



FACTORS AFFECTING DRUG ACTION



VARIATIONS IN DRUG RESPONSE DUE TO MANY REASONS –

- DIFFERENCE IN PHARMACOKINETIC HANDLING OF DRUGS – VARIABILITY IN PLASMA CONC.
- RECEPTOR NO. OR STATE DIFFERENCE
- OTHER HOST AND ENVIRONMENTAL FACTORS

KNOWLEDGE CAN GUIDE THE CHOICE OF APPROPRIATE DRUG AND DOSE FOR AN INDIVIDUAL PATIENT.

FACTORS AFFECTING DRUG ACTION

- BODY SIZE
- PREGNANCY
- LACTATION
- AGE – PEDIATRIC & GERIATRIC
- GENETIC FACTORS
- DISEASE STATES – KIDNEY & LIVER
- ROUTES OF DRUG ADMINISTRATION
- ENVIRONMENTAL FACTORS
- PSYCHOLOGICAL FACTORS
- TOLERANCE & RESISTANCE

FACTORS INCLUDE

BODY SIZE

- INFLUENCES THE CONCENTRATION OF DRUG ATTAINED AT THE SITE OF ACTION
- AVERAGE ADULT DOSE FOR – MEDIUM BUILT
- FOR EXT.OBESE OR LEAN INDIVIDUAL –
- $\text{INDIVIDUAL DOSE} = \text{BW(kg)}/70 \times \text{AVERAGE ADULT DOSE}$

- BODY SURFACE AREA (BSA) PROVIDES A MORE ACCURATE BASIS FOR DOSE CALCULATION
INDIVIDUAL DOSE = $BSA (m^2) / 1.7 \times AV. ADULT DOSE$
- **$BSA(m^2) = BW(Kg)^{0.425} \times HEIGHT(cm)^{0.725} \times 0.007184$**
- OBTAINED FROM CHART FORM OR SLIDE RULE NOMOGRAMS BASED ON BW AND HEIGHT. AVAIL. FOR SOME DRUGS.




DRUG THERAPY IN PREGNANCY

- MOST DRUGS CAN CROSS THE PLACENTA AND EXPOSE THE DEVELOPING EMBRYO AND FETUS TO THEIR PHARMACOLOGIC AND TERATOGENIC EFFECTS .
- AS A RULE TRY TO AVOID GIVING ANY DRUG DURING PREGNANCY, IF POSSIBLE .




FACTORS AFFECTING PLACENTAL DRUG TRANSFER AND DRUG EFFECTS ON FETUS

- THE PHYSICOCHEMICAL PROPERTIES OF DRUG.
- RATE AT WHICH DRUG CROSSES THE PLACENTA AND AMOUNT OF DRUG REACHING THE FETUS.
- DURATION OF EXPOSURE TO DRUG.

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- DISTRIBUTION CHARACTERISTICS IN DIFFERENT FETAL TISSUES.
 - STAGE OF PLACENTAL AND FETAL DEVELOPMENT AT THE TIME OF EXPOSURE TO DRUG.
 - THE EFFECTS OF DRUGS USED IN COMBINATION.

LIPID SOLUBILITY

- DRUG PASSAGE ACROSS THE PLACENTA IS DEPENDENT ON
- **LIPID SOLUBILITY AND**
- **DEGREE OF DRUG IONIZATION .**
- LIPOPHILIC DRUGS DIFFUSE READILY ACROSS THE PLACENTA AND ENTER THE FETAL CIRCULATION
- **FOR EXAMPLE- THIOPENTAL , DRUG USED FOR CEASARIAN SECTION (CS) CROSSES THE PLACENTA ALMOST IMMEDIATELY AND CAN PRODUCE SEDATION OR APNEA IN NEWBORN.**

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- HIGHLY IONIZED DRUGS LIKE SUCCINYLCHOLINE, ALSO USED FOR CS, CROSSES THE PLACENTA SLOWLY AND ACHIEVES VERY LOW CONC. IN FETUS.
 - **IMPERMEABILITY OF PLACENTA TO POLAR COMPOUNDS IS RELATIVE NOT ABSOLUTE .**
 - IF HIGH ENOUGH MATERNAL - FETAL CONC. GRADIENTS ARE ACHIEVED, POLAR COMPOUNDS CROSS THE PLACENTA IN GOOD AMOUNTS.

