UNIT 30 CHELATING AGENTS, IMMUNOSUPPRESSIVES, ANTISEPTICS AND DISINFECTANTS, AND ENZYMES

Structure

30.0 OBJECTIVES

After completing this unit, you should he able to understand:

- different types of Chelating agents:
- immunosuppressives used in ophthalmology; and
- indications and uses of antiseptics and disinfectants with their side effects.

30.1 INTRODUCTION

There are various agents that are used for prevention and cure of diseases. In addition to drugs, these include chelating agents, immunosuppressive agents, disinfectants, and enzymes. Chelating agents remove metallic ions and metals, immunosupprossive agents modulate immunity, antiseptics and disinfectants act against microbial agents, and enzymes dissolve organic structures.

30.2 CHELATING AGENTS

Chelating agents are substances that combine with the metallic ion and change the metal into a soluble complex that is rapidly excreted by the kidneys.

Common chelating agents are:

- Ethylene Diamine tetra acetate
- Desferrioxamine mesylate
- British anti-lewisite (BAL)
  Penicillamine
- Alpha cysteine

30.2.1 Ethylene Diamine Tetra Acetate (EDTA)

EDTA is a chelating agent with a high affinity for many metals. It is a useful chelating agent in the treatment of band keratopathy and lime injury.

Edetate sodium is available in 15 per cent concentration. It is diluted to prepare 0.35 per cent, 0.7 per cent and 1.85 per cent concentrations.

The sodium salt in 0.3 per cent solution is useful after removing corneal epithelium in treatment of band keratopathy. Lime injury (e.g., painters) is treated with a similar EDTA preparation. Prompt irrigation of the epithelium-denuded cornea with EDTA should be, a past of the emergency treatment of alkali burns especially if discrete particles of alkali are superficially embedded within the tissues.

30.2.2 Desferrioxarnine

Desferrioxamine is a specific potent iron chelating agent. It produces a stable bond with ferric ions.

Superficial corneal iron deposits may be removed by treatment with a 10 per cent solution (in 0.5 per cent methylcellulose) four times daily for several weeks. Desferrioxamine acts by chelating free iron ions or those that may bc loosely attached to the acid mucopoly saccharides of the vitreous.

Clinically it is used for non-surgical chemical removal of iron stains. It is also applicable to the treatment of small corneal rust stains.

30.2.3 British Anti-Lewisite (BAL)

British anti-lewisite is an effective anti-arsenic agent that is of definite value in civilian practice as well as in treatment of war gas casualties, BAL treatment reduces corneal damage to only slight residual scarring. The longer the interval between lewisite burn and BAL application, the less effective is the therapeutic effect.

30.2.4 Penicillamine

This chelating agent for copper, mercury, zinc and lead may be used to treat toxicity from these metals. Another possible use for this drug stems from its ability to prevent cross-linking of collagen fibers. Such cross linkage is the basis for the tensile strength of the collagen.

30.2.5 Alpha Cysteine

A 0.2 molar solution of cysteine will irreversibly inhibit collagenase. It acts by chelating divalent ions and by disrupting disulfide bonds. It is used in the treatment of alkali hums.

Check Your Progress 1

1) What are the commonly used chelating agents'?

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2) How is EDTA prepared?

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30.3 IMMUNOSUPPRESSIVES

Immunosuppressive drugs modulate the immunity and arc used in various immunological disorders and conditions like corneal transplantation to contain the body's immune response.

Commonly used immunosuppressive drugs include:

- Azathioprine
- Mercaptopurine
- Methotrexate
- Mechlorethamine
- Chlorambucil
- Cyclophosphamide
- Triethylene thiophosphoramide
- Mycophenolate mofetil
- Cyclosporine

30.3.1 Azathioprine

Description

Azathioprine is a derivative of 6-inereaptopurine in which substitution of the sulfhydryl group has been achieved to impede degradation of the compound in vivo,

Actions

Like-6 mercaptopurine, azathioprine is an antimetabolite that acts by interfering with nucleic acid synthesis. It has been used in the treatment of thrombocytopenic purpura, autoimmune hemolytic anemia, glomerulonephrilis, lupus erythematosus, polymyositis, Crohn's disease, and rheumatoid arthritis. Antibody formation is inhibited by azathioprine, for this reason the drug has been used in suppressing immune reactions after whole organ transplantation.

