FACTORS MODIFYING DRUG DOSE-RESPONSE RELATIONSHIP

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Therapeutic Window
Factors Altering The Response to Drug Therapy

Predictable Influencing Factors

BODY SIZE
AGE
GENDER
ROUTE OF ADMINISTRATION
TIME OF ADMINISTRATION
PATHOLOGICAL STATE
TOLERANCE
GENETIC FACTORS
PRESENCE OF OTHER DRUGS
BODY SIZE

• Body weight and composition
  ▶ Drug achieves a higher concentration in smaller people given the same dosage (will produce a more intense effect)
  ▶ The “body surface area” calculation is better than body weight because it takes into account weight as well as how fat or lean the person is (% body fat)
  ▶ Dosages must be adapted to size

Drugs and Age of Patients

* Most drugs are developed and tested in young to middle-aged adults

* Drug consumption is different

* Dosage regimen cannot be based on body weight or surface area extrapolated from adult dosage

* Therapeutic disasters: 
  - Gray Baby Syndrom: chloramphenicol
  - Thalidomide: Teratogenic effect
  - Isotretinion (Accutane®): Teratogenic effect
AGE PERIODS

Populations have several groups

– Premature infants : < 36 weeks gestation
– Full-term infants : 36-40 weeks gestation
– Neonates : 1st 4 weeks post-natal
– Infants : 5-32 weeks post-natal
– Children : 1-12 years
– Adolescents : 12-16 years
– Geriatrics : > 65 years

Changes in Body Proportions with Age

<table>
<thead>
<tr>
<th>Age</th>
<th>Minerals</th>
<th>Protein</th>
<th>Water</th>
<th>Fat</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2.0%</td>
<td>12.0%</td>
<td>80.0%</td>
<td>6.6%</td>
</tr>
<tr>
<td>Premature (2 kg)</td>
<td>3.2%</td>
<td>13.4%</td>
<td>70.0%</td>
<td>13.4%</td>
</tr>
<tr>
<td>Full term (3.5 kg)</td>
<td>3.0%</td>
<td>13.4%</td>
<td>61.2%</td>
<td>22.4%</td>
</tr>
<tr>
<td>1 yr (10 kg)</td>
<td>4.2%</td>
<td>17.3%</td>
<td>64.8%</td>
<td>13.7%</td>
</tr>
<tr>
<td>10 yr (31 kg)</td>
<td>4.3%</td>
<td>18.1%</td>
<td>64.6%</td>
<td>13.0%</td>
</tr>
<tr>
<td>15 yr (50 kg)</td>
<td>5.5%</td>
<td>16.5%</td>
<td>60.0%</td>
<td>18.6%</td>
</tr>
<tr>
<td>Adult (70 kg)</td>
<td>4.0%</td>
<td>12.0%</td>
<td>54.0%</td>
<td>30.0%</td>
</tr>
<tr>
<td>Elder (65 kg)</td>
<td></td>
<td></td>
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</tr>
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</table>
Developmental Changes in Drug Clearance

- High body water: >70% OF BW
- Decrease in binding to plasma proteins: increase in unbound drug in serum
- Metabolism is slower: pathways of drug metabolism develop variably over the first year
- Limited metabolic clearance: glucuronidation pathway is not developed the first year
- Lower body fat: Highly lipid-soluble drugs distribution is diminished (Diazepam)
- Diminished renal function
- Undeveloped BBB
Age-Dependent of Diazepam Elimination

Elimination half-life of Diazepam is shortest in the infant and longest in the elderly

PEDIATRIC PHARMACOLOGY

CHILDREN ARE NOT SMALL ADULTS!
PEDIATRIC PHARMACOLOGY

- Liver metabolizing enzymes are increased: metabolism faster than adults

![Liver metabolizing enzymes graph]

