PHARMACOLOGY

Tolerance / Dependence & Adverse Drug Reactions

OBJECTIVES:

- Distinguish the difference between tolerance and desensitization (tachyphylaxis) and reasons for their development.
- Recognize patterns of Adverse Drug Reactions (ADR)

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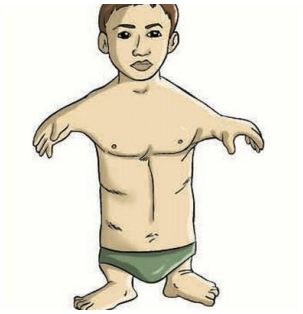
Phocomelia: it,s a disease caused by Thalidomide (a drug was marketed in 1958 in West Germany as a hypnotic & for morning sickness during pregnancy). newborn babies(40000-100000 cases)
This is called **Iatrogenic disease** (caused by the doctor)



These should be distinguished from Resistance (the loss of effectiveness of antimicrobial agents).

Diminution of a response
ways of diminishing a response

Tachyphylaxis/ Desensitization

- Rapid (takes few minutes)

Tolerance

- Gradual (few days to weeks)

Phenomenon of variation in drug response, whereby there is a gradual diminution of the response to the drug when given continuously or repeatedly

Tolerance

A need for markedly increased amounts of the substance to achieve intoxication (addictive agents) or desired effect.

OR

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

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 (cancel out) of drug response by a physiological adaptive homeostatic response

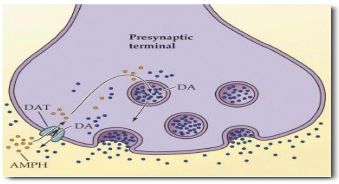
Example:

Antihypertensive effects of ACEIs (Angiotensin Converting Enzyme Inhibitors) become nullified by **activation** of Renin Angiotensin System **(RAS)** by NSAIDs (NonSteroidal Anti-Inflammatory Drugs)

Events at Receptors

Exhaustion of mediators

Depletion of mediator stores by amphetamine



Binding alteration

1. Phosphorylation of receptor by ß-adrenoceptors → causes reduced activation of AC (Adenyl Cyclase) to related ionic channel [functional defect]
2. Desenzation of Ach receptor

Down regulation

Decrease in number of receptors.

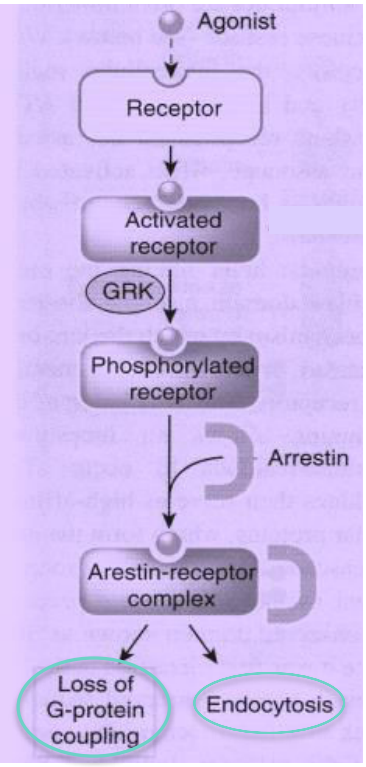
Example:

isoprenaline activation to β receptors → Increase in receptor recycling by endocytosis [structural defect]

Down Regulation and Binding Alteration

G protein-coupled receptor kinases (GRKs) : regulate the activity of GPCRs by phosphorylating their intracellular domains after their associated G proteins have been released and activated.

Arrestin is a protein that prevent the re-association of the G proteins with their receptors, thereby **preventing** reactivation of the signaling pathway.



Binding alteration

Down regulation

Addiction

A chronic, relapsing brain disease

Characterized by:

- Compulsive behaviour of a person (loss of control)
- Continue taking drugs despite their many adverse. health and negative consequences.
- Craving: dysphoric and feels very bad.

It involves two components:

1- **Physical** dependence (withdrawal symptoms),Neurons adapt to the repeated drug exposure and only function normally in the presence of the drug.

2- **Psychological** dependence. (craving)

Drugs of Addiction

Stimulants	• stimulate the central nervous system. • amphetamines, cocaine, nicotine.
Depressants	• depress the CNS • alcohol, barbiturates, benzodiazepines.
Analgesics	• powerful painkillers • from opium poppy , morphine, heroin.
Hallucinogens	• dramatically alter perception • LSD, cannabis, Marijuana.

Adverse Drug Reactions (ADR)

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

Types of ADR:

1. Type A (Augmented)
2. Type B (Bizarre)
3. Type C (Continuous)
4. Type D (Delayed)
5. Type E (End-of-Use)

Types of ADR

1. Type A (Augmented)

- 80% of ADRs
- (Predictable)
- consequence of the drug's primary pharmacological effect (Occurs consequent but in excess of drug primary pharmacological effect of quantitative nature).

2. Type B (Bizarre)

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

3. Type C (Continuous)

Occurs during chronic drug administration.

e.g. 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**

4. Type D (Delayed)

- Occurs after long period of time even after drug stoppage.
- **Long after patients can show:**

- Teratogenicity after retinoid
- Carcinogenicity after tobacco smoking

Types of ADR

5. Type E (End-of-Use)

- Occurs upon sudden stoppage of chronic drug use due to existing adaptive changes.
- **e.g. Patients on stoppage of**

- Clonidine develop rebound hypertension
- Morphine develop withdrawal syndrome
- anxiety, insomnia develop Withdrawal of diazepam

	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
Incidence & Morbidity	High	Low
Mortality	Low	High
Treatment	Dose adjustment or substitute by more selective Antagonize unwanted effect of first drug	Stop Drug Symptomatic treatment
Example	Bradycardia: Beta-ADR Blockers Hemorrhage: Warfarin	Apnea: Succinylcholine Thrombocytopenia: Quinine Penicillin: Anaphylactic shock

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

- 1st Exposure to a Drug → Sensitization
- Repeated Exposures → Hypersensitivity Reaction

Hypersensitivity Reactions

Characteristics	Type-1 (Anaphylactic)	Type-2 (cytotoxic)	Type-3 (immune complex)	Type-4 (Cell mediated /delayed type)
Antibody	IgE- mediated	Antibody-dependent IgG, IgM	IgG, igM	Not antibody-mediated
Antigen	Re-exposure by a specific antigen (exogenous)	On patient's own cell surface that is perceived as foreign, leading to cellular destruction	Soluble in the blood, so they're not completely removed by macrophages	Tissue and organs
Response time	FAST- Occurs in minutes (15-30 minutes)	Hours to a day	Hours to days	Two to three days
Histology (Type of the 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-In severe cases, It might lead to death	-	It get deposited in various tissue (typically the skin, kidney and joints)	cytotoxic T cells cause direct damage whereas T-helper secrete cytokines
EXAMPLE	Allergic asthma, high fever, rhinitis, and Anaphylaxis (Most Severe)	Drug-induced haemolytic anemia, thrombocytopenia	Serum sickness (fever, arthritis, enlarged lymph nodes, urtcaria)	Contact dermatitis
CAUSED BY	**Penicillin**, streptomycin	Penicillin, **Quinidine**	**Sulphonamides**, penicillin, streptomycin	**Local anesthetic creams**, anti-histamine creams &topical antibiotics

THANK YOU FOR CHECKING OUR WORK

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