Ophthalmic: Uses

Azathioprine has been used experimentally and in a limited number of clinical cases to suppress immune reactions in the cornea and uvea.

Adverse Effects

Azathioprine may produce nausea, vomiting, leukopenia and bone marrow depression. Increased susceptibility to many common infections develops.

Preparation

Azathioprine tablet is available in 50 mg tablets. Azathioprine sodium is available as a 100 mg powder (lyophilized) for intravenous use.

30.3.2 Mercaptopurine

Description

Mercaptopurine is **an** analogue and metabolic antagonist of adenine, a nucleic acid constituent.

Actions

Mercaptopurine interferes with nucleic acid synthesis. It is used in the treatment of acute leukemia and chronic myelocytic leukemia. Mercaptopurine suppresses antibody synthesis and has been used in the treatment of serious immune reactions.

Ophthalmic Uses

Mercaptopurine has been used to treat severe cases of uveitis unresponsive to corticosteroid and ACTH therapy.

Adverse Effects

Mercaptopurine is **a** cytotoxic agent and can produce many serious side effects, including bone marrow depression, liver damage with jaundice, gastrointestinal irritation and ulceration, nausea, vomiting and anorexia. This drug can produce abortion and teratogenic effects, so whenever possible, it should be avoided during the first trimester of pregnancy.

Preparation

It is prepared in the form of 50 mg tablets.

Dosage

The dosage is 2.5 to 5 mg/kg of body weight/day. Low doses should be used initially and increased if no clinical improvement occurs. Larger doses are used in the treatment af non-hematological malignancies.

30.3.3 Methotrexate

Mechanism of Action

Inhibits enzyme dihydrofolate reductase, which is important in maintaining the levels of tetrahydrofolate cofactor necessary for one-carbon transfer reactions in the synthesis of purines and thymidylate.

. Its immunosuppressant action is due to inhibition of T-cell and B-cell proliferation.

Description

Methotrexate is a competitive inhibitor of the enzyme folic acid reductase, which reduces folic acid to tetrahydrofolic acid.

Actions

Tetrahydrofolic acid is very important in DNA synthesis and cellular replication. Methotrexate inhibits the formation of tetrahydrofolic acid. Methotrexate is effective in the treatment of leukemias, Burkitt's tumour and various cascinoinas. It is also used in the treatment of severe psoriasis.

Ophthalmic Uses

Methotrexate has been used in the treatment of severe forms of uveitis, including sympathetic ophthalrnia.

Adverse Effects

Methotrexate may produce serious side effects including stomatitis, hemorrhagic enteritis, bone marrow suppression and hepatic dysfunction.

Preparations

Methotrexate is prepared in tablets 2.5 mg, powder 20 mg, solution 2 and 2.5 mg/ml.

Dosage

Orally 2.5 to 5 mg/kg of body weight daily for 4 to 5 days, or twice weekly.

30.3.4 Mechlorethamine

Actions

Mechlorethamine hydrochloride is a cytotoxin that has an affinity for cancer cells and other rapidly growing cells. The precise action of the drug is unknown. However, it interferes with growth and mitotic cell division. It is also used as a palliative agent in patients with Hodgkin's disease, lymphosarcoma, reticular cell sarcoma, and bronchogenic carcinoma.

Ophthalmic Uses

Mechlorethamine hydrochloride has been used in combination with X-ray therapy for the treatment of retinoblastoma. However, it has not been used as extensively in the treatment of this disorder as has triethylene melamine (TEM).

Adverse Effects

Nausea, vomiting, anorexia and thrombophlebitis are the common side effects. Others include lymphocytopenia, granulocytopenia, thrombocytopenia and anemia. Extravasation outside the vein leads to severe local inflammation and sometimes to sloughing of the overlying tissues.

Preparation

The preparation for injection is powder 10 mg.

Dosage

The dosage is 0.1 to 0.3 mg/kg of body weight by intravenous injection daily for 4 days.

30.3.5 Chlorambucil

Description and Actions

Chlorambucil is a derivative of nitrogen mustard. It is cytoioxic and has been used in the treatment of chronic lymphocytic leukemia, lymphomas, lymphosarcomas, and Hodgkin's disease. It is thought to be less toxic to the hemopoietic system than nitrogen mustard.

