Drug allergy

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Lecture 9

Drug allergy

- Adverse reaction to a drug by a specific immune response either:
  - **Directly to the drug**
  - **One or more of its metabolites alone**
  - **Drug bound to a body protein such as albumin, (Hapten).**
- No correlation with known pharmacological properties of the drug
- No linear relationship with drug dosage

Drug allergy

- Drug allergy is an uncommon and unwanted side effect of medication.
- Reactions to drugs range:
  - Rasha (mild localized)
  - Angioedema
  - the serum sickness syndrome
  - anaphylaxis and asthma (serious effects on vital systems)
- The body’s response can affect many organ systems, but the skin is the most frequently involved.

Classifications

- Adverse drug reactions are classified as
  - **A predictable drug reaction:**
    - related to the pharmacological actions of the drug.
  - **An unpredictable reaction:**
    - related to immunological response (hypersensitivity reactions) or nonimmunological response

Features of allergic drug reactions

- Require an **induction period** on primary exposure
- Disappear on stop of therapy
- Reappear after re-administration of a small dose
- Occur in a minority of persons receiving the drug
- De-sensitization may be possible

The classification of the hypersensitivity

- Type I
  - **Antigens combine with specific IgE antibodies** that are bound to membrane receptors on tissue mast cells and blood basophils
  - It causes the rapid release of **potent vasoactive and inflammatory mediators**
  - It produces **vasodilatation,** increased capillary permeability, glandular hypersecretion and smooth muscle spasm.
- Type II
  - **Cytotoxic reactions** (activation of killer T cells or macrophages to produce cytotoxicity)resulting when antibody reacts with antigenic components of a cell or tissue elements or with antigen or hapten that is coupled to a cell or tissue.

The classification of the hypersensitivity

- **Type III (Immune complex (IC) reactions)**
  - resulting from deposition of soluble circulating antigen-antibody ICs in vessels or tissue.
  - It causes polymorphonuclear cell migration and release of lysosomal proteolytic enzymes and permeability factors in tissues, **resulting in acute inflammation**
- **Type IV**
  - Cell mediated, delayed hypersensitivity reactions caused by sensitized T lymphocytes after contact with a specific antigen.

The most common drug to cause allergy

- **Analgesics:**
  - Codeine
  - Morphine
  - NSAIDs, such as ibuprofen or indomethacin
  - aspirin
- **Antibiotics** such as penicillin, sulfa drugs, and tetracycline

Risk factors for Drug Allergy

- Frequent exposure
- Large doses
- injection
- Family tendency

Most common allergic reactions

- Rash
- Fever
- Muscle and joint aches
- Lymph node swelling
- Inflammation of the kidney
- Anaphylactic shock

Anaphylactic Reaction

- Life threatening
- occur within 4 hours of the first dose of the drug ,or within 1 hour of taking the drug, and many occur within minutes or even seconds.

Complication of Anaphylactic shock

- Skin reaction - RASH, redness/flushing,
- sense of warmth, itching
- Difficulty breathing - Chest tightness, wheezing, throat tightness
- Fainting أغماء or loss of consciousness due to shock
- Rapid or irregular heart beat
- Swelling of face, tongue, lips, throat, joints, hands, or feet

The causative antigens causing anaphylaxis

- Blood products
- ß-lactam antibiotics
- X-ray contrast agent
- Other drugs

Management

- **Immediate treatment** with adrenaline
  - Adrenaline is an antagonist to the effects of the chemical mediators on smooth muscle, blood vessels and other tissues.
- **For mild reactions** (e.g. angiodema, mild wheezing, nausea and vomiting)
  - 0.3-0.5 ml adrenaline 1:1000 should be given
  - After symptoms resolve, an oral antihistamine should be given for 24 hr.

Management

- For more severe reactions (massive angioedema but without evidence of cardiovascular involvement)
  - Diphenhydramine 50-100 mg IV
  - 0.005mL/kg of an aqueous suspension of long acting adrenaline 1:200 can be given for its 6-8hr effect
  - Oral antihistamine should be given for the next 24hr

Management

- For asthmatic reactions that do not respond to adrenaline
  - IV fluids should be started
  - Theophylline 5mg/kg IV can be given over 10-30 min
  - Endotracheal intubations or tracheotomy with oxygen administration if necessary
- Hypotension (caused mainly by hypovolemia):
  - fluid replacement/ vasopressor drugs e.g. dopamine, noradrenaline if necessary

Urticaria

- It is local wheals and erythema in the superficial dermis
- Urticaria induced by drug is generally acute and is limited to the skin and subcutaneous tissues.

