Toxicological aspects of medicine

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“The dose makes the poison.” (Paracelsus)

Alle Ding' sind Gift und nichts ohn' Gift; allein die Dosis macht, das ein Ding kein Gift ist.”  
“All things are poison and nothing is without poison, only the dosage makes a thing not poison.”
Dose-response relationship

\[
[AR] = \frac{[R_0][A]}{K_D + [A]}
\]

A: agonist, R: receptor, KD: dissociation constant

Linear Scale

Semilog Scale

% Biological Effect

[Drug] (M/L)

Log [Drug] (M/L)

EC\(_{50}\)
Quantal vs. cumulative dose-response curves

Responsiveness/sensitivity of individuals is variable, follows normal distribution.
Pharmacology and toxicology

**Therapeutic window**: concentration range within which the drug exerts the wanted therapeutic effect, without toxic side effects.

**Therapeutic index**: median toxic dose/median therapeutic dose
Dose-response relationship

<table>
<thead>
<tr>
<th>The importance of dose</th>
<th>The importance of size</th>
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<tbody>
<tr>
<td><img src="image1" alt="Dose illustration" /></td>
<td><img src="image2" alt="Size illustration" /></td>
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Gilbert, 2005

Harris & Goonetilleke, 2004
Adverse drug effects

Incidence of adverse drug effects in normal population 0.5-1%
Incidence in hospitalised patients ≈ 15%!

Causes of adverse drug effects:
• Interactions between drugs
• Different metabolic rate
• Special sensitivity – foetus, neonate, elderly, chronic disease...
• Allergy/hypersensitivity
• Addiction (CNS drugs, anxiolytics, stimulants...)

inadequate dosing

(mostly overdose)
Interactions

Addition
Synergy ≈ Potentiation
Antagonism

Isobolograms of drugs A and B
I: synergy
II: addition
III: antagonism
Interactions

Background mechanisms of drug interactions

**Pharmacokinetic interactions**
- Competition for plasma protein binding, specific transporters
- Metabolism, enzyme induction
- Elimination – competition for transporters in kidney

**Pharmacodynamic interactions**
- Same system as target for multiple drugs
Factors affecting metabolism

• Enzyme induction/inhibition
  - occurs for phase I and phase II enzymes
  - mechanism: “xenobiotic sensors” (transcription factors, steroid receptor-like receptors) → transcription of enzymes ↑
  - induction: carbamazepine (antiepileptic) → halflife decreases dramatically in a few weeks → increasing dose
  - chronic alcohol induces enzyme responsible for production of toxic paracetamol metabolite
  - inhibition: erythromycin
  - basis for drug interaction!
Factors affecting metabolism

- Genetic variability, enzyme polymorphisms - isoforms
- Species (animal studies!)
- Diseases (liver, kidney, gastrointestinal, infection)
- Sex (female slower metabolism for certain drugs)
- Age – in babies, liver metabolism is much slower than in adults (caffeine half-life: days, in adults: 4 hours), elderly also slower
- Environmental pollutants (heavy metals, PAH), nutrition (grapefruit juice cytochrome inhibitor)
Factors affecting metabolism

Zanger & Schwab, 2013
Genetic variability in CYP

Clinically relevant enzyme polymorphisms – CYP2C, CYP2D

Poor, intermediary, extensive and ultra-rapid metabolisers

ADR: adverse drug response ↔ non-responders

Antidepressants, antipsychotics, antitumour agents, immunosuppressants, antiepileptics...

