Basic pharmacological terms, definitions.

Physiological and pathological factors influencing drug effects.

Adverse drug effects.

Jan Juřica

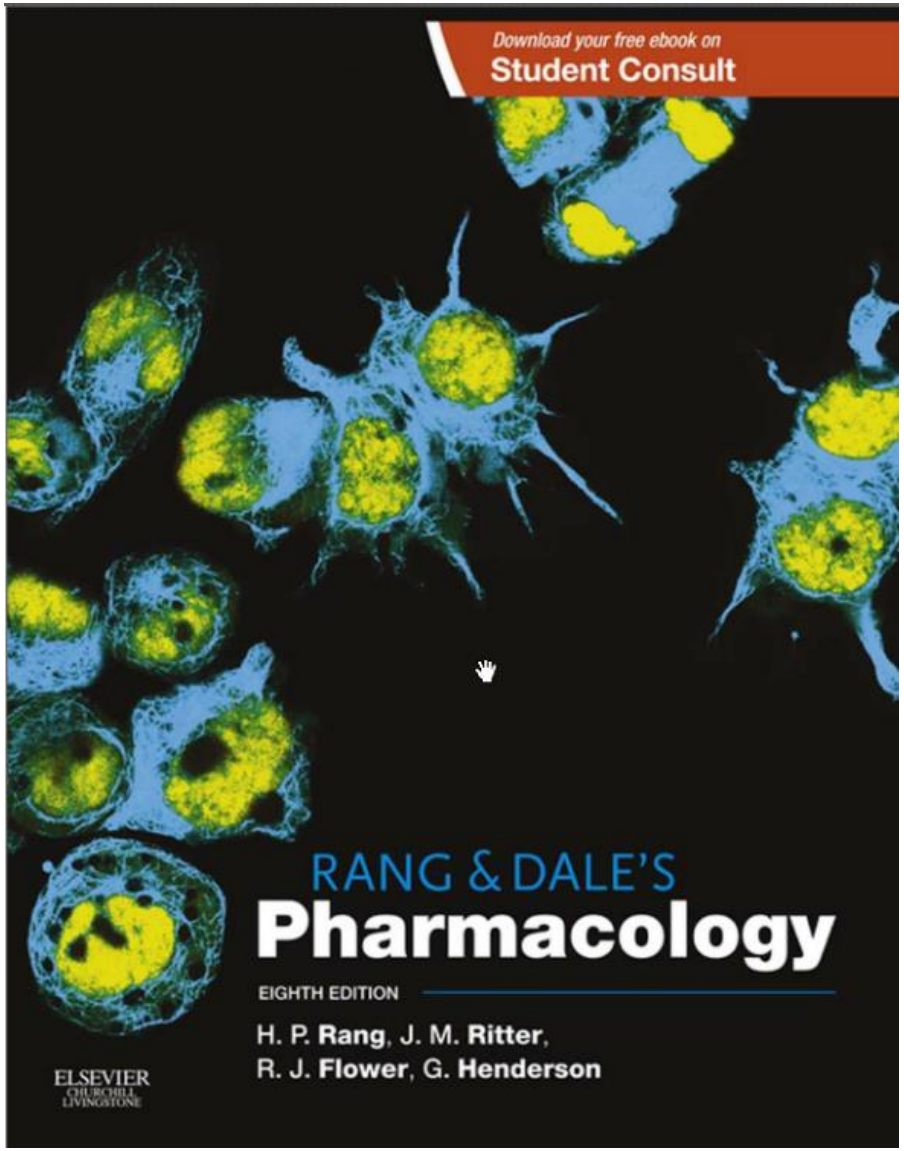
RECOMENDED LITERATURE

Rang & Dale's pharmacology 8th Edition:with student consult online access. Edited by H. P. Rang. : Churchill Livingstone, 2016.

- Ritter, James M. - Lewis, Lionel D. - Mant, Timothy G.K. - Ferro, Albert. **A Textbook of Clinical Pharmacology and Therapeutics**, 5th Ed., Hodder Arnold, 2008. 465 s. ISBN 978-0-340-90046-8
- Waller, Derek - Renwick, Andrew G. - Hillier, Keith. **Medical pharmacology and therapeutics.** 3rd ed. New York : Elsevier Saunders, 2009. ix, 744 p. ISBN 0-7020-2991-2.

RECOMENDED LITERATURE

https://ezdroje.muni.cz/



WHAT IS PHARMACOLOGY

from the Greek **pharmakon** (φάρμακον) means „remedy"

logos (λόγος) means "science")

Definition: Pharmacology is the science that **deals with interactions between substances** (xenobiotics) **and a living organism,** at all levels (molecular, cellular, organ and whole organism)

WHAT IS PHARMACOLOGY

Greek word ***pharmakon***

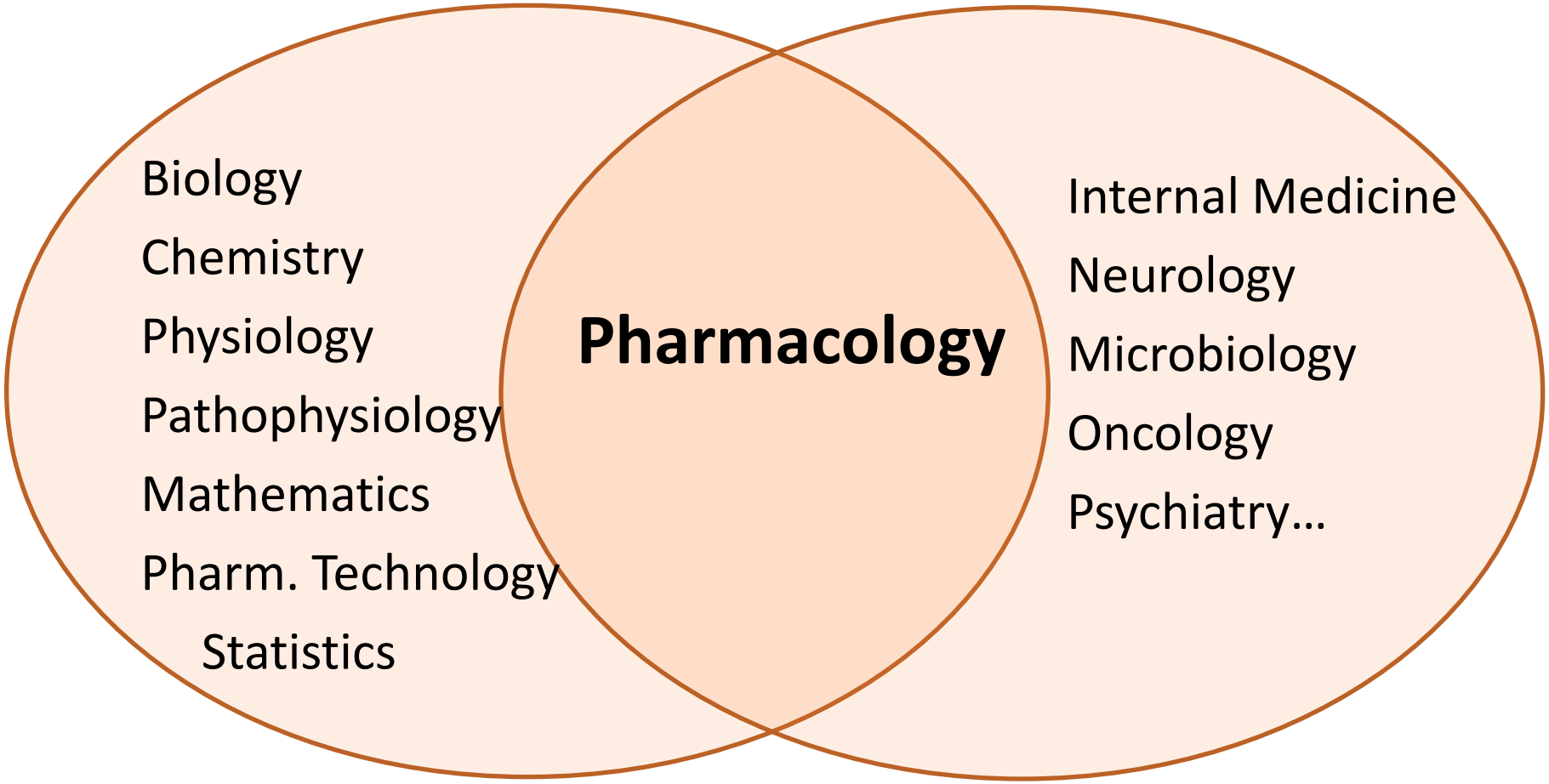
- originally meant a magic charm for

treating disease.

Later, ***pharmakon*** came to mean a remedy or „drug“.

- Pharmacology is (and has to be) interdisciplinary science
  - interdisciplinary collaboration with the preclinical and clinical disciplines

What is Pharmacology



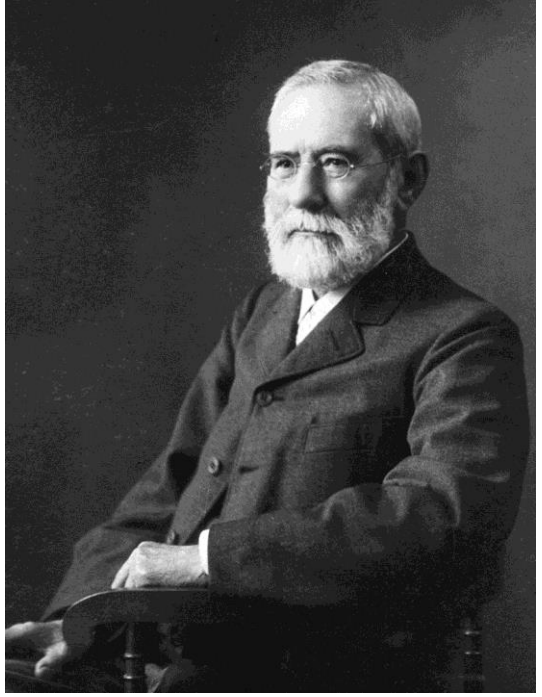
History of modern Pharmacology

The pharmacology as the exact science was founded in the fifties of the 19th century…

Prof. Rudolf Buchheim (1820-1879) - founder of experimental pharmacology

- 1847 - Rudolf Buchheim became the first professor of a separate Department of Pharmacology, University of Dorpat, Estonia

History of modern Pharmacology



Oswald Schmiedeberg (1838 – 1921)

was a Baltic German pharmacologist.

referred to as the

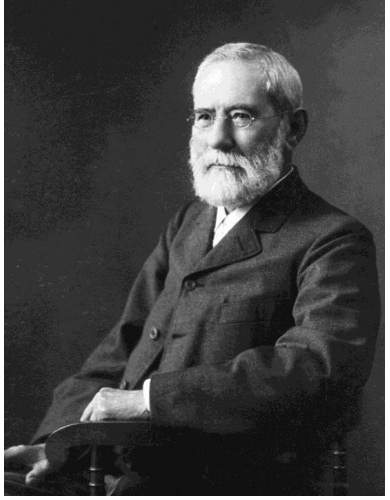
"Father of Modern Pharmacology."

Searched for the correlation between the chemical structure and effectiveness.

Together with his pupil **Hans Horst Meyer** he discovered glucuronic acid - conjugation partner in xenobiotic metabolism.

Later found that glucuronic acid was also a component of cartilage and occurred as a disaccharide of chondroitin sulfate

History of modern Pharmacology



Oswald Schmiedeberg (1838 – 1921)

graduating in 1866, then worked at the same University
as a Professor. Buchheim, respectively under his
leadership.

- 1872 - Professor of Pharmacology at the University of Strasbourg

"Muscarinic effects" are comparable with electric stimulation n.vagus ...

- 1878 - publication of results in the **Outline of Pharmacology**

History of modern Pharmacology

- huge development of the drugs 20th century, mainly after 2 WW
- from „simple chemicals“ to the current treatment including „***targeted“*** or ***„biological therapy***“, advanced therapy (gene and cell therapy, tissue engineering)…
- progress in cellular, molecular medicine and methods, era of pharmacogenomics, pharmacogenetics, proteomics and metabolomics….
- new challenge - how to harmonize the new sciences with the ‘old’ pharmacology

IUPHAR, EPHAR, EMA, SUKL

- IUPHAR = International Union of Basic and Clinical Pharmacology

  http://www.iuphar.org/

- EPHAR = the Feredration of European Pharmacological Societies

  http://www.ephar.org/home.html

- EMA = European Medicines Agency

  http://www.ema.europa.eu/ema/

- SUKL = State Institute for Drug Control

  http://www.sukl.eu/index.php?lang=2

A SUBSTANCE ?

A substance shall mean any matter irrespective of origin which may be of :

a) human origin, e.g. human blood, its constituents, and human blood products;

b) animal origin, e.g. micro-organisms, toxins, whole animals, parts of organs, animal secretions,extracts or blood products;

c) plant origin

d) chemical origin

A MEDICINAL PRODUCT /DRUG/ ?

a) a substance or combination of substances

having therapeutic or preventive properties in the case of human or animal diseases;

or

b) any substance or combination of substances which may be used or administered to human beings or used or administered to animals with a view to **restoring, correcting or modifying the physiological functions by means of a pharmacological, immunological or metabolic effect or with a view to making a medical diagnosis.**

A MEDICINAL PRODUCT /DRUG/ ?

- vaccines, toxins, serums or allergen products
- human autogenic vaccines prepared for a specific patient from pathogens or antigens obtained exclusively from this patient;
- homeopathic products prepared in accordance European Pharmacopoeia
- radiopharmaceuticals, when ready for use, contain one or more radionuclides (radioactive isotopes) included for a medicinal purpose;
- Blood derrivatives
- Herbal medicines

Regulatory issues

REGULATORY ISSUES

Why we need the regulation?

- **International regulations**
- **Safety of the patients**
- **Efficacy approved in controlled trials**
- **…..???**

The area of the regulation..

- **research, production, preparation, distribution and disposal of drugs**
- **registration, post-marketing surveillance, prescribing and dispensing of medicinal products**
- **keeping records of the above activities**

European legislation

- Directive 2001/83/EC of the European Parliament and of the Council on the Community code relating to **medicinal products for human use**
- Directive 2001/20/EC of the European Parliament and of the Council on the approximation of the laws, regulations and administrative provisions of the Member States relating to implementation of **good clinical practice in the conduct of clinical trials on medicinal products** for human use
- Directive 2002/98/EC of the European Parliament and of the Council, setting standards of **quality and safety for the collection, testing, processing, storage and distribution of human blood and blood components**

European legislation (2)

- Directive 2004/10/EC of the EP and of the Council on the harmonisation of laws, regulations and administrative provisions relating to the application of the principles of **good laboratory practice**
- Council Directive 2001/18/EC of 12 March 2001 on the deliberate release into the environment of **genetically modified organisms** and repealing Council Directive 90/220/EEC.
- Council Directive 96/23/EC of 29 April 1996 on **measures to monitor certain substances and residues** thereof in living animals and animal products.
- Council Directive 2003/85/EC of 29 September 2003 on Community measures for the **control of foot-and-mouth disease** repealing Directive 85/511/EEC

European legislation (3)

• Regulation (EC) No 1901/2006 of the European Parliament and of the Council on **medicinal products for paediatric use** and amending Regulation (EEC) No 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No 726/2004.

• Council Regulation (EC) No 141/2000 on **orphan medicinal products.**

Czech legislation

- Czech legislation
- ACT of 6 December 2007 on Pharmaceuticals and on Amendments to Some Related Acts (**the Act on Pharmaceuticals**)

Czech regulatory authority – SUKL (State institute for drug control)

Act on Pharmaceuticals 378/2008

- Definitions , terms
- Nomenclature of Human medicinal products
- Earmarked drugs
- Regulation of prescription –Rx, OTC
- Registration
- Harmonization of registration procedures wihtin EU
- Pharmacovigilance
- Traditional herbal medicines

- Farmakovigilance (PRAC)
- E- prescription

- Non-registered medicines- use in Individual cases (approval)

Specific treatment programs
Clinical trials

SUKL

The mission:

- only those pharmaceuticals which are of **good pharmaceutical quality, efficacy, and safety, are applied in practice** and during clinical trials
- that **quality and safe raw materials be used in the manufacture** and preparation of pharmaceuticals
- Only **safe and functional medical devices** with information describing objectively established properties **are used**
- that **data from the research** of pharmaceuticals, raw materials, and devices **are credible and obtained in an ethical manner**.

