



# PHARMACOVIGILANCE & ADVERSE DRUG REACTIONS

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Done by:

Salma Al Nazzal  
Lama Nawasreh

Corrected by:

Dina Hajjaj

Doctor:

Nashwa Aborayah

# PHARMACOVIGILANCE & ADVERSE DRUG REACTIONS

## ADVERSE (when therapeutic dose cause the problem) DRUG REACTION:

always Harmful or unpleasant reaction

which is:

- ✓ Due to a drug
- ✓ At doses normally used in man
- ✓ May requires treatment or decrease in dose or stop it
- ✓ Caution in the future use of the same drug

## SIDE EFFECTS (not always harmful)

- UNWANTED UNAVOIDABLE PHARMACOLOGICAL EFFECTS OF THE DRUG
- OCCUR AT THERAPEUTIC DOSES
- PREDICTABLE

### • EXAMPLES

**1-H<sub>1</sub> ANTI-HISTAMINICS: SEDATION = causes drowsiness**

We use Antihistamine drugs for allergy but it cause sedation (not side effect when I use it for sleeping, considered side effect when I don't want it)

**2-ASPIRIN (anti-inflammatory drug): ANTITHROMBOTIC**

**EFFECT (side effect BC it may cause bleeding tendency, may used in some indication as therapeutic drug)**

Aspirin can cause peptic ulcer this is a adverse effect it always harmful, also aspirin can cause renal failure which is (adverse effect)

An effect may be therapeutic in one context but side effect in another context

## ▪ **INCIDENCE OF ADR MORE**

• **POLYPHARMACY**(using more than one drug at the same time---> increase adverse effect +drug interaction may occurs)

• **ELDERLY**(the metabolism is weak which increase the adverse effects)

• **CHILDREN**(metabolism of liver is under developed which increase the adverse effect)

## ▪ **PATIENT WITH MULTIPLE DISEASES**

▪ **PREGNANCY**(the pregnancy do change the physiological of the body, considering 1) the mother 2) fetus--->some drug can be transformed through placenta and cause " teratogenic effect")

• **MALNOURISHED**(decrease immunity+not healthy organs -->increase adverse effects)

• **IMMUNOSUPPRESSION**(1\_ with organ transplantation -->this is patient take immuno suppressant drug to avoid organ rejection 2- cancer patients -->immunosuppress+ chemotherapy 3-AIDS patients+ patients with autoimmune diseases as rheumatoid +systemic lupus)

▪ **DRUG ABUSERS AND ADDICTS**(Bc there drug source is not legal and maybe manipulated or contaminated )

## ▪ **DEVELOP**

▪ **IMMEDIATELY**(as allergy)

▪ **PROLONGED MEDICATION**(

▪ **AFTER STOPPING**(after using a pain killer for long time as peptic ulcer)

## ▪ GRADING OF SEVERITY OF ADVERSE DRUG REACTIONS

- MINOR: NO THERAPY IS REQUIRED (as sedation, but if used by a driver it will be dangerous)
- MODERATE: REQUIRES CHANGE IN DRUG THERAPY, SPECIFIC TREATMENT OR PROLONGS HOSPITAL STAY.
- SEVERE: **POTENTIALLY** LIFE-THREATENING, CAUSES PERMANENT (as renal failure + anaphylactic shock with penicillin) DAMAGE OR REQUIRES INTENSIVE MEDICAL TREATMENT.
- LETHAL: DIRECTLY OR INDIRECTLY CONTRIBUTES TO DEATH OF THE PATIENT (as anaphylactic shock)

## ▪ CLASSIFICATIONS OF ADR

- •A(AUGMENTED)
- •B(BIZARRE)
- •C(CONTINUOUS)
- •D(DELAYED)
- •E(ENDING USE)
- •F(FAILURE OF RESPONSE)
- Broadly
- Type-A (Predictable) **preventable** - Based on pharmacological properties
- Type-B (Non-predictable) - Based on Immunological response and genetic makeup of person

### Type A-Augmented

- If its pharmacological action increased a lot. It can be transformed to an adverse effect
- THESE ARE BASED ON THE PHARMACOLOGICAL ACTIONS OF THE DRUG SO CAN BE PREDICTED
- THEY ARE COMMON AND ACCOUNT FOR 75% OF ADRS.
- DOSE-RELATED AND PREVENTABLE MOSTLY REVERSIBLE (When stopping the drug the body will return to its normal)
- Increase dose increase augmented type

## EXAMPLES:-

**ANTICOAGULANTS (E.G., WARFARIN, HEPARIN) – BLEEDING** (If there action increased this will lead to bleeding)

**ANTI-HYPERTENSIVES (E.G., A1-ANTAGONISTS) – HYPOTENSION** it supposed to normalize the tension but if it action increased hypotension occurs

