

# TOLERANCE AND ADRS

## 442

EDITING FILE



- Important
- Main text
- Male slide
- Female slide
- Extra info
- Doctor notes

# OBJECTIVES

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

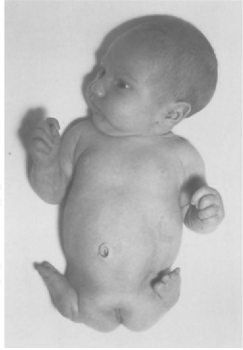


Fig. 1 Partur 2 at birth; note phocomelia of both

# PHOCOMELIA

iatrogenic disease:  
disease caused by a  
prescribed drug  
(iatrogenic disease)

Other names for Phocomelia:

- iatrogenic disease
- Thalidomide crisis

Teratogenicity

Doctor's Note:

Thalidomide is a  
teratogenic drug (441)

Teratogen: an  
agent or  
factor that  
causes  
malformation  
of an embryo

## 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 newborn babies  
(40,000-100,000 cases)

The body  
limbs look  
like seal  
limbs



Hypnotic:  
sleep  
inducing

# LECTURE DEFINITIONS



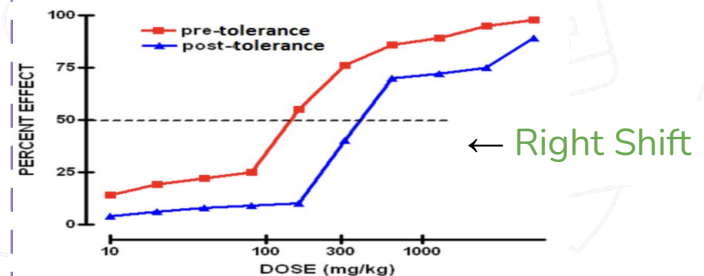
## ADVERSE DRUG REACTIONS (ADRS)

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

note: When you take a drug for a long time (chronic use), efficacy will decrease (not the same as the beginning)

## TOLERANCE & DESENSITIZATION

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



# TOLERANCE AND DESENSITIZATION



These should be distinguished from **resistance** (loss of effectiveness of antimicrobial agent). **Doctor's Note:** Resistance is only for antibiotics and bacteria

## Diminution of a Response

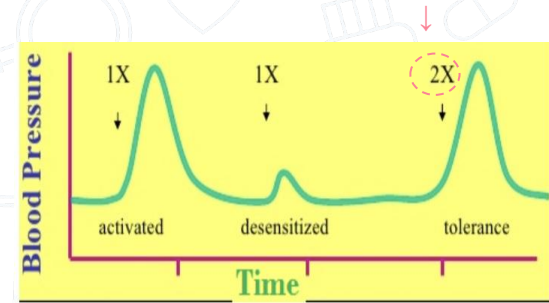
### Tachyphylaxis/Desensitization

Rapid, in the course of few minutes

### Tolerance

Gradual, in the course of few days to weeks (Dose is doubled to get the same effect)

Dose is doubled to reach same response



Both reduction of response but the difference is time



# REASONS FOR DEVELOPMENTS OF TOLERANCE

Refractoriness:  
not yielding to  
treatment



## Pre-Receptor Events (changes in pharmacokinetics)

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

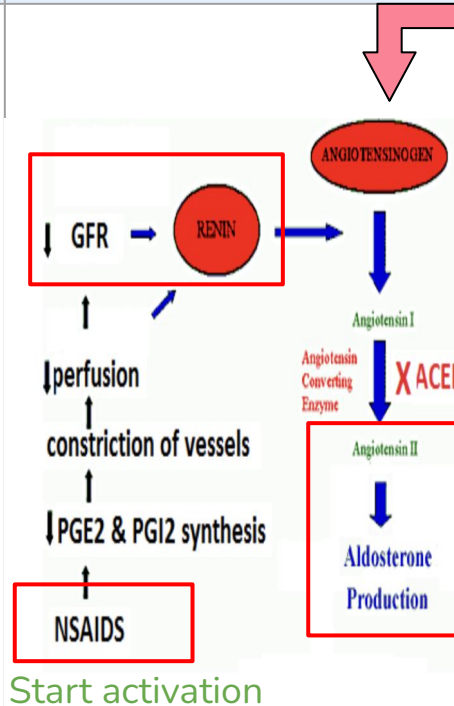
**Drug becomes:**

- 1- > metabolized or excreted (increase)
- 2- < absorbed (decrease)
- 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 (information on next slide)



## Post-Receptor Events (deletion of response)

**Nullification** (cancelling out) 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**

**Result in LOSS OF THERAPEUTIC EFFICACY -Refractoriness-**

Doctor's explanation of picture: There is refractoriness; although the person is taking drugs there is recurrence of disease because the person is taking a drug that is antagonizing ACEI, i.e. canceling the effects of the drug

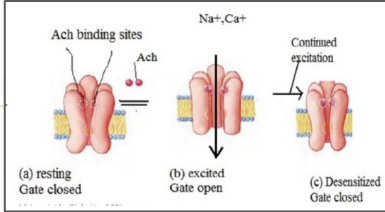


1-Phosphorylation of receptors i.e. tight binding of  **$\beta$ -adrenoceptors agonists** → reduce activation of AC (Adenylyl Cyclase)