SUKL

- Approval for clinical trials
- Monitors the use of unregistered medicines and on specific treatment programs
- Supervises the manufacture, distribution, preclinical testing, clinical evaluation, and operation of pharmacies selling restricted drugs, including the authorization of certain activities and issuance of certificates
- Supervises advertising on drugsnad medicinal preparations and devices

Basic Pharmacological terms

The therapeutic effect: primary effect intended that is the reason the drug is prescribed

(such as morphine sulfate is analgesia)

Side effect: secondary effect of the drug is one that unintended, side effects are usually predictable and may be either harmless

(such as sedation, breathing depression after morphine)

Three Phases of Drug Action

I. PHARMACEUTICAL PHASE

II. PHARMACOKINETIC PHASE

III. PHARMACODYNAMIC PHASE.

I. PHARMACEUTICAL PHASE

A solid drug (tablet) has to disintegrate before it can be absorbed

The process where a solid drug (tablet) goes into solution is called as dissolution

All drugs must be in solution to cross biological membranes

I. PHARMACOKINETIC PHASE

- What the body does to the drug- refers to the study of how the body processes drugs

- It includes the 4 basic components of :

  Absorption , Distribution, Metabolism

  (Biotransformation) , Excretion

- Acronym ADME

I. PHARMACODYNAMIC PHASE

- refers to the study of the mechanism of drug action on living tissue. (What a drug makes with the body)

- Drugs *may increase, decrease or replace endogenous substances,* inhibit enzyme functions, hormones or body metabolic functions.

- Chemotherapeutic drugs alter an abnormal parasite or growth on the body such as bacteria, viruses or neoplastic tissue. *examples: antibiotics and antineoplastic drugs*.

- Drugs may be also effective trough their non-specific action (e.g. Antiacids, alkylating drugs…)

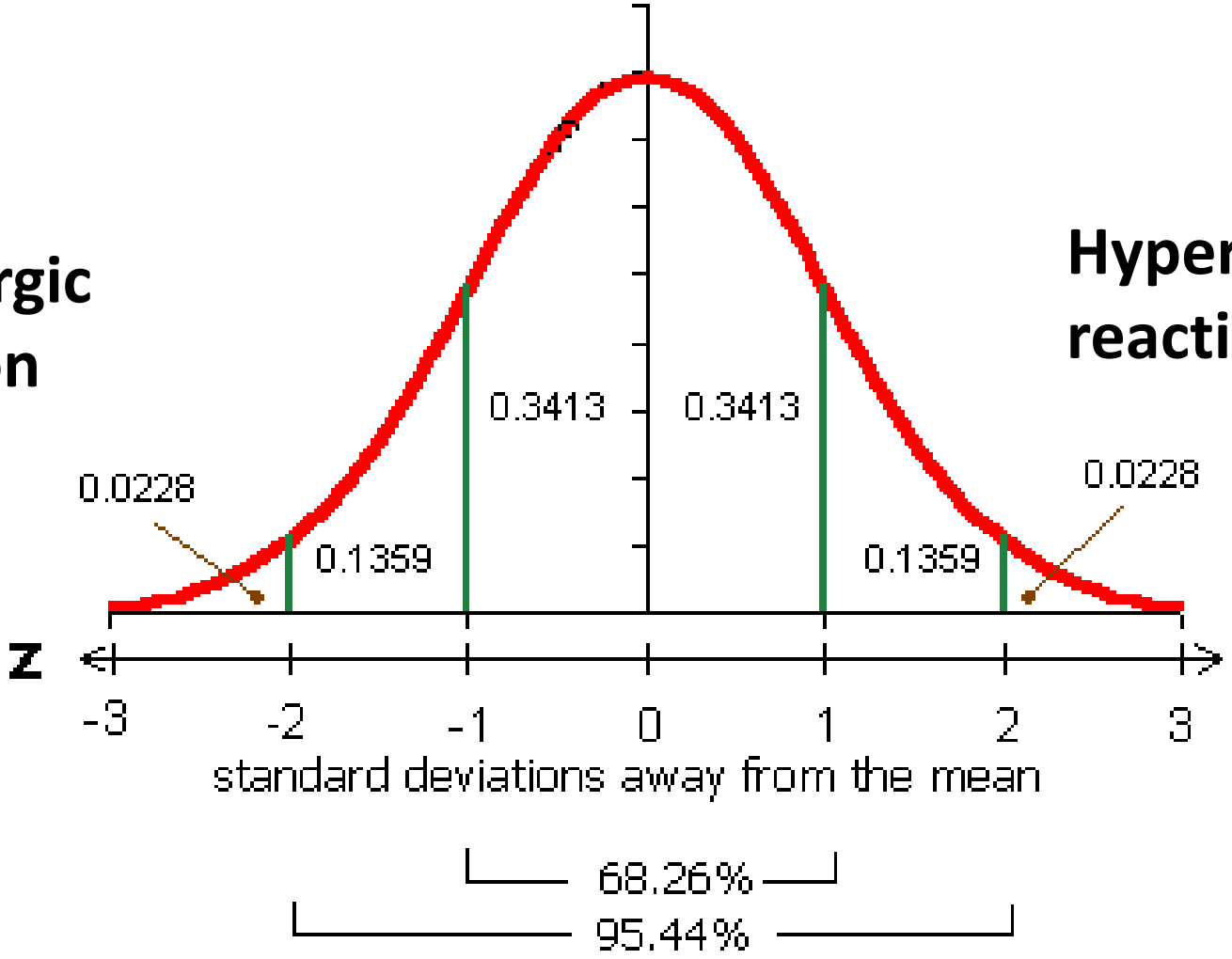
Physiological and pathological factors influencing drug effects.

Factors influencing drug effects

Normoergic reaction

Hypoergic reaction

Hyperergic reaction



Factors influencing drug effects

1. Factors related to the drug

2. Factors related to the drug and organism

3. Factors related to the organism

1.Factors related to the drug

A Physico-chemical properties

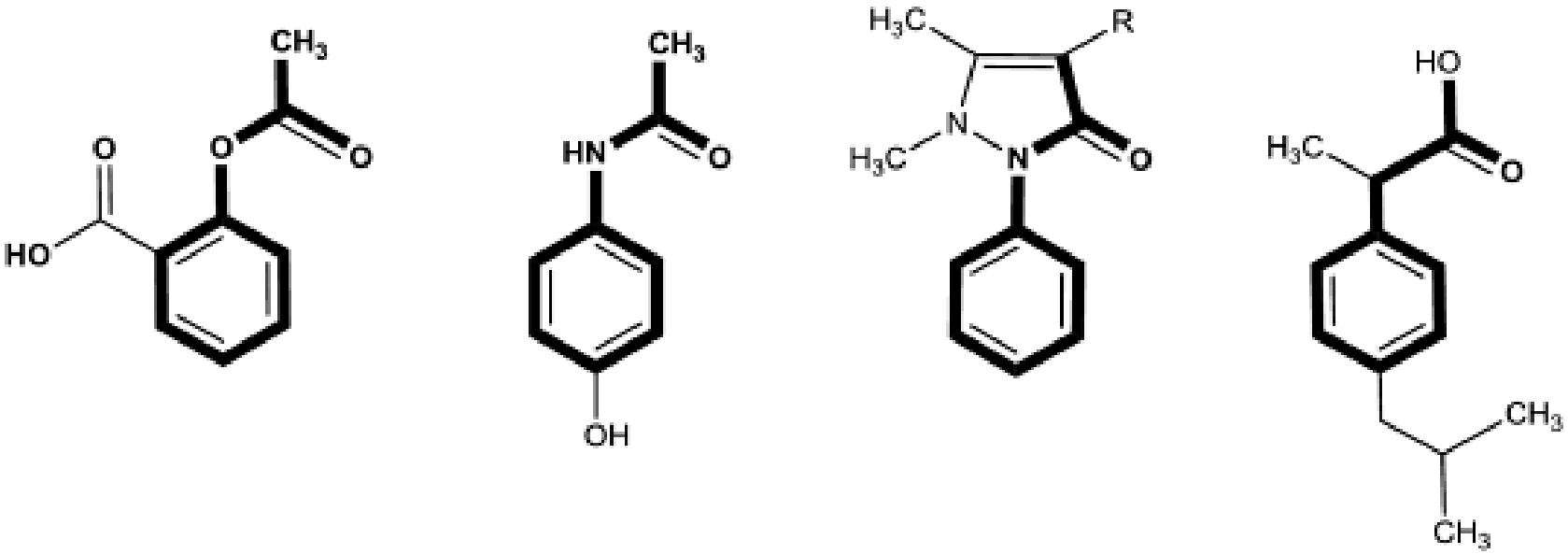
B Drug dosage form and way ofadministration

C Effect of meal, nutrients

A Physico-chemical properties

- Lipid and water solubility
  onset of action, distribution ...
- The size and shape of the molecule
- Chemical configuration
- Acid-base properties

The relationship of chemical structures and the nature of the effect

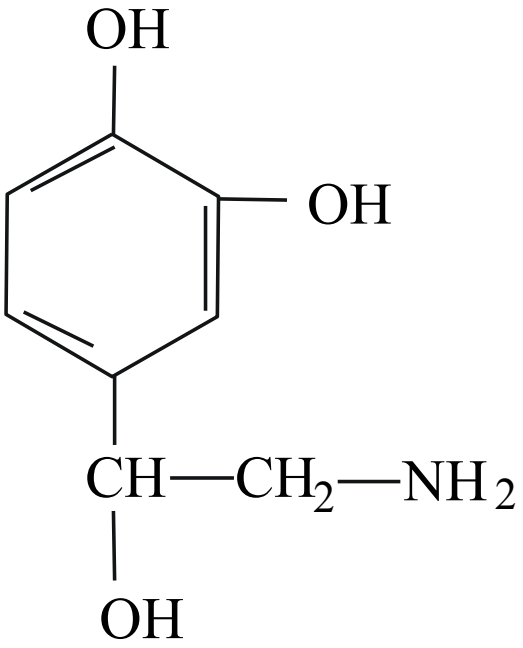


acetylsalicylová kys. deriváty acetanilidu deriváty pyrazolonu ibuprofen

Základní strukturní typy analgetik-antipyretik

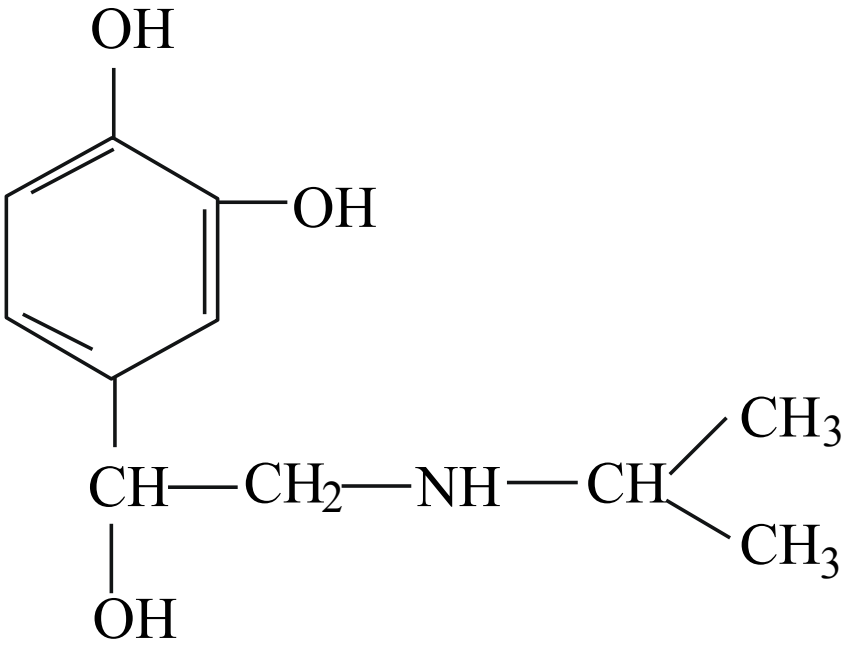
ASA **anilide derrivative** **pyrazolone derrivative** **ibuprofen**

The relationship of chemical structures and the nature of the effect



Norepinephrine

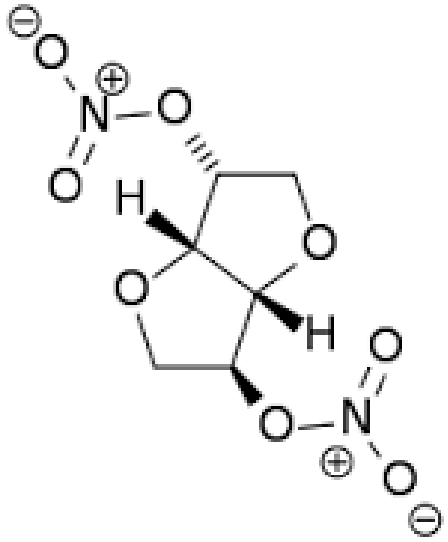
(mostly α mimetic effects)

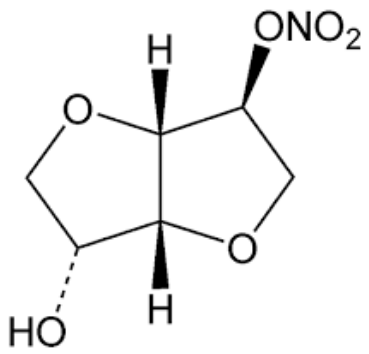


Isopropylnorepinephrine

(mostly β mimetic effects)

The relationship of chemical structures and the nature of the effect





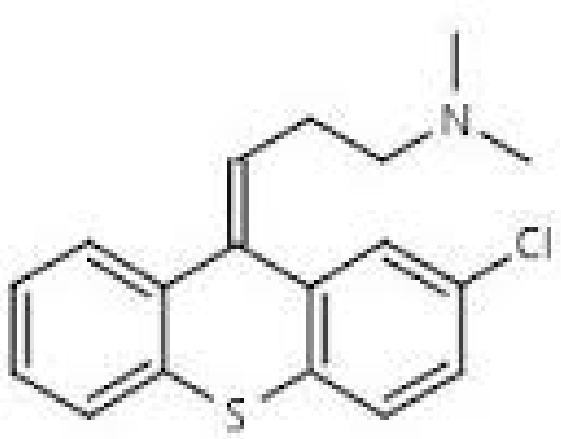
ISDN more lipophilic than the **ISMN**

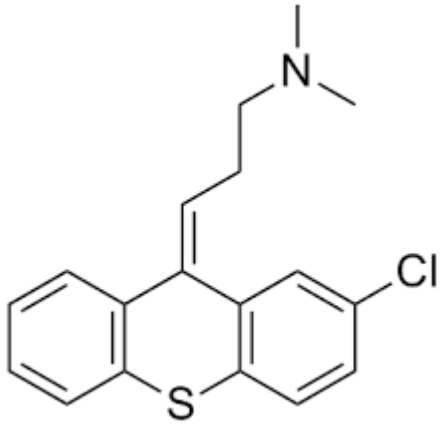
- ISDN can be given sublingually
- ISMN almost does not undergo hepatic FPE
- Another example: atenolol x metoprolol

Hydrophilic vs. lipophilic

longer vs. shorter half-life

Cis-trans isomers



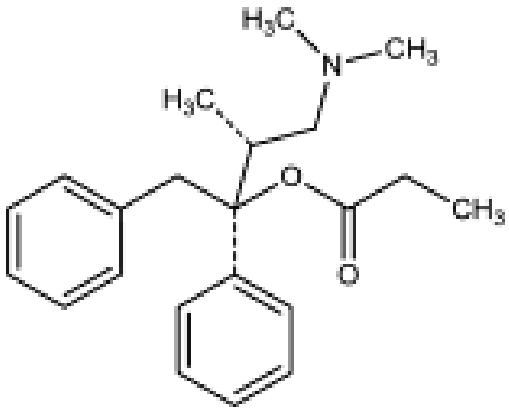


Cis -trans isomerism : only the cis form chlorprothixene is effective

Chirality

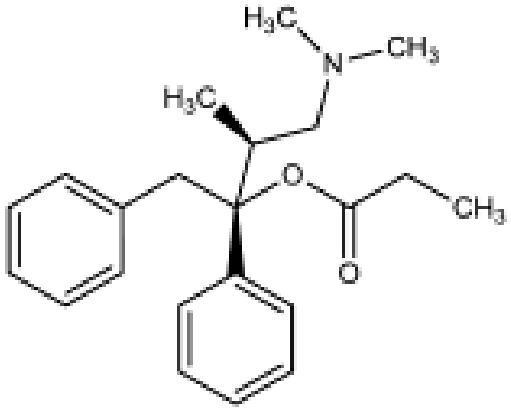
Levopropoxyphene - 2 = 4 chiral carbon isomers

