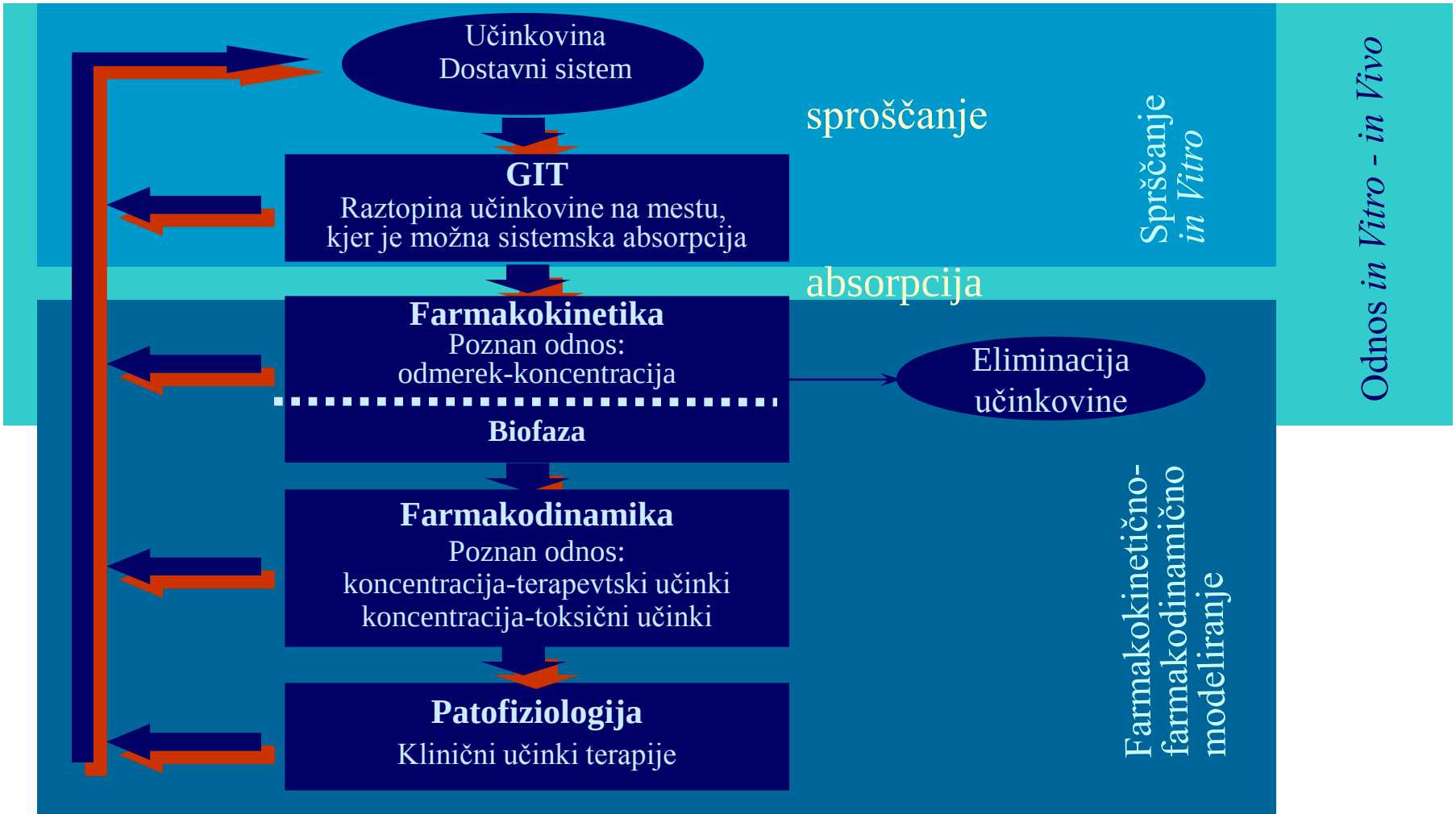
Enovit Magistrski Študij Farmacije

Biofarmacija s farmakokinetiko

Predstavitev področja in predmeta

Mrhar Aleš

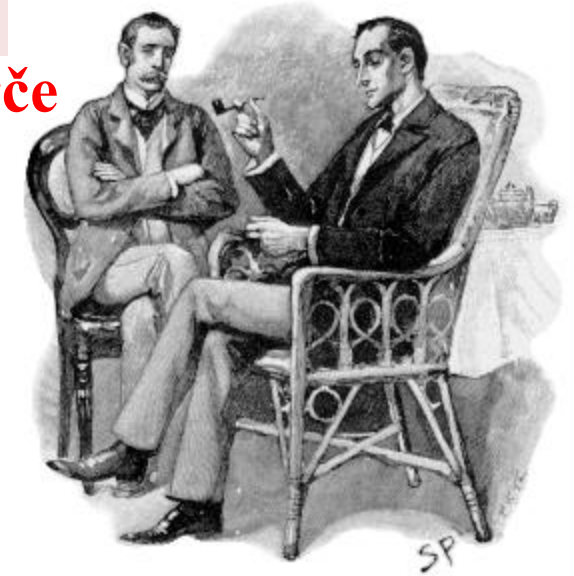
Odnos med učinkovino/dostavnim sistemom, farmakokinetiko, farmakodinamiko in kliničnimi učinki



