Tolerance and Adverse Drug Reactions

Lecture no. 10

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Editing File

(اللَّهُمَّ انفَعْنِي بِمَا عَلَّمْتَنِي، وَعَلِّمْنِي مَا يَنْفَعُنِي وَزِدْنِي عِلمًا)

Objectives

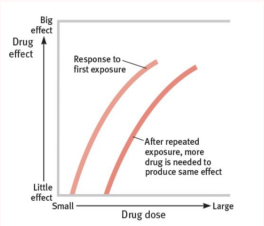
- **Distinguish difference between tolerance and desensitization (tachyphylaxis) and reasons for their development .**

- **Recognize patterns of adverse drug reactions (ADRs)**

Tolerance and Desensitization

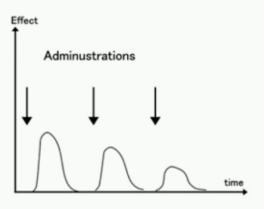
Drug Tolerance

Phenomenon of variation in drug response, whereby there is a gradual diminution of the response to the drug when given continuously or repeatedly. You need to increase the dose to get the same effect.



Tachyphylaxis/ Desensitization

A rapid decrease in response to repeated doses of a drug over a short period of time.



Extra info. for understanding from Team 443:

Diminution of a Response

Tachyphylaxis/ Desensitization

Rapid, in the course of few minutes

Both reduction of response but the difference is the time (442)

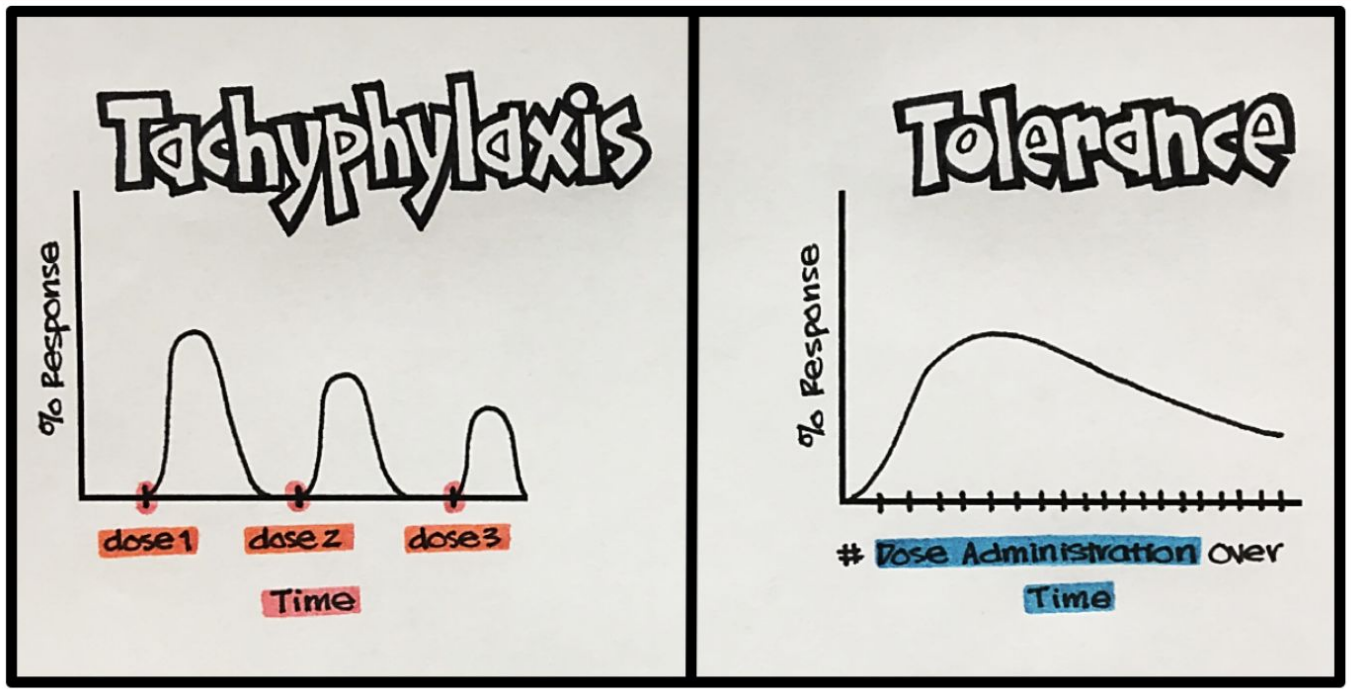
Tolerance

Gradual in the course of days to weeks

Resistance

These should be distinguished from resistance (loss of effectiveness of antimicrobial agent).