Ophthalmic Uses

Chlorambucil has been used in the treatment of severe immune inflammatory disorders such as uveitis and retinal vasculitis that have been unresponsive to corticosteroid therapy.

Adverse Effects

Bone marrow depression, including leukopenia, thrombocytopenia and anemia often occurs. This toxicity appears to be dose related and is usually reversible. Patients receiving chlorambucil should be monitored with regular blood counts. The drug is teratogenic and should not be used during the first trimester of pregnancy.

Preparation and Dosage

Chlorambucil 2 mg tablets should be given orally, usually adult dosage is 0.1 to 0.2 mg/kg of body weight for 3 to 6 weeks. Further treatment is defined by the response of patient and toxic reactions.

30.3.6 Cyclophosphamide

Cyclophosphamide is an antineoplastic drug related to nitrogen mustards. It is classified as an alkylating agent.

Actions

The exact mechanism of action of cyclophosphamide is unknown, it is probable that the drug acts by interfering with DNA replication and cell division. It is useful in the treatment of Hodgkin's disease, lymphosarcoma, reticulum cell sarcoma, multiple myeloma and some forms of leukemia. It has a palliative effect on some solid carcinomas. The drug has also been used to suppress severe immune reactions including those after whole organ transplantation and severe disabling rheumatoid arthritis.

Ophthalmic Uses

Cyclophosphamide has been used to suppress severe immune reactions of the uvea that are unresponsive to other drugs. It has also been used in the treatment of rctinoblastoma.

Adverse Effects

Alopecia is a common side effect, this is reversible. Leukopenia and bone marrow depression generally occurs. Other side effects include nausea, vomiting, anorexia, weight loss, diarrhoea and mucosal ulceration. The drug is highly teratogenic.

Preparations

Preparations include the following: Vials of 100 mg and 200 mg for injection and tablet 25 mg and 50 mg.

Dosage'

For anti-inflammatory therapy, 50 mg is given daily and increased by 50 mg every four weeks until there is clinical improvement. The maintenance dose is 50 to 100 mg daily. A blood count should be obtained weekly and the leukocyte count maintained between 2500 and 5000hnm^3.

30.3.7 Triethylene Thiophosphoramide

Description

Triethylene thiophosphoramide is an alkylating agent related to nitrogen mustard.

Actions

The drug is used as a palliative agent in the treatmént of neoplastic disease. Its action is believed to result from the release of ethylenimine radicals and their effects on dividing cells. The drug may be injected into local sites or given intravenously for the treatment of neoplasms.

Ophthalmic Uses

Triethylene thiophosphoramide has been applied topically to prevent recurrence of pterygium after surgical removal. It has also been used topically to prevent corneal vascularization after chemical burns.

Adverse Effects

The drug is radiomimetic and is highly toxic to the hematopoietic system when given systemically. Other possible side effects include vomiting, anorexia, headache, and allergic reactions. There are no significant systemic side effects with topical therapy, changes in skin pigmentation of eyelids have occurred in blacks. Occlusion of the lacrimal puncta may occur.

Preparation

The drug is prepared in 15 mg vials.

Dosage

As prophylaxis against recurrence of pterygium, a 1:2000 solution is applied to the eye every 3 hours during the day for 6 to 8 weeks. Treatment is started within a few days after surgical removal of the pterygium.

30.3.8 Mycophenolate Mofetil

Mycophenolate Mofetilb is the 2-morpholinoethyl ester of mycophenolic acid. It is can immunosuppressive agent, acts by inhibiting inosine monophosphate dehydrogenase enzyme. It inhibits, proliferative responses of T and B lymphocyte to both mutagenic and allospecific stimulation.

Indications

- Scleritis
- Uveitis
- Ocular pemphigoid
- Corneal transplantation

Adverse Effects

Systemic use : Diarrhoea, Leukopenia,Vomiting, Infections.

Dosage

1 gm twice a day. Its efficacy is similar to cyclosporin. Available for oral administration in 250 mg and 500 mg tablets, suspension, injection.

