

Lecture (10)

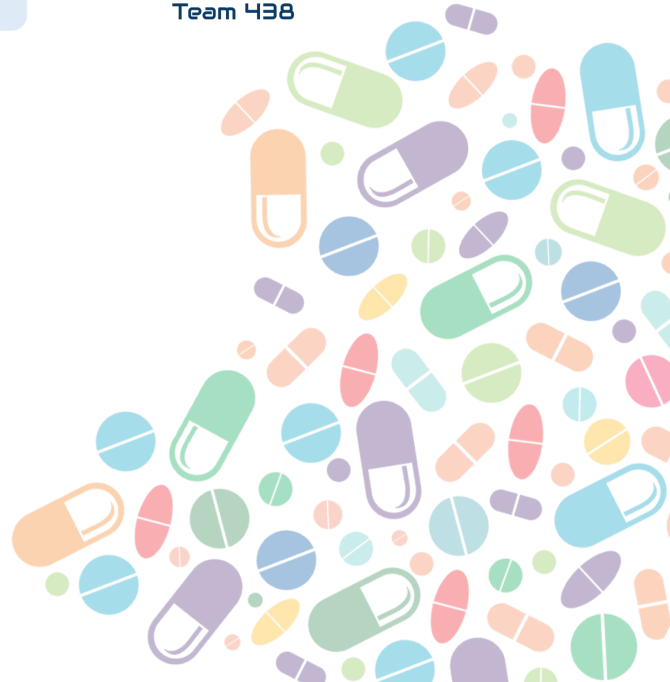
Tolerance and adverse drug reaction



- Red : important
- Black : in male / female slides
- Pink : in girls slides only
- Blue : in male slides only
- Green : notes, Extra

Editing File:

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Objectives :

- Distinguish difference between tolerance and desensitization (tachyphylaxis) and reasons for their development.
- Recognize patterns of adverse drug reactions (ADRs)



Variation in drug responsiveness

Decrease in drug effects or **Development of side effects**
and it happens either:

- Between **different** individuals
- Within the **same** individual

Diminution of a response:

Diminution of a response

These should be distinguished from **Resistance** (loss of effectiveness of antimicrobial agent)

**Tachyphylaxis /
Desensitization**

Rapid (takes a few minutes)

Tolerance

Gradual (few days to weeks)

Phenomenon of variation in drug response, where by there is a **diminution** of the response to the drug when given continuously or repeatedly



Definitions:

- **Adverse drug reactions [ADR]:** Harmful or seriously unpleasant effects occurring at doses intended for therapeutic effects.
- **Tolerance:**
 - A need for markedly **increased amounts** of the substance to achieve intoxication or desired effect.
 - A markedly **diminished effect** with continued use of the same amount of the substance.

Reasons for Development of Tolerance:

1. Pre-receptor Events
2. Events at Receptors
3. Post Receptor Events



Tolerance

reasons for development of tolerance:

Pre-receptor Events

- Reduced drug availability at the relevant receptors due to pharmacokinetic variables.

Drug becomes:

- More metabolized or excreted.
- Less absorbed.

Causing an altered distribution to tissues.

Example:

Barbiturates (enzyme inducers) increase metabolism of **Contraceptive pills** which reduces its availability.



Both result in **Refractoriness**
Loss of therapeutic efficacy

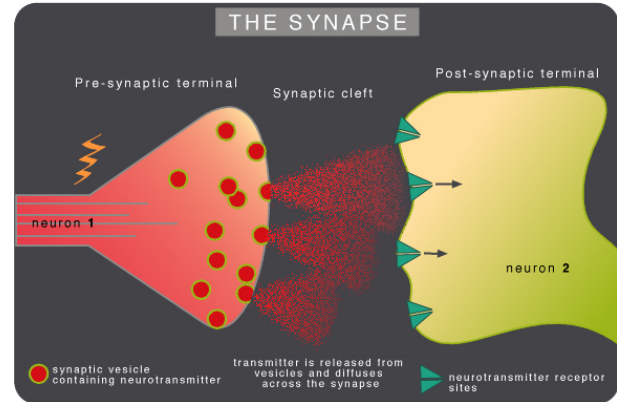
Post Receptor Events

- Nullification of drug response by a physiological adaptive homeostatic response

Example:

Antihypertensive effects of **ACEIs** become nullified by activation of Renin Angiotensin System (RAS) by **NSAIDs**

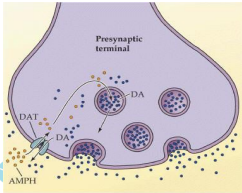
A membrane action potential arriving at the terminal opens axonal Ca channels; Ca inflow releases neurotransmitter molecules from many vesicles by fusing the vesicle membranes to the nerve terminal membrane. Membrane fusion generates an opening through which the molecules are expelled into the synaptic cleft via exocytosis