2-Desensitization of Ach-receptors

[functional defect]

2-Binding alteration



Continued excitation means chronic use → even though ACh is bound to a receptor, it is not open

# EVENTS AT RECEPTORS



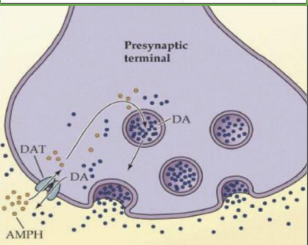
memories  
-e.g  
-result

1-Exhaustion of mediators

Amphetamine is a CNS drug that causes release of dopamine. Over time, there will be a depletion of dopamine (mediator) → no response

Depletion of mediator stores by **amphetamine**

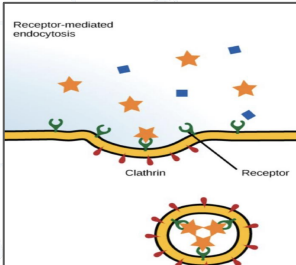
note: amphetamine is a drug that increases drug activity



3-Down Regulation

Decrease Number of receptors. E.g: **Isoprenaline** activation to  **$\beta$**  receptors → Increase receptor recycling by endocytosis [structural defect]

Increased use of isoprenaline causes endocytosis which decreases the number of receptors



# TYPES OF ADRS

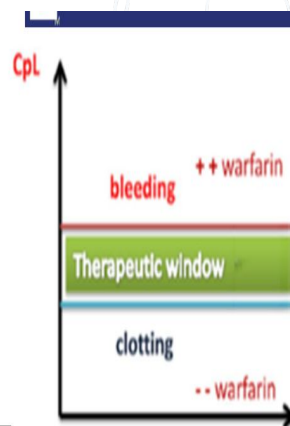
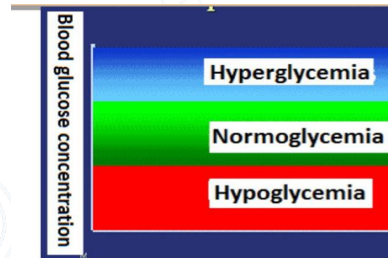
## Adverse drug reaction (ADRS)

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

- 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 (not deadly)
- 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 C Chronic

- Occurs during chronic drug administration (long-term use)
- chronic corticosteroid intake -> Osteoporosis (هشاشة العظام)
- Consequence to primary effect (it just took longer time to show side effect).



# TYPES OF ADRS



## TYPED 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

## TYPED End of use

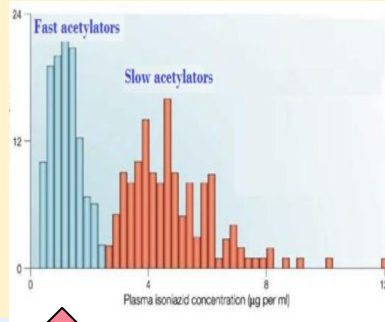
- Occurs after **sudden stoppage** of a chronic drug use due to existing adaptive changes
- Withdrawal syndrome -> **morphine**
- Increases body ache, insomnia, diarrhea, goose flesh, lacrimation (**secretion of tears**)
- Withdrawal of diazepam -> anxiety and insomnia, vomiting

# TYPE B BIZARRE



Important slide

- 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



# HYPERSENSITIVITY REACTIONS

Must know each example for what type



## Type I Anaphylaxis

- Release of mediators from mast cells or blood basophils ( few minutes)
- Urticaria rhinitis, bronchial, asthma caused by **penicillin**

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## Type II Cytotoxic

- Antibody- directed cell-mediated lysis (hours to days)
- Haemolytic anemia, thrombocytopenia by **Quinine**

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## Type III immune complex

- 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**

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## Type IV cell mediated

- Interaction release cytokines that attract inflammatory cell infiltrate (long time)
  - Contact dermatitis by **Local anaesthetics creams**
- 
- 
- 

# MCQ

**Q-1 Serum sickness that caused by sulfonamides is considered as?**

A) TYPE I. B) TYPE II. C) TYPE III. D) TYPE IV

**Q-2 Haemolytic anaemia is caused by ?**

A) Penicillin. B) Sulphonamides. C) Quinine. D) Streptomycin

**Q-3 Both of Pre & Post Receptor Events result in ?**

A) Osteoporosis. B) Refractoriness. C) Adverse drug reaction. D) Tolerance

**Q-4 Which of the following considered "Delayed"**

A) -anxiety due to diazepam  
C) - bleeding due to warfarin

B) - Teratogenicity due Retinoids  
D) -thrombocytopenia due to quinine

1-C

2-C

3-B

4-B

The logo for the Short Answer Question (SAQ) section, consisting of the letters 'SAQ' in a bold, blue, sans-serif font. The background of the slide is a light blue pattern of various medical icons including syringes, pills, hearts, and first aid kits.

# SAQ

Q-1 Nullification of drug response happen at ?

Q-2 Loss of effectiveness of antimicrobial agent is called?

## Answers

1- Post Receptor Events

2- Resistance

Thanks to med 39

The logo for the Short Answer Question (SAQ) section, consisting of the letters 'SAQ' in a bold, blue, sans-serif font.

# SAQ

Q3-type B bizarre is usually due to?from the dr

## Answers

immunological response  
or  
patient's genetic defect



You GOT  
THIS!

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