Drug Action Modifiers
&
Adverse Drug Reactions

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Drug Action Modifiers

The common causes of variation among individuals in response to the same dose of a drug:

I. Pharmacokinetic differences: varying drug concentrations in the plasma/target site.

II. Pharmacodynamic differences: number/state of receptors & signal transduction components.

III. Secondary Factors (e.g., Patient Noncompliance, Neurogenic/Hormonal Tone, etc).

1. Body weight and composition (Vd dependent on body mass; obese vs. muscular)

2. Age:

- **Children** often require larger (per body weight) drug doses
  - ↑ elimination rates ⇒ drug dose adjustment on the basis of body surface area
- **Geriatric patients** show changes in responsiveness to drugs: hyper- or hypo-reactivity
  - ↓ renal & hepatic function ⇒ use lower drug doses
  - ↓ plasma albumin ⇒ ↓ plasma protein binding of drugs ⇒↑ free drug
  - ↓ motility and blood flow to intestines ⇒ slower drug absorption
  - changes in receptor responsiveness (e.g., ↓ sensitivity of beta-adrenergic)

3. Sex & Pregnancy:

- **Females:** ↑susceptibility to drug interactions by systemic contraceptives;
  ↑ risk of drug- induced cardiac arrhythmias;
- **Pregnancy:** ↑ drug metabolism;
  ↑ renal excretion (↑cardiac output & GFR);
  ↓ binding to albumin

4. Race: Differences in EC_{50} of drugs (e.g., ↑ EC_{50} of atropine and beta-blockers in blacks).

5. Genetics: Drug metabolizing enzyme isoforms; SNPs in structure of enzymes/receptors.

Drug Action Modifiers (Cont'd)

6. Pathological & Psychological States:

A. GI Diseases: ↓ absorption of orally-administered drugs (e.g., achlorhydria, diarrhea, coeliac disease).

B. Liver Dysfunction (specific hepatic disease, infection, reduced blood flow to the liver, etc):

i)↓ hepatocellular function ⇒ ↑ bioavailability of drugs with high first-pass metabolism,

ii) ↓ serum albumin ⇒ ↓ protein binding of drugs (e.g., Diclofenac, Warfarin)⇒ ↑drug in free form,

iii) ↓ drug metabolism and elimination (e.g., Lidocaine, Morphine) ⇒ ↑ plasma drug concentration &↑ duration of drug action (⇒ ↑ drug half-life),

iv) Prodrugs with hepatic metabolism for activation (e.g., Bacampicillin) may become less effective,

v) ↓ biliary excretion of drugs

vi) Insidious effects of drugs that are potentially toxic to their primary organs of elimination (e.g., Acetaminophen accumulation⇒ hepatic necrosis⇒ further impairment of drug metabolism)

C. Kidney Disease:

i) ↓ clearance of drugs that are primarily excreted unchanged⇒↑ drug half-life (⇒↑ dosage interval),

ii) ↓ serum albumin ⇒ ↓ protein binding of acidic drugs ⇒ ↑ drug in free form,

iii) ↓ excretion of inactive metabolites ⇒ ↑ risk of untoward reactions,

iv) renal failure ⇒ ↑ permeability of blood-brain barrier ⇒ ↑ effectiveness of centrally-acting drugs (e.g. opiates, barbiturates, benzodiazepines); GFR ↓↓↓⇒ loop and thiazide diuretics ineffective.

D. Congestive Heart Failure:

i) mucosal edema, vasoconstriction ⇒ ↓ drug absorption from the GI tract,

ii) ↓ perfusion⇒↓ Vd (but ↑ Vd for some drugs due to ↑extracellular fluid),

iii) ↓ liver perfusion, ↓GFR/↑tubular reabsorption ⇒↓ drug elimination⇒ ↑ drug half-life

E. Thyroid Disease (non-pharmacokinetic effects): Hypothyroidism ⇒↑sensitivity to CNS depressants; Hyperthyroidism ⇒↑ systemic effects of Epinephrine; ↓ potency of morphine

F. Anxiety: ↑ requirement for general anesthetics

Drug Action Modifiers (Cont'd)

7. Drug Factors:

- **Variables in Drug Administration** - *the only factors that are totally under the control of the clinician*
  - Dose, Drug Formulation, Route of Administration
  - Timing of Administration
    - Avoidance of disturbing side effects if a sedative agent can be given shortly before sleep (e.g., the vestibular component of nausea associated with opioid analgesics);
    - Scheduling of doses with (↓ gastrointestinal upset) or between (↑absorption) meals

- **Drug Tolerance:** A state of decreased responsiveness ⇒ ↑ drug dose to produce a given response.