**ANTI-DIABETICS (E.G., INSULIN) – HYPOGLYCEMIA** it supposed to \_ normalize but if augmented then increase occur

## TYPE B- BIZZARE

Fatal+serious adverse seen in this type but un common

Main difference between B and A types

**HAVE NO DIRECT RELATIONSHIP TO THE DOSE OF THE DRUG**

**DEVELOP ON THE BASIS OF:**

- **IMMUNOLOGICAL REACTION TO THE DRUG (ALLERGY)** --> Can be avoided by sensitivity test

When give a patient a penicillin the symptoms vary (rash, swelling...till anaphylactic shock) Allergy occurs because antigen antibody reaction antigen (penicillin) , antibody (IgE in mast cells.) which will cause it's degradation ,so histamine will leak out side and cause the symptoms. to solve this problem we use adrenaline , which is a physiological antagonist (one system with 2 types : H1 for histamine and B for adrenaline)

In the anaphylactic shock we give the patient adrenaline + antihistamine + cortisone. Or just antihistamine +cortisone if there is no adrenaline.

- **GENETIC PREDISPOSITION (IDIOSYNCRACY) ABNORMAL DRUG REACTIONS**
- **EXAMPLES????**

As(succinylcholine apnea) when a person take succinylcholine ( a relaxant) and his body doesn't contain (pseudocholinesterase )which lead to paralysis of respiratory muscle.

Favism which is (G-6-PD deficiency ) when a person with this disease take aspirin (hemolytic anemia) will occur .

- **MORE SERIOUS CLINICAL OUTCOMES WITH HIGHER MORTALITY AND MORBIDITY** fatal ,serious adverse, effect seen in this type But un common . Main difference between B and A types

- **MOSTLY REQUIRE IMMEDIATE WITHDRAWAL OF THE DRUG**
- **UNCOMMON**

## **TYPE C – CHRONIC (CONTINUOUS) USE**

**THEY ARE MOSTLY ASSOCIATED WITH CUMULATIVE- LONG TERM EXPOSURE**

**EXAMPLE:- ANALGESIC (NSAID) as aspirin morphine – INTERSTITIAL NEPHRITIS, PAPILLARY, SCLEROSIS which will lead to renal failure and then lead to death**

## **TYPE D – DELAYED**

**some drugs after a long time of usage appear cancer Or a drug can cause a genetic mutation and this mutation will appear after years or will not appear and can be transformed to the next generation.**

**THEY MANIFEST THEMSELVES WITH SIGNIFICANT DELAY •**

**TERATOGENESIS -THALIDOMIDE – PHOCOMELIA (FLIPPER-LIKE LIMBS) •**

**MUTAGENESIS •**

**CANCEROGENESIS**

## **TERATOGENICITY (TERATOS- MONSTER)**

**It appears after pregnancy that's way it is delayed.**

**DRUG TO CAUSE FOETAL ABNORMALITIES WHEN ADMINISTERED TO THE PREGNANT MOTHER.**

**•DRUGS CAN AFFECT THE FOETUS AT 3 STAGES- (I) FERTILIZATION AND IMPLANTATION-CONCEPTION TO 17**

**DAYS-FAILURE OF PREGNANCY WHICH OFTEN GOES**

**UNNOTICED(Because the mother doesn't know that she is pregnant so if she take a drug can cause end of pregnancy.**



## First 2 week)

(II) ORGANOGENESIS-18 TO 55 DAYS OF GESTATION MOST VULNERABLE PERIOD, DEFORMITIES ARE PRODUCED. **Because it is a period of organogenesis malformation of an organ can occur because of drug causes anomalies**

(III) GROWTH AND DEVELOPMENT-56 DAYS ONWARDS DEVELOPMENTAL AND FUNCTIONAL ABNORMALITIES CAN OCCUR **Because taking a drug that causes anomalies. Growth retardation)**

E.G. ACE INHIBITORS(GROWTH RETARDATION) , THALIDOMIDE, WARFARIN (EYE AND HAND DEFECTS, ANTIEPILEPTIC DRUGS (CLEFT LIP/PALATE)(**THALIDOMIDE (دواء مهدئ للاحوامل)** all babies that there mothers took this drug born with a deformity that is called phocomelia ( no upper limb , no lower limb)