30.3.9 Cyclosporine

Description

Belongs to a chain of medicines known as immunosuppressants. It works on humoral immunity but is most effective against T- cell dependent immune mechanism. It is water insoluble and for topical use should be prepared in olive oil or corn oil. It is used alone or as a steroid sparing agent.

Indications

a) ***Oral***

When other therapies or drugs cannot be employed like in:

- Uveitis
- Behcet's disease
- Scleritis
- Orbital inflammatory disease

b) ***Ocular***

- Prevention of corneal graft rejection
- Treatment of graft rejection
- Dry eyes
- Vernal keratoconjunctivitis
- Adenoviral keratoconjunctivitis.

Adverse **Effects**

Ocular: Burning of the eye, blurred vision, pain, redness, superficial punctate keratitis, conjunctivitis.

Systemic: Kidney dysfunction, Hypertension, Gingival hyperplasia, hypertrichosis, elevation of serum cholesterol levels.

Precautions

While on topical therapy of cyclosporine, systemic side effects should be looked for as blood levels of upto 64 mg/ml have been observed after topical use.

Dosage

It is available as topical 0.05 per cent ophthalmic emulsion.

Systemic dose is 5-7 mg/kg body wt/day.

Check Your Progress 2

1) Name the various immunosuppressive agents.

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2) Mention the common ocular indications of their usage.

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38.4 ANTISEPTICS AND DISINFECTANTS

Antiseptics and disinfectants are the agents having antimicrobiol property, used to sterilise body surfaces (antiseptics) and instruments (disinfectants).

30.4.1 Betadine (Povidone-Iodine 0.5 per cent w/v)

Description

It is a broad-spectium anti-microbial agent with well-established clinical efficacy, and is used worldwide. Povidone-iodine is an iodophore. An iodophere is a loose complex of elemental iodine with a carrier that serves not only to increase the solubility of iodine, but also to provide a sustained release reservoir of the element. In povidone-iodine, povidone (polyvinyl pyrolidine) acts as a carrier for iodine. The germicidal property of the preparation is due to the presence of elemental iodine, which possesses marked anti-microbial action.

Mechanism of Action

Betadine releases elemental iodine slowly fomn the complex of polyvinyl pyrolidine. This free iodine is lethal to several strains of bacteria, fungi, protozoa,

yeasts and viruses. The spectrutn of povidone-iocline (betadine) includes several gram-negative and gram positive bacteria, fungi, viruses, protozoa and other organisms. Povidone-iodine exerts microbial action against susceptible pathogens.

Properties of Betadine

- Betadine has a broad anti-microbial spectrum.
- Betadine exerts a sapid lethal action against susceptible pathogens killing them within 1 to 2 minutes.
- Pathogens do not develop resistance to betadine.
- Betadine does not lose its activity in the presence of pus. blood and tissue fluid.
- Topical application of betadine does not cause systemic toxicity.
- Supra infection does not develop during therapy with betadine because of its broad anti-microbial spectrum.
- Betadine does not cause sensitization and the incidence of hypersensitivity reaction with betadine is extremely low.
- Betadine is non-irritating to the skin.

Usage in Ophthalmology

- Dilute Betadine with saline (equal amount) is used to clean eyelids, eyelashes, eyebrows, skin of Sorehead, cheek as a part of pre operative preparation.
- Diluted solution used to irrigate the eye.
- A strong solution of iodine (containing 7 per cent iodine and potassium iodide) is sometimes used in the treatment of acute herpetic keratitis.

30.4.2 Chlorocresol

This is a potent bactericide. It is used at 0.03 to 0.05 per cent concentration, when it is predominantly bacteriostatic. Some people may find this concentration painful on instillation. The solution should be protected from light.

30.4.3 Cetrimide

This is a cationic quaternary ammonium compound with an activity similar to benzalkonium chloride. It may be used for preserving eye drops at a concentration of 0.005 per cent. It is also used for cleansing skin, pre operative hand washing and in contact lens work.

30.4.4 Cresol

An apparently effective solution for chemical sterilization of sharp instruments contains the following constituents:

Liquor crcsol compound .....8 ml.
Oil of lavender .....2 ml.
Thymol crystals .....2 g.
Ethyl alcohol .....88 ml.