Events at Receptors

Exhaustion of mediators

Depletion of mediator stores by **amphetamine**



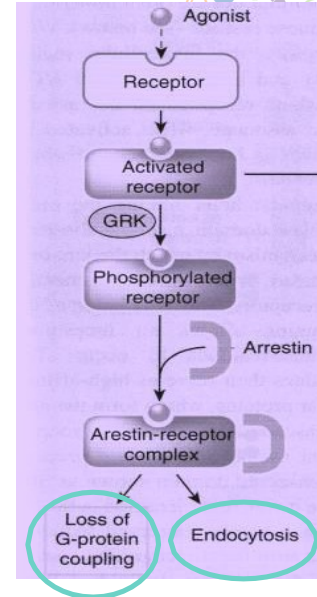
Binding alteration

Phosphorylation of receptor by **β -adrenoceptors** \rightarrow causes reduced activation of AC (Adenyl Cyclase) to related ionic channel **[functional defect]**

Down regulation

Decrease in number of receptors.

Example: **isoprenaline** activation to β receptors \rightarrow Increase in receptor recycling by endocytosis **[structural defect]**



Binding alteration

Down regulation

Adverse drug reactions [ADR] :

Harmful or seriously unpleasant effects occurring at doses intended for **therapeutic effects**

Type A (Augmented) :

- Predictable
- Occurs consequent but in excess of drug primary pharmacological effect. Of **quantitative nature**

Type B (Bizarre) :

- Unpredictable
- Occurs different [heterogenous / idiosyncratic] to known drug pharmacological effect usually due to patient's genetic defect or immunological response. Of **qualitative nature**

Type C (Continuous) :

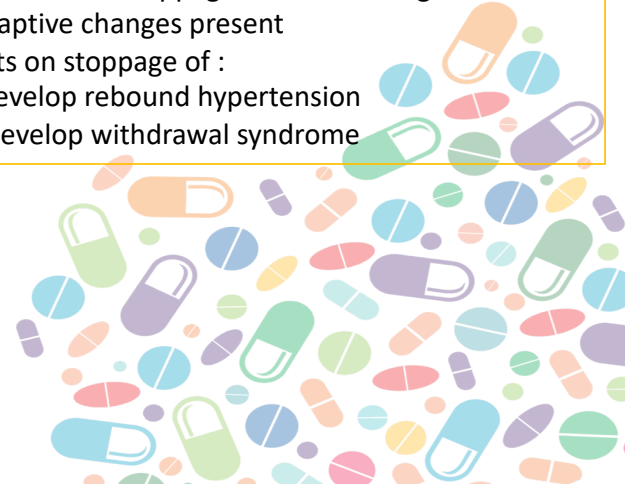
- Occurs during chronic drug administration
- Patients can develop :
 1. **Osteoporosis** : secondary to chronic corticosteroid intake
 2. **Dependence**
 - a. **Psychological [Craving]** as by cannabis
 - b. **Psychological [Craving] + Physical withdrawal manifestations (syndrome)** = Addiction as by morphine

Type D (Delayed) :

- Occurs after long period of time even after drug stoppage.
- Examples:
 - Teratogenicity** after retinoids.
 - Carcinogenicity** after tobacco smoking.

Type E (End of use) :

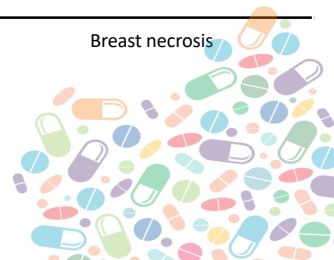
- Occurs after sudden stoppage of chronic drug use due to existing adaptive changes present
- e.g. Patients on stoppage of :
 - **Clonidine**: develop rebound hypertension
 - **Morphine**: develop withdrawal syndrome





	Type A Augmentation	Type B Idiosyncratic
Predictability	Yes	No
Nature	Quantitative (Extension of pharmacology effect)	Qualitative (Immune or Genetic base)
Dose-Dependent	Yes (Dose response relationship present)	No (Dose response relationship absent)
Onset of Symptoms	Usually rapid	Usually delayed
Mortality	Low	High
Treatment	<ul style="list-style-type: none"> Dose adjustment or substitute by more selective Antagonize unwanted effect of first drug 	<ul style="list-style-type: none"> Stop Drug Symptomatic treatment
Example	Bradycardia: β -ADR Blockers Hemorrhage: Warfarin	Apnea: Succinylcholine Thrombocytopenia: Quinine