α dextropropoxyphene



analgesic

αLevopropoxyphene (1R 2S)



antitussive

Chirality – other examples

Esomeprazole

Dextrometorphan

Escitalopram

Levodropropizine

Thalidomide

B Drug dosage forms

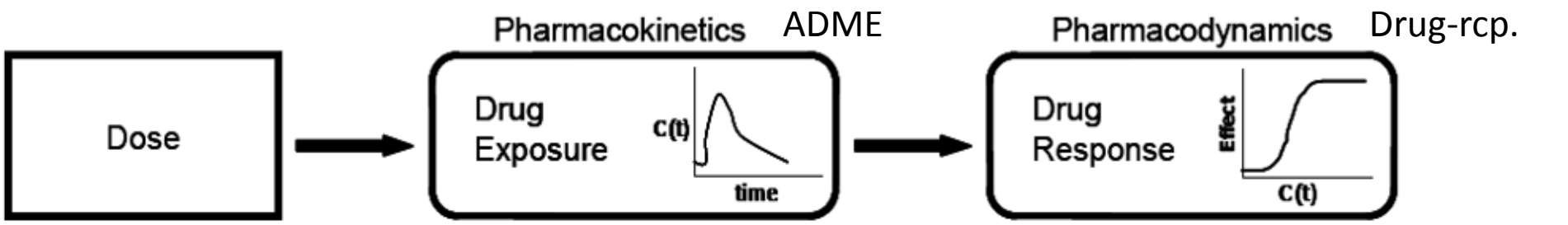
definition:

" The ultimate form of processing of active substances and excipients,

the composition and the shape predestiny the intended use

influences **pharmaceutical availability**

Pharmaceutical stage Pharmacokinetic stage Pharmacodynamic stage



Desagregation, desintegration disolution

Sources of Variability
Gender, Race, Body size
Renal/hepatic function
Gastric pH
Drug-Drug Interactions
Environmental factors
Concomitant Diseases
Drug Metabolism polymorphisms
Medication Compliance

Sources of Variability
Gender, Race
Drug-Drug Interactions
Environmental Factors
Concomitant Diseases
Placebo effect
Drug receptor or enzyme polymorphisms
Tolerance, Tachyphylaxis

DRUG DOSAGE FORM GENERATIONS

1. **generation – <u>conventional DDF</u>**

2. **generation with <u>controlled release</u>**

   with prolongated release (SR,XR...)*

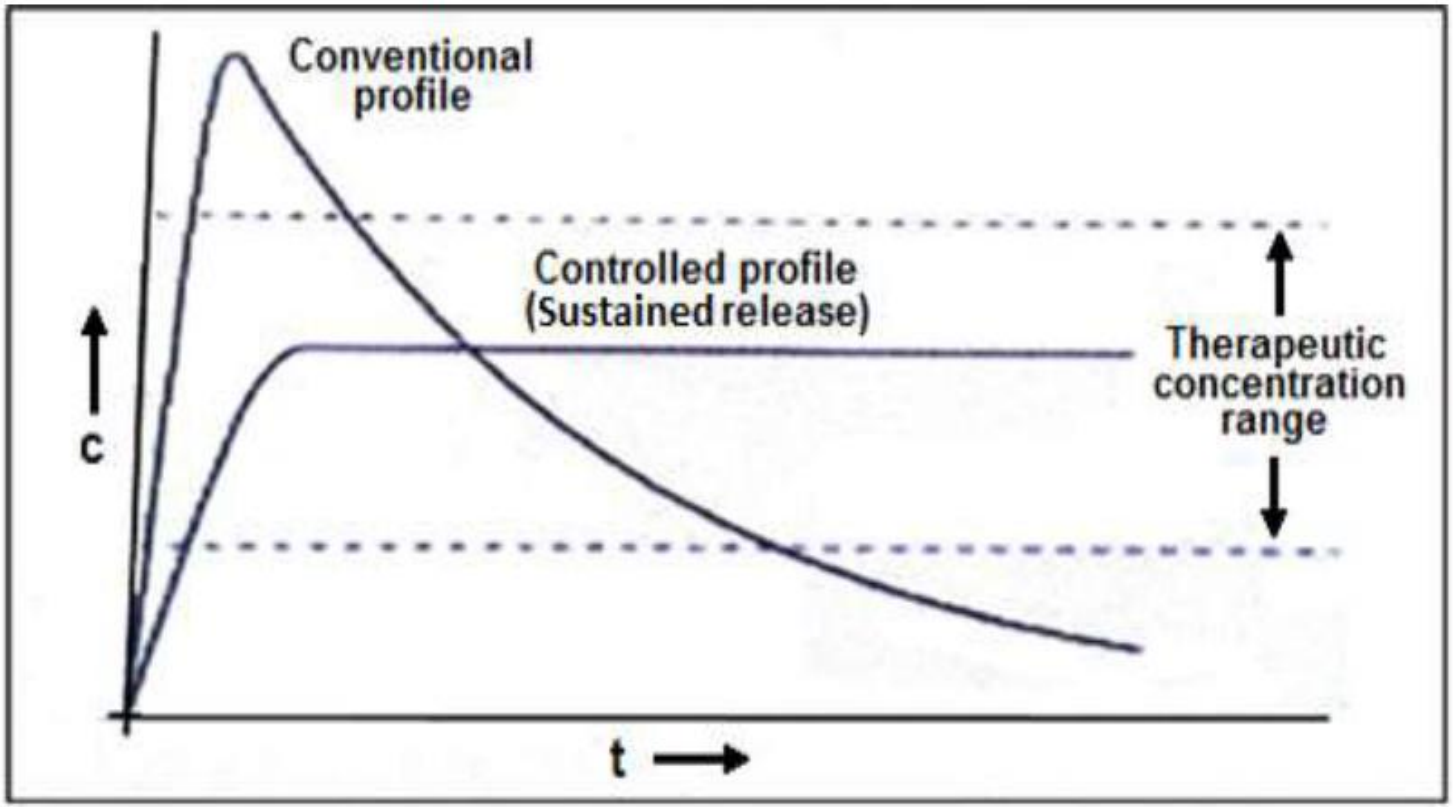
   transdermal therapeutic system

   gastrointestinal therapeutic system

3. **generation with <u>targeted drug delivery</u>**

***SR=sustained release, slow release**
LA=long acting, SA=slow acting, XR=extended release
CR=continuous (controlled) release, retard atd.

Plasma concentrations of drug administered in conventional dosage form and the dosage form with prolonged release



3. generation „Drug targeting“

Targeted therapy - selective action on specific cellular or subcellular targets

- some liposomal LF

- most of biological drugs (MAb)

- antibody drug conjugate (ADC) - e.g brentuximab –vedotin delivers an antineoplastic agent that results in apoptotic cell death selectively in CD30-expressing tumour cells.

- antisense therapies

- gene therapy

C Concomitant food + drug intake

PD interactions

- non-selective inhibitors of MAO increase the bioavailability of tyramine from food (fermented food is risky, e.g. some cheese, red wine, smoked meat, bananas).

There is a menace of excessive wash out of catecholamines and hypertense crisis.

- food with high content of vitamin K (e.g. broccoli) can decrease the effect of warfarin (vitamin K antagonist)

PK interactions

- more often- influence at the level of absorption, but also at the site of metabolism and excretion

PK interactions

Food can:

slow down the absorption without the change of extension of bioavailability
(inappropriate in analgetics, hypnotics…)

decrease bioavailability
increase bioavailability

Principles of administration of meal and drugs

Together YES, if:

↑ bioavailability of some basic drugs ,
subject to presystemic elimination
metoprolol, labetalol, verapamil

slow release from the dosage form :
hydrochlorothiazide, lithium

On empty stomach (2hrs after/ 1 hour before), if it is possible to

- ↑ rate of absorbtion: hypnotics, analgesics, ATB, NSAIDs
- ↑ F by decreasing adsorption on components of meal: furosemide, ampiciline

Avoid to combine with specific meal

e.g..

- tetracycline antibiotics with dairy products, antacids
  (Formation of nonabsorbable chelates with Ca ++ , Fe ++ , Mg ++)

- flavonoids of grapefruit juice inhibit CYP P450 3A4 =
  ⇑F other substrates : felodipine , verapamil , cyclosporin

- foods high in vitamin K (broccoli , green leafy vegetables) with oral anticoagulants - antagonists vit .K
  (Warfarin)