This solution is not corrosive to metal instruments and does not dull sharp edges. Surgical instruments experimentally contaminated by bacteria are invariably sterilized within 2 minutes of immersion in this solution and usually within 60 seconds. The thymol and oil of lavender are added to disguise the unpleasant odour of cresol.

30.4.5 Ultra-Violet Light

The germicidal properties of ultra-violet light are well known and widely used for sterilization. Before the discovery of antibiotics, UV radiation was successfully employed in treatment of corneal ulcers caused by micro-organisms. Resistance of

viruses, fungi and many bacteria to antibiotics and the development of new ultraviolet radiation sources suggest re-evaluation of this old method of therapy. Peak germicidal activity occurs at a wavelength of about 2650 Å (most effective wavelength against bacteria). Nucleoprotein absorption of ultraviolet light has a similar peak, which suggests that the germicidal effect is a result of nucleoprotein destruction. Experimental studies with 2537Å UV light indicates that dosage of 1250 microwatt sec/cm^2 can be tolerated by human cornea in a single dosage without causing permanent scarring.

UV radiation is used for sterilization of disposable hypodermic equipment, blood collection tubes, gloves, plastic lab-ware, cotton, bandages, respiratory care products, parenteral solutions.

30.4.6 Ethylene Oxide

The current belief is that no chemical method will effectively sterilize instruments contaminated with spores with the exception of ethylene oxide. The sharp instruments used in eye surgery tend to be dulled by autoclaving, which was the reason for the past extensive use of sterilizing solutions (which inadequately sterilize spores). Ethylene oxide sterilization has been shown to be as efficacious as autoclaving and yet not to damage sharp edges, glass or plastic. This gas, in a concentration of 10g/L of space will sterilize even resistant organisms and spore? within a 2 how period. Mixing it with hydrocarbon gases eliminates the explosive properties of pure ethylene oxide. The gas is toxic and should be handled with reasonable care. Even a sniff of the gas can he fatal. The ethylene oxide gas sterilizer is a standard equipment in many hospitals. A small portable sterilizer has been developed and is practicable for private ophthalmic use.

This gas is thus used for the sterilisation of surgical equipment and dressing material.

30.4.7 Ethanol

Ethyl alcohol, commonly used as "spirit", has a weak action against spores and viruses. It is commonly used in the concentration of 70 per cent. It is mainly used for sterilisation of instruments and tonometers.

30.4.8 Formaldehyde

It is a highly effective germicide, kills all spores and viruses. It is used in a concentration of 4 per cent for the sterilisation of operation theatres (fumigation) and of articles which can not bc wetted. However, it has the side effect of being extremely irritant to mucus membranes and is hence being superseded by newer chemicals for the purpose of fumigation.

30.4.9 Glutaraldehyde

It is also a gaseous agent, which is bactericidal, fungicidal, sporicidal and virucidal. It is commonly used in the concentration of 2 per cent for the sterilisation of sharp instruments.

30.4.10 Benzalkonium

This chemical is bactericidal to **gram** positive and gram negative bacteria. It is used in pre operative skin preparation and as a preservative in eye drops. The commonly used concentrations are 1:1000, 1:5000 and 1:20000.

30.4.11 Phenol (Carbolic Acid)

This is bactericidal and fungicidal, but not effective against virus and spores. It is now used rarely as better agents are available.

30.4.12 Acetone

This agent is an effective bacteriocidc, fungicide and sporicide. It is used in a concentration of 99 per cent for the sterilisation of sharp instruments in eye camps.

Check Your Progress 3

What arc the agents commonly used for sterilisation?

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30.5 ENZYMES

Enzymes are complex proteins produced by living cells that catalyze specific biochemical reactions at body temperatures.

30.5.1 Alpha Chymotrypsin

Description

It is a lyophilized form of crystalline alpha chymotrypsin, a proteolytic enzyme obtained from the pancreas of ox. The dilucnt is a sterile balanced salt solution to be used for reconstituting the crystals. Package includes one vial alpha chymotrypsin 750 Units and a 9 ml vial of diluent.

Clinical Pharmacology

When instilled into the posterior chamber of the cyc, its enzymatic action causes dissolution of zonular fibers attached to the lens.

Indications and Usage

For enzymatic zonulysis in intracapsular lens extraction.