**Figure 1. A:** Traditional view of cytochrome P450 development.

Table 11-3 ADVERSE DRUG REACTIONS UNIQUE TO PEDIATRIC PATIENTS

<table>
<thead>
<tr>
<th>Drug</th>
<th>Adverse Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Androgens</td>
<td>Premature puberty in males; reduced adult height from premature epiphyseal closure</td>
</tr>
<tr>
<td>Aspirin and other salicylates</td>
<td>Severe intoxication from acute overdose (acidosis, hyperthermia respiratory depression); Reye’s syndrome in children with chickenpox or influenza</td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td>Gray syndrome (neonates and infants)</td>
</tr>
<tr>
<td>Glucocorticoids</td>
<td>Growth suppression with prolonged use</td>
</tr>
<tr>
<td>Fluoroquinolones</td>
<td>Tendon rupture</td>
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<tr>
<td>Hexachlorophene</td>
<td>CNS toxicity (infants)</td>
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<tr>
<td>Nalidixic acid</td>
<td>Cartilage erosion</td>
</tr>
<tr>
<td>Phenothiazines</td>
<td>Sudden Infant death syndrome</td>
</tr>
<tr>
<td>Sulfonamides</td>
<td>Kernicterus (neonates)</td>
</tr>
<tr>
<td>Tetracyclines</td>
<td>Staining of developing teeth</td>
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Compliance problem
  • Poor communication
  • Inconvenient dosage forms
  • Unpalatability
  • Unreliable measurement
  • Spillage, etc

Medication dosage: BW versus BSA

Body Surface Area for Drug Dosage

• Calculations based on the child’s weight are inaccurate
• Physiological differences (body water, fat): larger doses of some drugs on a mg/m2 basis
• BSA is calculated from height and weight (nomogram)
• The surface area rule is the most accurate
Body Surface Area for Drug Dosage

Approximate child’s dose =
Body surface area of the child \times \text{adult dose}

\[ 1.73 \text{ m} \]

GERIATRIC PHARMACOLOGY

Drug Therapy in Geriatric Patients
Drug Therapy in Geriatric Patients

- Elderly constitute 12% of the population but consume 31% of prescribed drugs in US
  - Elderly more sensitive to drugs and exhibit more variability in response
    - Altered pharmacokinetics
    - Multiple and severe illnesses
    - Multiple drug therapy and usage
    - Poor compliance

“Individualization of treatment is essential: each patient must be monitored for desired responses and adverse responses, and the regime must be adjusted accordingly”

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Physiological Changes in Geriatric Patients

- **Increased body fat**: reduces plasma levels of lipid soluble drugs
- **Decreased total body water**: increases concentration of water soluble drugs and intensity of response
- **Reduced concentration of serum albumin**: malnourishment decreases albumin and results in increased drug levels

Altered Pharmacokinetics in Geriatric Patients

- **Metabolism**: hepatic functions decrease in elderly and drug levels increase (amount of dysfunction variable)
- **Excretion**: decline of renal function in elderly (variable)-therefore increase drug levels in plasma
Drugs With Reduced Metabolism or Elimination in The Elderly

Altered Pharmacodynamics in Geriatric Patients

- Pharmacodynamic Changes:
  - Alterations in receptor levels may change on a number of cells, but mostly unknown
  - Example: Beta-adrenergic blocking agents are less effective in the elderly patients.
  - Greater response with CNS-acting drugs (depressants: Valium)
Adverse Drug Reactions in Geriatrics

- Seven times more likely in elderly
- 16% of hospital admissions
- 50% of all medication-related deaths
  - Drug accumulation secondary to reduced renal function
  - Polypharmacy: dangerous practice (drug-drug interactions)
  - Greater severity of illness
  - Presence of multiple pathologies
  - Increased individual variation
  - Inadequate supervision of long-term therapy
  - Poor patient compliance

Polypharmacy

I’m a walking drugstore!

"I feel a lot better since I ran out of those pills you gave me."
Polypharmacy

- Seniors accounts for 25% prescriptions
- Over 75 year old take on average nearly 3 prescribed medications and 1.5 across the counter meds daily!
- In day hospitals, average number of active medications ranges from 5.5-8.3 per day
- Increase in drug-drug interactions and ADR

Gender and Drug Variability

- Factors that influence drug responses are:
  - Sex
  - Pregnancy
  - Breastfeeding
Sex and Drug Variability

- Response is different to same drug and dosage between men and women
- Some are more effective in men, some are more effective in women
- Until recently (1977), all drug research done in males
- **Known difference**: Alcohol is metabolized more slowly in women; women are more sensitive to cardio-toxic effects of terfenadine (seldane) than are men.
- **Hormonal effects?**

Drug Therapy During Pregnancy and Breastfeeding

- 1/3 to 1/2 of pregnant women take at least one prescription drug and most take more
  - Some used to treat pregnancy side effects
    - Nausea
    - Pre-eclampsia
    - Constipation
  - Some medications used to treat chronic disorders
    - Hypertension
    - Diabetes
    - Epilepsy
    - Cancer
    - Infectious Diseases
  - Drugs of abuse
Drug Therapy During Pregnancy and Breastfeeding

• Physiological changes in pregnancy that impact drug dosing are in the:
  – Kidney
  – Liver
  – Gastrointestinal tract
• All drugs cross the placenta
• Drug transfer is
  – Easier—lipid soluble drugs
  – Difficult—ionized, highly polar or protein-bound drugs

Drug Therapy During Pregnancy and Breastfeeding

• Effect of a teratogen is highly dependent on when the drug is given during the pregnancy.

