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 – PEADIATRIC & 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 –
- INDIVIDUAL DOSE = \( \frac{BW(kg)}{70} \times AVERAGE\ ADULT\ DOSE \)
• BODY SURFACE AREA (BSA) PROVIDES A MORE ACCURATE BASIS FOR DOSE CALCULATION

INDIVIDUAL DOSE = BSA \( (m^2) \)/1.7 X AV. ADULT DOSE

• BSA\( (m^2) \) = BW(Kg)\(^{0.425}\) X HEIGHT(cm)\(^{0.725}\) X 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 PHARMAKOLOGIC 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.
- 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, a drug used for cesarian section (CS) crosses the placenta almost immediately and can produce sedation or apnea in newborn.
• 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 $\alpha_1$ 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
• 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.....
• **YOUNG’S FORMULA –**
  CHILD DOSE = \( \frac{\text{AGE}}{\text{AGE} + 12} \times \text{ADULT DOSE} \)

• **DILLING’S FORMULA –**
  CHILD DOSE = \( \frac{\text{AGE}}{20} \times \text{ADULT DOSE} \)

• **DOSE CALCULATION ON THE BASIS OF BODY SURFACE AREA**
• 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 SUCCINYLCHOLINE 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.
• 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.
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.
• 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
- FLUCYTOSINE
- 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, hydrochlorthiazide
- ↑ 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
• 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 \( \alpha \) 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.
• 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 LESSENED**
  - 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