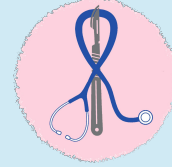




Revised & Reviewed
by
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MED441
KING SAUD UNIVERSITY

Tolerance and ADRs

• **Important**

• Main Text

• Male slides

• female slides

• Extra information

• Doctors notes

For any future corrections [Editing file](#)

If you didn't understand any part from this lecture [Click here](#)

Objectives

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

We can call phocomelia by other names which are latrogenic disease, Thalidomide crisis

Teratogenicity
Doctor note: Thalidomide
Is teratogenic drug

Phocomelia

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

In 1961 a report of outbreak of phocomelia in the newborn babies(40000-100000 cases)

540



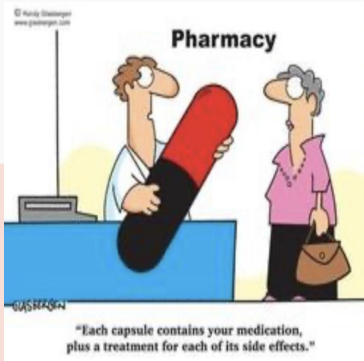
Fig. 1 Patient 7 at birth note phocomelia of both legs

The body
limbs look like
seals limbs



ADVERSE DRUG REACTIONS [ADRS]

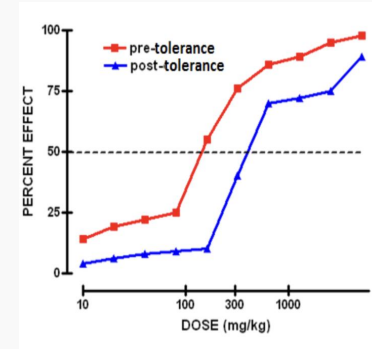
Harmful or seriously unpleasant effects occurring at doses intended for therapeutic effects.



The Definitions for this lecture

TOLERANCE

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



Tolerance and Desensitization

Diminution of a response

Tachyphylaxis/
Desensitization

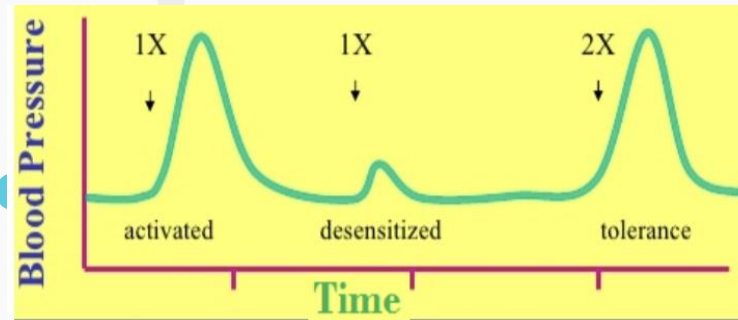
Rapid, in the course of few minutes

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

TOLERANCE

Gradual in the course of few days to weeks

Doctor note: Dose is doubled to get the same effect



REASONS FOR DEVELOPMENT OF TOLERANCE

PRE RECEPTOR EVENTS

Decrease **Drug availability** at the relevant receptors due to pharmacokinetic variables
Drug becomes:

1. > metabolized or excreted (**increase**)
2. < absorbed (**decrease**)
3. altered distribution to tissues

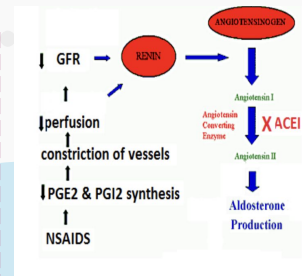
e.g. **Barbiturates increase metabolism of Contraceptive pills = decrease its availability**

Doctor note: **increase metabolism = decrease efficacy**

EVENTS AT RECEPTORS

POST RECEPTOR EVENTS

Nullification of drug response by a physiological adaptation homeostatic response
e.g. Antihypertensive effects of ACEIs become nullified by activation of renin-angiotensin system by **NSAIDs**