• Sensitivity of fetus to drug is dependent upon developmental stage and when drug is given in relation to the developmental stage

• Gross malformations
  – Cleft palate
  – Clubfoot
  – Hydrocephalus
  – Spina bifida
  – Behavioral and biochemical anomalies
Effects of Teratogens at Specific Stages of Fetal Development

Drugs & Pregnancy

Table 10-1 DRUGS THAT SHOULD BE AVOIDED DURING PREGNANCY BECAUSE OF PROVEN OR STRONGLY SUSPECTED TERATOGENICITY

<table>
<thead>
<tr>
<th>Drug</th>
<th>Teratogenic Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticonvulsants/antidepressant Drugs</td>
<td>CNS malformation, secondary cases</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>CNS and limb malformations</td>
</tr>
<tr>
<td>Lithium</td>
<td>Neuronal tube defects</td>
</tr>
<tr>
<td>Valproic acid</td>
<td>Growth retardation; CNS deficits</td>
</tr>
<tr>
<td>Sex Hormones</td>
<td>Maceration of the female fetus</td>
</tr>
<tr>
<td>Steroids</td>
<td>Vaginal carcinoma in female offspring</td>
</tr>
<tr>
<td>Alcohol (in high doses)</td>
<td>Fetal alcohol syndrome, stillbirth, spontaneous abortion, low birth weight, neural retardation</td>
</tr>
<tr>
<td>Antiprotease enzymes (exhibitors)</td>
<td>Renal failure; umbilical dysgenesis, skull hypoplasia (from exposure during the second and third trimesters)</td>
</tr>
<tr>
<td>Antithyroid drugs (propylthiouracil, methimazole)</td>
<td>Goiter and hypothyroidia</td>
</tr>
<tr>
<td>Neuroleptics and anti-inflammatory drugs</td>
<td>Premature closure of the ductus arteriosus</td>
</tr>
<tr>
<td>Lithium</td>
<td>Eisenmenger's anomaly (cardiac defects)</td>
</tr>
<tr>
<td>Antihyperglycemic drugs (e.g., tolbutamide)</td>
<td>Neuronal hypoplasia</td>
</tr>
<tr>
<td>Vitamin A derivatives (tocopherol, retinoids, megadoses of Vitamin A)</td>
<td>Multiple defects (CNS, craniofacial, cardiovascular, others)</td>
</tr>
<tr>
<td>Thalidomide</td>
<td>Tooth and bone anomalies</td>
</tr>
<tr>
<td>Warfarin</td>
<td>Shortened limbs, internal organ defects</td>
</tr>
<tr>
<td></td>
<td>Skeletal and CNS defects</td>
</tr>
</tbody>
</table>

CNS = central nervous system.

*The absence of a drug from this table does not mean that the drug is not teratogenic; it only means that teratogenicity has not been proved. The most proven teratogens are the result of a completed study in only 10%.
FDA Pregnancy Categories

1983 FDA classified drugs into 5 categories according to probable risks to fetus:

- A. Remote risk of fetal harm
- B. No risks in animals studies; no well-controlled human studies
- C. Risks in animals studies; no well-controlled human studies
- D. Proven risk of fetal harm - Potential benefits versus risk
- X. Proven risk of fetal harm - Drugs should not be used

Pregnant women should avoid drugs completely.

If PG woman has been exposed:

Find out exactly when drug was taken – if not during weeks 2-8 then patient should be reassured that risk of malformation is minimal & 3% of all babies have some kind of malformation.
Drug Therapy during Breast Feeding

- Drugs get through breast milk and can effect infant
- Little research done on this aspect because of dangers involved in these studies - Adverse effects are described (penicillin, tetracycline)
- Concentration of drugs differ in milk. Lipid soluble drugs are in higher concentration
- Generally most drugs are in too low a concentration to be harmful to infant - However consider:
  - Volume of milk consumed
  - Age of the infant
  - Liposolubility of the drug
  - Some drugs are contraindicated because of known risk: nicotine, amphetamines, lithium, marijuana, anticancer drugs, ...

