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IMMUNOTROPIC AND
ANTIALLERGIC AGENTS

Types of hypersensitivity reaction

Immediate-type hypersensitivity

1. Anaphylaxis – results from cross-linking of membrane-bound IgE on blood basophils or tissue mast cells by antigen. This interaction causes cells to degranulate, releasing substances (histamine, leukotrienes)

Examples: hay fever, anaphylactic shock.

2. Cytotoxic reaction – results from the formation of antigen-antibody complexes between foreign antigen and immunoglobulins. It results in lysis of cells that keep antigen.

Examples: blood transfusion reactions and in hemolytic disease of the newborn; aplastic anemia from chloramphenicol

Immediate-type hypersensitivity

3. Immune complex reaction – is due to the presence of elevated levels of antigen-antibody complexes. The formation of these complexes activates complement to produce components that increase vascular permeability and recruit neutrophils to the site of complex deposition.

Examples: skin rashes, serum sickness, glomerulonephritis.

Delayed-type hypersensitivity – is characterized by the influx of the activated macrophages and neutrophils; and release copious amounts of enzymes that contribute to the extensive tissue damage and local inflammation.

Examples: parasitic granuloma; tuberculin skin test.

Development of drugs hypersensitivity has three stages:

- conversion of drug's substance into form that can interact with proteins;
- conjugation of incomplete antigen with host protein that lead to formation of complete antigen;
- immune reaction of the organism on certain drug-protein complex that became alien.

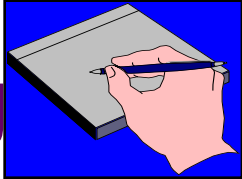
!N.B. 71% of side effects of pharmacotherapy is the drugs hypersensitivity.

Peculiarity of allergic reactions:

- ✓ mismatch of drugs pharmacological properties and clinical manifestations of hypersensitivity;
- ✓ even minimal dose of a drug could cause any allergic reaction

ANTIALLERGIC AGENTS

I. For the treatment of **IMMEDIATE-TYPE** reaction:

- ↓ synthesis and release of histamine and other active substances – cromolyn, ketotifen, glucocorticoids
- H₁-histaminoblockers – dimedrole, diprazin, diazolin, loratidine etc.
- agents that bind with histamine – histag  n
- ↓ manifestations of hypersensitivity – adrenomimetics, M-cholinoblockers, zafirlucast, euphylline
- ↓ tissue alteration –steroid and non-steroid anti-inflammatory agents

II. For the treatment of **DELAYED-TYPE** reaction

- *immunosuppressant* – cyclosporine, azathioprine
- ↓ *tissue alteration* – anti-inflammatory steroid and non-steroid, slowly-acting agents (chloroquine, gold-containing agents, dalson etc.)

HISTAMINE RECEPTORS

recept ors	localization	Effects of activation	blockers:
H₁	bronchial sm. muscles	↑ tonus	Dimedrol Diprazin Diazolin etc.
	intestinal sm. muscles	↑ tonus	
	heart	↓ AV	
	vessels	↓ arteries, ↑ veins	
	capillary	↑ permeability	
	nerve endings	↑ pain perception and itching	
	CNS	different	
H₂	gastric glands	↑ secretion	Cimetidine, Famotidin etc.
	heart	+ ino- and chrono-	
	arteries	↓ tonus	

H₁(HISTAMINE)-BLOCKERS

AGENTS	antihistamine activity			sedative	M-cholinolytic	irritative
	onset	strength	duration, hrs			
dimedrol	fast	++	3-5	++	++	+
diprazin	-»-	++++	6-8	+++	+++	+
suprastin	-»-	++	4-6	++	+	+
tavegil	-»-	+++	8-12	+	+	+
diazolin	slow	++	>24	-	-	+
fencarol	-»-	++	6-8	+	+	+
terfenadin	-»-	++	12-24	+	-	-
loratidin	-»-	++	24	+	-	-

Other H₁-blockers:

- ❖ Antiemetic (diprazin, dimedrol)
- ❖ Antiparkinsonic (diprazin, dimedrol)
- ❖ Alpha-adrenoblocking (diprazin)
- ❖ Local anesthetic (dimedrol)

Therapeutic uses:

- ✓ Allergic dermatitis, itching; allergic rhinitis; anaphylaxia
- ✓ Motion sickness prevention, hyposomnia

Adverse effects:

- Sedation, drowsiness; rare – excitation (in children)
- Atropine-like effects
- Local irritative action
- Feto- and embriotoxicity
- Potentiation of alcohol, neuroleptics action

Cromolyn sodium –inhibits mast cell release of histamine, leukotrienes.

Uses: bronchospasm prevention.

Ketotifen – acts like cromolyn and blocks H₁-receptors.

Readily absorbed in GIT. T_{1/2}=20 hours.

Uses: allergic bronchitis, hay fever, allergic dermatitis.

Adverse effects: drowsiness, thrombocytopenia.

Histaglobulin – is a preparation of the human γ -globulin. Increases the production of antihistamine antibodies.

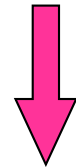
Uses: bronchial asthma, allergic dermatitis and different allergic disease.

