



King Saud University
College of Medicine
Foundation Block

Tolerance and Adverse Drug Reaction

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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 diminution of the response to the drug when given continuously or repeatedly.

DIMINUTION OF A RESPONSE

Rapid, in the course of few minutes

Tachyphylaxis
(desensitization)

Gradual in the course of few days to weeks

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

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 anti-inflammatory drugs) such as Aspirin

Events at Receptors

Refractoriness:
Loss of therapeutic efficacy

Down Regulation

↓ number of receptors.

Isoprenaline activation to β receptors → ↑ R recycling by endocytosis [**structural defect**]
Arestin has a role in down regulation

Binding Alteration

Phosphorylation of receptor i.e. β -adrenoceptors → ↓ 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)

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.

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)

Comparison between type A & B ADRs

	Type A Augmentation	Type B Idiosyncrotic
Pharmacological predictability	Yes	No
Nature	<u>Quantitative</u> [extension of pharmacology effect]	<u>Qualitative</u> [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
Mortality (نسبة الوفيات)	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

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

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**

Type D
(**Delayed**)
Occurs after long period of time even after drug stoppage.

Long after patients can show:
-Teratogenicity after **retinoids**
-Carcinogenicity after **smoking tobacco**
(cancer development after smoking, even after quitting smoking.)

Type E
(**End-of-Use**)
Occurs upon sudden stoppage of chronic drug use due to existing adaptive changes present.
(in case of addiction)

e.g. Patients on stoppage of
- **Clonidine** develop rebound hypertension
- **Morphine** develop withdrawal syndrome

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 <u>during</u> chronic drug administration	Occurs after long period of time <u>even after drug stoppage</u>	Occurs by <u>sudden stoppage</u> 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

MCQS

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 stoppage of chronic drug use.
- D- Depletion of mediator stores.

2) Phosphorylation of a receptor by β -adrenoceptors causes:

- A- Decrease of adenylyl 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- Thrombocytopenia
- 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



THIS WORK WAS DONE BY :



Tolerance + ADR

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