## MUTAGENICITY AND CARCINOGENICITY

CAUSE GENETIC DEFECTS AND CANCER RESPECTIVELY

MUTAGENICITY: REACTIVE INTERMEDIATES WHICH AFFECT GENES AND MAY CAUSE STRUCTURAL CHANGES IN THE CHROMOSOMES( **when drug release a toxic metabolites which cause mutations in chromosomes and genes which can appear in a person later on Or in other generations.**)

### Cells مهينة to cancer

• **CARCINOGENICITY: CERTAIN CHEMICALS CAN PROMOTE MALIGNANT CHANGE IN GENETICALLY DAMAGED CELLS, RESULTING IN CARCINOGENESIS.(When a person is treated by isotopes Or when persons take anti cancer drugs , after a period if time a new cancer can appear in his body)**

• **EXAMPLES- ANTICANCER DRUGS, RADIOISOTOPES, ESTROGENS (cause breast cancer), TOBACCO(cause lung cancer)**

## TYPE E – END OF USE

### DRUG WITHDRAWAL SYNDROMES AND REBOUND PHENOMENONS

#### EXAMPLE – SUDDEN WITHDRAWAL OF LONG TERM THERAPY

#### WITH $\beta$ -BLOCKERS CAN INDUCE REBOUND TACHYCARDIA

AND HYPERTENSION( patient with hypertension was treated by B-blockers as (metoprolol) .. if the patient felt fine and stopped the drug this can cause rebound hypertension . Which is an adverse reaction of Beta blocker when

sudden end of use.

Occur because the up regulation of the receptor = increase number of receptors . Which is a result of prolonged use of antagonistic (beta B blockers : bind to (B receptors )and when B blocked the pressure increase)) when sudden withdrawal of receptors will bind to adrenaline +nor adrenaline , cause severe hypertension which cause myocardial infraction and death

The solve of this problem gradual withdrawal.

)

## TYPE F- FAILURE OF RESPONSE (TOLERANCE)

### FAILURE OF RESPONSIVENESS TO THE USUAL DOSE

OF A DRUG(so we keep increasing dose till it reach toxicity)

• TYPES: 1- ACQUIRED 2- CONGENITAL

IT OCCURS ON REPEATED ADMINISTRATION OF THE DRUG. •

MORE DOSES ARE NEEDED TO OBTAIN THE ORIGINAL EFFECT. •

IT IS REVERSIBLE: IT DISAPPEARS WHEN THE DRUG IS STOPPED FOR SOME TIME. •

EXAMPLES OF DRUGS CAUSING TOLERANCE: MORPHINE, NITRATES,

XANTHINES AND BARBITURATES(NITRATES used in the treatment of angina. As the doctor give them a free day from the drug ,so the body return the enzyme +mechanism of the drug , so it keep useful

XANTHINES for treating bronchial asthma)



## • MECHANISM OF ACQUIRED TOLERANCE:

1. DECREASED INTESTINAL ABSORPTION OF DRUGS.-----> in

pharmacokinetic

2. INCREASED RENAL EXCRETION OF DRUGS.-----> in pharmacokinetic

3. INCREASED METABOLISM OF DRUGS DUE TO ENZYME

INDUCTION-----> in pharmacokinetic

4. CELLULAR ADAPTATION TO THE PRESENCE OF THE DRUG.-->in

pharmacodynamic When stopping the drug a period of time the mechanism return

back ( as enzymes of metabolism and Carriers of absorption )

will be regenerated

+ receptors will restore there sensitivity

## • SPECIAL TYPES OF ACQUIRED TOLERANCE

1. TACHYPHYLAXIS: (Acquired tolerance)

• IT IS ACUTE RAPID DEVELOPMENT OF ACQUIRED

TOLERANCE.(So the tolerance will occur after the first dose) •

THE ORIGINAL EFFECT CAN NOT BE OBTAINED BY INCREASING THE DOSE.

• EXAMPLE: TACHYPHYLAXIS TO ACTION OF EPHEDRINE ON

BLOOD PRESSURE (It affect one time and then even if we increased the dose there will be no effect)

MECHANISM OF TACHYPHYLAXIS TO EPHEDRINE:

• A - RATE OF DISSOCIATION OF EPHEDRINE(Decrease the blood pressure) IS MODERATE SO FEWER AND FEWER RECEPTORS ARE AVAILABLE.