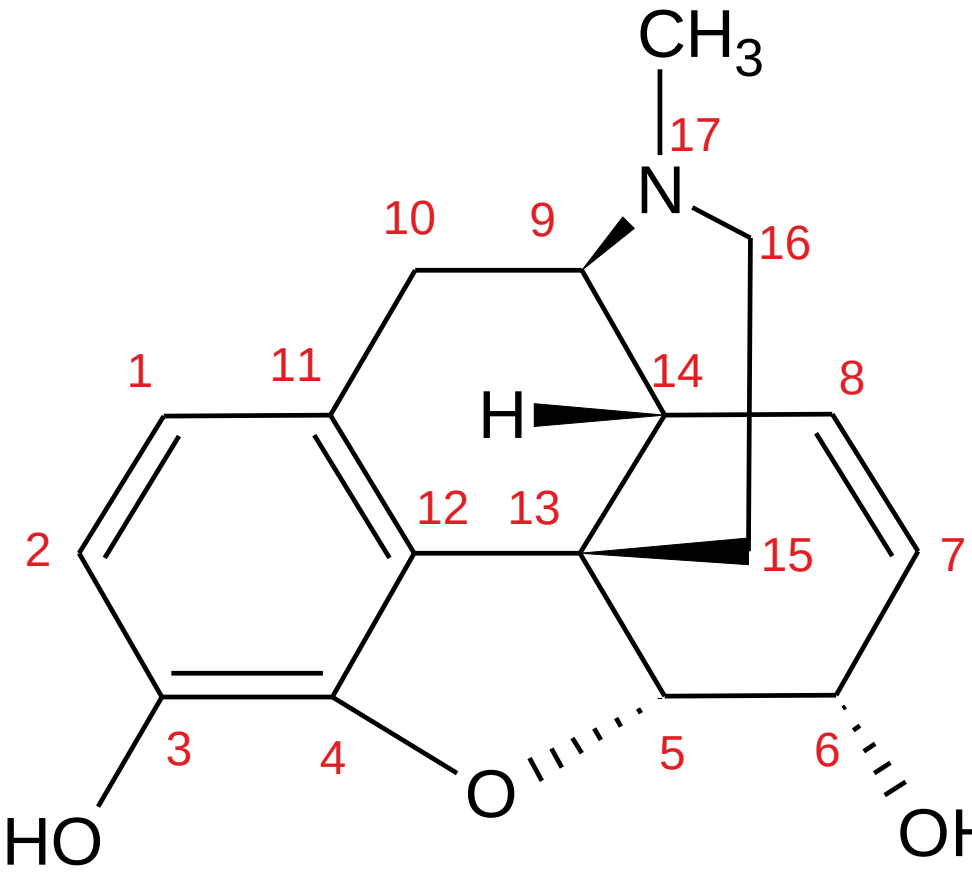
Od mehanizmov delovanja zdravil do njihovih kliničnih učinkov

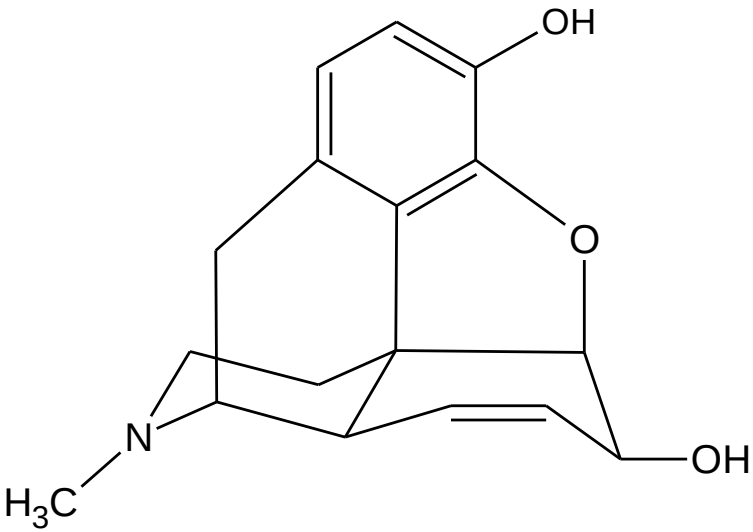
- ***Nivo celega organizma*** (merljivi klinični učinki kot posledica postreceptorskih dogodkov po aplikaciji zdravila, ki pride v kri)
- ***Nivo organov*** (v katerih organih so tarče, kako pride učinkovina do organov?)
- ***Celični nivo*** (kje v celici so tarče, kako pride učinkovina do tarč?)
- ***Molekularni nivo*** (interakcija učinkovina - tarča, kaskada postreceptorskih dogodkov, ki se na koncu manifestirajo v obliki merljivih kliničnih učinkov - primarnih in sekundarnih, želenih in neželenih)