PHARMACOTHERAPY OF ANAPHYLACTIC SHOCK:

- ✓ **Adrenomimetics (adrenaline, ephedrine, noradrenaline, mesaton)**
- ✓ **Glucocorticoids (prednisolone, hydrocortisone, dexamethasone)**
- ✓ **H₁- blockers (diprazin, dimedrol, suprastin)**
- ✓ **Miotropic agents (euphylline)**
- ✓ **Analeptics (cordiamine, sulfocamphocaine)**

IMMUNOPHARMACOLOGY –

types of immune correction:



specific & non-specific



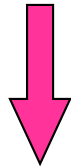
stimulative



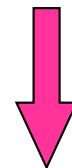
substitutive



inhibiting



**infections,
tumor**



immunodeficit



allergy

CLASSIFICATION OF IMMUNO-SUPPRESSANT & CYTOTOXIC AGENTS

- ▶ **antimetabolites:** mercaptopurine, azathioprine, methotrexate, and fluorouracil
- ▶ **alkylating agents:** cyclophosphane, chlorbutine, sarcolysin, myelosan, etc
- ▶ **antibiotics:** cyclosporin A, actinomycin, dactinomycin, rubomycin, doxorubicin
- ▶ **hormones and their antagonists :** prednisolone, dexamethasone, phosphoestrol etc.
- ▶ **antibodies:** antilymphocytic globulin (ALG)
- ▶ **NSAIDs:** butadion, indomethacin etc.
- ▶ **miscellaneous:** vincristin, vinblastin, asparaginase; chloroquine.

1. Alkylating agents

Mechanism of action: alkylations of DNA within the nucleus

Indications: leukemia, Hodgkin's disease, ovarian and breast cancer

2. Antimetabolites

Mechanism of action : analogs of physiologic metabolites. **Mercaptopurine** and **azathioprine** – analogs of purines; **methotrexate** – folic acid; fluorouracil – pyrimidines. Inhibit DNA and protein synthesis.

Indications: leukemia; intestinal cancer, breast and gastric cancer; organs transplantation; autoimmune diseases

3. Antibiotics

Mechanism of action : inhibit DNA synthesis. Also cyclosporin inhibits T-lymphocytes differentiation, caused antigen action.

Indications: breast, endometrial, and thyroid carcinoma; cancer of lungs and kidney; organs transplantation; autoimmune diseases

4. Periwinkle alkaloids (**vincristin, vinblastin**)

Mechanism of action : mitosis inhibition.

Indications: leukemia, Hodgkin's disease.

5. Enzymes (**L-asparaginase**)

Mechanism of action : splitting of L-asparagine.

Indications: lymphosarcoma, leukemia.

ADVERSE EFFECTS OF IMMUNOSUPPRESSANTS

initial:

- disturbance of bone marrow function
- disturbance of GIT function
- predisposition to infections
- allergic reactions

postponed:

- cancerogenic (cytotoxic agents)
- disturbance of reproductive system (10-70%) and teratogenic effect
- growth retardation in children
- others: hyperpigmentation, lungs fibrosis, hemorrhagic cystitis, alopecia; hepatotoxicity (antimetabolites)



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CLASSIFICATION OF IMMUNOSTIMULATORS

<i>group</i>	<i>agents</i>
mainly stimulate nonspecific immunity	derivatives of purine and pyrimidine (methyluracil, pentoxyl)
mainly stimulate monocytes (macrophages)	sodium nucleinate, zymozan, vaccines (BCG), pyrogenal, prodigiosane
mainly stimulate T- lymphocytes	dibazol, thymalin, tactivin, vilozen, zinc agents, interleukines (IL-2)
mainly stimulate B-lymphocytes	myelopid, taficin, rigin, dalargin, amastin etc.
mainly stimulate NK and K-cells	interferons, filgrastim, molgramostim, placenta extract
others (plant origin, hormones, vitamins etc.)	adaptogens; vitamins C,E,A; anabolic steroids and non-steroids

1. Stimulators of nonspecific immunity – methyluracil, pentoxyl.

- ✓ **Effects:** hasten cellular regeneration, wound closing; stimulate cellular and humoral immunity.
- ✓ **Indications:** mild leucopenia, badly closed wounds, burns, bone crash.
- ✓ **Adverse effects:** usually well-tolerated.

2. Stimulators of macrophages and T-lymphocytes – sodium nucleate, BCG, pyrogenal.

Obtaining: sodium nucleate is obtained by hydrolysis of yeast; pyrogenal – microbial polysaccharide from *Pseudomonas aeruginosa*.

Therapeutic uses:

sodium nucleate – different diseases with leucopenia;

BCG – leukemia; carcinoma of breast, urinary bladder, intestine;

pyrogenal – chronic prostatitis, chronic inflammation of female reproductive system; inflammation and damage of peripheral and central nervous system.

3. Mostly stimulate NK & K-cells

Interferons possess antimicrobial, antiproliferative and anticancer activity.

There are **three types of interferons:**

- ❖ α -(leukocyte)
- ❖ β -(fibroblast)
- ❖ γ -(T-lymphocyte)

Uses:

- ✓ **Natural α -interferon** are used locally for common cold, herpes keratitis.
- ✓ **Recombinant α -interferon (reaferon, laferon)** are used for hepatitis B & C; leukemia; carcinoma of urinary bladder and intestine.
- ✓ **Recombinant β -interferon (betaferon)** – for multiple sclerosis.

Cytokines with colony-stimulating properties:

- granulocyte colony-stimulating factor (filgrastim);
- granulocyte-macrophage colony-stimulating factor (molgrastim).

Filgrastim stimulates formation of granulocytes;
molgramostim – mixed granulocyte-macrophage colony. They hasten recovery from neutropenia in patients after chemotherapy and after bone marrow transplantation.

Poludan, amixin – stimulates the synthesis of endogenous interferon. Poludan is used locally for viral ophthalmic disease; amixin - at hepatitis B & C.