MOLECULAR SIZE

- MOL. WT. OF DRUG ALSO INFLUENCES THE RATE OF TRANSFER AND AMOUNT OF DRUG TRANSFERRED ACROSS THE PLACENTA.
- e.g. **HEPARIN** , A VERY LARGE POLAR MOLECULE IS UNABLE TO CROSS THE PLACENTA WHILE **WARFERIN** CAN CROSS & IS TERATOGENIC, SHOULD BE AVOIDED DURING FIRST TRIEMESTER.



- **PLACENTAL TRANSPORTERS –**

- P GLYCOPROTEIN TRANSPORTER PUMPS BACK INTO THE MATERNAL CIRCULATION A VARIETY OF DRUGS , INCLUDING ANTICANCER DRUGS.
- DRUGS ACHIEVE LOW CONC. IN FOETAL CIRCULATION.

- **PROTEIN BINDING –**

- DEGREE OF PP BINDING AFFECTS THE TRANSFER OF DRUGS THAT ARE POORLY LIPID SOLUBLE AND IONIZED.
- VERY LIPID SOLUBLE DRUGS DIFFUSE ACROSS PLAC. MEMBRANE VERY RAPIDLY AND FREELY , NOT AFFECTED BY PP BINDING.

P/Ds

- **MATERNAL DRUG ACTION –**
- **PHYSIOLOGICAL CHANGES AFFECT DRUG DISPOSITION -**
- **CARDIAC OUTPUT & RENAL BLOOD FLOW**
- **EXPANSION OF E.C.F AND PLASMA VOLUME**
- **FALL IN PLASMA ALBUMIN AND INCREASE IN α_1 ACID GLYCOPROTEIN – UNBOUND FRACTION OF ACIDIC DRUGS INCREASES, BASIC DRUGS DECREASES.**
- **HEPATIC MICROSOMAL ENZYME INDUCTION**



TOXIC DRUG REACTIONS IN FOETUS

- ANGIOTENSIN CONVERTING ENZYME INHIBITORS DURING PREGNANCY CAN RESULT IN SIGNIFICANT AND IRREVERSIBLE RENAL DAMAGE IN FOETUS , C/I IN PREG.
- **DELAYED ADVERSE EFFECT** – FEMALE FETUS EXPOSED TO DIETHYL STILBESTEROL, ARE AT INCREASED RISK FOR ADENOCARCINOMA OF VAGINA AFTER PUBERTY .

TERATOGENIC DRUG ACTIONS

- A SINGLE INTRA-UTERINE EXPOSURE TO A DRUG CAN AFFECT THE FETAL STRUCTURES UNDER-GOING RAPID DEVELOPMENT AT THE TIME OF EXPOSURE .
- EXAMPLE - **THALIDOMIDE** - PHOCOMELIA (SEAL LIMBS)
- **VIT A ANALOGUES** – TERATOGENIC , AFFECTS TISSUE DIFFERENTIATION.
- **HIGH DOSES OF ETHANOL** – FETAL ALCOHOL SYNDROME, CNS EFFECTS , GROWTH , FACIAL DEVELOPMENT AFFECTED.
- **TERATOGENIC RISK QUANTIFIED ---**
- **A(SAFE) -X(DEFINITIVE HUMAN TERATOGENICRISK)**



DRUG USE DURING LACTATION

- MOST DRUGS DETECTABLE IN BREAST MILK.
- But in low conc.
- Less than therapeutic dose .
- If must , timing- 30-60 min after nursing, 3-4 hrs before the next feed.
- This allows many drugs to be cleared from mother's blood.
- Avoid , if no safety data available.