Struktura molekule → **Transport do tarče**
Vezava na tarčo

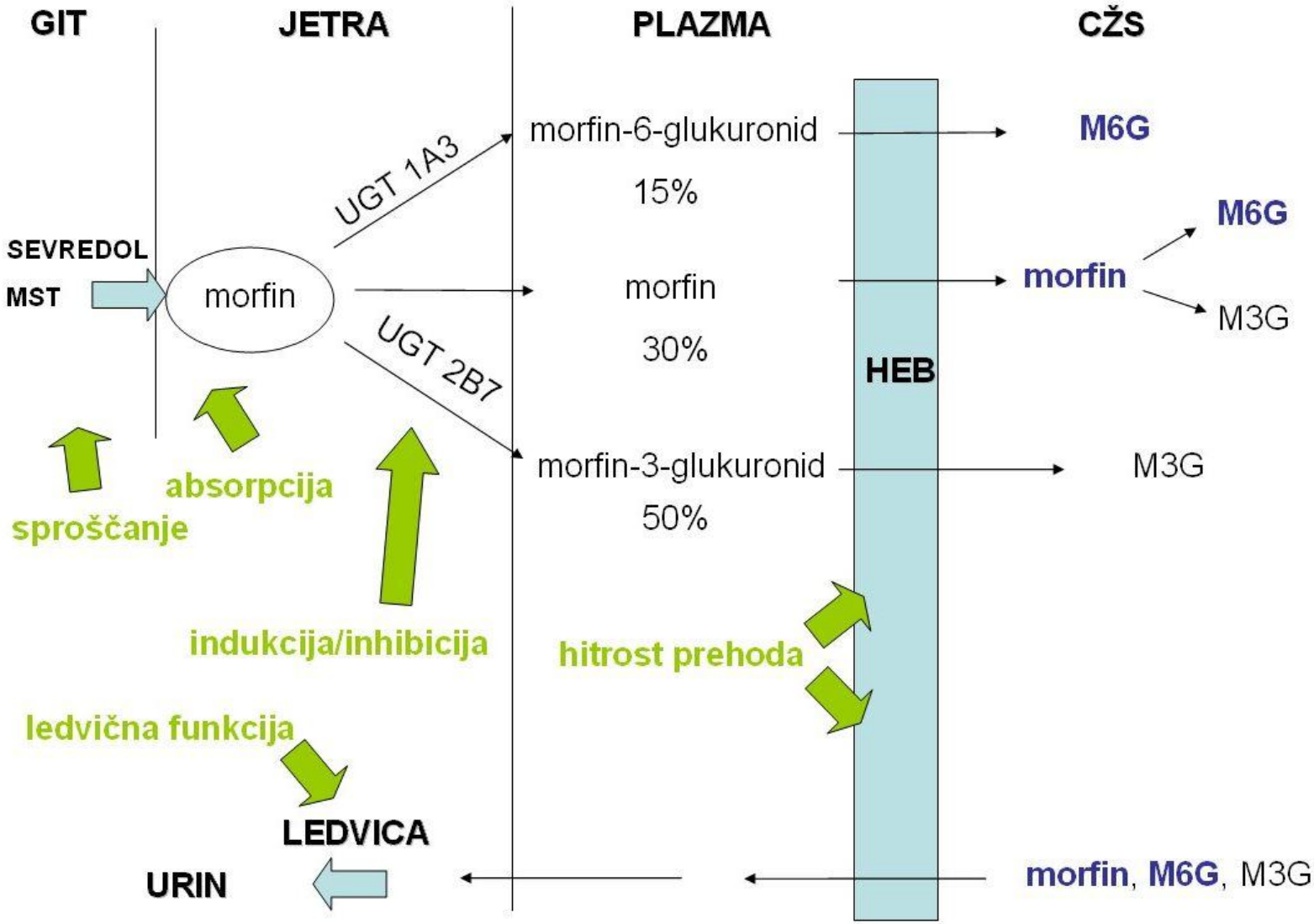


morfin





Transport morfina do tarče



Vezava morfina na tarčo

a) agonistično delovanje na μ-receptorjih v CŽS, stimulacija μ1 inducira dihanje, stimulacija μ2 pa inhibira dihalni center **(analgezija, depresija dihanja)**

b) agonistično delovanje na κ- in δ-receptorjih v CŽS **(navzea, bruhanje, mioza)**

c) agonistično delovanje na μ-receptorje v GIT **(zaprtje)**

d) dve učinkoviti molekuli: morfin in morfinijev-6-glukuronid

1) morfinijev-6-glukuronid je 2-4 krat močnejši agonist kot morfin

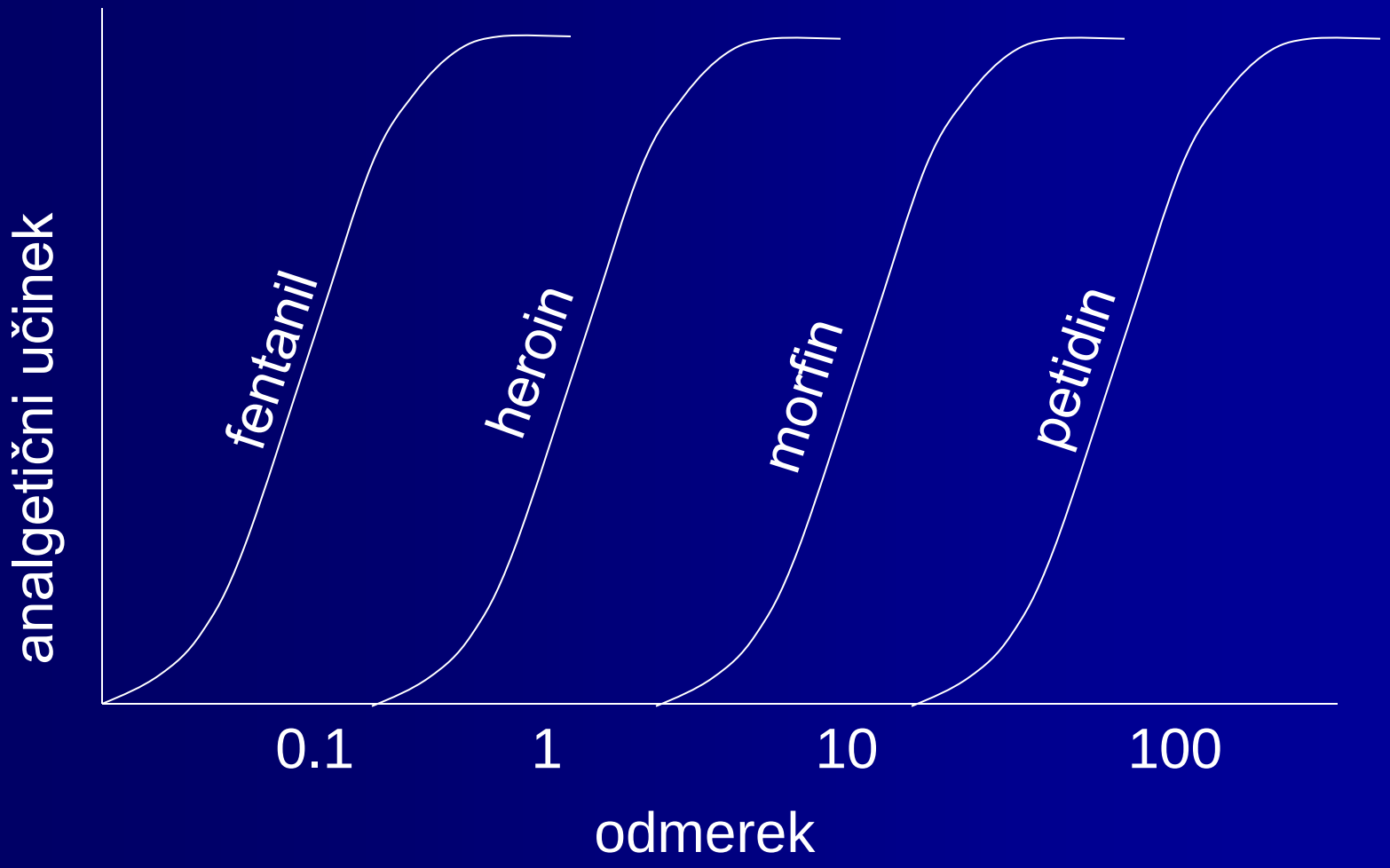
2) morfinijev-6-glukuronid ima večjo afiniteto do μ1 kot do μ2 receptorjev