- Signs and symptoms
  - Pruritus حكة (generally the first symptom)
  - Crops of rash

- Treatment for acute urticaria
  - Symptoms subside in 1 to 7 days, treatment is chiefly palliative ملطف.
  - All nonessential drugs should be stopped until the reaction has subsided.
  - Symptoms can be relieved by oral antihistamine and glucocorticoid.

Management for Chronic Urticaria

- Certain drugs e.g. aspirin may be increase symptoms and should be avoided.
- Oral antihistamines
- H2 blockers

Angioedema

- Diffuse and painful swelling of:
  - loose subcutaneous tissue of hands or feet eyelids, lipsand mucous membranes.
- Edema of the upper airways may produce respiratory distress

Management for Angioedema

- Glucocorticoid (e.g. prednisone 30-40mg/day)
- Adrenaline 1:1000, 0.3ml
- IV antihistamine (e.g. diphenhydramine 50-100mg) to prevent airway obstruction
- Intubations or tracheotomy and oxygen administration may be necessary

Penicillin Allergy

- Symptoms
  - Fever
  - Rash
  - Urticaria
  - Angioedema
  - Nephritis
  - Lymphadenopathy

Mechanism of Penicillin Allergy

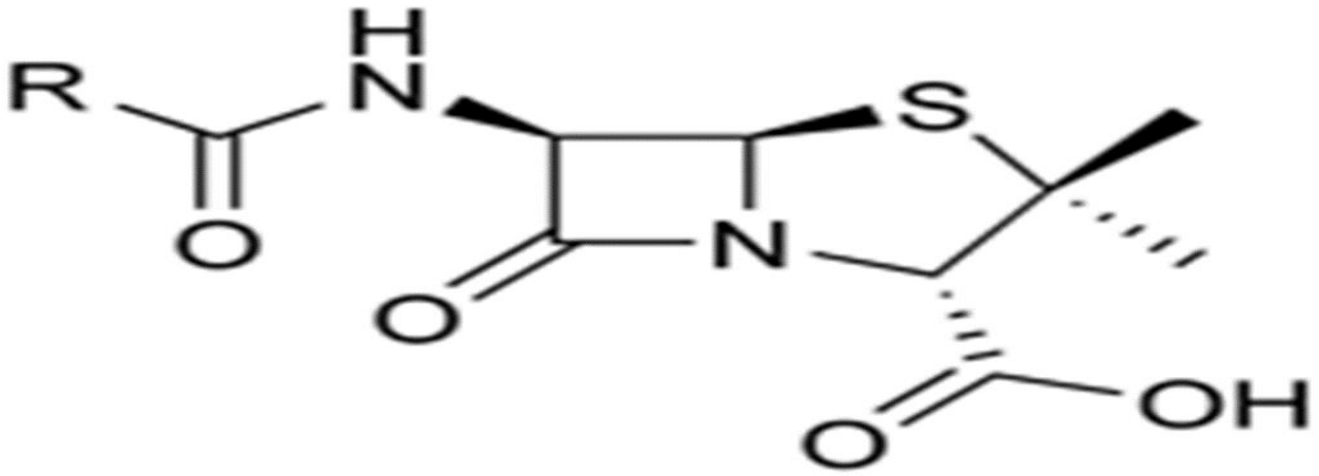
- The drug, or one of its metabolites must be chemically reactive with protein can act as haptens and bond covalently to proteins.

- The breakdown products can bond to ε-amino groups of lysine residues, most importantly globulins.

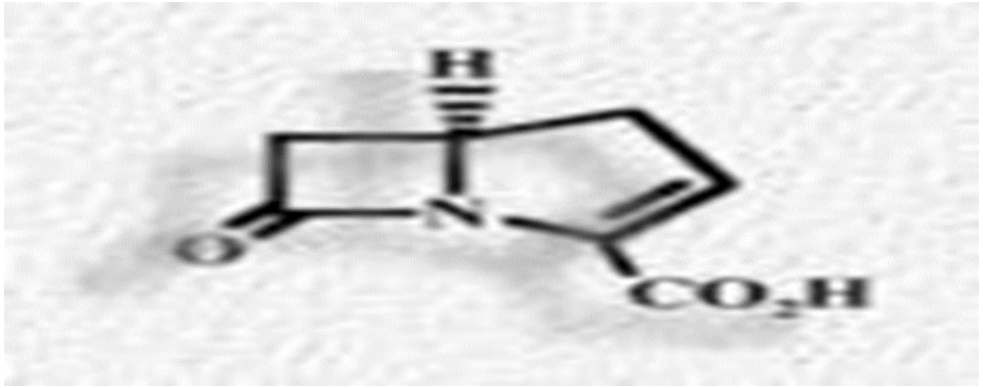
- This binding leads to a spectrum of potentially immunologically active moieties on serum proteins that can cross-link with a variety of preformed anti-penicillin IgE bond to mast cells