DRUG USE DURING LACTATION

- Most antibiotics detected in milk. e.g. tetracycline concentrations in breast milk are 70 % of maternal serum conc. , present a risk of permanent tooth staining in infant.
- Isoniazid – pyridoxine deficiency in infant.
- Diazepam – sedative effect.
- Mothers taking anticancer therapy should avoid breast- feeding.


DRUG THERAPY IN PEDIATRIC PATIENTS

- **INFANTS & CHILDREN ARE NOT SMALL ADULTS IN THE WAY THEIR BODIES HANDLE DRUGS .**
- **RAPID AND IMPORTANT AGE RELATED PHYSIOLOGIC CHANGES IN DRUG METABOLISM AND ELIMINATION OCCUR IN CHILDREN ESP. DURING FIRST YEAR OF LIFE .**
- **A KNOWLEDGE OF AGE-RELATED CHANGES IN DRUG ABSORPTION , DISTRIBUTION , AND CLEARANCE IS ESSENTIAL TO OPTIMIZE DRUG EFFICACY AND TO AVOID TOXICITY.**

P/K PRINCIPALS IN NEONATES AND INFANTS AND CLINICAL RELEVANCE

DRUG ABSORPTION

- **ABSORPTION FROM GIT-**
- **↓ INTESTINAL MOTILITY AND DELAYED GASTRIC EMPTYING IN NEONATES AND INFANTS RESULTS IN LONGER PERIODS OF TIME FOR A DRUG TO REACH SIMILAR PLASMA CONC. AFTER ORAL ADMINISTRATION .**
- **ORAL ABSORPTION OF ACETAMINOPHEN, PEN.G, PHENOBARBITAL – LOWER IN INFANTS**

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- DIFFERENT FLORA COLONIZE THE STERILE FETAL INTESTINE .
 - GI ENZYME ACTIVITIES ARE LOWER IN NEWBORN THAN IN ADULTS .
 - LOW CONC. OF BILE ACIDS, DECREASES THE ABSORPTION OF LIPID SOLUBLE DRUGS .

DRUG DISTRIBUTION

- NEONATE HAS A HIGHER % OF ITS BODY WT. IN THE FORM OF WATER (70-75%) THAN ADULTS (50-60%) .
- EXTRACELLULAR WATER IS 40 % OF LEAN BODY WT. COMPARED WITH 20 % IN ADULTS .
IMPORTANT FOR CONC. OF WATER SOLUBLE DRUGS.
- **PROTEIN BINDING OF DRUGS IS LESS IN NEONATES . AFFECTS - LA , DIAZEPAM, PHENYTOIN .**

DRUG METABOLISM


- DRUG METABOLIZING ACTIVITIES OF CYTOCHROME P₄₅₀ DEPENDENT MIXED FUNCTION OXIDASES AND CONJUGATING ENZYMES ARE SUBSTANTIALLY LOWER IN EARLY NEONATAL LIFE THAN LATER .
- GLUCURONIDE FORMATION REACHES ADULT VALUES B/W THIRD AND FOURTH YEARS OF LIFE.
- SLOW CLEARANCE RATES AND PROLONGED ELIMINATION HALF LIVES.

DRUG EXCRETION

- GFR MUCH LOWER IN NEWBORNS, UPTO FIRST FEW DAYS OF LIFE.
- 30-40 % OF ADULT VALUE .
- EVEN LOWER IN PREMATURE INFANTS
- IT AFFECTS THE CLEARANCE OF MANY DRUGS.
- e.g . Penicillins, digoxin .


Pediatric drug dosage

- SIMPLE PROPORTIONATE REDUCTION IN ADULT DOSE MAY NOT BE ADEQUATE TO DETERMINE A SAFE AND EFFECTIVE PEDIATRIC DOSE .
- MOST OF DRUGS HAVE LEAFLET WITH PEDS DOSE WRITTEN IN - mg/kg
- IF NOT AVAILABLE , CALCULATE ON THE BASIS OF AGE , WT, SURFACE AREA BY USING ONE OF FOLLOWING FORMULAS.....