Učikovitost/jakost

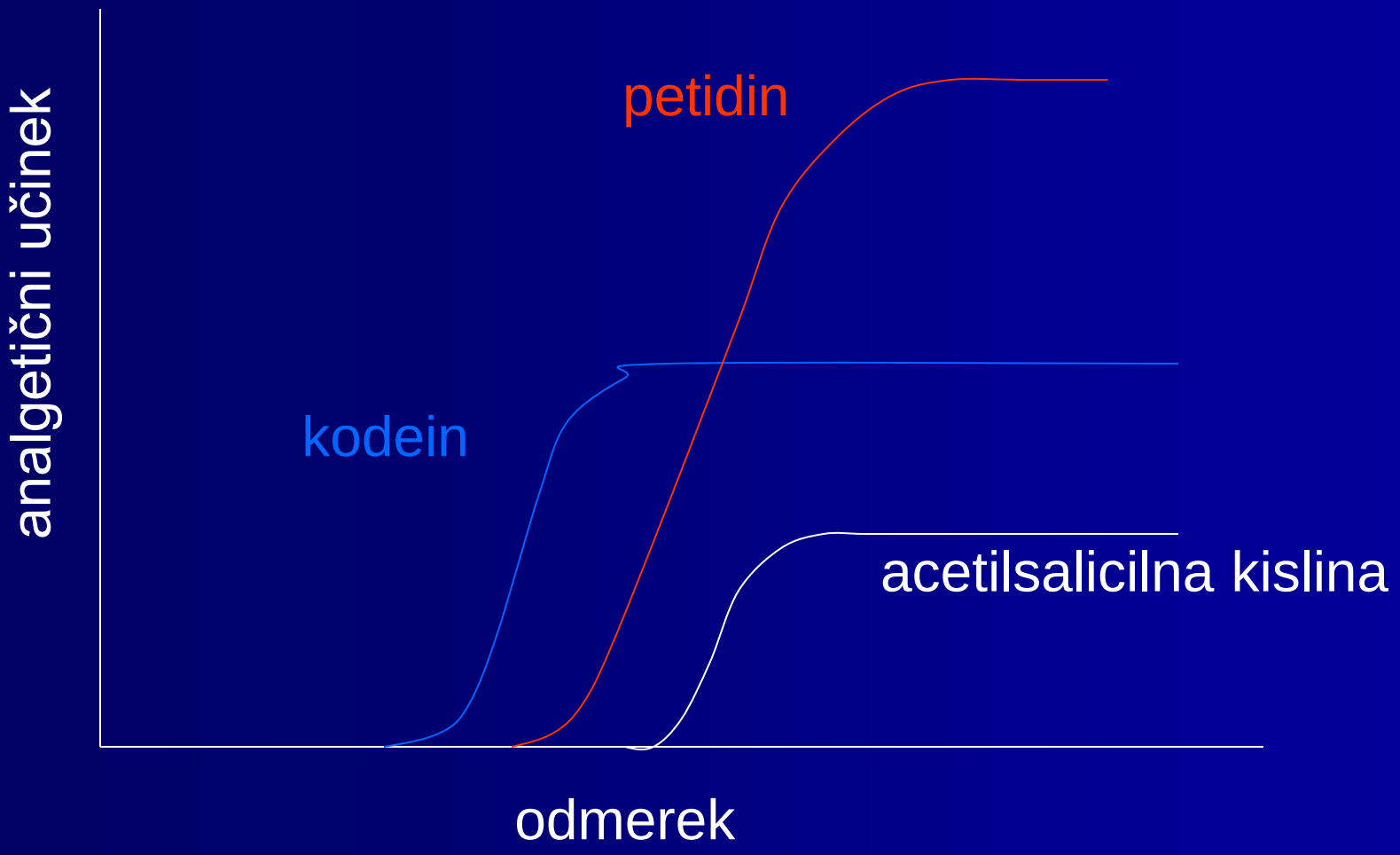
- Jakost (Potency): pri primerjavi večih učinkovin z istim delovanjem primerjamo ED_{50}. Učinkovina z najmanjšo ED_{50} je najmočnejša, z največjo ED_{50} pa najšibkejša

- Učinkovitost (Efficacy): pri primerjavi večih učinkovin primerjamo E_{max}. Najučinkovitejša je tista, ki daje pri danem odmerku največji E_{max}, najmanj učinkovita pa tista z najmanjšim E_{max}

