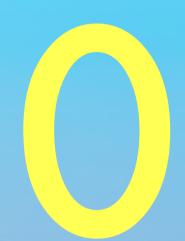


King Saud University College of Medicine Foundation Block

Tolerance and Adverse Drug Reaction

The Last Lecture ©

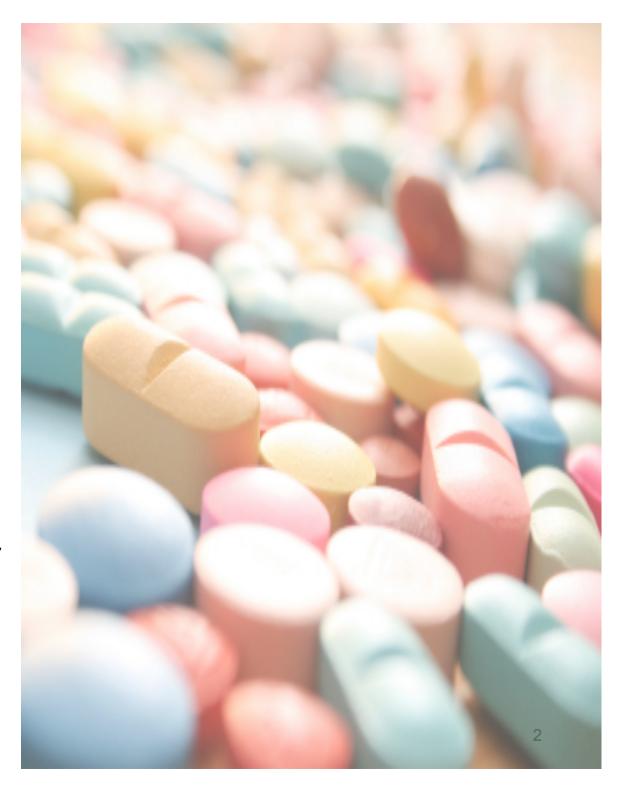


OBJECTIVES:

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

KEY WORDS:

Tolerance, Desensitization, Adverse, Refractoriness, Morbidity, Mortality, Anaphylaxis.



VARIATION IN DRUG RESPONSIVENESS

Decrease in drug effects or Development of side effects Between different individuals or within the same individual.

Tolerance and Desensitization

Phenomenon of variation in drug response, where by there is a gradual <u>diminution of the response</u> to the drug when given continuously or repeatedly.

DIMINUTION OF A RESPONSE

Rapid, in the course of few minutes

<u>Gradual</u> in the course of few days to weeks

Tachyphylaxis (desensitization)

Tolerance

These should be distinguished from: Loss of effectiveness of antimicrobial agent (Resistance)

Reasons for Developing of Tolerance

Pre-Receptor Events

Drug-Drug interaction

↓ drug **availability** at the relevant receptors due to pharmacokinetic variables

Drug becomes:

- *More metabolized or excreted
- *Less absorbed
- *altered distribution to tissues

e.g.. Barbiturates

metabolism of Contraceptive pills =

it availability

Post-Receptor Events

Loss of therapeutic efficacy

Refractoriness:

Drug-body interaction

Nullification of drug response by a physiological adaptative homeostatic response

Antihypertensive effects of ACE Is become nullified by activation of renin angiotensin system by NSAIDs (Non-steroidal antiinflammatory drugs) such as Aspirin

Events at Receptors

Down Regulation

↓ number of receptors.

Isoprenaline activation to β

receptors $\rightarrow \uparrow R$ recycling by

endocytosis [structural defect] Arestin has a role in down regulation

Binding Alteration

Phosphorylation of receptor i.e. β -adrenoceptors \rightarrow ↓ activation of AC to related ionic channel [functional defect]

Exhaustion of Mediators

Depletion of mediator stores

by Amphetamine produce the effect by displacing dopamine

Adverse drug reactions [ADR]:

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

TYPES OF (ADR)
(A, B, C, D, E)

Type A

(Augmented)

PREDICTABLE (because the ADR is related to the drug action)

Type B
(Bizarre)
UNPREDICTABLE

Occurs consequent but in excess of drug main pharmacological effect (Of quantitative nature)

For example: The therapeutic effect of giving a drug to a hypertensive patient is to decrease the pressure back to normal, but if the patient become hypotensive this is called extension of pharmacological effect.