A. ***Natural:*** Individual is inherently less sensitive to the drug (e.g., blacks are tolerant to mydriatics),

B. ***Acquired:*** Loss of therapeutic efficacy after prolonged/intensive use of a drug
- **Pharmacokinetic**: the effective drug concentration is diminished; e.g. metabolic enzyme induction
- **Pharmacodynamic**: the reaction to a given drug concentration is reduced (e.g., ↓ receptors)
- **Immune**: antibodies bind to the drug

C. ***Cross-Tolerance:*** The development of tolerance to pharmacologically related drugs (e.g. alcoholics are tolerant to barbiturates and general anesthetics).

D. ***Tachyphylaxis****:* rapid development of tolerance when doses of a drug are repeated quickly

Drug Interactions

For patients taking 2 drugs, the risk of a toxic drug interaction is approximately 15%.
This risk increases to 40% and 80% (!!!) when the patient takes 5 and 7(+) drugs, respectively….

The Most Dangerous Drug Combinations Relevant to Dentistry:

Epinephrine in Local Anesthetics with:
Propranolol (non-selective beta-adrenergic antagonist)

NSAIDs with:
Diuretics and Renin-Angiotensin-Aldosterone System inhibitors (triple therapy)
Lithium (mood stabilizer-Bipolar Disorder)

Warfarin (anticoagulant) with:
Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)
Metronidazole and Fluconazole
Sulfonamides, Macrolide and Quinolone antibiotics

Mechanisms:
- A competition leading to pharmacologic interaction resulting in a detrimental response
  - Cytochrome P450 enzyme system polymorphisms, enzyme inhibition or induction;
- A medication prescribed in excessive amounts;
- Untoward consequences despite being correctly prescribed
  - Absorption and Metabolism variability:
    Age, Genetic variation, pH in the GI tract, other health conditions, etc.

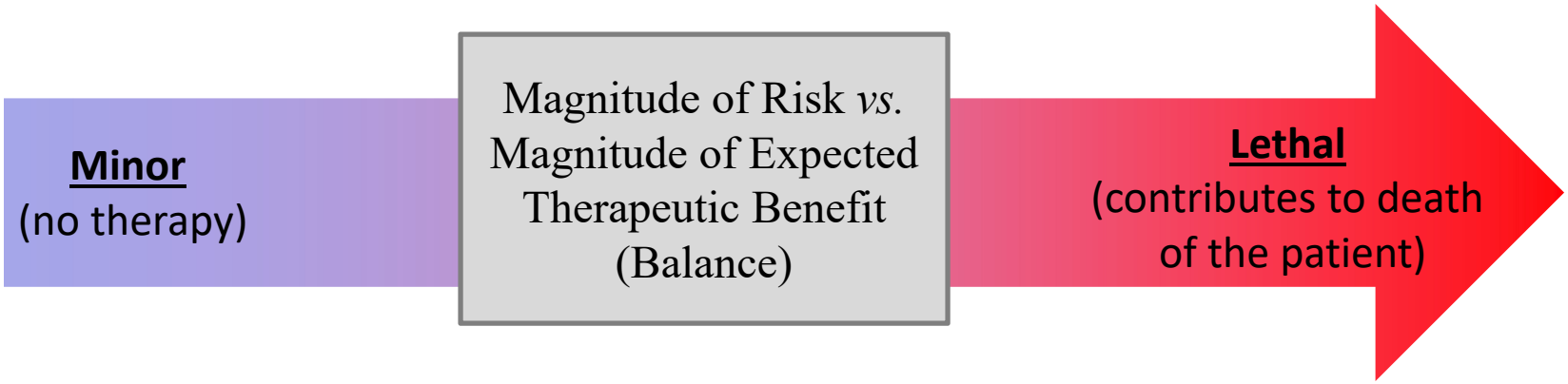
Adverse Drug Effects

Definition

Any undesirable consequence of drug administration.