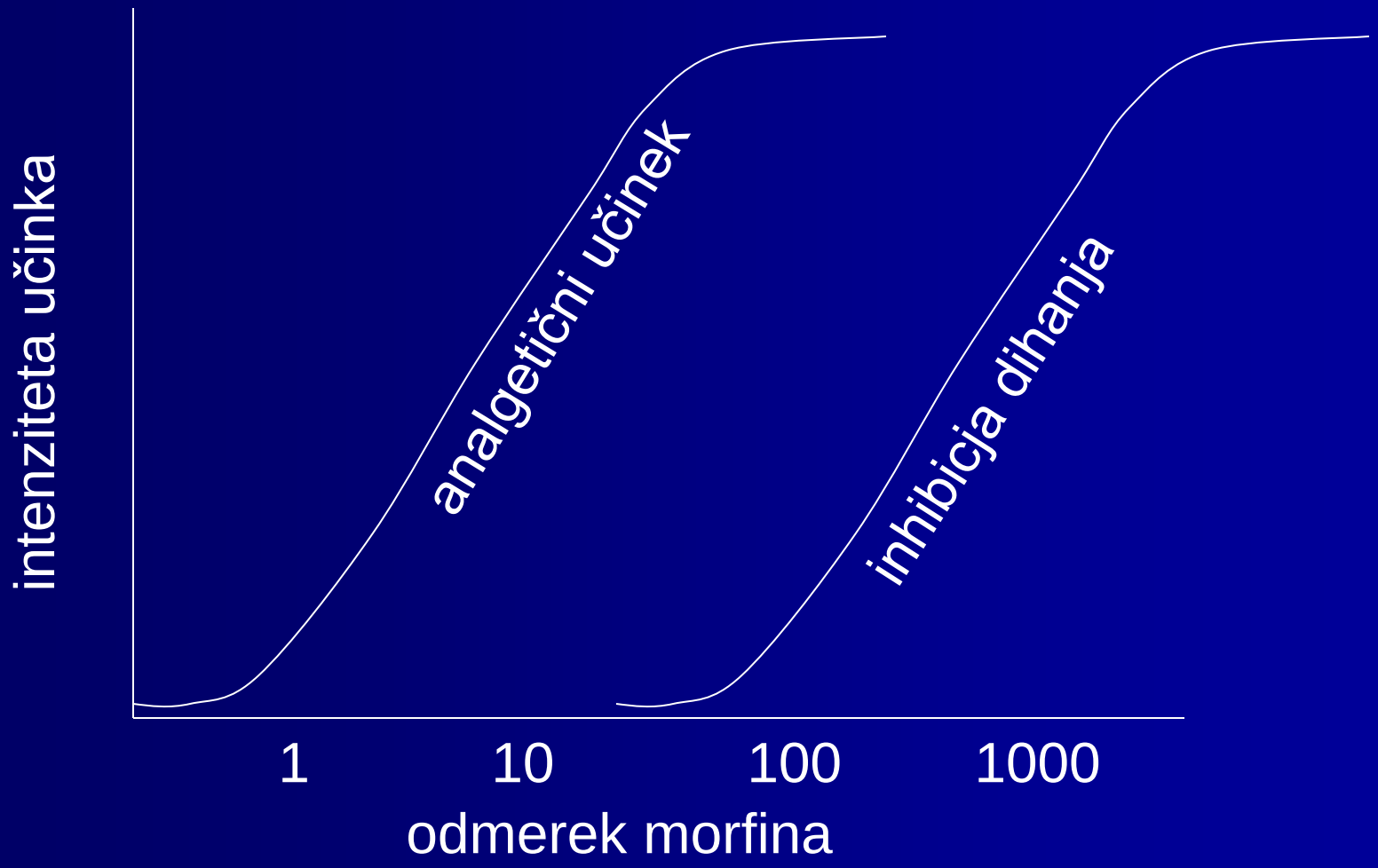
Jakost


analgetični učinek
fentanil
heroin
morfin
petidin
0.1
1
10
100
odmerek

Učinkovitost



Odvisnost različnih učinkov od odmerka



Pharmacodynamic (PD) behaviour of a drug is altered by:

- **Pharmacokinetic (PK) processes**

  Systemic: distribution, metabolism, elimination

  Nonsystemic: release, absorption

  Cp-t profile of a parent drug.

  Cp-t profile of active metabolite

- **Biophase distribution**

  The extent and rate depend on the anatomical location of the target tissue, its perfusion rate and its permeability to the drug (metabolite) to reach the receptor

  Kinetics of biophase distribution determinates E-t profile

  Cp-t profile good predictor for E-t profile if distribution is fast

  Cp-t profile poor predictor for E-t profile if redistribution is slow

- **Drug-receptor interaction**

  Sigmoid E_{max} model

- **Transduction processes**

  Include all biological events following drug-receptor binding

  Binding to extracellular receptors

  Binding to intracelluar receptors

  (i.e., glucocorticoids have to transfer the cell membrane and interact with soluble receptors; the drug-receptor complex then translocates into the nucleus and interferes with the transcription of nuclear DNA or the translation mechanism)

  Transduction kinetics can be faster or slower than biophase distribution kinetics

- **Secondary postreceptor events**

  Primary, drug induced biological responses occur at the cellular level

  Most PD effects are measured (observed) at the level of the organism, i. e. animals, humans

  (i.e. a vasoconstrictor agent may shorten the length of a series of cells in arterial muscular level, thereby reducing the vessel diameter and increasing the resistance of the local vascular bed and then increasing systemic vascular resistance; the observed PD effect is elevation in arterial blood pressure)

- Farmakokinetika:

  Prehod učinkovin skozi telo v prostorskem in časovnem smislu

  1. Difuzija
  2. Konvekcija

- Biofaza (Tarče)

- Farmakodinamika:

  Interakcije med učinkovinami in tarčami

  1. Receptorji
  2. Encimi
  3. Ionski kanali
  4. Prenašalci

Pharmacokinetic measurements of plasma and urine levels of

- **the drug and/or**
- **metabolite(s)**

are obtained by an **analytical method** with defined specificity, accuracy, repeatability, sensitivity, linearity, limit of detection, limit of quantification

Pharmacodynamic measurements of effects such as

- **haemodynamic**
- **electrocardiogramic**
- **electroencephalogramic**
- **hormones suppression**
- **muscle relaxation**
- **pain rating**
- **natriuresis**

are obtained by different methods which should meet the criteria: objectivity, sensitivity, repeatability, continuity