Difference between Tolerance and Tachyphylaxis



Sr. No.	Tolerance	Tachyphylaxis
1	Develops slowly	Develops rapidly
2	High doses cause tolerance	Does not depends on dose.
3	Effect can be received after increasing the dose.	Even after increasing the dose there will be no effect.
4	e.g. barbiturates	e.g. ephedrine

REASONS FOR DEVELOPMENTS Of TOLERANCE

Pre-Receptor Events

-Reduced Drug availability at the relevant receptors due to pharmacokinetic variables (ADME)

Drug becomes:
1. >metabolized or excreted
(increased metabolism increases drug breakdown thus decreasing availability)
2. <absorbed
(decreased absorption will reduce availability)
3. Altered distribution to tissues
(increase metabolism = decrease efficacy)
e.g. Barbiturates (works on CNS) ↑metabolism of contraceptive pills = ↓its availability (can cause pregnancy).

-Result in LOSS OF THERAPEUTIC EFFICACY(Refractoriness)

Events at Receptors

- **Exhaustion/depletion of mediators**

- **Binding alteration (functional defect like desensitization of Rs)**

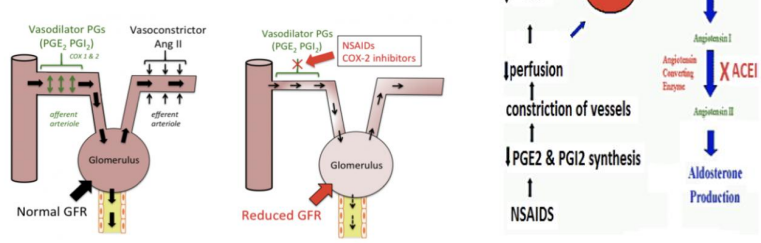
- **Down Regulation (structural defect like endocytosis)**

Post-Receptor Events

-Nullification(cancelling out) of drug response by a physiological adaptative homeostatic response.

e.g : Antihypertensive effects of ACEIs Angiotensin converting-enzyme inhibitors (L9) become nullified by activation of renin angiotensin system by NSAIDs (Non-Steroidal anti-inflammatory drugs).

-Result in LOSS OF THERAPEUTIC EFFICACY (Refractoriness)



- NSAIDs increase renin so it will activate the pathway and stop ACEI effect .
- NSAID & ACEI work Opposite each other

ADVERSE DRUG REACTIONS (ADRs)

Adverse drug reactions (ADRs)

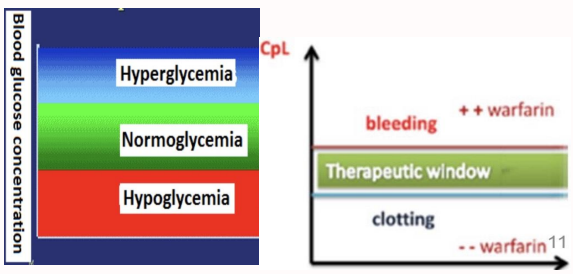
Harmful or seriously unpleasant effects occurring at doses **intended for therapeutic effects.** ≠toxicity which occurs due to ⬆️ drug conc.

Types of ADRs

(A) Augmented
(B) Bizarre
(C) Chronic
(D) Delayed
(E) End of use

Type A: Augmented

- A consequence of the primary effect of the drug. (تضاعف التأثير)
- High incidence 80% of ADRs (most common).
- Predictable.
- The ADR is **Quantitatively** different from the primary effect.
- Dose dependant.
- Not mortal (immortal)
- Treated by stopping or changing(lowering) the dose.



Examples:
-hypoglycemia from hypoglycemic drugs.
-bleeding from warfarin. (anti-coagulant).

Type B: Bizarre

- Occurs different to known drug pharmacological effect (idiosyncratic).
- Idiosyncratic reactions are drug reactions that occur rarely and unpredictably amongst the population (Unknown mechanisms).
- **Usually due to:**
  1-immunological response.
  2-patient genetic defect.
- The ADR is Qualitatively different from the primary effect.
- Dose independent.
- It is mortal
- Treated by stopping the drug and using another one and give antidote and treat symptoms.

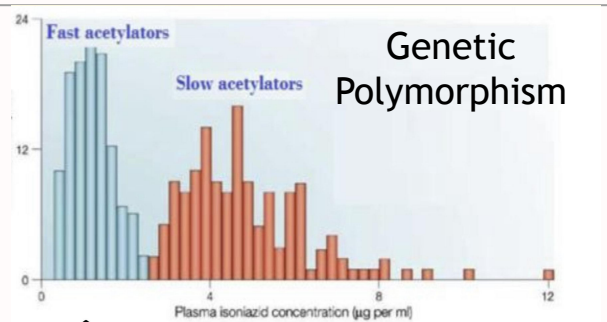
Examples:
-penicillin → anaphylactic shock.
-Quinine → Thrombocytopenia.