1.2 Factors related to the drug and organism

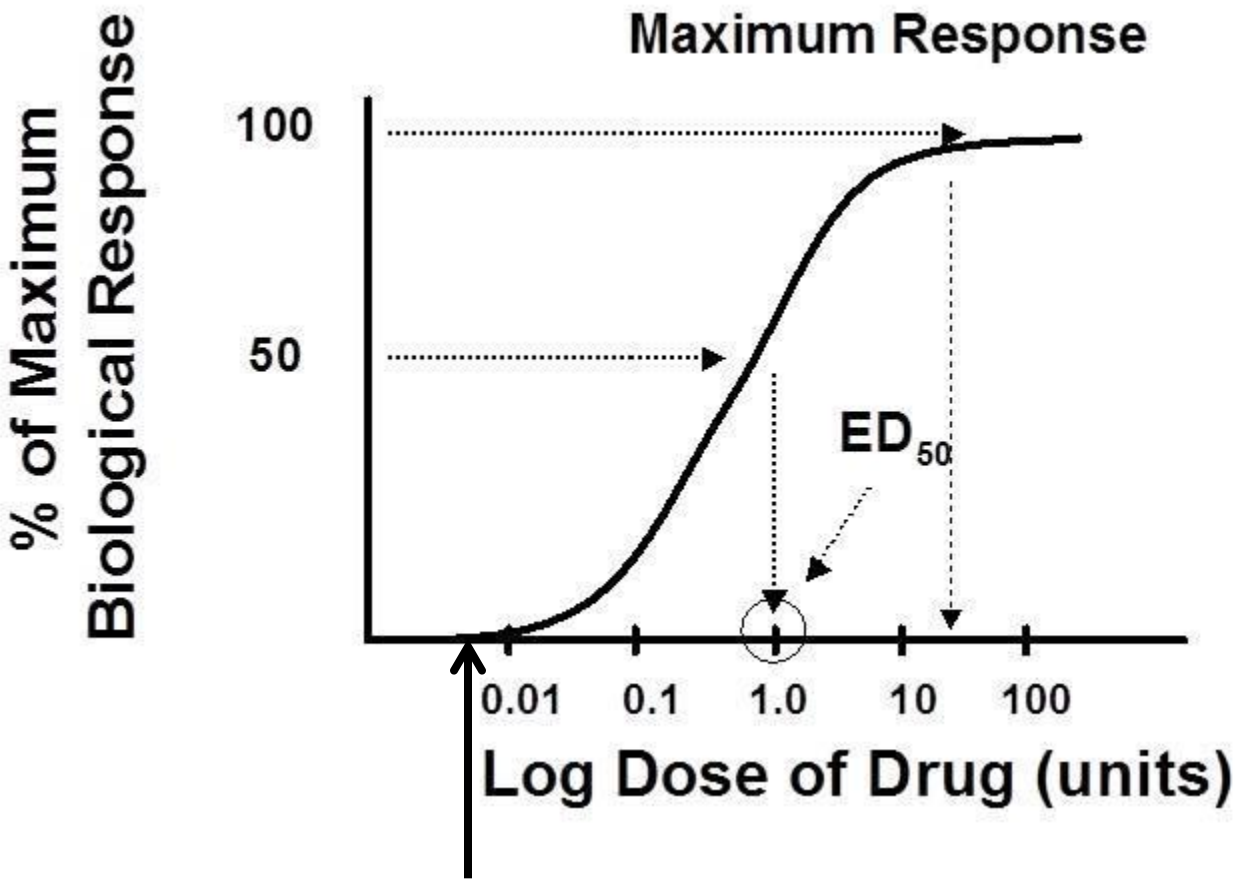
A Dose

B Drug Combinations

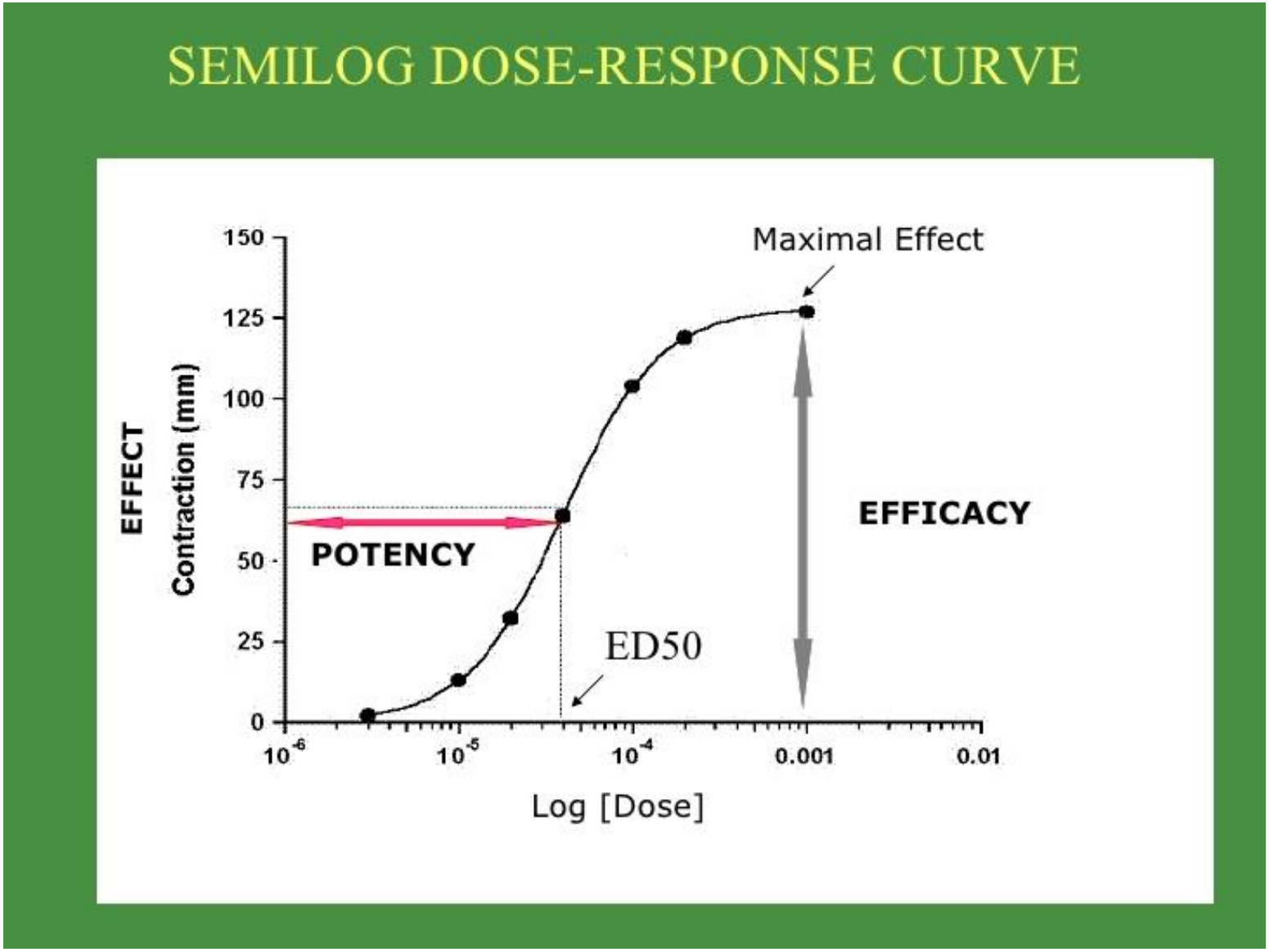
C Repeated administration

D Delayed effects

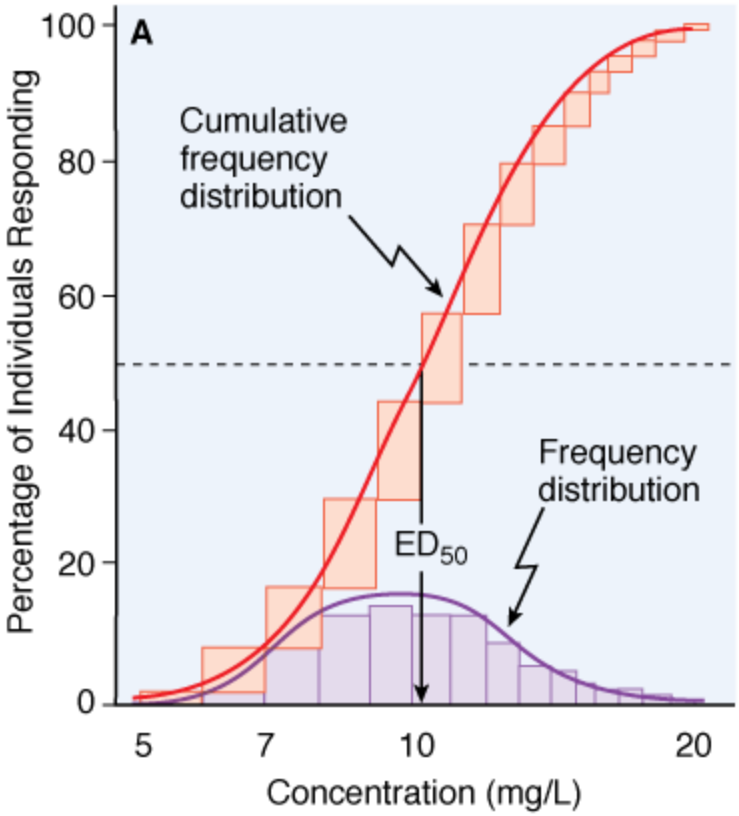
Dose-response curve

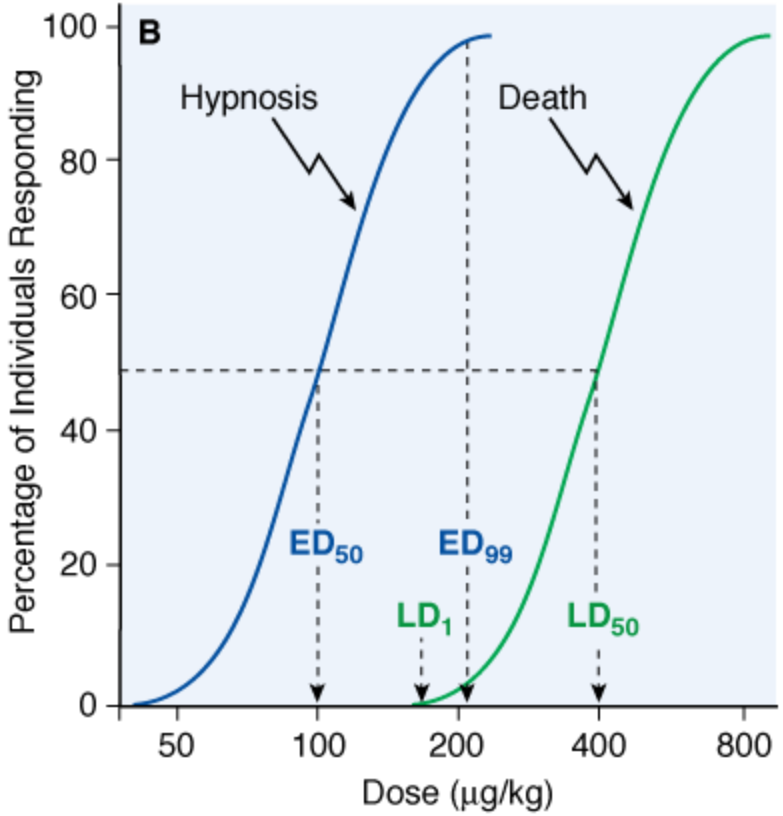


Dose-response curve

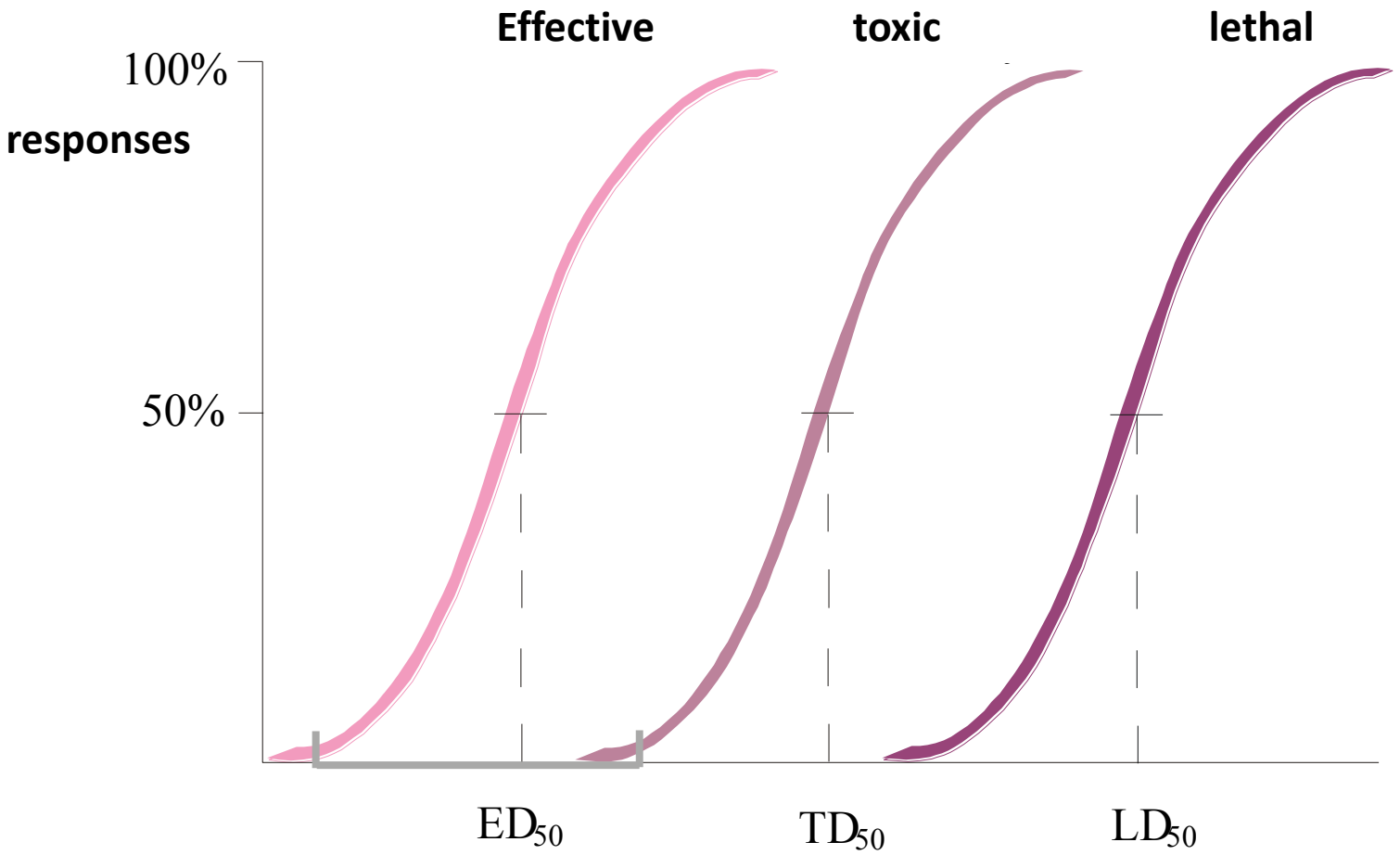


Therapeutic Index: $\frac{LD_{50}}{ED_{50}} = \frac{400}{100} = 4$





Quantal curves



$$TI = \frac{LD_{50}}{ED_{50}}$$

Therapeutic Index

- Similar to the ED50 in quantal curve (intherapeutic effects)
- is TD50 – medium toxic dose
- LD50 – medium letal

- ratio TD50 / ED50 (resp. ratio LD50 / ED50) = therapeutic index, Ti

Therapeutic Index

- Difference TD_{50} (LD_{50}) - ED_{50} = therapeutic range

- limitations therapeutic index :

  LD_{50} is found in animal experiments

  most drugs has more toxic effects → more values TD_{50} and thus more therapeutic index values,

  a number of drugs , there is a more ED50 → e.g. ED_{50} of the analgesic effect of NSAID is less than ED_{50} of antirheumatic effect

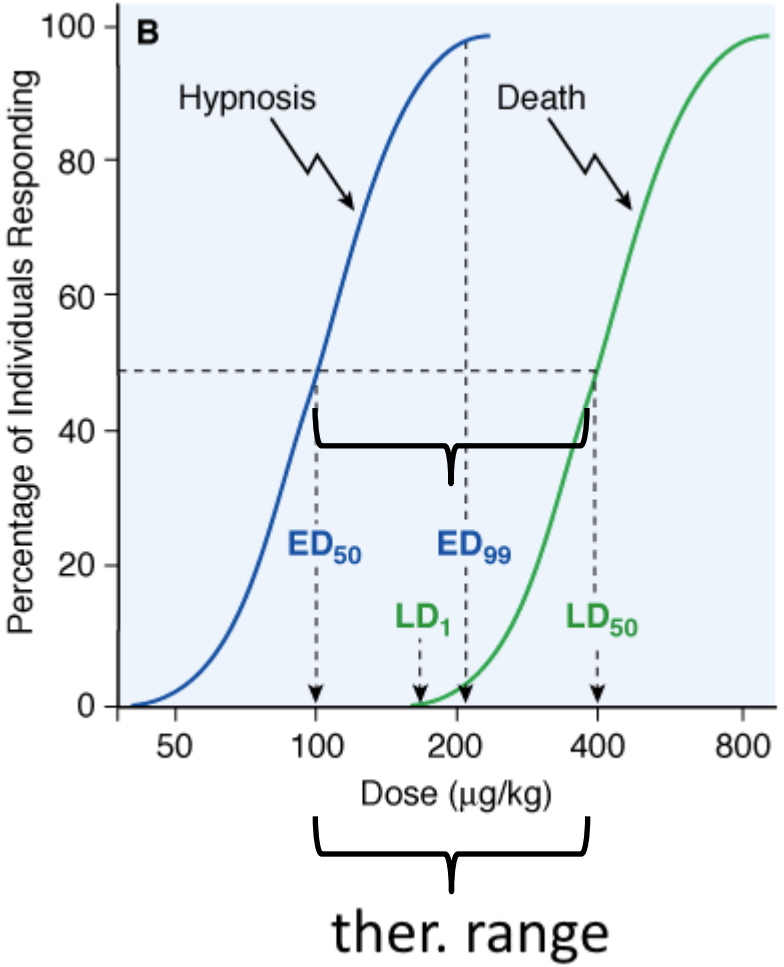
  in some of animal experiments, toxic effectscan not be not reliably detected

Therapeutic Index/range

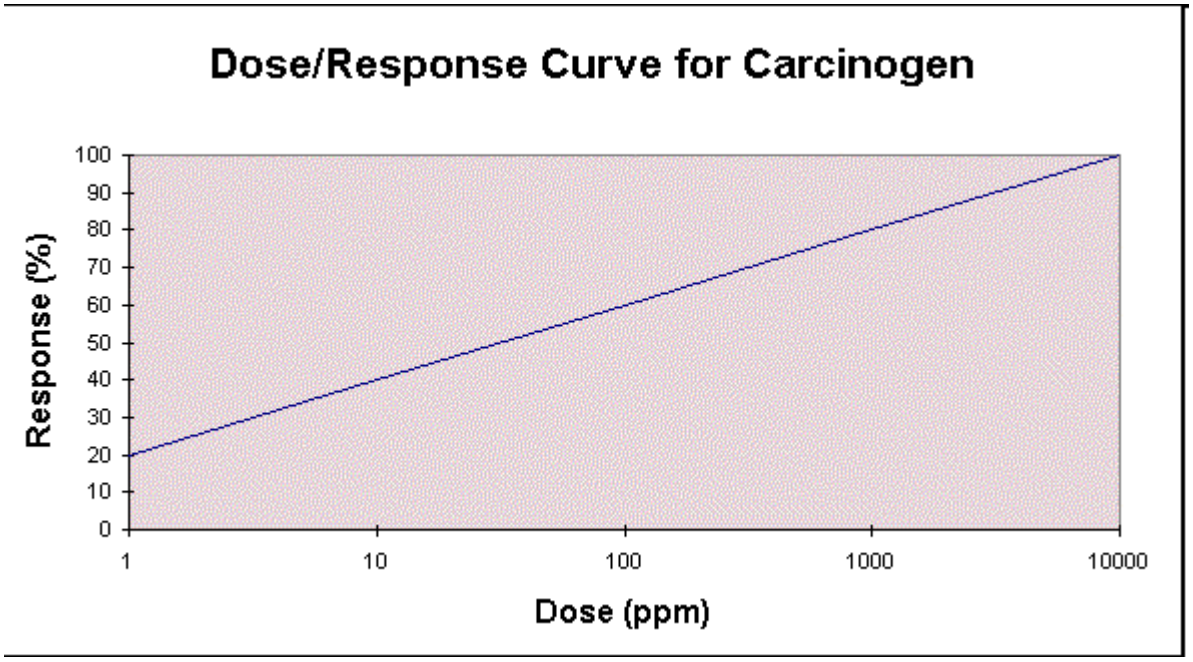
Drugs with Ti ≤ 2.0 can not be used in practice

drugs, where the value of Ti is about 2.5 is suitable monitoring of plasma concentrations (therapeutic " Drug Monitoring ")

index > 10 is resembles relatively safe medications



The relationship dose - for non-specifically acting drugs



Doses in pharmacology

In preclinical trials

In clinical trials phase I: MTD (maximal tolerated dose)

Doses in pharmacology

dosis pro dosi (d. singula) - for one administration
dosis pro die - daily dose
dosis curativa - therapeutic dose
(Cumulative)
dosis therapeutica maxima - maximal therapeutic dose

Doses for children

Doses for children

by age (Joung rule)

$$\text{infant dose} = \text{adult dose} \times \frac{\text{Age (Years)}}{\text{Age + 12}}$$

by weight (Clarke's rule)

$$\text{infant dose} = \text{adult dose} \times \frac{\text{Weight (kg)}}{70}$$

Doses for children

Doses divided into 3 age groups

0-1 1-6 6-15

Calculation according to the body surface area (most precise)

$$\text{Dose for children} = \frac{\text{body surface}[m^2]}{1{,}73} \times \text{adult dose}$$

$$\text{Body surface } [m^2] = \frac{7 * \text{age (yrs)} + 45}{100}$$

Information on dosing ?