Cross-reactivity

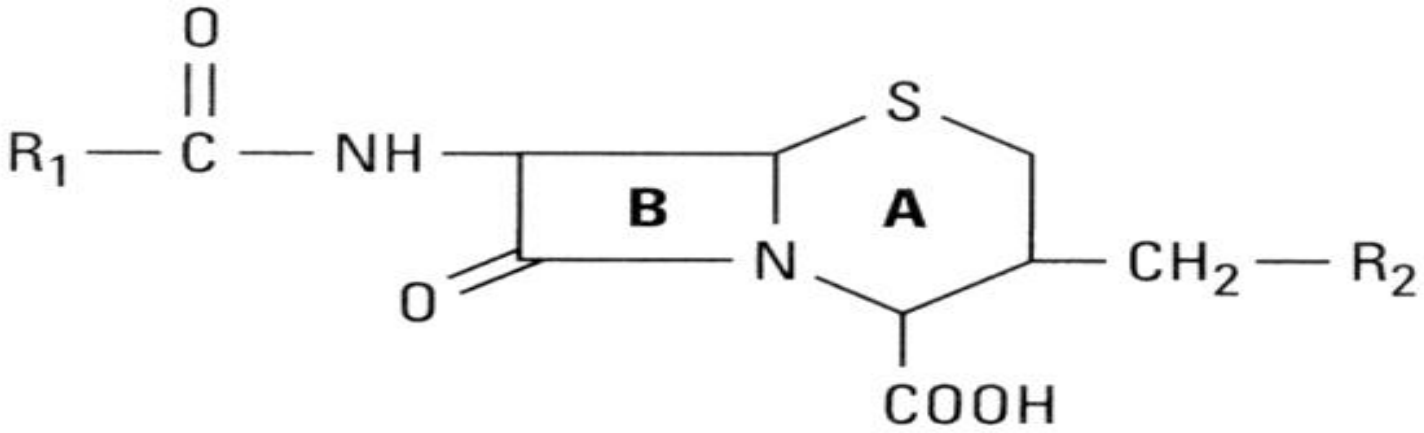
- The most important part of penicillin antigen appears to be the core structure
- The structure of the penicillin is a β-lactam ring with the five-membered thiazolidine ring



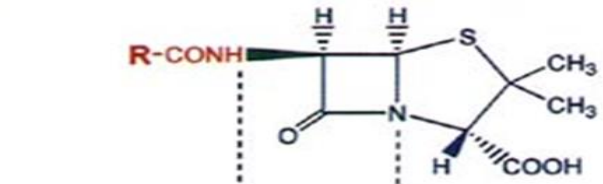
- **Carbapenems** have a bicyclic nucleus containing β-lactam ring and an adjacent five-membered ring.
- It showed 50% cross-reactivity in allergy skin testing between penicillin and the analogous Carbapenems reagents.
- Patients especially with positive penicillin skin test should withhold carbapenems



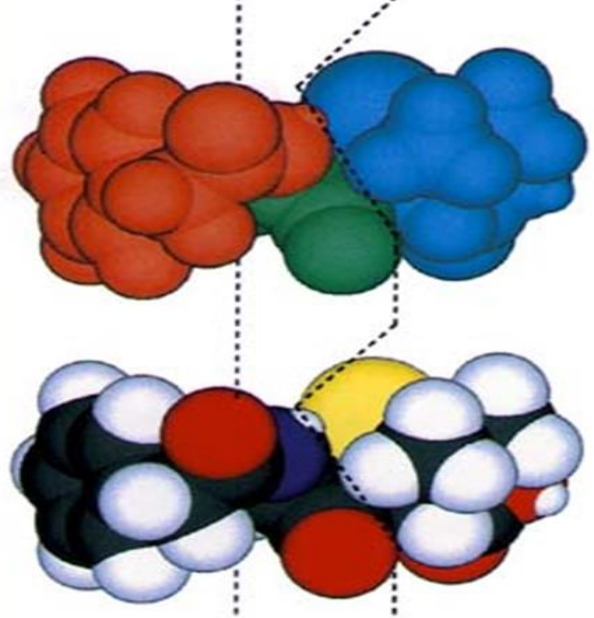
- The structure of **cephalosporin** contains a β- lactam ring with a six-membered dihydrothiazine ring.
- Side chain antigens may be more significant and probably dominate in cephalosporin (patients with positive penicillin skin test results who were given cephalosporin had a cross reaction rate of 10%-20%)