Pharmacogenetics, personalized therapy

![Diagram showing genetic variability in CYP enzymatic activity](TRENDS in Pharmacological Sciences)

Ingelman-Sundberg, 2004
Genetic variability in CYP

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Genetic Mechanisms</th>
<th>Pharmacokinetic Effects</th>
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<tbody>
<tr>
<td>Poor Metabolizer (PM)</td>
<td>2 inactive alleles</td>
<td></td>
</tr>
<tr>
<td>Intermediate Metabolizer (IM)</td>
<td>2 decreased-activity alleles OR one active allele and one inactive allele OR one decreased-activity allele and one inactive allele</td>
<td></td>
</tr>
<tr>
<td>Extensive Metabolizer (EM)</td>
<td>2 functional alleles (wild type)</td>
<td></td>
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<tr>
<td>Ultrarapid Metabolizer (UM)</td>
<td>Gene duplication in the absence of inactive or decreased alleles</td>
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Genetic mechanisms for CYP450 metabolic phenotypes and their pharmacokinetic implications (van der Weide et al., 2005)
Teratogenic effects

Embryonic development
1-12 weeks

Foetal development
13-38 weeks

Organogenesis
Severe teratogenesis

Differentiation (maturation), growth
Milder, delayed teratogenic effects

Tortora & Derrickson, 2012
Exposition in utero

- Placental barrier
- Small, lipophilic molecules cross (drugs!)
- Foetal metabolism limited
- Foetal blood-brain barrier not developed (human neonatal period)

Teratogenic agents: disrupt developmental processes
Ethanol – foetal alcohol syndrome

- Limb malformations, heart defects, slow prenatal + postnatal growth, structural brain abnormalities
- Neurological deficits: hearing loss, poor fine motor skills, eye-hand coordination
- Mental retardation, behavioural problems
- Characteristic facial features in childhood, no other marker
- Estimated incidence: 3-4/1000

Sampson et al., 1997
Teratogenic effects

Other teratogens

- Irradiation – first trimester
- Illegal drugs – cocaine
- Antibiotics
- Anticoagulants, antitumor agents, antiepileptics, thyroid drugs....
- Cigarette smoking – low weight, higher risk of infant mortality, heart and respiratory problems

Many drugs can pass into mother’s milk and can harm the baby during nursing!
Thalidomide (Contergan®)

Marketed in 1957
Sedative, anxiolytic, antiemetic agent for pregnant women
>10000 malformations worldwide until withdrawal in 1961
Largest drug disaster ever → stricter protocols in pharmacological toxicology
Now prescribed against leprosy, certain cancer types

www.toxipedia.org
helix.northwestern.edu
Thalidomide (Contergan®)

Mechanism of effect still not clear
- ROS (reactive oxygen species) generation
- Inhibits formation of blood vessels
- DNA damage of S-stereoisomer (R-S conversion)
- Differences in metabolism
- Rodents – resistant, rabbit, chicken, zebrafish – sensitive
- Rodent cell/tissue cultures sensitive! (ROS, blood vessel effect)

Ito, 2011
Medication allergies

- Hypersensitivity reaction, drug behaves as antigen, antibodies produced
- Symptoms: skin rash, itching → anaphylactic shock
- Most common: penicillin allergy (10-15% of patients, but 80-90% may not be truly allergic!)
- Desensitisation, resensitisation may occur, skin test
- Cross-allergy: derivatives, similar compounds (amoxicillin, cephalosporins) – matter of debate

[Diagram of anaphylactic reaction]

www.experimentalphysiology.gr
Headache

- 8% of headache patients may suffer due to medication!
- headache is a frequent side effect of many drugs: drugs acting on blood vessels, antidiabetics, anti-inflammatory drugs, antidepressants, antiepileptics, hormonal drugs...
- “medication overuse headache” or “rebound headache”
  - painkillers taken on a daily basis for years → chronic headache may develop, especially in migraine-prone patients

www.rbforhealth.co.uk
Neurological symptoms

Movement disorders

• 1/3 of Parkinson cases is caused by medicines!
• Neuroleptics, antidepressants, antiepileptics
• Parkinson medication – mostly levodopa

Grosset & Grosset, 2004
Neurological symptoms

Cognitive deficits

- anticholinergic drugs (Parkinson medication)
  
Tremor, hyperexcitation

- drug causing cholinergic excess (Alzheimer medication)