Contraindications

Contraindication in those persons who have shown hypersensitivity to any component of this preparation,

Warnings

Do not use the reconstituted solution if cloudy or if it contains a precipitate. Do not autoclave the powder or the reconstituted solution, excessive heat, alcohol and other chemicals used for sterilization inactivate the enzyme. After the operation discard any unused portion, including the diluent.

Precautions

Alpha chymotrypsin may produce an acute rise in intra-ocular pressure following surgery. Use of this preparation is not advised in patients under 20 years of age.

Adverse Reaction

Transient increase in intra-ocular pressure, moderate uveitis, corneal edema and striate keratitis has been reported.

Note

If the zonules are still intact, irrigate with additional alpha chymotrypsin and wait an additional two minutes before flushing with the diluent.

30.5.2 Urokinase

Description

It is a thrombolytic agent used to dissolve blood clots.

Indication

It is useful for removal of blood clot of hyphema which is then removed with ringer lactate. Microcatheter urokinase infusion has been used to treat central retinal artery occlusion (CRAB).

Contraindication

Ocular infections and ocular malignancy.

Dosage

5000 units of urokinase are dissolved in 2ml of normal saline and injected into the anterior chamber.

Dose for CRAO is 100,000-900, 000 IU over 10-90 minutes into the Ophthalmic artery.

30.5.3 Hyaluronidase

Description

It is an enzyme that acts by depolymerizing hyaluronic acid a component of the intercellular ground substance which determines the permeability of tissues.

Indications

- Used with local anesthetics for regional anesthesia. It is also used to hasten the onset of local anesthesia.
- Sub-conjunctival hemorrhage.
- Hyphema

Contraindication

Ocular infections and ocular malignancy are contraindication to its use.

Adverse Reaction

It is antigenic and may sometimes produce allergic reactions.

Dosage and Administration

It is available as an odorless fluffy powder containing 300 units of activity per mg. For local anesthesia one ampoule of 1500 units is reconstituted with 2 per cent lignocaine and lml of this solution is mixed with the 30 ml vial. The fresh prepared solution rapidly loses activity at room temperature and the solution should be used within 12 hours.

Check Your Progress 4

1) Which enzyme is used to break zonules?

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2) Which enzyme is used mixed with local anesthetics?,

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30.6 LET US SUM UP

In this unit you have learned that chelating agents combine with metallic ions and help in their removal from the body. EDTA is nseful for the treatment of band keratopathy and in alkali burns.

You have also learned that iminunosuppressive agents are used to suppress the immunity during tissue transplant and also when excessive inflammation is to be controlled. Enzymatic dissolution of tissue using enzymes like urokinase, hyaluronidase or chymotrypsin. Antiseptic agents and disinfectants are used to eliminate infections on animate and inaminate objects.

30.7 ANSWERS TO CHECK YOUR PROGRESS

Check Your Progress 1

1) The commonly used chelating agents are:
   - Ethylene Diamine tetra acetate
   - Desferrioxamine mesylate
   - British anti-lewisite (BAL)
   - Penicillamine
   - Alpha cysteine

2) Edetate sodiurn is available in 15 per cent concentration. It is diluted to prepare 0.35 per cent, 0.7 per cent and 1.85 per cent concentrations.

Check Your *Progress* 2

1) The various immunosuppressive agents are:
   - Azathioprine
   - Mercaptopurine
   - Methotrexate
   - Mechlorethamine
   - Chlorambucil
   - Cyclophosphamide
   - Triethylene thiophosphoramide
   - Mycophenolate mofetil
   - Cyclosporin.

2) The common ocular indications of immunosuppressant drugs are:
   - Uveitis
   - Scleritis
   - After pterygium surgery/corneal transplantation
   - Retinoblastoma
   - Severe dry eye
   - Unresponsive cases of vernal keratoconjunctivitis
   - Orbital inflammatory diseases
   - Ocular pemphigoid

Check Your Progress 3

The agents commonly used for sterilisation are:

- Betadine
- Chlorocresol
- Formaldehyde
- Glutaraldehyde
- Ethanol
- Acetone
- Cetrimide
- Benzalkonium chloride
- Phenol
- Cresol
- Ultra-violet light
- Ethylene oxide

Check Your Progress 4

1) Alpha Chymotrypsin

2) Hyaluronidase

30.8 FURTHER READINGS

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