Occurs different [heterogenous / idiosyncratic] to known drug pharmacological effect, usually due to patient's genetic defect or immunological response (Of qualitative nature)

Comparison between type A & B ADRs

	Type A Augmentation	Type B Idiosyncrotic	
Pharmacological 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 and morbidity	High	Low	
(نسبة الوفيات) Mortality	Low	High	
Treatment	Dose adjustment or Substitute by > selective + Antagonize unwanted effect of 1st drug	Stop drug + Symptomatic treatment	
Example	Bradycardia →β- ADR Blockers Hemorrhage →Warfarin	Apnea →succinylcholine Thrombocytopenia →Quinine	

Type C 2- DEPENDENCE: (Continuous) e.g Patients can Occurs during chronic a. Psychological [Craving] as develop by cannabis drug administration. b. Psychological [Craving] + 1- Osteoporosis secondary to chronic manifestations (syndrome) corticosteroid intake = ADDICTION as by Morphine Type D Long after patients can show: (Delayed) -Teratogenicity after retinoids Occurs after long -Carcinogenicity after smoking tobacco period of time even after drug stoppage. Type E (End-of-Use) Occurs upon sudden e.g. Patients on stoppage of stoppage of chronic - Clonidine develop rebound hypertension drug use due to - Morphine develop withdrawal syndrome existing adaptive changes present.

(in case of addiction)

SUMMARY

Recognize patterns of adverse drug reactions (ADR)

	Type A	Type B	Type C	Type D	Type E
Name	Augmented (Predictable)	Bizarre- heterogenous -idiosyncrotic (Unpredictable)	Continuous	Delayed	End-of-Use
Explanation	Occurs consequent but in excess of drug primary pharmacological effect of quantitative nature.	Occurs different to known drug pharmacological effect. Usually due to patient's genetic defect or immunological response.	Occurs during chronic drug administration	Occurs after long period of time <u>even after drug</u> <u>stoppage</u>	Occurs by sudden stop- page of chronic drug use due to existing adaptive changes
Example	Hemorrhage → Warfarin	Thrombocytopenia → Quinine	Osteoporos is → chronic corticosteroid intake	Teratogenicity → retinoids carcinogeniciy → tobacco smoking	Withdrawal syndrome → Morphine

Distinguish difference between tolerance and desensitization (tachyphylaxis) and reasons for their development:

Diminution of a response:

*Tolerance: Gradual in the course of few days to weeks.

*Desensitization: Rapid, in the course of few minutes.

-Reasons for development of tolerance :

- 1- Pre-Receptor events
- 2-Events at Receptors
- 3-Post-Receptor events

2-events at receptors:

- *Exhaustion of mediators
- *Binding alteration
- *Down regulation



1) One of the reasons for the development of tolerance in pre receptor event is the :

- A- Decrease drug availability at the relevant receptors due to pharmacokinetic.
- B- Nullification of drug response by a physiological adaptive homeostatic response.
- C- Sudden stop- page of chronic drug use.
- D- Depletion of mediator stores.

2) Phosphorylation of a receptor by \(\mathbb{B}\)-adrenoceptors causes:

- A- Decrease of adenyl cyclase activation.
- B- Increase in receptor recycling.
- C- Increase metabolism of Contraceptive pills.
- D- Affect renin angiotensin system.

3) The other name for Bizarre (type B of ADR):

- **A-** Predictable
- B- Heterogeneous
- C- End-of-Use
- D- Augmented

4) Sudden stoppage of chronic drug like Morphine can cause :

- A- Thromb<u>ocytopenia</u>
- **B-** Osteoporosis
- C- Hemorrhage
- D- Withdrawal syndrome

5) A drug that causes Osteoporosis during chronic drug administration .

is:

- A- Warfarin
- B- Morphine
- C- Corticosteroid
- D- Quinidine

6) Hemorrhage is a predictable response for :

- A- Quinidine
- B- Warfarin
- C- Morphine
- D- Corticosteroid

7) Tobacco smoking could lead to _____ that could happen after a long period of time after stopping.

- A- Carcinogenicity
- **B-** Teratogenicity
- C- Osteoporosis
- D- Hemorrhage

8) The Incidence and morbidity of Type A (Augmentation) of ADR is :

- A- High
- B- Low
- C- Normal
- D- Unknown

9) The nature of Type B (Idiosyncratic) is:

- A- Quantitative
- **B-** Qualitative
- C- Usually Rapid
- D- Unknown

10) Penicillin could lead to anaphylactic reaction like:

- A- Bronchial asthma
- B- Haemolytic
- C- Anemia
- D- Thrombocytopenia



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We hope that we made this lecture easier for you Good Luck!