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- **YOUNG'S FORMULA –**
 - **CHILD DOSE = $\text{AGE} / \text{AGE} + 12 \times \text{ADULT DOSE}$**

 - **DILLING'S FORMULA –**
 - **CHILD DOSE = $\text{AGE} / 20 \times \text{ADULT DOSE}$**

 - **DOSE CALCULATION ON THE BASIS OF BODY SURFACE AREA**

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- SOLID DOSAGE FORMS AND AEROSOL INHALATION ARE DIFFICULT TO ADMINISTER TO YOUNG CHILDREN .
 - MANY DRUGS PREPARED FOR CHILDREN ARE IN THE FORM OF ELIXIRS OR SUSPENSIONS.
 - **ELIXIRS** ARE ALCOHOLIC SOLUTIONS IN WHICH THE DRUG MOLECULES ARE DISSOLVED AND EVENLY DISTRIBUTED. NO SHAKING IS REQUIRED.
 - **SUSPENSIONS** CONTAIN UNDISSOLVED PARTICLES OF DRUG THAT MUST BE DISTRIBUTED THROUGHOUT THE VEHICLE BY SHAKING .

- COMPLIANCE
- TEASPOONFUL – 2.5- 7.8 ml
- INCORRECT PLACEMENT OF DECIMAL POINT
- INADEQUATE ANTIBIOTIC USE

- **SPECIAL ADVERSE EFFECTS –**
- **SUPPRESSION OF GROWTH WITH CORTICOSTEROIDS .**
- **ANDROGENS MAY PROMOTE EARLY FUSION OF EPIPHYSIS SO STUNTING OF STATURE.**

GENETICS

- DOSE OF A DRUG TO PRODUCE THE SAME EFFECT MAY VARY BY 4-6 FOLD AMONG DIFFERENT INDIVIDUALS **BECAUSE OF -**
- **DIFFERENT RATE OF METABOLISM-** DUE TO DIFFERENCE IN THE AMOUNT AND ISOFORM PATTERN OF DRUG METABOLISING ENZYMES WHICH IS GENETICALLY CONTROLLED.
- **DIFFERENCES IN TARGET ORGAN SENSITIVITY**

SPECIFIC GENE DEFECTS

- CAN LEAD TO VARIATION IN DRUG RESPONSES -
- e.g.
- **ATYPICAL PSEUDO-CHOLINESTERASE -**
PROLONGED SUCCINYLMCHOLINE INDUCED APNOEA
- **G-6 PD DEFICIENCY -**
- HEMOLYSIS WITH PRIMAQUINE AND OTHER OXIDIZING DRUGS LIKE SULPHONAMIDES , DAPSONE, QUININE , CHLOROQUINE, NALIDIXIC ACID, NITROFURANTOIN

SPECIES & RACE

- DIFFERENCES IN RESPONSIVENESS TO DRUGS AMONG DIFFERENT SPECIES -
- RABBITS ARE RESISTANT TO ATROPINE
- RATS & MICE TO DIGITALIS
- IMP. TO KNOW WHILE EXTRAPOLATING RESULTS FROM EXPERIMENTAL ANIMALS TO MAN
- RACIAL DIFFERENCES IN HUMAN BEINGS - BLACKS REQUIRE HIGHER AND MONGOLS REQUIRE LOWER CONC. OF ATROPINE & EPHEDRINE TO DILATE THE PUPIL .