Modeling of Pharmacokinetic/Pharmacodynamic (PK/PD) Relationships

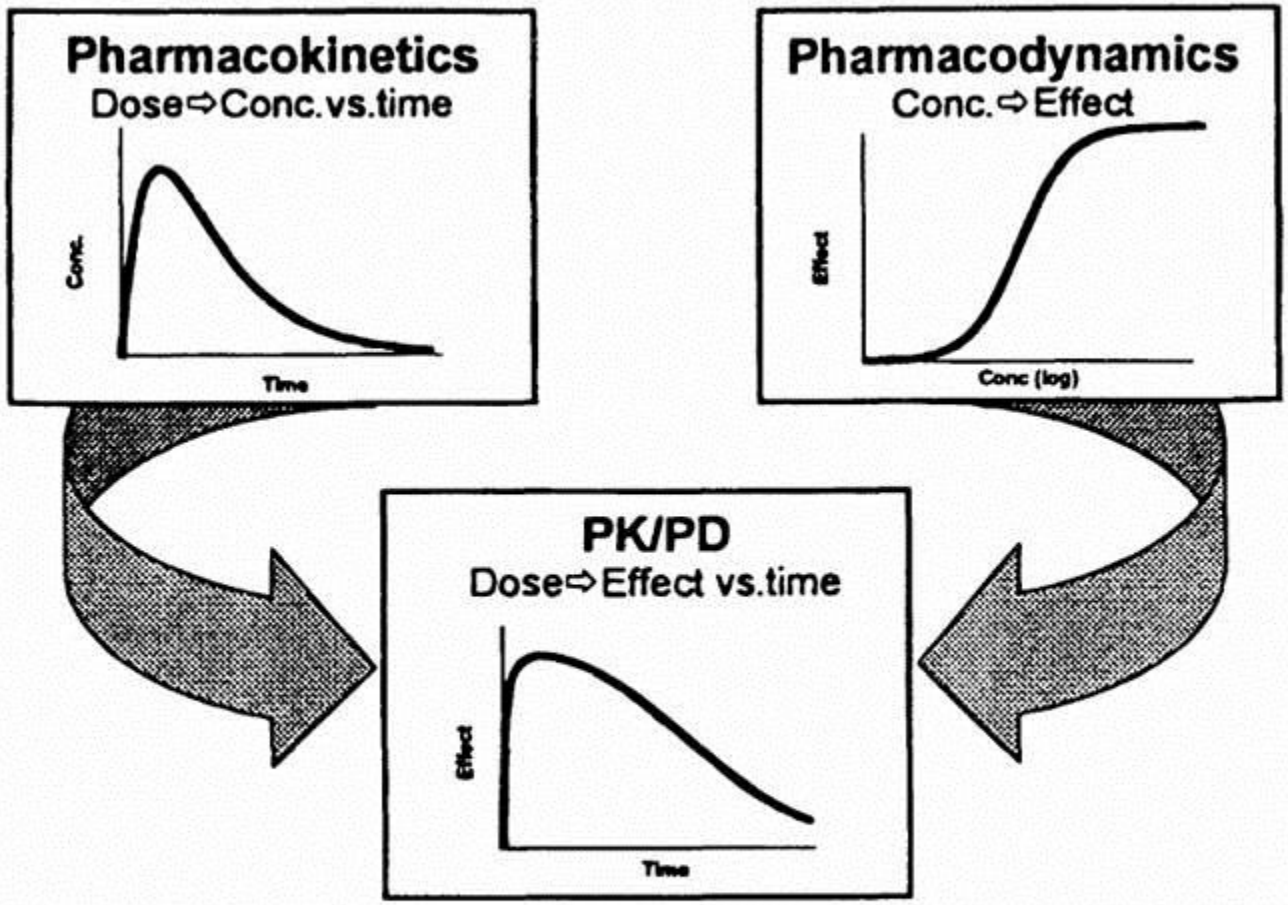


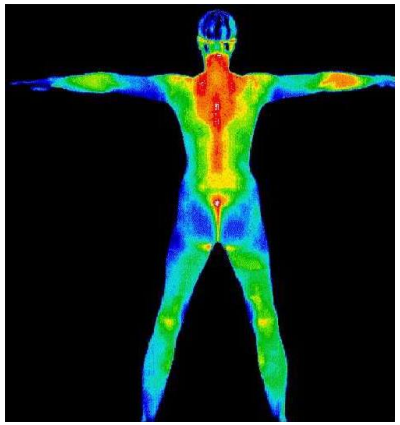
Fig. 1. Pharmacokinetic/pharmacodynamic (PK/PD) modeling as combination of the classic pharmacological disciplines pharmacokinetics and pharmacodynamics (modified from (15), reproduced with permission).

Transport, interakcije in metabolizem učinkovin v LADME sistemu

- določanje mehanizma procesov
- določanje kinetike procesov

PD

PK



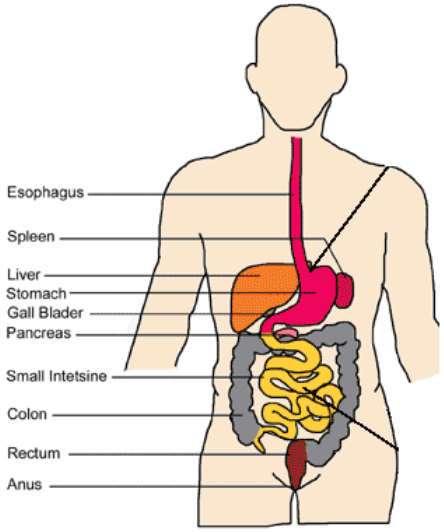
Modeliranje in simulacija

Model
(*in vitro*)