Ephedrine: works in 2 ways: 1- direct on receptor

2- indirect ..by releasing noradrenaline

b. DOWN REGULATION OF RECEPTORS(With each dose more down regulation will occur )

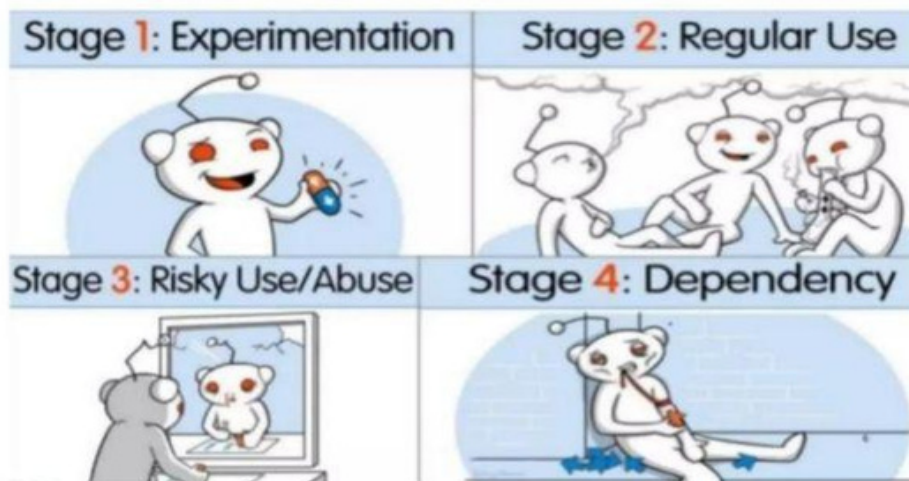
c. DEPLETION OF NORADRENALINE STORES ( because the nerve still didn't release more)

1. CROSS-TOLERANCE:TOLERANCE FOR DRUGS OF RELATED GROUPS E.G. MORPHINE AND PETHIDINE.
2. TISSUE TOLERANCE:TO SOME ACTIONS OF THE DRUG. E.G. MORPHINE TOLERANCE TO ANALEGESIC AND RESPIRATORY(Which leads to increase the dose) DEPRESSANT ACTIONS BUT NOT TO ITS MIOTIC (Pinpoint pupil eyes appear on the addiction) AND CONSTIPATING ACTIONS AND CONSTIPATING ACTIONS . (if tolerance doesn't occur he will die )
3. BACTERIAL RESISTANCETO ANTIBIOTICS

## CONGENITAL TOLERANCE

1. RACIAL: EPHEDRINE (Causes mydriasis( dilation of eye pupils ) in normal people.) IS NOT MYDRIATIC IN NEGROS
2. SPECIES: RABBITS TOLERATE LARGE AMOUNTS OF ATROPINE (Also causes mydriasis in normal cases .)AS RABBITS' BLOOD AND PLASMA CONTAIN ATROPINASE ENZYME WHICH RAPIDLY DETOXICATE ATROPINE
3. INDIVIDUAL TOLERANCE(Caused-by genetic of individuals)

## STAGES OF ADDICTION



patient in this stage take the drug because of his bad mood or for pain. Increase dose to reach the effect

## TOP TEN DRUGS

- MARIJUANA

- HEROIN

- COCAINE(CNS stimuli while morphine is CNS depressed .)

ALCOHOL

TOBACCO

LSD (Lysergic acid diethylamide)

SPEEDBALL(( morphine +cocaine ) very dangerous because you take 2 drugs with there effect ..cause burden on lung)

- MDMA

KETAMINE

CRYSTAL-METH(Causes symptoms as symptom of schizophrenia  
(بسبب اوهام قد تؤدي الى ارتكاب جريمة)

## DRUG DEPENDENCE

- USE OF DRUGS FOR PERSONAL SATISFACTION PHYSICAL DEPENDENCE IT IS AN ALTERED PHYSIOLOGICAL STATE PRODUCED BY REPEATED ADMINISTRATION OF A DRUG WHICH NECESSITATES THE CONTINUED PRESENCE OF THE DRUG TO MAINTAIN PHYSIOLOGICAL EQUILIBRIUM

- DISCONTINUATION OF THE DRUG RESULTS IN A

CHARACTERISTIC WITHDRAWAL (ABSTINENCE) SYNDROME(The opposite of the action of the drug for example morphine is CNS depressant so it's Abstinence lead to CNS stimuli appear as shouting , angry)

Also person under cocaine( CNS stimuli )effects be : angry ....

But when he under abstinence ( CNS depressant) effects the person will be quite

# DRUG ABUSE

(Abused; wrong use of drugs):

REFERS TO USE OF A DRUG BY SELF-MEDICATION IN A MANNER AND AMOUNT THAT DEVIATES FROM THE APPROVED MEDICAL AND SOCIAL PATTERNS IN A GIVEN CULTURE AT A GIVEN TIME. • DRUG ADDICTION

Marijuana is legal in some countries so in this state it's not considered as drug abuse. But abuse if used inside the class.