ROUTE OF ADMINISTRATION

- GOVERNS THE SPEED AND INTENSITY OF DRUG RESPONSE.
- USE & ACTION MAY VARY WITH ROUTE,
e.g. MAGNESIUM SULFATE -GIVEN ORALLY
CAUSES PURGATION
- APPLIED ON INFLAMMED AREAS - ↓SES
SWELLING
- I.V. – PRODUCES C.N.S. DEPRESSION AND
HYPOTENSION




ENVIRONMENTAL FACTORS

- EXPOSURE TO INSECTICIDES , CARCINOGENS, TOBACCO SMOKE , CHARCOAL BROILED MEAT INDUCE DRUG METABOLISM.
- TYPE OF DIET CAN ALTER DRUG ABSORPTION
- SET UP IN WHICH DRUG IS TAKEN – HYPNOTICS WORK BETTER WHEN TAKEN AT NIGHT IN QUIET SURROUNDINGS.


PSYCHOLOGICAL FACTORS

- DRUG'S EFFICACY CAN BE AFFECTED BY PATIENT'S EXPECTATIONS AND ATTITUDE .
- ANXIOUS PATIENT REQUIRES MORE GENERAL ANESTHETIC.

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- **LATIN TERM – PLACEBO – MEANS _ I SHALL PLEASE**
 - **A MEDICINE WHICH HAS NO INHERENT PHARMACOLOGIC ACTIVITY BUT IS INTENDED TO BE EFFECTIVE ONLY BY VIRTUE OF FACTOR OF SUGGESTION , USED FOR ITS SYMBOLIC EFFECT .**

PLACEBO

- FOR CONDITIONS THAT CAN NOT BE EXPLAINED ON A PATHO-PHYSIOLOGIC BASIS OR FOR WHICH NO SPECIFIC TREATMENT IS AVAILABLE,
- PHYSICIAN-PATIENT RELATIONSHIP HAS A MAJOR ROLE IN PLACEBO EFFECT.

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- PLACEBO RELEASES ENDORPHINS IN BRAIN – CAUSING ANALGESIA.
 - CAN SUPPLEMENT PHARMACOLOGICAL EFFECTS
 - HIGHLY VARIABLE EVEN IN SAME INDIVIDUAL.
 - e.g. may induce sleep on the first night ,not subsequently.


DISEASE STATES

GIT DS.

- CAN ALTER THE ABSORPTION OF ORALLY ADMINISTERED DRUGS .
- DRUG ABSORPTION CAN BE INCREASED OR DECREASED.
- e.g. ACHLORHYDRIA DECREASES ASPIRIN ABSORPTION BY CAUSING ITS IONIZATION.

LIVER DISEASES

- BIOAVAILABILITY OF DRUGS HAVING HIGH FIRST PASS METABOLISM IS INCREASED DUE TO LOSS OF HEPATOCELLULAR FUNCTION .
- SERUM ALBUMIN IS REDUCED – PROTEIN BINDING OF ACIDIC DRUGS IS REDUCED AND MORE DRUG IS PRESENT IN FREE FORM.

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- METABOLISM OF SOME DRUGS DECREASED, THEIR DOSE REDUCED/USE ALTERNATIVES. MORPHINE, PENTOBARBITONE, LIDOCAINE, PROPRANOLOL
 - PRO-DRUGS REQUIRING HEPATIC METABOLISM FOR ACTIVATION ARE LESS EFFECTIVE .
PREDNISOLONE , BACAMPICILLIN .

KIDNEY DISEASES

- P/K AND DRUG EFFECTS AFFECTED
- WITH DECREASE IN CREATININE CLEARANCE , CLEARANCE OF DRUGS THAT ARE EXCRETED UNCHANGED IS REDUCED .
- MAINTENANCE DOSE OF SUCH DRUGS SHOULD BE REDUCED .
- SOME DRUGS WORSEN THE EXISTING CLINICAL CONDITIONS IN RENAL FAILURE e.g. NSAIDs CAUSE FLUID RETENTION .
- NEPHROTOXIC ANTIBIOTICS SHOULD BE AVOIDED--

NEPHROTOXIC ANTIBIOTICS

- **AVOIDED EVEN IN MILD FAILURE OR DOSE REDUCTION NEEDED.**
- AMINOGLYCOSIDES
- CEPHALEXIN
- ETHAMBUTOL
- VANCOMYCIN
- AMPHOTERICIN - B
- FLUCYTOCINE
- ACYCLOVIR