Opazujemo

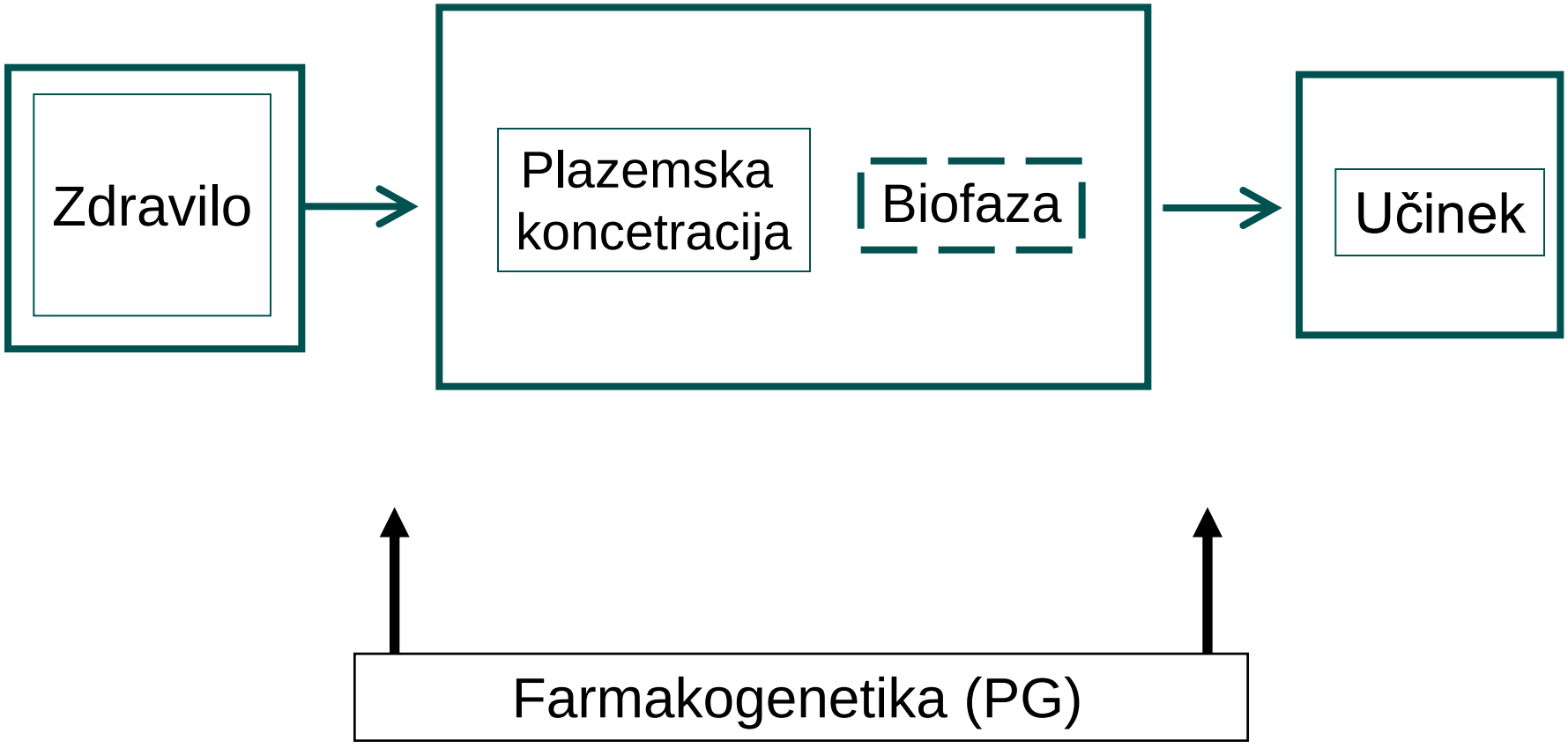
Napovedujemo

Sistem
(človek, žival)