Route & Forms of Administration

Route & Forms of Administration

• Variability in Absorption
  – Differences in manufacturing processes affect rate of absorption of drug
• Factors that influence bioavailability:
  – Product preparations
    – Tablet (Example: next slide. 4 diff preparation)
    – Enteric coating
    – Sustained release formulations (capsule)
    – Routes of administration
Variations in Bioavailability Among Digoxin Preparations

Lindenbaum, Mellow, Blackstone, Butler, 1971.

Fig. 4-5. Penicillin G (3 mg/kg) was administered intramuscularly to the same individual on different occasions as an aqueous solution (I.M.) and as procaine penicillin in oil (P-I.M.) and in oil with aluminum monostearate (AP-I.M.). The differing rates of decline of the plasma concentration of penicillin G point to an absorption rate-limitation when this antibiotic is given as the procaine salt in oil. Distinction between rate-limited absorption and rate-limited disposition following intramuscular administration of the aqueous solution can only be made by giving penicillin G intravenously (1 mg/L = 3.0 μM). (Modified from Marsh, D.F., Outline of Fundamental Pharmacology, Charles C. Thomas, Springfield, Ill., 1951.)
Food-Drug Interaction

- Timing of Drug administration and Meals
  - Drug-food interactions may decrease absorption:
    - Calcium containing foods and tetracyclin
    - High fiber foods reduce absorption
  - Drug-food interactions may increase absorption:
    - High calorie food more than doubles the absorption of squinavir
  - Drug may cause upset stomach if taken without food
    - Choose alternative drug?
    - Increase dose if taken with food?
    - Take shortly before or after meal?
Food-Drug Interaction

➢ Grapefruit juice may inhibit metabolism of certain drugs, raise the blood levels (co-administration of grapefruit juice produce a 40% increase in blood levels of felodipine—drug for hypertension), and lead to toxicity level.

➢ Grapefruit juice may inhibits cytochrome P450 enzymes and decrease metabolism of certain drugs: One glass (200 ml) is sufficient

Grapefruit & Drug Effects

Effect of Grapefruit Juice on Felodipine Plasma Concentration

PATHOLOGICAL STATE & DRUGS

• Pathophysiology: how disease affects responses to drugs

• Kidney
  – Reduce drug excretion: drugs accumulate in body
  – Must decrease dosage of drug until kidney function back to normal

• Liver
  – Site of drug detoxification and metabolism
  – Drug will accumulate to toxic levels in body
PATHOLOGICAL STATE & DRUGS

- Changes in response to "normal" drug level
  - Increased sensitivity to respiratory depressants in respiratory disease
  - Altered sensitivity in thyroid disease
    - a. To CNS depressants and opiates (reduced sensitivity in hyperthyroid patient, increased sensitivity in hypothyroid patient)
    - b. To cardiovascular and CNS stimulants (increased sensitivity)
  - Increased sensitivity to cardiovascular stimulants in cardiovascular disease and in adrenocortical imbalance

TOLERANCE & DRUGS

- Decreased responsiveness to a drug due to repeated drug administration. Patients require higher doses to produce the same effects (that could be achieved with lower doses).
- Four categories of drug tolerance
  - Pharmacodynamic (Cellular): morphine
  - Metabolic (Dispositional): barbiturates
  - Behavioral (Learned): drugs of abuse
  - Tachyphylaxis (Rapid Tolerance): nitroglycerine
GENETIC FACTORS & DRUGS

- Genetics (*idiosyncratic effects*)
  - Mostly through rate of metabolism of drug
  - Some effects due to differences in enzyme levels in organs (RBCs, liver, etc…)

- Idiosyncratic Effect: “uncommon drug response resulting from a genetic predisposition”
  - In most patient, paralysis due to succinylcholine is brief, lasting only a few minutes. But genetically predisposed individuals may become paralyzed for hours

Drug-Drug Interactions

- Occurs whenever a patient take more than one medication
  - Includes OTC drugs as well as prescription
  - Intensification of effects one or both drugs (Synergism):
    - *two drugs act to increase the effect of each other to a level greater than the additive effect of either one alone (may be harmful or beneficial)*
  - Reduction of effects of one or both drugs (Antagonism)
  - Addition or summation

- Mechanisms of drug-drug interactions
  - Direct chemical or physical
  - Pharmacokinetic
  - Pharmacodynamic
THE END