SPC (SMPC) = Summary of (Medicinal) Product Characteristics

available within :

EMA (European Medicines Agency)

Medicines.org.uk

AISLP -Information System of Medicinal Products (Czech)

SÚKL (State Institute for Drug Control)

PIL patient information leaflet

Czech Pharmacopoeia/Eur. Pharmacopoeia

Drug combination

Increased effect

S y n e r g i s m

Summation: both drugs have the same (similar) effect and, if we combine them, the final effect is a total of effects, which the drugs would have when administered in monotherapy

one-sided : analgetics anodynes + narcotics

two-sided : combination of cytostatics

Potentiation

one-sided : Ca^{2+} + digoxin

two-sided : digoxin + thiazide diuretics

Drug combination

Decreased effect

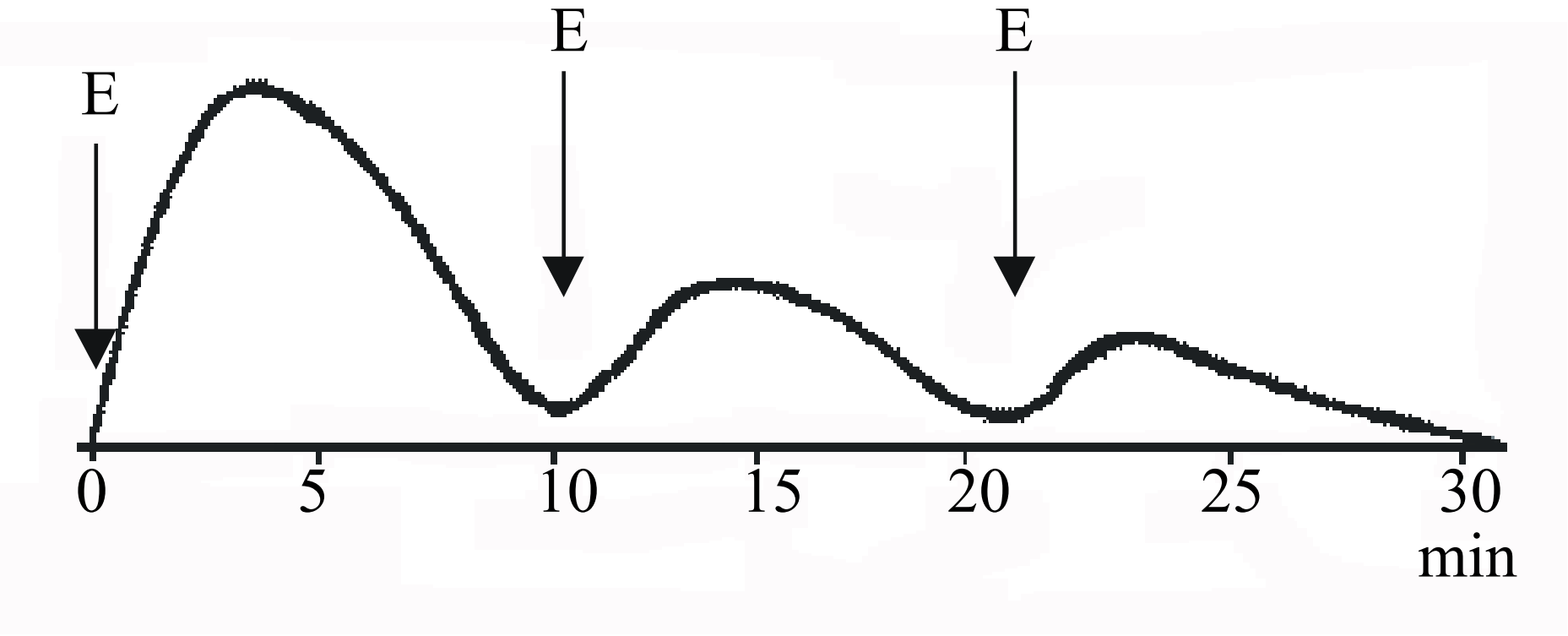
Antagonism

- pharmacological — ACh + atropine
- physiological — ACh + adrenaline; HIS+adrenaline
- chemical — heparine+ protamine; Fe+ deferoxamine

Repeated administration

- potentiating effect - accumulation - loading dose
- sensitization
- weakening effect - tolerance , tachyphylaxis
- drug addiction

Tachyfylaxis after repeated administration of efedrine (efect on blood pressure)



E = administration of efedrine

Lecture:
6th week, April, 8

Drug interactions. Assessment of the seriousness of drug interactions.

3. Factors related to the organism

- Age
- Sex
- Weight, physiognomy
- circadian rhythms
- Pathological condition of the body
- Genotype / phenotype

Drug administration in children

Children are not miniaturized adults !

- changes in PK
- changes in PD !!
- Qualitative and quantitative changes !

SPECIAL FEATURES PHARMACOKINETICS OF DRUGS IN A CHILD

Especially in neonates (especially preterm)

less binding to plasma proteins

a relatively large volume of extracellular fluid

incomplete development of blood-brain barrier

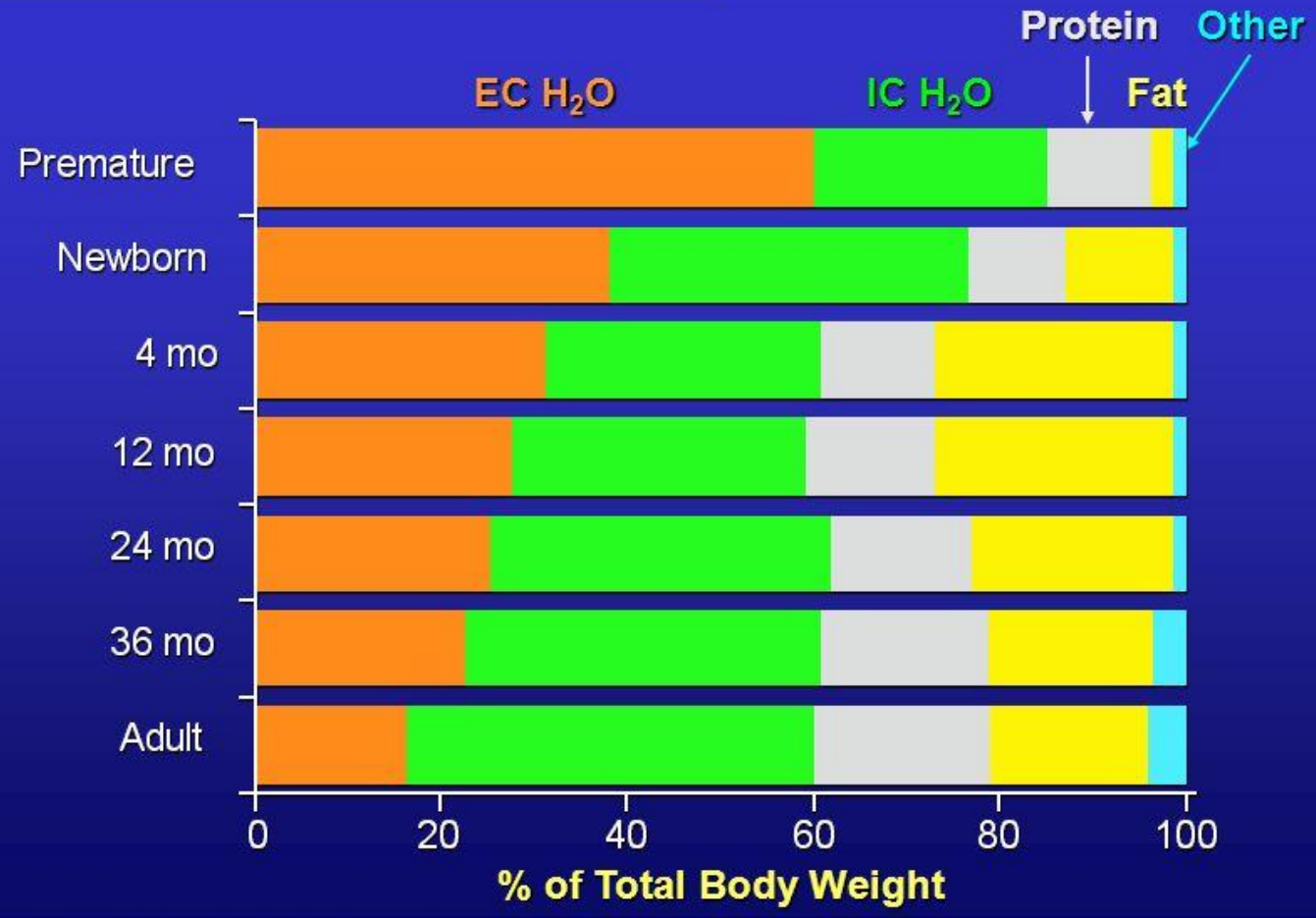
immaturity of enzymatic systems

immature renal function

ABSORPTION OF DRUGS IN THE NEONATAL AND CHILDHOOD

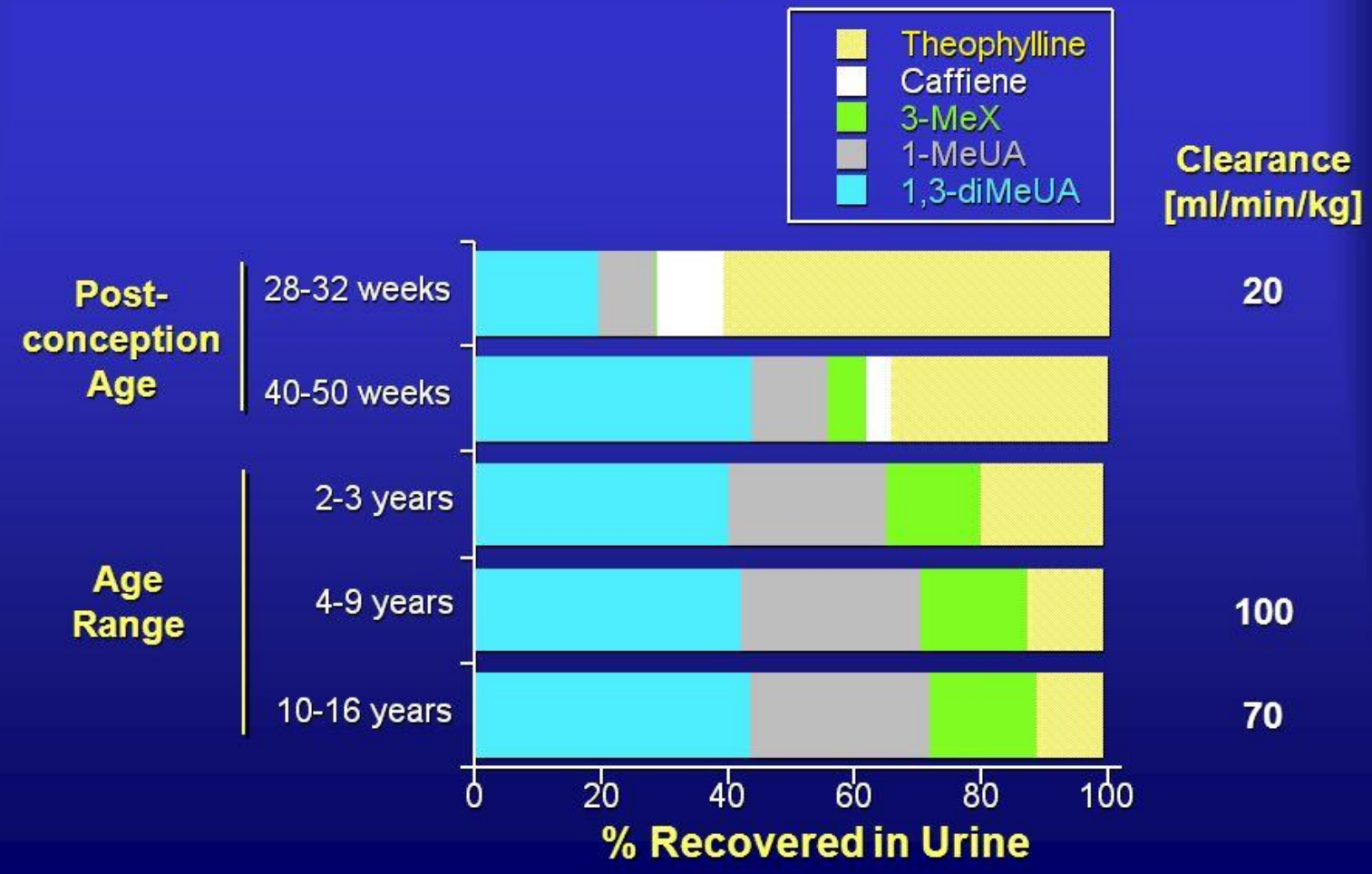
- decreased gastric acid secretion with a relative achlorhydria
- increased absorption of penicillin and conversely absorption of certain drugs is reduced (e.g. , phenobarbital , phenytoin , rifampin)
- delayed gastric emptying
- influenced by location, regurgitation , breastfeeding etc.
- variable bioavailability, greater level fluctuations than adults ;
- in particular lipophilic drugs, drugs with high presystemic elimination
- Administration on skin - higher ratio of body surface area / body weight
- greater absorption of acids: Boric acid, corticosteroids , aniline . dyes , hexachlorophene

Ontogeny of Body Composition

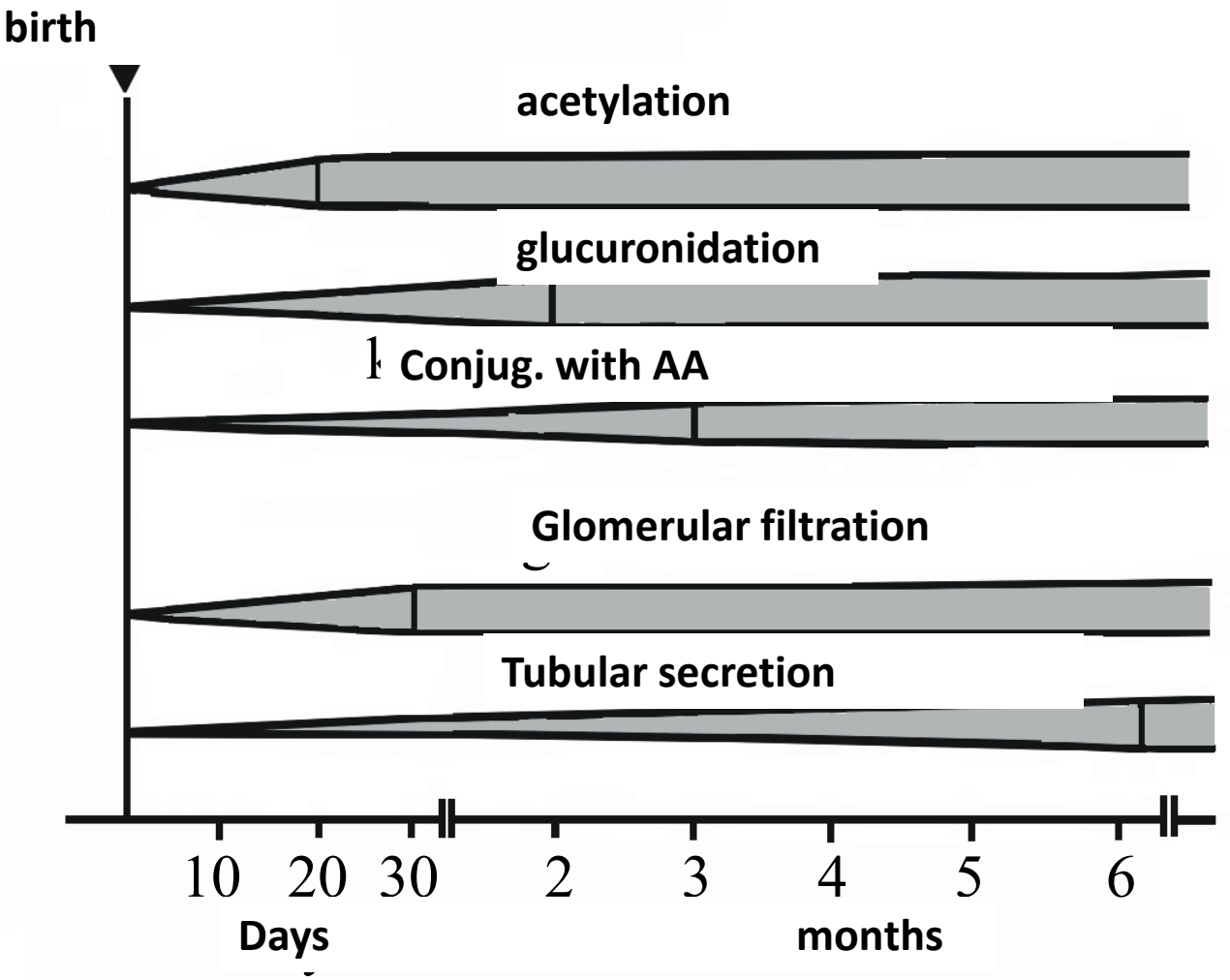


Kaufman, Pediatric Pharmacology (Yaffe & Aranda, eds) pp. 212-9, 1992

Theophylline Urinary Metabolites



POSTNATAL DEVELOPMENTAL CHANGES OF SELECTED LIVER AND RENAL FUNCTION .