DOSE REDUCTION IN SEVERE FAILURE

- CO-TRIMOXAZOLE
- CARBENICILLIN
- CEFOTAXIME
- NORFLOXACIN
- CIPROFLOXACIN
- METRONIDAZOLE

CONGESTIVE HEART FAILURE


- ↓ sed drug absorption from g.i.t. due to mucosal edema & splanchnic vasoconstriction.
e.g. procainamide , hydrochlorothiazide
- ↑ sed Vd for some due to expansion of e.c.f. or ↓ sed due to decreased tissue perfusion.
Loading doses of drugs like lidocaine should be decreased.
- ↓ sed elimination due to decreased g.f.r. ,
dosing rate of some drugs need to be lowered. e.g. lidocaine , procainamide, theophylline

DRUG INTERACTIONS

- DRUGS MAY MODIFY EACH OTHERS RESPONSE BY P/K OR P/D INTERACTION.
- **ADVERSE RESULTS -**
- FRUSEMIDE AND AMINOGLYCOSIDES – ENHANCED OTOTOXICITY
- DIURETICS CAUSE HYPOKALEMIA AND INCREASE DIGITALIS TOXICITY.

ELDERLY

- > 65 YEARS OF AGE
- IMP. CHANGES IN RESPONSE TO CERTAIN DRUGS WITH INCREASING AGE
- **GENERAL CHANGES –**
- INCREASED INCIDENCE OF DISEASE WITH AGE
- POLYPHARMACY
- NUTRITIONAL PROBLEMS
- REDUCED FINANCES
- DECREASED DOSING COMPLIANCE/
OVERCOMPLIANCE

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- **PHYSIOLOGIC CHANGES –**
 - MAJOR ORGAN SYSTEMS SHOW A DECLINE, BEGINNING IN YOUNG ADULTHOOD AND CONTINUING THROUGHOUT LIFE .
 - LINEAR DECREASE BEGINNING AROUND 45 YEARS OF AGE.
 - MOST IMP. IS **DECREASE IN RENAL FUNCTION.**

P/K CHANGES

ABSORPTION

- NO MAJOR ALTERATIONS
- CONDITIONS A/W AGE MAY ALTER THE RATE OF ABSORPTION
- ALTERED NUTRITIONAL HABITS
- GREATER CONSUMPTION OF NON-PRESCRIPTION DRUGS (ANTACIDS, LAXATIVES)
- CHANGES IN GASTRIC EMPTYING, SLOWER IN OLDER PERSONS, ESP. IN OLDER DIABETICS.

DISTRIBUTION


- REDUCED LEAN MASS .
- REDUCED BODY WATER, INCREASED FAT AS A PERCENTAGE OF BODY MASS .
- DECREASE IN SERUM ALBUMIN , WHICH BINDS MANY DRUGS ESP. WEAK ACIDS .
- INCREASE IN α ACID GLYCOPROTEIN, THAT BINDS BASIC DRUGS .
- RATIO OF BOUND TO FREE MAY BE ALTERED.
- MAY ALTER LOADING DOSE .

METABOLISM

- CHANGES ARE IN **PHASE I REACTIONS** i.e. THOSE CARRIED OUT BY MICROSOMAL P₄₅₀ SYSTEMS
- SMALLER CHANGES IN PHASE II REACTIONS
- CHANGES MAY BE DUE TO DECREASED LIVER BLOOD FLOW, IMP. FOR DRUGS WITH HIGH HEPATIC EXTRACTION RATIO.
- RECOVERY FROM INJURY DELAYED (DUE TO ALCOHOL OR VIRAL HEPATITIS)
- NUTRITIONAL DEF. MAY ALTER HEPATIC FUNCTION.