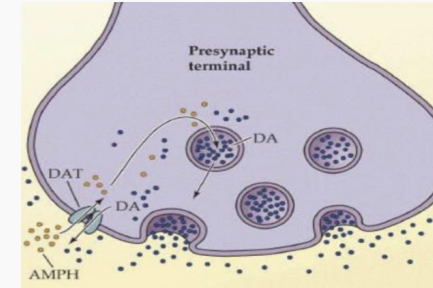
Both of Pre & Post Receptor Events result in **loss of therapeutic efficacy (Refractoriness)**

EVENTS AT RECEPTORS

1

EXHAUSTION OF MEDIATORS

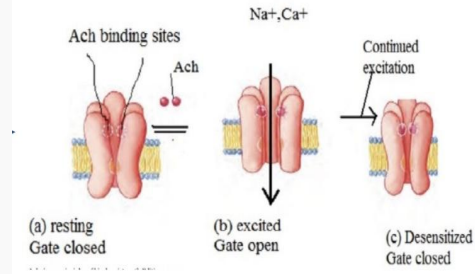
Depletion of mediator stores by **amphetamine**
Doctor note: **amphetamine** is drug that increase kinetic activity



2

BINDING ALTERATION

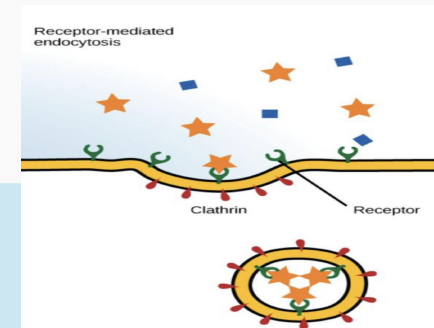
1-Phosphorylation of receptors i.e. Tight binding of **β -adrenoceptors agonists** \rightarrow \downarrow activation of AC
2-Desensitization of Ach- receptors
[Functional defect]



3

DOWN REGULATION

\downarrow Number of receptors. Isoprenaline activation to β receptors \rightarrow \uparrow receptor recycling by endocytosis
[Structural defect]



Adverse drug reaction (ADRS)

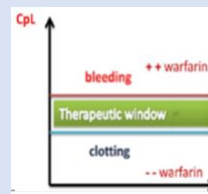
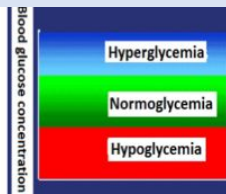
Harmful or seriously unpleasant effect occurring at doses intended for therapeutic effect (side effect)

TYPES OF ADRS

- A. Augmented
- B. Bizarre
- C. Chronic
- D. Delayed
- E. End of use

Type A Augmented

- Dose dependant
- 80% of ADRS
- Predictable (يمكن التنبأ به)
- A consequence of the primary effect of the drug
- Not mortal
- Treated by stopping or changing the dose
- Quantitatively different from the primary effect
- E.g. hypoglycemia from hypoglycemia drugs - bleeding from warfarin
- High incidence



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 or 2-patient's genetic defect
- Dose independent
 - qualitatively different from the primary effect
- Low incidence
- It is mortal
- Treated by stopping or using an antidote
- Penicillin cause Anaphylactic shock (hypersensitive)
- Quinine cause Thrombocytopenia



Genetics 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 **slow acetylators** (increase level of the drug)

Immunological response

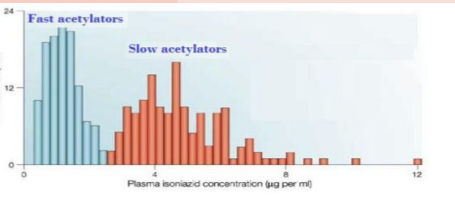
- 1st exposure to drug will lead to sensitization
- Repeated exposure will lead to **Hypersensitivity reactions**