Lecture:

10th week, May, 6

Drug therapy in children, general principles, pharmacokinetic and pharmacodynamic peculiarities.

Specificities of pharmacotherapy in the elderly.

Drug administration in elderly

- **60-74 age higher**
- **75-89 own age**
- **> 90 Longevity**

- physiological changes (fat/water, albumine, enzyme activity ...)
- multimorbidity
- polypharmacy (the administration of many drugs at the same time, increases the risk of medication, interactions)
- Higher incidence and severity of ADRs
- Beers list

DEMOGRAPHICS OF PHARMACOTHERAPY

seniors - about 15 % of the population

35-45 % of all drug expenses

People aged > 60 years use in 85 % at least one drug

aged > 75 years use in 97-99 % at least one drug

the average number of drugs :

Geriatric patient: 2-6 per patient

hospice patient: 3-9 per patient

CLINICALLY IMPORTANT CHANGES IN ELDERLY AND THEIR CONSEQUENCES

Composition of the body

- atrophy of tissues

- Increased fat and connective tissue → ↑ volume of distribution for lipophilic drugs

- ↓ water content in the body → reduction in volume of distribution for hydrophilic drugs (+inadequate fluid intake)

Musculoskeletal system

- A decrease in muscle mass → decline in muscle strength

- Loss of bone density

- The aging and wear of cartilage

- Impairment of motor coordination

The American Geriatric Society: updated Beers Criteria list based on evidence-based recommendations

Table 2. 2012 AGS Beers Criteria for Potentially Inappropriate Medication Use in Older Adults

Organ System/ Therapeutic Category/Drug(s)	Rationale	Recommendation	Quality of Evidence	Strength of Recommendation	References
Anticholinergics (excludes TCAs)					
First-generation antihistamines (as single agent or as part of combination products) • Brompheniramine • Carbinoxamine • Chlorpheniramine • Clemastine • Cyproheptadine • Dexbrompheniramine • Dexchlorpheniramine • Diphenhydramine (oral) • Doxylamine • Hydroxyzine • Promethazine • Triprolidine	Highly anticholinergic; clearance reduced with advanced age, and tolerance develops when used as hypnotic; increased risk of confusion, dry mouth, constipation, and other anticholinergic effects/toxicity. Use of diphenhydramine in special situations such as acute treatment of severe allergic reaction may be appropriate.	Avoid	Hydroxyzine and promethazine: high; All others: moderate	Strong	Agostini 2001 Boustani 2007 Guaiana 2010 Han 2001 Rudolph 2008
Antiparkinson agents • Benztropine (oral)	Not recommended for prevention of	Avoid	Moderate	Strong	Rudolph 2008

Changes of PK/PD in elderly

ATB aminoglycosides : lower doses (decrease in GF - correction by CL CR)

- Antihypertensives: orthostatic hypotension, mental changes (confusion)

- Anticoagulants: bleeding from GIT (decrease absorption vitamin K and reduced synthesis of prothrombin)

- NSAIDs : 25% melena or hematemesis

- anticholinergic compounds: higher toxicity , depression, confusion

(Decreasing the amount of mediator in the synapses of the CNS)

Sex differences in PK

absorption

distribution

biotransformation

excretion

On the basis of differences:

weight , plasma volume, gastric emptying , plasma proteins , CYP activity , activity of transport systems , clearance ...

Sex differences in PK

biorhythms
The heterogeneity of the female population :

Fertile
+ /- contraception

- progestin . contraception
- Combined contraception
- without contraception

- pregnancy
- breastfeeding
postmenopause

Sex diferences in absorbtion

- The slower gastric emptying and transit time in women (persists after menopause) difference increased by estrogen substitution (contraception, HRT)
- Slower absorption
- Lower intestinal CYP expression in women (in some CYPs)
- higher bioavailability and plasma levels of certain drugs in women
- PgP (MDR1) - increased hepatic expression in males
- Pgp activity (phenotype) identical - PgP apparently not affected by gender

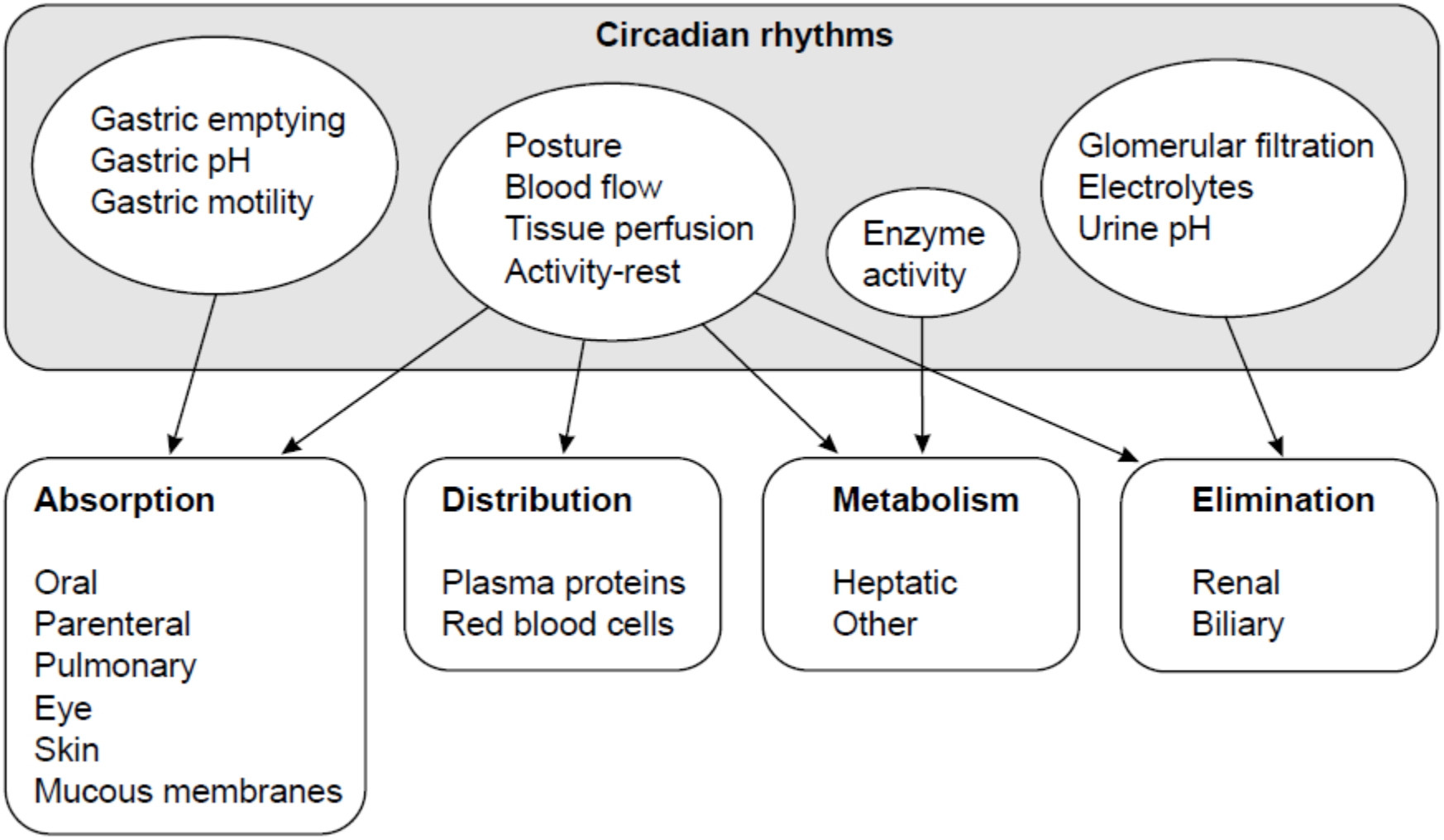
Circadian rhytms

Biorhythms in body functions depending on the day, season or time of year --- subject of study chronopharmacology and chronotherapy.

Example: the incidence of asthma attacks is highest in the early morning , (low sympathetic tone and low levels of endogenous glucocorticoids)

Cisplatin - lower toxicity at high bladder volume - circadian rhythms

melatonergic antidepressants


Circadian rhythms
Gastric emptying
Gastric pH
Gastric motility
Posture
Blood flow
Tissue perfusion
Activity-rest
Enzyme activity
Glomerular filtration
Electrolytes
Urine pH
Absorption
Oral
Parenteral
Pulmonary
Eye
Skin
Mucous membranes
Distribution
Plasma proteins
Red blood cells
Metabolism
Heptatic
Other
Elimination
Renal
Biliary

Genetic polymorphism

Genetic polymorphism = the existence of several
(At least two) alleles for the gene from which
At least part has a population frequency of at least 1 %

- Pharmacogenetics

focuses on the study of genetically conditioned variability in the response to a drug

- Pharmacogenomics examines the relationship of drug effect on the level of the whole genome, respectively transcriptome

GENETIC POLYMORPHISM OF BIOTRANSFORMATION ENZYMES

Polymorphism in the gene of ***N - acetyltransferase***

- Inactivation of drugs in the liver : slow x fast acetylators
- Isoniazide , procainamide, hydralazine
- Peripheral neuropathy (prevention - pyridoxine)

Polymorphism of ***thiopurine S - methyltransferase***

- the metabolism of azathioprine
- commercially available genetic test for determining the polymorphisms, prevention of serious adverse reactions

GENETIC POLYMORPHISM OF CYP2D6

Null alelles

- encode a nonfunctional protein

- In the homozygous state cause the phenotype PM

SNP (point mutations)

a chromosome deletion

mutation leading to loss of the fction of protein, but the length of protein is maintained

- * 4 allele (12-21 %) in Caucasian populations (most frequent 1846G > A)
- * 5 allele (2-7 %) causes loss of whole CYP2D6 gene
- allele * 13 and * 16 - 5'- CYP2D7P / CYP2D6-3' hybrid genes , deletion of various parts of CYP2D locus

GENETIC POLYMORPHISM OF CYP2D6

The alleles associated with decreased enzymatic function

encode an enzyme with reduced activity

in the homozygous state or with the null allele in the heterozygous state cause the IM phenotype

*** 10 (50-70 % Asian, 1-5% of the Caucasian population) 100C > T (disrupts normal folding of the protein → enzyme is very unstable and has a lowe affinity to a substrate**

Genetic polymorphism of CYP2D6

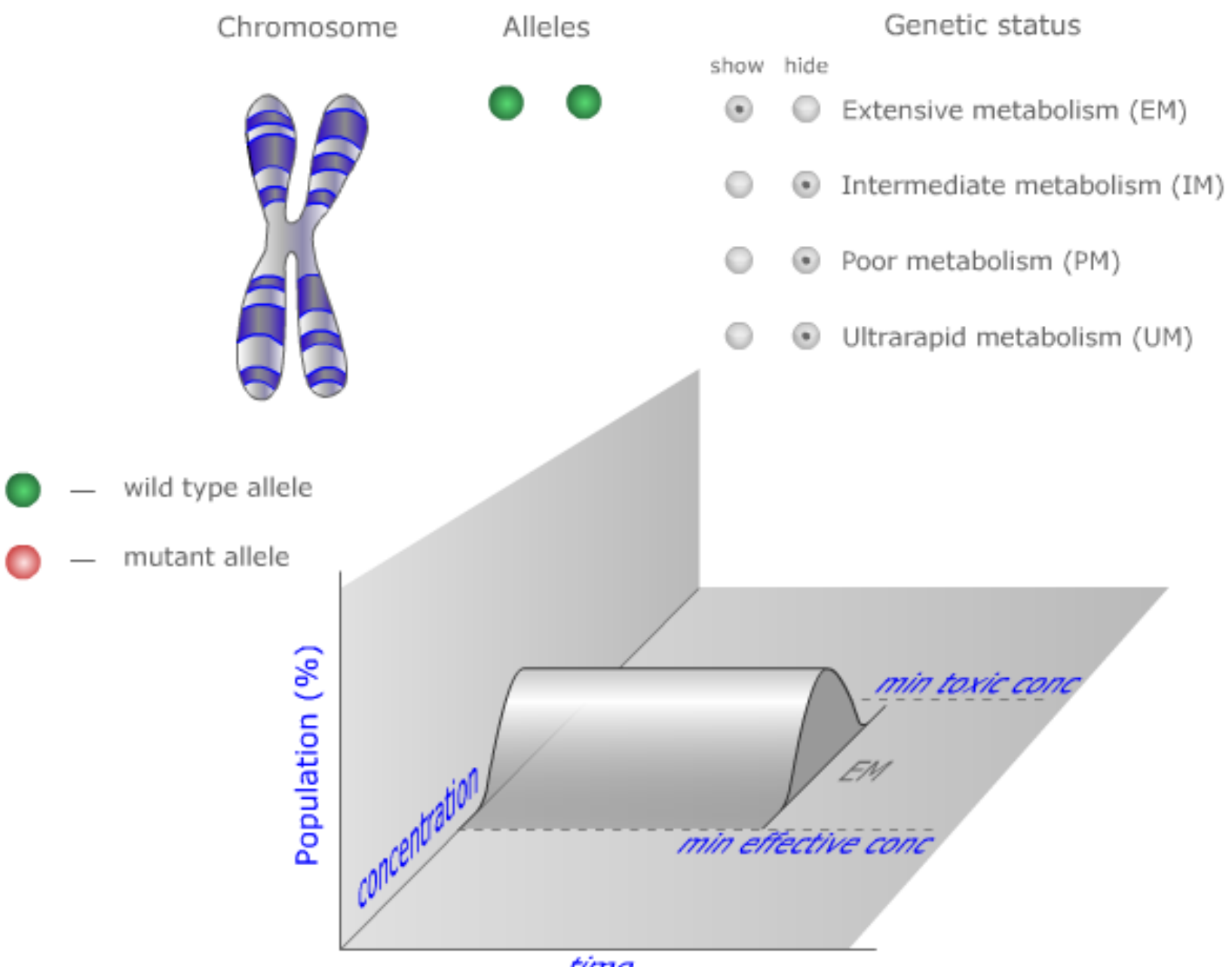
The alleles associated with increased enzyme function