ELIMINATION

- AGE RELATED DECLINE OF RENAL FUNCTIONAL CAPACITY
- GFR MAY FALL UPTO 50%.
- ↓ IN CREATININE CLEARANCE IN TWO THIRDS OF POPULATION
- MARKED PROLONGATION OF HALF LIFE OF MANY DRUGS (DRUGS THAT ARE SIGNIFICANTLY EXCRETED BY KIDNEY), ACCUMULATION TO TOXIC LEVELS IF DOSAGE NOT REDUCED IN SIZE OR FREQUENCY.

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- e.g. AMINOGLYCOSIDES, LITHIUM, DIGOXIN, CHLORPROPAMIDE, CIMETIDINE, SOME NSAIDs.
 - ELDERLY ARE LIKELY TO BE ON MULTIPLE DRUG THERAPY FOR HT , IHD , DIABETES , ARTHRITIS WHICH INCREASES THE CHANCES OF DRUG INTERACTIONS.
 - PROSTATISM IN ELDERLY MALES - VOIDING IS DIFFICULT WITH ANTICHOLINERGICS.



GEN.GUIDELINES OF GERIATRIC PRESCRIBING

- EVALUATE THE NEED FOR DRUG THERAPY
- TAKE A CAREFUL H/O HABITS & DRUG USE
- KNOW THE PHARMACOLGY OF DRUG PRESCRIBED
- BEGIN WITH RELATIVELY SMALL DOSES
- TITRATE DRUG DOSE WITH PATIENT RESPONSE
- SIMPLIFY THE DRUG REGIMEN & ENCOURAGE COMPLIANCE
- REGULARLY REVIEW THE TREATMENT PLAN & DISCONTINUE DRUGS NO LONGER NEEDED.
- REMEMBER THAT DRUGS CAN CAUSE NEW PROBLEMS OR EXACERBATE THE CHRONIC PROBLEMS.

TOLERANCE

- REQUIREMENT OF HIGHER DOSE OF A DRUG TO PRODUCE A GIVEN RESPONSE.
- **NATURAL** - INHERENTLY LESS SENSITIVE TO THE DRUG
- **ACQUIRED** – BY REPEATED USE OF A DRUG IN AN INDIVIDUAL WHO WAS INITIALLY RESPONSIVE . A CONTINUOUS PRESENCE OF DRUG IN THE BODY LEADS TO TOLERANCE.

CROSS-TOLERANCE

- DEVELOPMENT OF TOLERANCE TO PHARMACOLOGICALLY RELATED DRUGS .
- ALCOHOLICS TO BARBITURATES.
- CLOSER THE DRUGS , MORE COMPLETE IS THE TOLERANCE

MECHANISM OF TOLERANCE

- P/K – EFFECTIVE CONC. OF DRUG AT ACTIVE SITE DECREASED, BY INCREASED DRUG ELIMINATION ON CHRONIC USE e.g. barbiturates , carbamazepine, amphetamine.
- P/D – DRUG ACTION IS LESSENERD
CELLS OF TARGET ORGAN BECOME LESS RESPONSIVE e.g. morphine, barbiturates, salbutamol, nitrates. **Due to down regulation of receptors.**

TACHYPHYLAXIS

- **RAPID DEV. OF TOLERANCE** - DOSES OF A DRUG REPEATED IN QUICK SUCCESSION RESULT IN MARKED REDUCTION IN RESPONSE.
- USUALLY SEEN WITH INDIRECTLY OCCURRING DRUGS e.g. EPHEDRINE , TYRAMINE WHICH ACT BY RELEASING CATECHOLAMINES IN THE BODY , SYNTHESIS CAN'T MATCH RELEASE WHEN DOSES GIVEN IN QUICK SUCCESSION, STORES GET DEPLETED.

DRUG RESISTANCE

- TOLERANCE OF MICRO-ORGANISMS TO INHIBITORY ACTION OF ANTIMICROBIALS.
- e.g. STAPHYLOCOCCUS TO PENICILLIN G