Types of Hypersensitivity reactions

- 1- anaphylaxis
- 2- cytotoxic
- 3- immune complex
- 4- cell mediated

Type B is usually due to

- **Immunological response**
- **Patient genetic defect**



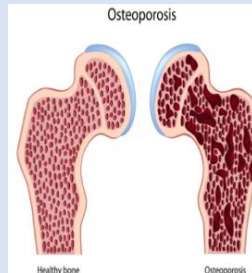
Hypersensitivity reactions

Type I Anaphylaxis	<ul style="list-style-type: none">• Release of mediators from mast cells or blood basophils (few minutes)• Urticaria rhinitis, bronchial, asthma caused by penicillin
Type II Cytotoxic	<ul style="list-style-type: none">• Antibody- directed cell-mediated lysis (hours to days)• Haemolytic anemia, thrombocytopenia by Quinine
Type III immune complex	<ul style="list-style-type: none">• Deposition of soluble antigen-antibody-complement complexes in small blood vessels (hours to days) Serum sickness (fever arthritis enlarged lymph node, urticaria) by Sulphonamides , streptomycin
Type IV cell mediated	<ul style="list-style-type: none">• Interaction release cytokines that attract inflammatory cell infiltrate (long time)• Contact dermatitis by Local anaesthetics creams

TYPES OF ADRS

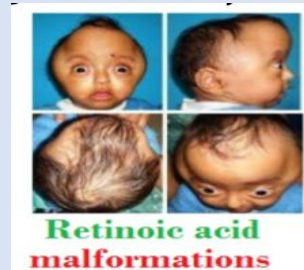
Type C Continued

- Occurs during **chronic** drug administration (**long-term use**)
- (**Osteoporosis**) -> **chronic corticosteroid intake**



Type D Delayed

- Occurs after long period of time even after drug stoppage (Delayed in onset)
 - Refers to carcinogenic and teratogenic effects
 - **teratogenicity** -> retinoids
 - **Carcinogenicity** -> tobacco consuming
- 436note - teratogenic drugs is an agent that disturb the development of the fetus



Type E End of use

- Occurs after **sudden stoppage** of a chronic drug use due to existing adaptive changes
- Withdrawal syndrome -> **morphine**
- Increases body ache, insomnia, diarrhea, goose flesh, lacrimation (**secretion of tears**)
 - Withdrawal of diazepam -> anxiety, insomnia.

MCQ

1Q.Nullification of drug response happen at?

- A.Pre Receptor Events
- B.Post Receptor Events
- C.Event at receptors
- D.Type B Bizarre

2Q. Where does structural defect happen?

- A.Binding alteration
- B.Exhaustion of mediators
- C.Pre Receptor Events
- D.Down regulation

Q3. which of the following drugs cause Type 2 hypersensitivity?

- A.Quinine
- B.Sulphonamide
- C.penicillin
- D.Local anaesthetics creams

Q4. serum sickness that caused by sulfonamide is considered as?

- A.type I
- B.Type II
- C. Type III
- D.Type VI

Answers

1	B
2	D
3	A
4	C

SAQ

1Q. Loss of effectiveness of antimicrobial agent is called?

2Q. Type B ADRS is usually due to?

3Q. Which type of hypersensitivity reaction cause enlarged lymph nodes by sulphonamide?

4Q. Which type of ADR occurs during chronic drug administration ?

Answers

1A. Resistance

2A. Immunological response , patient genetic defect

3A. Type III -immune complex

4A. Type C (Continued)

Thank you

Team leaders

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Female team members:

- Alanoud Albawardi
- Shaimaa Alqaoud
- Nada Alsaif
- Raneem Alanazi
- Ftoon Alenazi
- Areej Altamimi
- Sarah Alotaibi
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- Anas Alharbi
- Abdulrahman Alghamdi
- Abdullah Alotaibi
- Abdulaziz Aqusaiyer
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- Abdullah Alghamdi
- Mohammed Alsaqabi
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