- DRUG ADDICTION
- COMPULSIVE DRUG SEEKING AND USE DESPITE ADVERSE CONSEQUENCES

## • DRUG HABITUATION (PSYCHOLOGICAL DEPENDENCE)

- LESS INTENSIVE INVOLVEMENT WITH THE DRUG, SO THAT ITS WITHDRAWAL PRODUCES ONLY MILD DISCOMFORT.(not abstinence)
- CONSUMPTION OF TEA, COFFEE, TOBACCO, SOCIAL DRINKING ARE REGARDED HABITUATING, PHYSICAL DEPENDENCE IS ABSENT(While in morphine (for example) it contains 2 types of dependency ( physiological and physical)

## INTOLERANCE

- IT IS EXAGGERATED PHARMACOLOGICAL RESPONSE TO THE USUAL DOSE OF THE DRUG • EXAMPLE: ADRENALINE IN THYROTOXICOSIS(contain more beta receptor so when giving a dose of adrenaline its effect will be higher than usual Because of up regulation of receptor because of thyrotoxicosis)

## DRUG INDUCED DISEASES

- THESE ARE ALSO CALLED IATROGENIC (PHYSICIAN INDUCED) DISEASES, AND ARE DISEASE CAUSED BY DRUGS .(Here the physician who is the cause Because he had to give appropriately dose)

- EXAMPLES: • HEPATITIS BY ISONIAZID AND RIFAMPICIN • PEPTIC ULCER BY SALICYLATES (**Aspirin**)AND CORTICOSTEROIDS
- RETINAL DAMAGE BY CHLOROQUINE

## MANAGEMENT OF ADRS

- STOP THE SUSPECT DRUG(S)(**that causes the adverse effect**) OR
- REDUCE THE DOSE OF SUSPECT DRUGS(S)
- CONSIDER WHY THE DRUG THERAPY IS PRESCRIBED
- CONSIDER WHETHER ALTERNATIVE TREATMENT IS AVAILABLE
- AND TREAT THE SYMPTOMS (WHERE POSSIBLE)

## PREVENTION OF ADVERSE EFFECTS TO DRUGS

- AVOID INAPPROPRIATE USE OF DRUGS(**as antibiotics**)
- APPROPRIATE DRUG ADMINISTRATION (RATIONAL THERAPEUTICS)
  - DOSE
  - DOSAGE FORM
  - DURATION
  - ROUTE
  - FREQUENCY
  - TECHNIQUE
- ASK FOR PREVIOUS HISTORY OF DRUG REACTIONS AND ALLERGIES
- ALWAYS SUSPECT ADR WHEN NEW SYMPTOM (**Adverse effect**)ARISES AFTER INITIATION OF TREATMENT.
- ASK FOR LABORATORY FINDINGS LIKE SERUM CREATININE ETC

## PHARMACOVIGILANCE (DAUP)

THE 'SCIENCE AND ACTIVITIES RELATING TO THE DETECTION, ASSESSMENT, UNDERSTANDING AND PREVENTION OF ADVERSE EFFECTS OR ANY OTHER DRUG RELATED PROBLEMS'

THE INFORMATION GENERATED IS USEFUL IN EDUCATING DOCTORS AND IN THE OFFICIAL REGULATION OF DRUG USE. IT HAS AN IMPORTANT ROLE IN RATIONAL USE OF MEDICINES,

AS IT PROVIDES THE BASIS FOR ASSESSING SAFETY OF MEDICINES.

### VARIOUS ACTIVITIES INVOLVED IN PHARMACOVIGILANCE ARE

:

- POST MARKETING SURVEILLANCE AND OTHER METHODS OF ADR MONITORING SUCH AS VOLUNTARY REPORTING BY DOCTORS' PRESCRIPTION.
- DISSEMINATION OF ADR DATA THROUGH 'DRUG ALERTS', 'MEDICAL LETTERS,' ADVISORIES SENT TO DOCTORS BY PHARMACEUTICALS AND REGULATORY AGENCIES.
- CHANGES IN THE LABELLING OF MEDICINES INDICATING RESTRICTIONS IN USE OR WARNINGS, PRECAUTIONS, OR EVEN WITHDRAWAL OF THE DRUG.

فرصة جيّدة..

لإعادة النّظر في كلّ ما انشغلنا به سابقًا، لِكُلِّ فراغ أخذ من وقتنا، لكلّ تفاهةٍ شغلت أيماننا، لكلِّ متابعةٍ كانت لا تستحق، فرصة جيّدة للتّخفّف من أثقال الحياة، للتّركيز على الآخرة، للانتباه على الغاية والهدف.. عرّفتم الطّريق، فالزموا.

