biocide for disinfection, sterilization, and antisepsis.

- It is a clear, colorless liquid that is commercially available in a variety of concentrations ranging from 3 to 90%.

- H_2O_2 is considered environmentally friendly, because it can rapidly degrade into the innocent products water and oxygen. Although pure solutions are generally stable, most contain stabilizers to prevent decomposition.

- H_2O_2 demonstrates broad-spectrum efficacy against viruses, bacteria, yeasts, and bacterial spores.

Astringents

Astringents are protein precipitants with limited penetrative power. That is, they are able to coagulate protein primarily on the surface cells, an action that does not result in the death of the cell.

Astringent influences constriction of tissue e.g. small blood vessels but the action is only topical, no deeper effects occur.

Most topical astringents are salts of aluminum, zinc, and to some extent, zirconium.

Applications of astringents

1. Styptic, to stop bleeding from small cuts by promoting coagulation of blood and constricting small capillaries.
2. Antiperspirant, to decrease secretion of perspiration by constricting pores at the surface of the skin.
3. Restriction of the supply of blood to the surface of mucous membranes as a means of reducing inflammation.
4. Direct actions on skin to remove unwanted tissue (requires a higher concentration, termed corrosive).

Alum

- Alum N.F. can be either the ammonium salt (Aluminum Ammonium Sulfate) or the potassium salt (Aluminum Potassium Sulfate). The label on the container must indicate which salt is being dispensed.
- Astringent solutions of Alum usually contain between 0.5 and 5% of the compound.

Uses:

- Alum serves as a source of aluminum ion, making it useful as a topical astringent.
- The rather high astringency of the compounds makes it possible for certain preparations to be used as irritants or caustics.
- It can be used in footbaths as a means of toughening the skin.

- It is frequently the active ingredient in styptic pencils, where it is used to stop bleeding from small cuts.
- The protein precipitant properties of Alum are utilized in the preparation of precipitated diphtheria and tetanus toxoids.

Zinc Chloride

Zinc chloride is used for the activity of zinc ion, which is a very strong precipitant.

The compound is a powerful astringent in solution and a mild antiseptic.

It is thought that its antiseptic properties are due to an interaction of the metal with certain bacterial enzymes, inhibiting their function.

- The strong astringent properties of zinc chloride make the compound useful as an escharotic.

- The compound is applied as a solution containing from 0.5-2% of zinc chloride.

- The lower concentration may be applied to mucus membranes and is used as a nasal spray in office procedures to aid drainage from infected sinuses.

- The USP also recognizes the compound as a desensitizer of dentin. For this purpose, a 10% solution is applied topically to the teeth.

CREAMS AND OINTMENTS

- Creams are a mixture of roughly half water and half oil, they spread easily, are well absorbed, and wash off with water, they are usually packaged in a tube since they are too thick to be dispensed in a pump like a lotion.

- Ointments are 80% oil and 20% water, the oil component is made from hydrocarbons, such as mineral oil or petroleum jelly, ointments feel greasy and are “occlusive”, meaning they stay on the surface of the skin and are not well absorbed, the water and oil components of creams and ointments serve primarily as a “vehicle” to carry an active ingredient or medication.

Guidelines for deciding when to use an ointment and when to use a cream:

1.Creams are best when covering large areas of the skin or to avoid the greasiness associated with an ointment.
2.Wet or “weeping” skin lesions, such as eczema or poison, are best treated with a cream (or gel).
3.Ointments are best when treating dry skin conditions, such as psoriasis.
4.Ointments allow greater penetration of the active ingredient in the topical medication, whether it is an antibiotic, steroid, or anti-fungal medication.
5.The best moisturizers are in ointment form.
6.Ointments may be better to use on sensitive skin since many creams are manufactured with sensitizing preservatives.