- An increase in the number of active gene copy

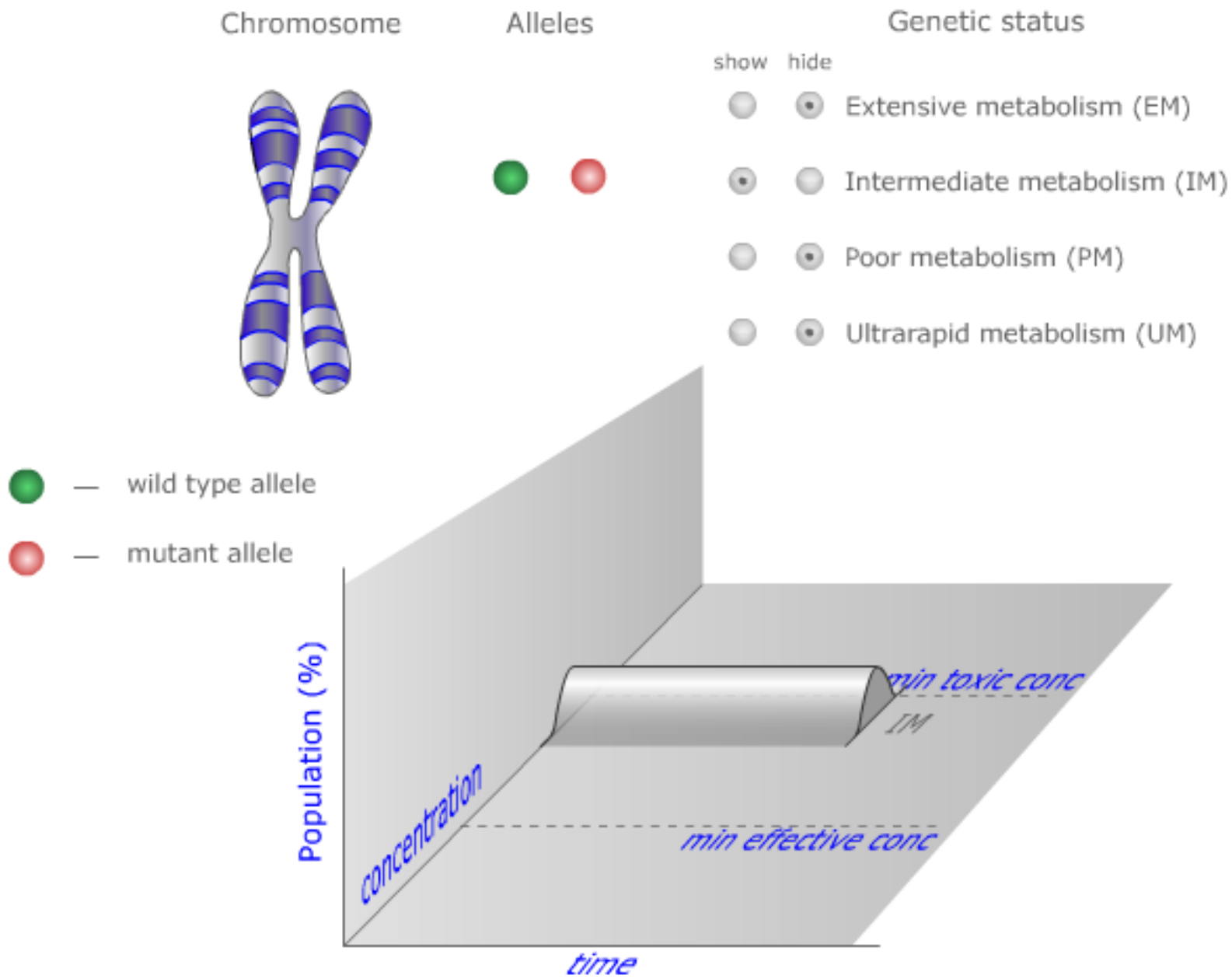
- Alleles * 1 , * 2 , 35 *

- The frequency of Caucasians 1-5%

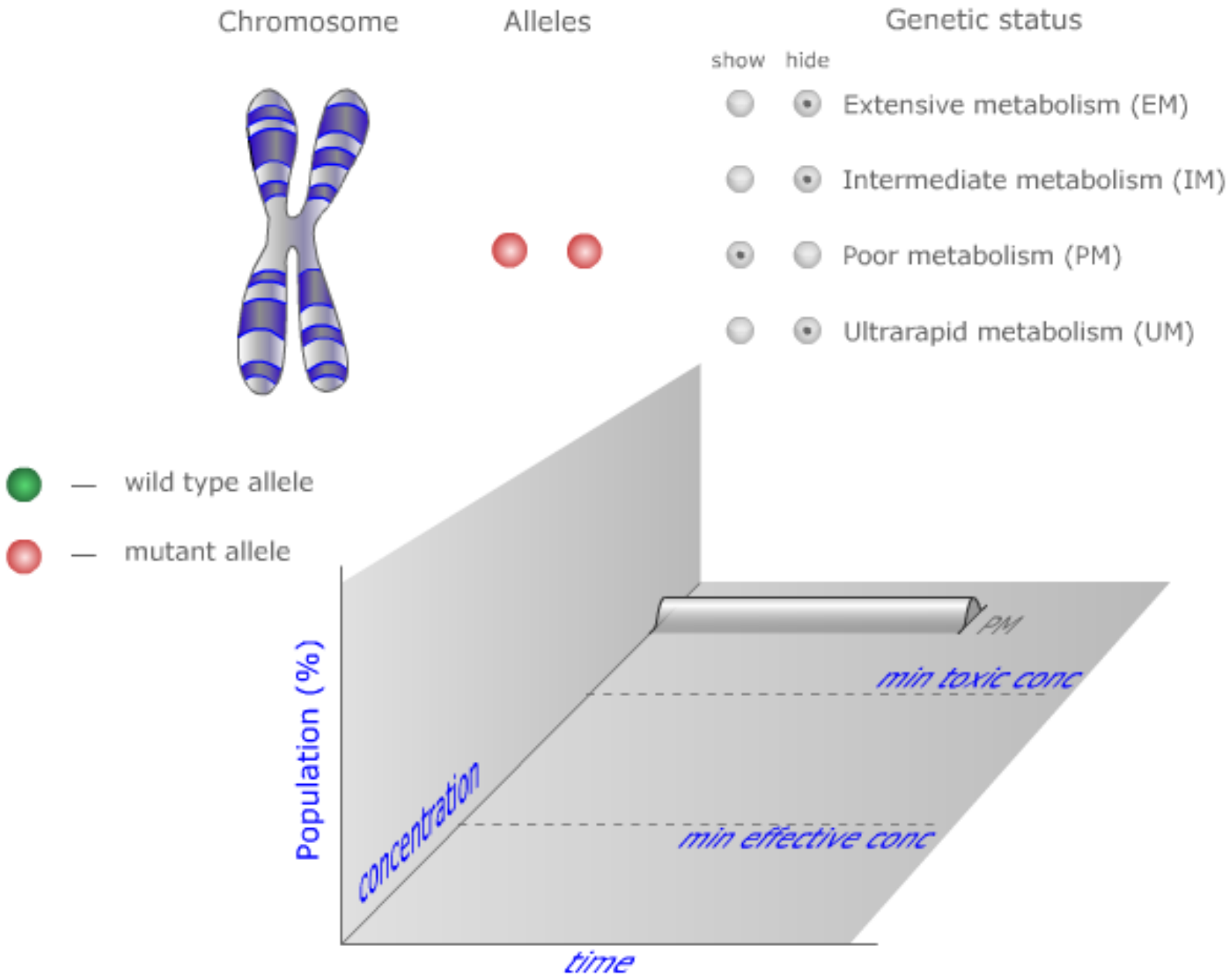
GENETIC POLYMORPHISM OF CYP2D6



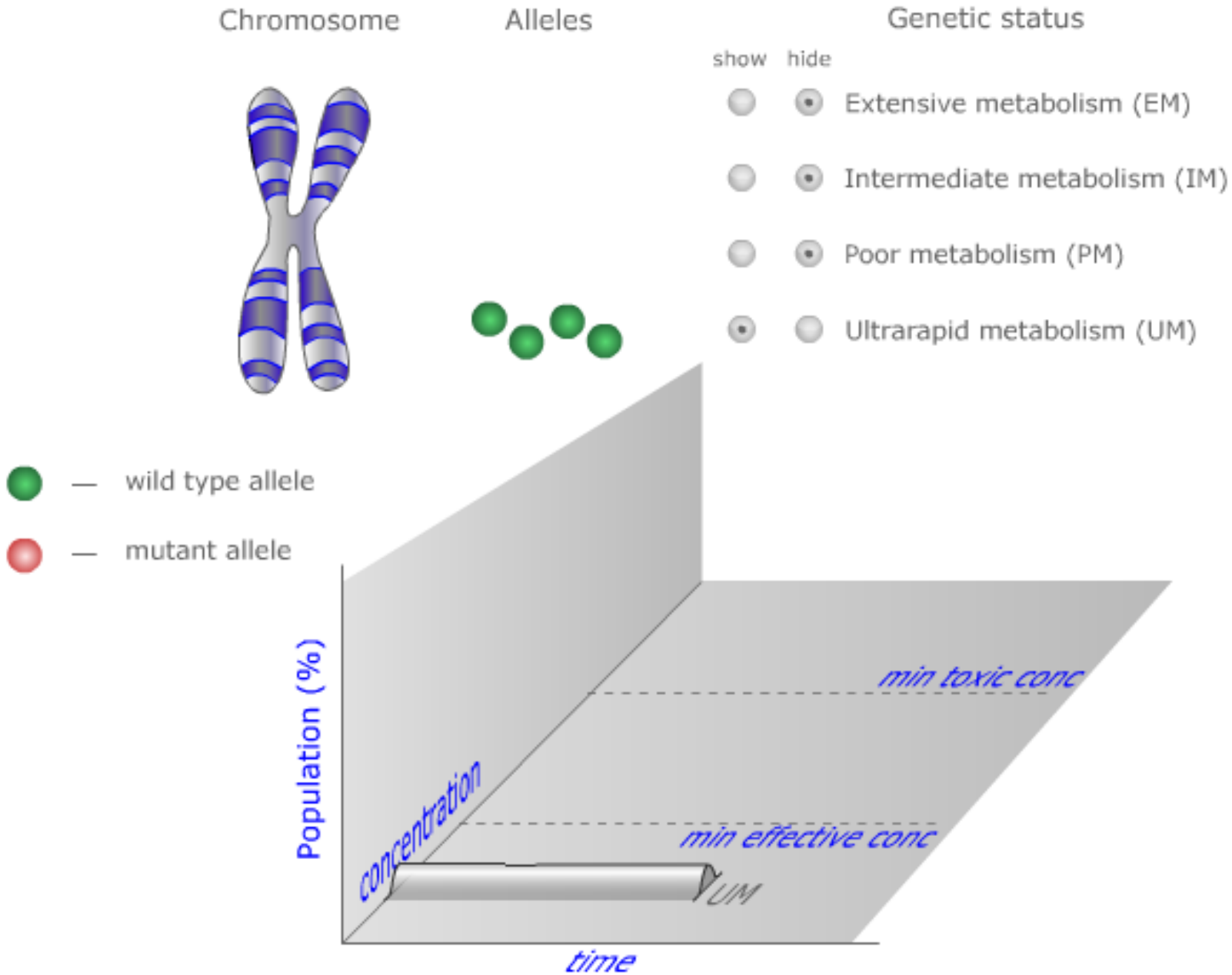
Genetic polymorphism of CYP2D6



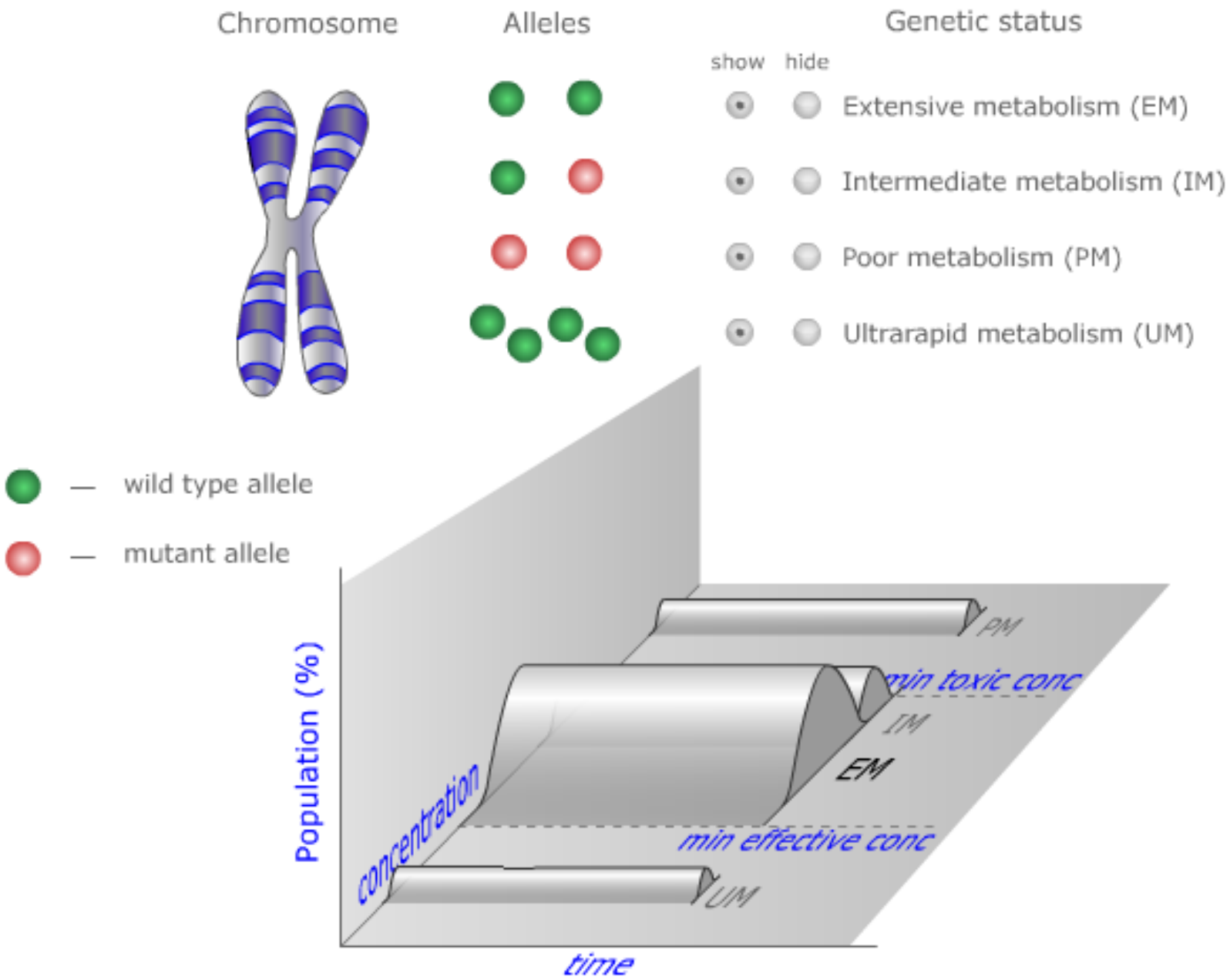
Genetic polymorphism of CYP2D6



Genetic polymorphism of CYP2D6



Genetic polymorphism of CYP2D6



Genetic polymorphism of CYP

- **CYP2D6** and antidepressants (especially classical) : significant

PK differences, difficult to adjust dose due to slower onset of effect, long-term drug therapy

- **CYP2C9** and oral antidiabetic drugs - derivatives

sulfonylureas (e.g. glimepiride, glipizide and tolbutamide)

In heterozygotes CYP2C9 * 1 / * 3 , the total clearance of 50 %

homozygotes and CYP2C9 * 3 / 20 * 3 % compared to WT

- **CYP2C9** and anticoagulants - (warfarin) in heterozygous

CYP2C9 * 1 / * 3, the total clearance of 70 %, and in

homozygotes CYP2C9 * 3 / 40 * 3 % compared to WT

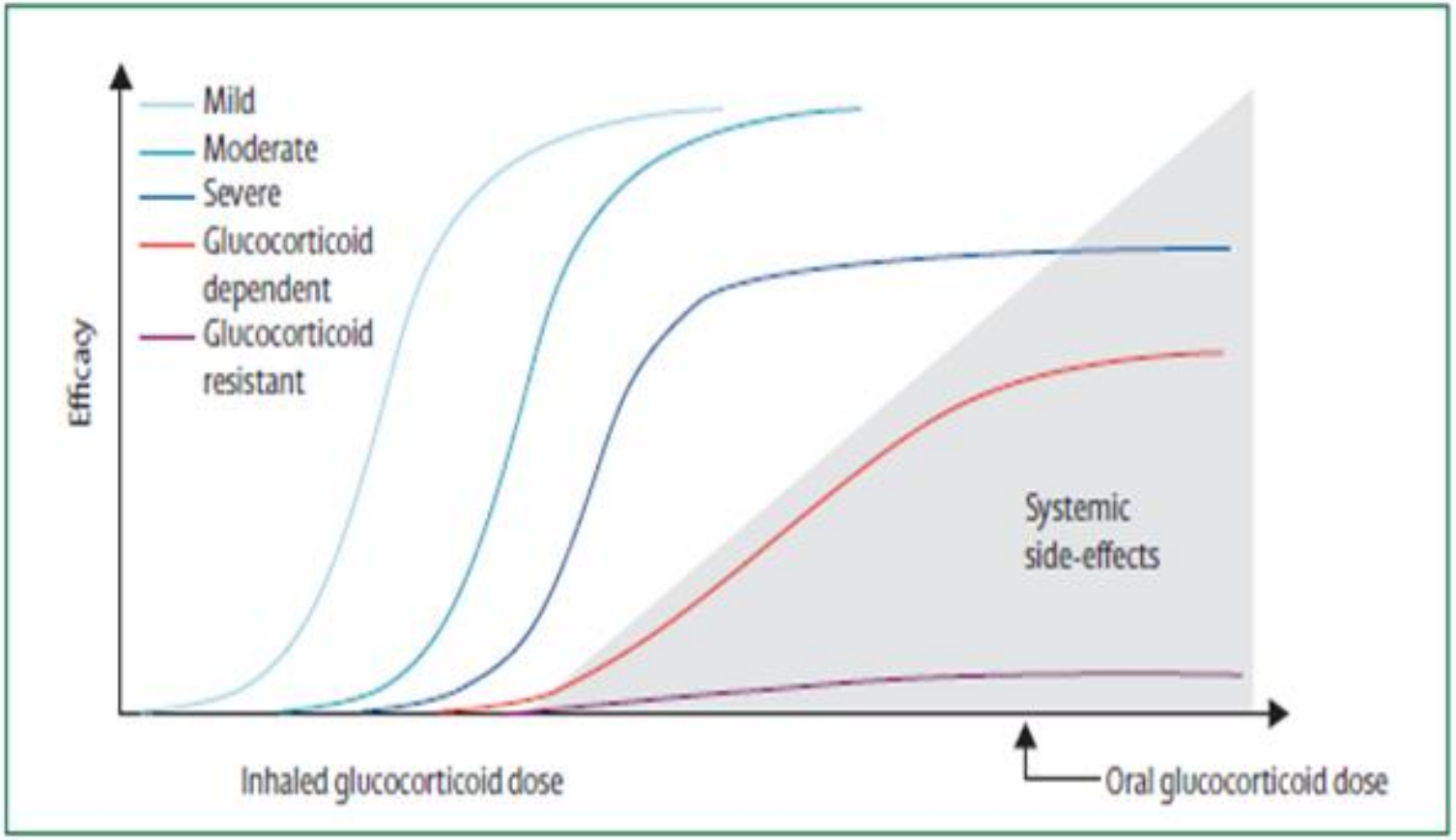
Pathological condition of the body
Effect of diseases on the effect of drugs

effect on the pathological condition on the pharmacodynamics of drugs
(Antipyretics, cardiotonics)

Effect of kidney , liver insufficiency, impairment, thyroid gland overctivity/hypofunction - pharmacokinetics consequences

Path. State as contraindication!