Causes of Type B: Bizarre

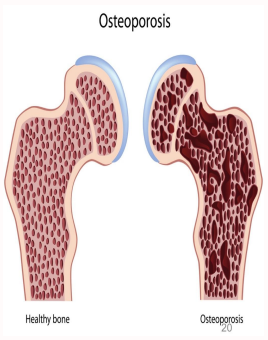
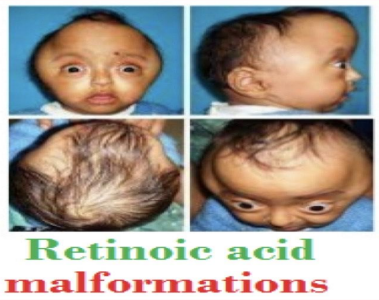
-1st exposure to drug will lead to sensitization.
-Repeated exposure will lead to Hypersensitivity reactions.

Type I, II, and III take 24 hours.
Type IV takes 72 hours.

Immunological response	**Type I Anaphylaxis:** **-Release of mediators from mast cells or blood basophils.** -Urticaria, rhinitis, bronchial asthma caused by penicillin.	**Type II Cytotoxic:** **-Antibody directed cell-mediated lysis.** -Haemolytic anemia, thrombocytopenia by Quinine.	**Type III immune complex:** -**Deposition of soluble antigen-antibody-complement** complexes in small blood vessels. -Serum sickness (fever, arthritis, enlarged lymph node, urticaria) by Sulphonamides, streptomycin.	**Type IV cell mediated:** -Interaction release **cytokines** that attract inflammatory cell infiltrate. -Contact dermatitis by Local anaesthetics creams.
Genetic defect	- When isoniazid is given in identical doses/kg, two distinct groups can be identified,a group with a low blood level acetylate the drug more rapidly " fast acetylators"& a group with with high blood level acetylate the drug slowly" slow acetylators". - Relapse of infection & hepatitis occur in fast acetylators (decrease level of the drug). - Isoniazid cause peripheral neuropathy in slow acetylators (increase level of the drug).			



Types of ADRs Cont..

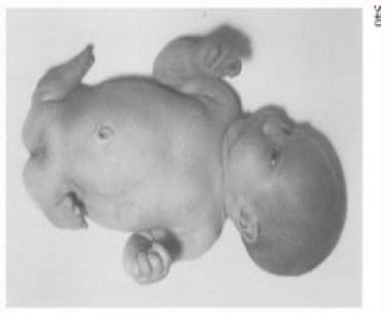
Type C: (Chronic)	Type D: Delayed	Type E: End of use
Occurs during chronic drug administration (long term use).	- Occurs after long period of time even after drug stoppage (delayed in onset).(not related to the dose). -Refers to **carcinogenic** and **teratogenic** effects. -436 note: teratogenic drugs is an agent that disturb the development of the fetus. -444note: (like Phocomelia).	Occurs after sudden stoppage of a chronic drug use, due to existing adaptive changes. (إذا أوقفته فجأة تظهر أعراض انسحابية لأن الجسم صار يعتمد عليه).
Example: Chronic corticosteroid intake→ **Osteoporosis**. 	Examples: -**Teratogenicity** -> Retinoids -**Carcinogenicity** -> Tobacco smoking. 	Examples: -Withdrawal syndrome -> **morphine** -> Increases body ache, insomnia, diarrhea, goose flesh, lacrimation (secretion of tears). -Withdrawal of **diazepam** (anti-anxiety) -> anxiety and insomnia,vomiting. 

Phocomelia

In 1961 a report of outbreak of phocomelia in the newborn babies (40,000-100,000 cases).

Thalidomide was marketed in 1958 in West Germany as a hypnotic & as for morning sickness during pregnancy.

Thalidomide is a teratogenic effect (Type D).



Other names for Phocomelia:
- Iatrogenic disease.
-Thalidomide crisis.

Iatrogenic disease: disease caused by a prescribed drug.

Hypnotic: sleep inducing.

The body limbs look like seal limbs.

MCQs

Q1.The most common ADRs:			
a) **Type B**	b) **Type C**	c) **Type A**	d) **Type E**

Q2.Which ONE of the following is an unpredictable adverse drug reaction:			
a) **Augmented**	b) **Chronic**	c) **Delayed**	d) **Bizarre**

Q3.Which of the following is correct about Type D of adverse drug reaction:			
a) **Dose dependent**	b) **Due to genetic defect**	c) **Delayed In onset**	d) **Hypersensitivity reaction**

Q4.Nullification of drug response happen at?			
a) **pre receptor events**	b) **post receptor events**	c) **events at receptors**	d) **none**

Q5.Where does structural defect happen?			
a)**Binding alteration**	b)**Exhaustion of mediators**	c)**Exhaustion of mediators**	d)**Down regulation**

Answers:

1)C
2)D
3)C
4)B
5)D

SAQs

What are the usual causes of Type B of adverse drug reaction?

?

1- Immunological response.
2- Genetic defect.

Loss of effectiveness of antimicrobial agent is called?

?

Resistance

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