Drug	Type A	Type B
Chlorpromazine	Sedation	Cholestatic jaundice
Naproxen	GIT haemorrhage	Agranulocytosis
Phenytoin	Ataxia	Hepatitis, lymphadenopathy
Thiazides	Hypokalaemia	Thrombocytopenia
Quinine	Tinnitus	Thrombocytopenia
Warfarin	Bleeding	Breast necrosis



Type B

- Genetic Variation
- Defect in immunological predisposition

Immunological Predisposition: The drug or its bi-product (protein macromolecules or haptens) react as antigens and provoke immune response that results in damage to the tissue → **Hypersensitivity Reaction**

First Exposure to a Drug → **Sensitization**

Repeated Exposures → **Hypersensitivity Reaction**



Hypersensitivity Reactions

Characteristics	Type-1 Immediate (Anaphylactic or atopic)	Type-2 cytotoxic	Type-3 immune complex	Type-4 Cell mediated Or delayed
Antibody	IgE- mediated	Antibody - dependent IgG, IgM	IgG, IgM	Not antibody - mediated
Antigen	Provoked by Re-exposure to a specific antigen	may be endogenous or exogenous chemicals (haptens) which can attach to cell membranes	Soluble immune complexes (aggregations of antigens and IgG and IgM antibodies) form in the blood and are not completely removed by macrophages	-
Response time	FAST- Occurs in minutes (15-30 minutes)	Hours to a day	Hours to days	2 to 3 days
Histology (Type of cell)	Basophil & Mast cells	-	-	T-cells (cytotoxic & helper)
Cell-mediators	Histamine, serotonin, leukotrienes	-	-	It is cell mediated response
FURTHER INFORMATION	1-The reaction can be local or systemic 2-Symptoms vary from mild (irritation) to death from anaphylactic shock.	The antibodies (IgM or IgG) bind to antigens on the patient's own cell surfaces that is perceived by the immune system as foreign, leading to cellular destruction.	It gets deposited in various tissue (typically the skin, kidney and joints)	cytotoxic T cells cause direct damage whereas T-helper secrete cytokines that attracts inflammatory cell infiltrate
EXAMPLE	Allergic asthma, Allergic conjunctivitis, Allergic rhinitis (hay fever), Urticaria (hives), Anaphylaxis.	Drug-induced haemolytic anemia, thrombocytopenia	Serum sickness (fever, arthritis, enlarged lymph nodes, urticaria)	Contact dermatitis
CAUSED BY	Penicillin, streptomycin	Penicillin, Quinidine	Sulphonamides, penicillin, streptomycin	Local anesthetic creams, anti-histamine creams & topical antibiotics



Quiz (MCQ) :

Q1. Which one of these has a gradual diminution of response ?

A) Tachyphylaxis B) Tolerance C) Desensitization

Q2. Which one of ADR types occurs after long period of time even after drug stoppage?

A) Type C B) Type D C) Type E

Q3. Which one of these is considered as “Augmented” ?

A) anxiety due to diazepam B) malformation due to retinoids C) hemorrhage due to warfarin

Q4. Which type of hypersensitivity reaction is considered as “allergic reaction” ?

A) TYPE I B) TYPE II C) TYPE IV

Q5. Which one of these does Not depend on antigen & antibody? From 437

A) TYPE II B) TYPE III C) TYPE IV

Q6. Serum sickness that caused by Sulphonamides is considered as ?

A) TYPE II B) TYPE III C) TYPE IV

ANSWER : 1)B - 2)B - 3)C - 4)A - 5)C - 6)B





Quiz (SAQ) :

Q1. Loss of effectiveness of antimicrobial agent is called ?

Q2. Which type of ADR the “Hypoglycemia from hypoglycemic drugs” referred to?

Q3. Which type of ADR occurs during chronic drug administration ?

For(4-5). A patient has Thrombocytopenia as adverse drug reaction due to Quinine drug.

Q4. What is the type of ADR in this case?

Q5. What will you do to the patient as a treatment?

Q6. Which type of hypersensitivity reaction cause releasing of histamine from the mast cells ?

Q7. Which type of hypersensitivity reaction cause contact dermatitis by local anesthetics creams ?

Q8. Which type of hypersensitivity reaction cause enlarged lymph nodes by Sulphonamide?

Q9. What are the possible causes of Anaphylaxis?





Answer(SAQ) :

1. Resistance

2. Type A - Augmented

3. Type C (Continuous)

4. Type B - Bizarre

5. Stop drug + Symptomatic treatment

6. TYPE I - Anaphylactic

7. Type IV (Cell-mediated)

8. Type III - Immune complex

9. Penicillin, Streptomycin



Good luck

Thanks to the pharma team 435



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