Effect of diseases on effect of drugs - other pathologies



Effect of diseases on the effect of drugs - other pathologies

Impact of liver disease

- There is no reliable quantitative measure of impaired liver elimination capability for drugs (CLcr analogy with kidney disorders); therefore - empirical approach

- liver function tests (ALT, AST, albumin, clotting factors) are not a good guide for the dosage of drugs - nonspecific

EFFECT OF DISEASES ON THE EFFECT OF DRUGS - OTHER PATHOLOGIES

In people with liver diseases

- Think about the possibility of impaired elimination of drugs which are eliminated mainly via the liver (> 60-70 %)
- Reduce the dosage in advanced liver diseases:

  diazepam, paracetamol, phenobarbital, phenytoin, valproic acid mesocaine, morphine, theophylline, calcium channel blockers
- carefully: antidiabetics, diuretics,anticoagulants, antihypertensives (follow accomplishments

  effect)
- Monitoring the levels (TDM)- appropriate for antiepileptic drugs, theophylline, cytostatics (low TI), AMG antibiotics, antipsychotics…

EFFECT OF DISEASES ON THE EFFECT OF DRUGS - OTHER PATHOLOGIES

Heart failure (centralization of circulation)

- possible slowdown and reduced absorption after p.o. admin.
- possible increase biol . availability of substances with extensive first pass effect
- Slow down the absorption after IM

Gastrointestinal disorders (malabsorption , gastric ulcers and conditions inducing nausea , vomiting)

Thyroid disorders (hyperfunction is generally increased

the intensity of metabolism) x hyperthyroidism may potentiate the effect of warfarin

- **Fever (↑ ventilation and GF, increased elim. of gentamicin)**
- **Edema (↑ Vd gentamicin)**
- **Obesity**

ADVERSE DRUG EFFECTS

= adverse unintended response on a drug administration

excessive effect (therapeutic)

independent on the main (mechanism) effect

The incidence of 1-30 % of treated patients

0.5 to 0.9 % - lethal ADE

ADVERSE DRUG EFFECTS

PHARMACOVIGILANCE

Monitoring of adverse drug reactions in routine clinical practice - the active drug safety

SÚKL
Státní ústav pro kontrolu léčiv

+420 272 185 111
telefonní seznam

Léčiva | Zdravotnické prostředky | Lékárny | Zdravotnická zařízení | Farmaceutický průmysl | Distribuce | SÚKL

gentura pro konopí pro
použití
činnosti
ormace
leska

Úvod / SÚKL / Úřední deska

Úřední deska

Posláním Státního ústavu pro kontrolu léčiv je v zájmu ochrany zdraví občanů zajistit, aby se v praxi a při klinickém hodnocení používala pouze farmaceuticky jakostní, účinná a bezpečná léčiva, jakostní a bezpečné suroviny pro výrobu a přípravu léčiv a bezpečné a funkční zdravotnické prostředky s informacemi popisujícími jejich objektivně zjištěné vlastnosti a aby údaje z výzkumu léčiv, surovin a prostředků byly věrohodné a byly získávány eticky.

7th week, April, 15

Principles of pharmacovigilance, duties of physicians and pharmaceutical companies, general rules in drug promotion.

Uninteded drug reactions

- Up to 20 % hospitalizations in elderly are suspected to be due to ADE

- ≥ 2/3 NÚL are dose-related, predictable, avoidable

Intensity of ADR

- mild
  - No action needed
- moderate
  - Results in change of dosing or treatment
- severe
  - Potentional harm
  - necessity of drug withdraval
- lethal

LEGISLATION

Pharmaceutical act (378/2007 SB.)

- SADR – serious adverse reaction
- UADR – unexpected adverse drug reaction
- USAR – unexpected serious adverse reaction
- SUSAR - suspected unexpected serious adverse reaction

- Adverse event

ADVERSE DRUG EFFECTS

Classification according to frequency

Very frequent	≥1/10 patients
frequent	≥1/100 patients
Less frequent	1/100 - 1/1 000 patients
Rare	1/1 000 - 1/10 000 patients
Very rare	≤ 1 / 10 000 patients

ADVERSE DRUG EFFECTS

A – **augmented** – (95 %) caused by the same mechanism as pharmacotherapeutical effects.

B – **bizzare** – (5 %)„pacient's reaction" –are caused by a genetic mechanism (idiosyncrasy) or by an imunological mechanism (allergies).

C – **chronic** – are caused by a long term taking

D – **delayed** – show after a longer period of latency

E – **end-of-use** -syndrom caused by discontinuing a drug

A – AUGMENTED

caused by the same mechanism as the pharmacotherapeutical effects. Induced by unappropriate dosage or by change in pharmacokinetics as a result of pathological process.

- predictable
- directly dependent on the dose
- frequent, seldom fatal

Insulin > hypoglycaemia

Anticoagulants> bleeding

beta-blockers > bronchi-constriction > astmatic attack

B - BIZZARE

Caused by a genetic mechanism (idiosyncrasy) or by an imunological mechanism (allergies).

- unpredictable
- do not depend on the dose
- less frequent (1:1 000 až 1:10 000)
- higher mortality

Idiosyncrasy – reaction on the first dose, without previous sensibilisation (suxamethonium in individuals with atypical cholinesterase), polymorfisms.

Allergic reaction - reaction after a previous sensibilisation.

C - CHRONIC

- **caused by a long term drug administration**

- e.g. analgetics > nefropathy
- prednisolon > iatrogenic Cushing's syndrome
- laxatives > dysfunction of GIT.

D - DELAYED

- become apparent after a longer period of latency (or in children of the treated patients)
  -mutagenesis, teratogenesis and cancerogenesis

    Decreased fertility

    Developmental toxicity =

    accumulation of drugs in the breastmilk

    Immunosuppression → immunosuppressants ca liver, biliary tract

Common characteristics:

- change of the genetic information because of the effect on DNA
- sensibility of the dividing and growing tissue
- ireversibility of the induced changes

E – END OF USE

Appears after the administration of a drug is finished. Like a syndrom caused by discontinuing a drug
(rebound fenomen, withdrawal syndrome).
up/down-receptors regulation

- Examples:
- Tachycardia after discontinuing betablockers.
- Adrenocortical insufficiency after discontinuing glucocorticoids.
- Seizures after discontinuing antiepileptics.

F- THERAPEUTIC FAILURE

treatment failure

primarily ineffectiveness despite:

The correct dosage , correct indication

Correct MO sensitivity to antibiotics

TOXIC EFFECTS OF DRUGS

—> after administration of inappropriately high doses

Increased quantity of effect - heparin - bleeding
changed quality of action - phenacetin - nephropathy

Toxic reactions:
pharmacological
- may be decreased with lower doses (hypnotics)
pathological
- Lead to tissue damage
genotoxic
- DNA damage

TOXIC EFFECTS OF DRUGS

Signs of toxicity may appear as a consequence of

Early toxicity – aucite toxicity

In repeated administration -subacute toxicity

Delayd – chronic toxicity – teratogenity, cancerogenity, mutagenity

toxicity: topical x systemic

acute x chronic

TOXIC EFFECTS OF DRUGS

mostly occur in drugs with narrow therapeutic index

Antihypertensives

cardiac glycosides

antiarrhythmics

anticoagulants

Cytostatics, immunosuppressants

aminoglycoside antibiotics

Categories of the risks during pregnancy

Essential tool in assessing the risks of drug use in pregnancy

it is always necessary to assess the situation comprehensively

expected development of the disease **without treatment**

the risk sourcing from non-administration of the drug to the mother and fetus

the expected duration of treatment and the expected dose

Categories of the risks in pregnancy

US - divides the drug into five groups (A, B, C, D, X)

- Medicines "A" = proved to be safe
- The drug "X" = proven teratogens

AUSTRALIA - the same division,
subgroup B divided into subgroup B1, B2 and B3

GERMANY - 11 subgroups

- subgroup 11 = proven teratogens

Thalidomide Scandal

Thalidomid - Contergan©

1950 – 1960 hypnosedative, antiemetic used in pregnancy

Teratogenic !!

between 5,000 and 7,000 infants were born just 40% of these children survived

Throughout the world, about 10,000 cases were reported only 50% of the 10,000 survived

Thalidomide Scandal

Malformations - "phocomelia", i.e. agenesis arms or legs

dose causing malformations in humans is very low (about 0.1 mg / kg), whereas in most animal species is much higher (20 to 300 mg / kg).

TERATOGENIC EFFECTS OF DRUGS

Thalidomide isomere R and S,

R is used to treat morning sickness, S is highly teratogenic.

Thalidomide – very effective in patients with multiple myeloma.
tested in a number of other hematological and oncological diagnoses.

It is also used to treat leprosy and tested in other indications.

OTHER ADRs

- **CNS**
  - drowsiness, dizziness, headache, depression
- GIT
  - dyspepsia, flatulence, peptidic ulcers, diarrhea, constipation, vomiting, anorexia
- UGT
  - erectile dysfunction, changes in vaginal secretion
- RT
  - dyspnoea, bronchoconstriction
- CVS
  - arrhythmia, hypotension, hypertension, palpitations

Reasonable Pharmacotherapy

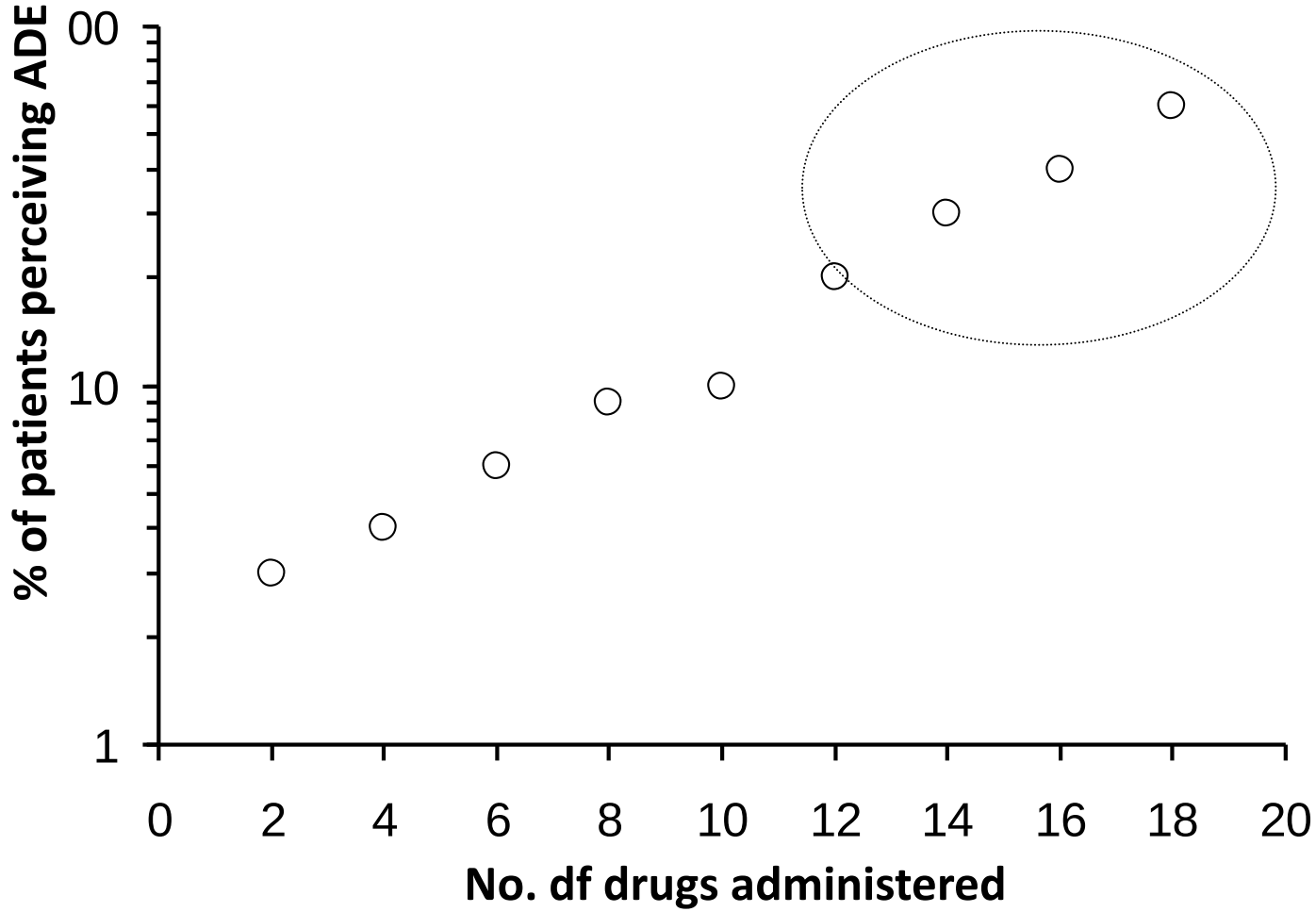
- = correct selection of drug for distinct patient at right time
- Approved indication
- Suitable indication
- Avoidance of polypharmacy and ADR

Polypharmacy

- irational concomitant use of more drugs
- Some are non-essential
- Increases the risk of inappropriate interactions and ADRs
- Higher risk in elderly

Adverse effects and number of administered drugs

No. of drugs



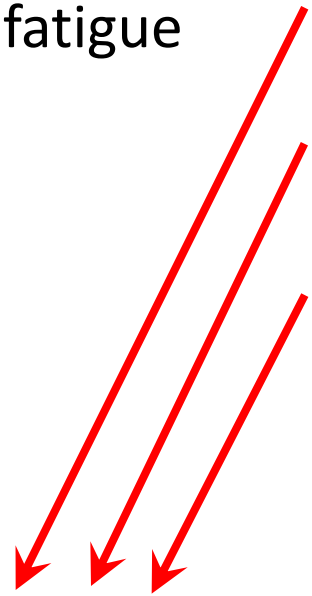
Polypharmacy

Response to medication may mimic some signs of aging:

drowsiness, dizziness, fatigue

falls insomnia
nervousness
incontinence
confusion

malaise
depression



Some may indicate a psychiatric treatment
→ The indication of psychotropic drugs

Thank you for attention

2nd week, March, 11

Drug delivery approaches, routes of administration, prolonged release preparations. The management of poisoning.