ALL drugs are capable of producing adverse effects.
The risk increases with **increasing the dose, multiple drug therapy** & **in the elderly**.

"It is the dose which distinguishes a remedy from a poison"
Paracelsus (1493-1541)



Adverse drug effects can be minimized by:

1. Using appropriate dose, route and frequency of drug administration based on patient's parameters;
2. Adopting correct drug administration techniques (e.g., **NSAIDs** not to be given on empty stomach);
3. Considering patient's past history of drug reactions and allergic diseases ($\Rightarrow\uparrow$ risk of drug allergies);
4. Eliminating the possibility of drug interactions when the patient takes other medication;
5. Carrying out laboratory monitoring (e.g., prothrombin time/INR with **Warfarin**).

Adverse Drug Effects

Major Categories

Side Effects, Secondary Effects, Toxicity/Poisoning/Extension Effects, Intolerance, Idiosyncrasy, Allergy, Photosensitivity, Dependence & Withdrawal Reactions, Terato-/Carcino-/Muta-genicity, Drug-Induced Diseases (Iatrogenic)

Selected Categories

1. Side Effects

- Can be predicted from the pharmacological profile of a drug, occur at therapeutic doses and reduction in dose usually ameliorates the symptoms (dose-dependent).
- May be based on the same action as the therapeutic effect (e.g., *Xerostomia* by **Atropine**; *gastric mucosal damage* by **NSAIDs**; *cardiac depression* by **Lidocaine**).
- May also be based on a different facet of action (e.g., *sedative effect* of **Promethazine**, unrelated to its anti-allergic action).
- An effect may be therapeutic in another context (e.g., *Xerostomia induced by* **Atropine** *in control of salivation; Constipation* by **Codeine** in *traveler's diarrhea*).

2. Toxicity / Poisoning/ Extension Effects

- Excessive pharmacological action of the drug due to over-dosage or prolonged use.
- Absolute over-dosage: accidental, homicidal, suicidal (analgesics, antidepressants, alcohol).
- Relative over-dosage: usual dose, but decreased elimination (e.g., renal failure).
- May result from extension of the therapeutic effect (e.g., **Insulin** - *hypoglycemia;* **Warfarin, Heparin** – *spontaneous bleeding*; **Furosemide** - *hypovolemia*)

Adverse Drug Effects
Selected Categories (Cont'd)

3. Drug Allergy

- Immunologically-mediated reaction producing stereotype symptoms (similar to food/protein allergy, allergic diseases) which are unrelated to pharmacodynamic effects of the drug.
- Allergic reactions can occur with very small doses (dose-independent; 'drug hypersensitivity').
- Allergic reactions cannot be produced in not sensitive individuals at any dose.
- Prior sensitization is necessary; a latent period (>1-2 weeks) after the first exposure.
- Drugs of importance to dentistry and commonly implicated in allergic reactions:
  Penicillins, Sulfonamides, Cephalosporins, Tetracyclines, Local Anesthetics, Salicylates

4. Teratogenicity

- The capacity of a drug to cause fetal abnormalities when administered to the pregnant woman.
- No drug can be declared to be absolutely safe during pregnancy – all drugs should be avoided unless there are compelling reasons for their use.
- In contrast to adults, drug effects on embryo are often irreversible:
- *Failure of pregnancy* (0-20 days);
- *Deformities* (21 days-the end of the First Trimester-the most vulnerable period–Organogenesis)
  ⇒ Emergency Dental Tx only; **Avoid Benzodiazepine Sedatives**- known human teratogens)
- *Developmental & Functional Abnormalities* (56 days -)

(e.g., *discolored/deformed teeth* and *retarded bone growth* by **Tetracyclines**;
cleft lip/palate by **Phenytoin** and **anticancer drugs (Methotrexate)**;
premature closure of ductus arteriosus by **NSAID**s)