PENICILLINS

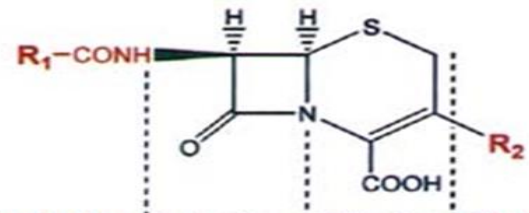


Side-chain R-CONH- | β-Lactam ring | Thiazolidine ring

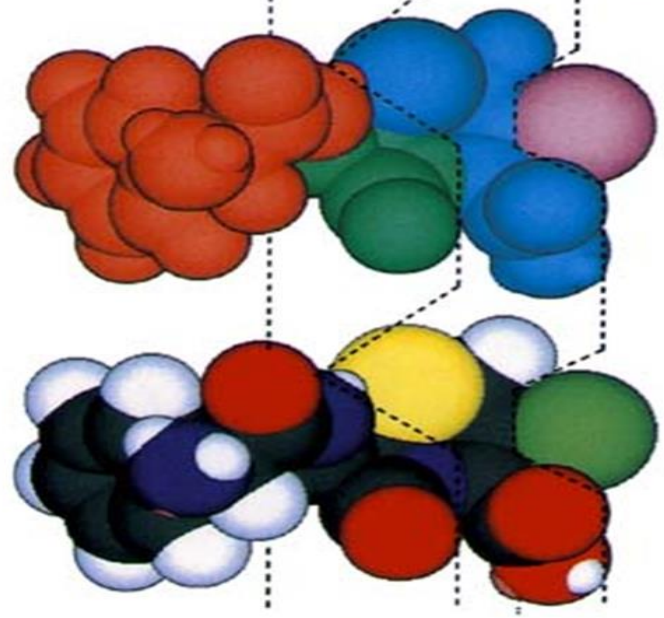


e.g. Benzylpenicillin

CEPHALOSPORINS



Side-chain R_1-CONH- | β-Lactam ring | Dihydro-thiazine ring | Side-chain R_2-



e.g. Cefaclor

Prophylaxis of Penicillin Allergy

- **Skin test**
  - The major degradation product of penicillin, benzylpenicillenic acid, can combine with tissue proteins to form benzylpenicilloyl (BPO), the major antigenic determinant of penicillin
  - A BPO-polylysine conjugate and penicillin G in a concentration of 1000U/ml are available for skin testing
  - performed by prick technique-a drop of a dilute allergenic extract

- If the patient has a history of a severe reaction, the reagents should be diluted 100-fold for initial testing.
- Intradermal test
  - 0.5 or 1 ml dilute is injected
  - Each set of skin tests should include the diluents alone as a negative control and histamine as a positive control.
- A skin test is considered positive if it produces a wheal and flare reaction in 15 min with a wheal diameter at least 5 mm larger than the control.

Caution with the skin test

- Antihistamines, tricycle antidepressants and adrenergic drugs can **inhibit** skin tests results and should be discontinued before the testing procedure.

- Patients using β-adrenergic blocking drugs or angiotensin-converting enzyme inhibitors at the same time of skin testing **may not respond** to emergency treatment with adrenaline if a systemic reaction occurs.

Aspirin and NSAIDs allergy

- Signs and symptoms
  - Respiratory tract symptoms (bronchospasm)
  - urticaria/angioedema
  - GIT (nausea, vomiting, diarrhea)

How do NSAIDs cause allergy?

- NSAIDs inhibit the enzyme cyclo-oxygenase 1 (COX-1), which produces prostaglandins such as PGE2
- PGE2 are necessary to protect against excessive leukotriene release in susceptible individuals.
- The release of leukotriene from the affected target organs cause the clinical symptoms

Allergic reactions to vaccines

- Sensitivity reactions can occur when egg-allergic patients are vaccinated with vaccines containing egg protein.
- These vaccines include yellow fever, influenza and rubella
- Severe anaphylactic reactions to influenza vaccination have been reported to occur at a rate of 0.024 per 100,000 vaccinations
- Egg-sensitive individuals should not receive such vaccinations unless the need is great.
- Influenza vaccines can be contraindicated to patients who are allergic to the preservatives of the vaccine, e.g. neomycin

Latex allergy

- Latex is derived from natural rubber, composed of various polymers of isoprene.
- latex-allergic reactions could be mistakenly interpreted as medication allergies or allergic reactions to general anesthesia.
- Such reaction is IgE mediated
- Signs and symptoms
  - Urticaria
  - Flushing
  - Angioedema
  - Asthma (inhalation of the powder absorbed with latex protein allergens)
  - anaphylaxis

How to Distinguish Drug Allergy and Drug Toxicity

- Reduction in fever within 48h withdrawal of drug strongly suggests that suspected drug causing allergy.
- If fever is accompanied by granulocytopenia, drug toxicity is more likely than allergy and is much more serious.