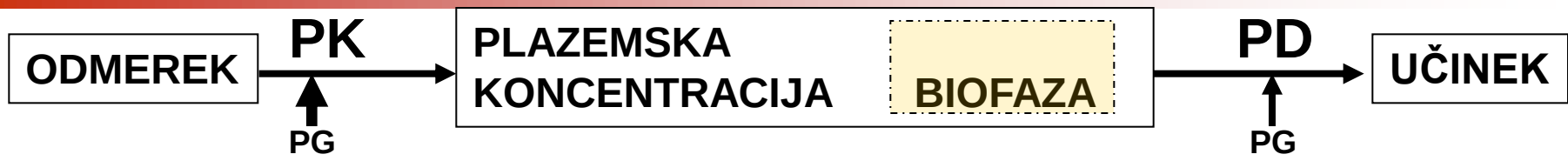


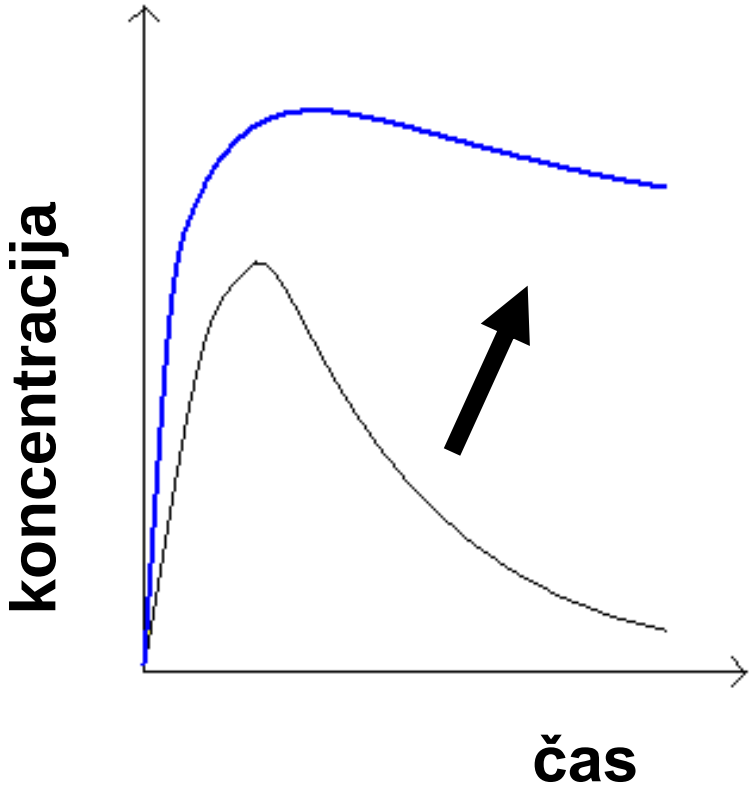
Sistem PK / PD

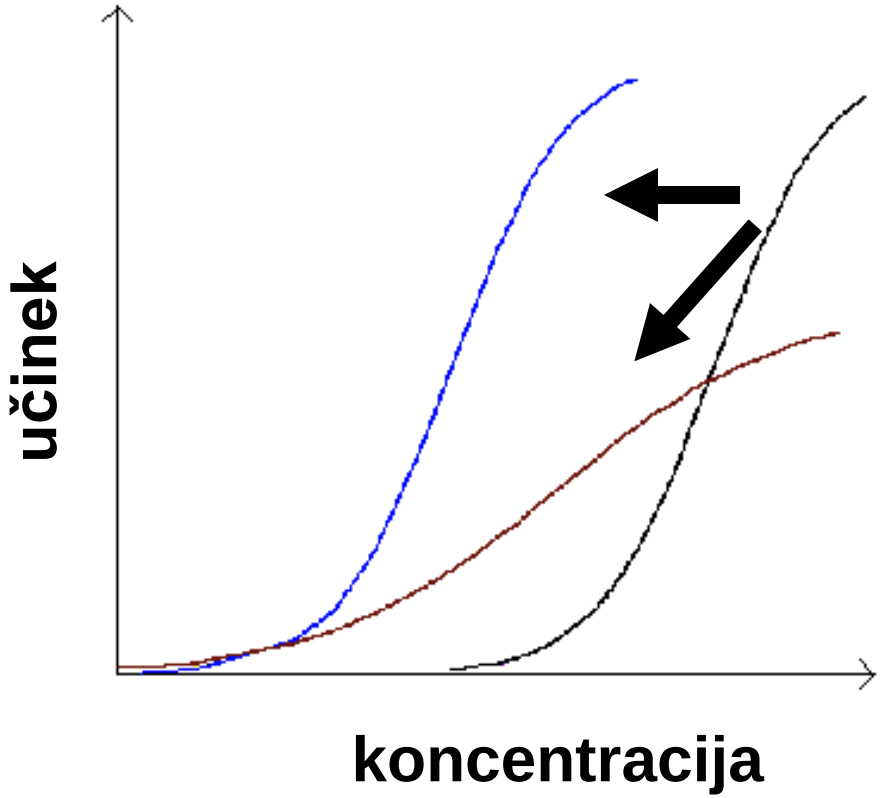
Farmakokinetika (PK) Farmakodinamika (PD)

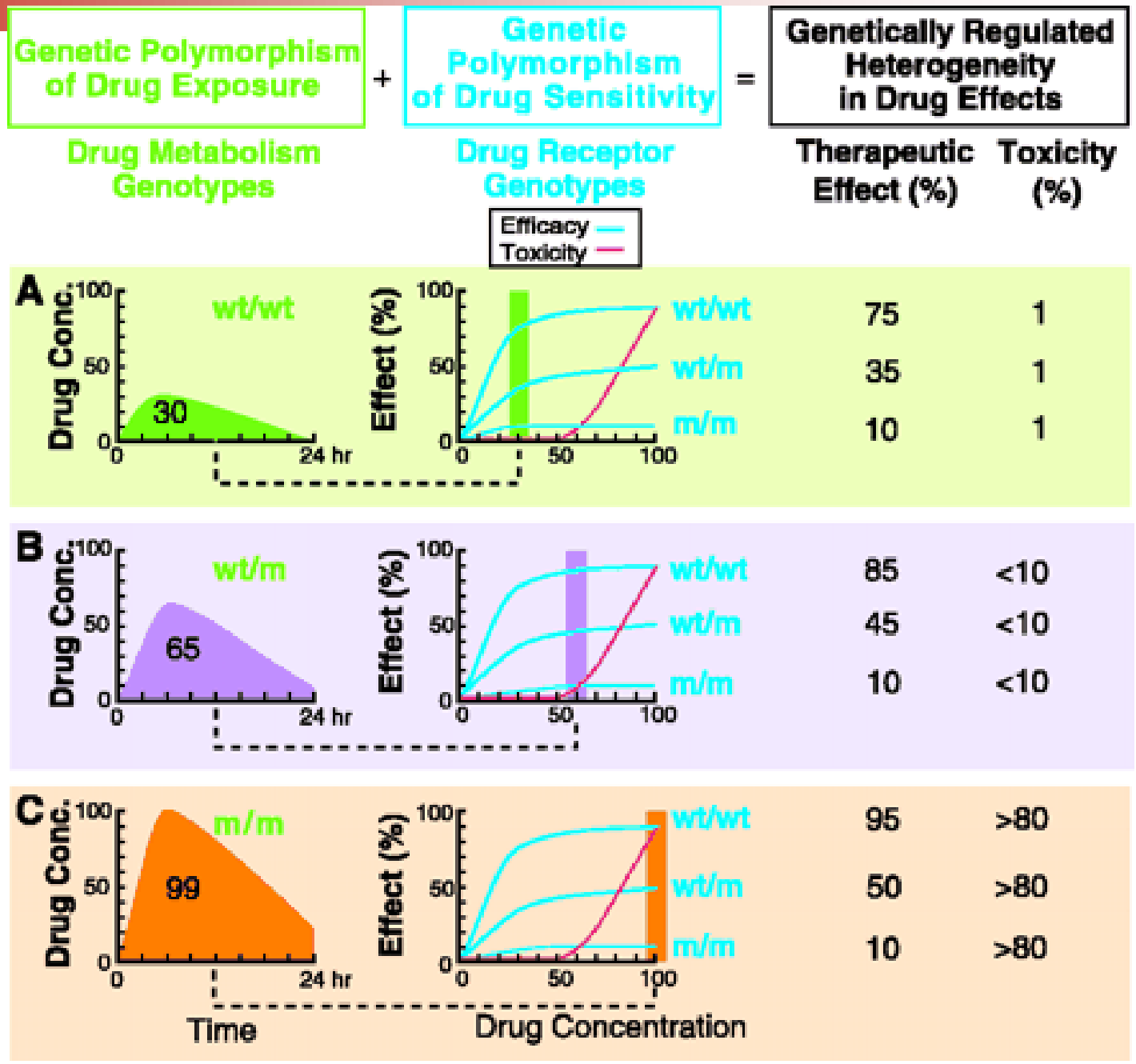


Prirejeno po Rowland and Tozer, *Clinical Pharmacokinetics: Concepts and Applications*, 3rd ed., 1995


ODMEREK
PK
PG
PLAZEMSKA KONCENTRACIJA
BIOFAZA
PD
PG
UČINEK


koncentracija
čas


učinek
koncentracija



From: Evans WE, Relling MV. *Science* 286:487-491, 1999.

Farmakogenetika / Farmakogenomika

- Farmakogenetika

  Veda, ki preučuje vpliv genotipa (enega gena) posameznika na njegov odgovor na določeno zdravilo. Cilj je individualizirana terapija.
- Farmakogenomika

  Preučuje medsebojni vpliv zdravila in več genov ter njihovih produktov na veliki populaciji. Vključuje znanje farmakogenetike in genomike.

⇓

- geni, ki karakterizirajo “podkategorijo” bolezni
- geni, ki kodirajo “tarčo” delovanja učinkovin
- geni, ki kodirajo proteine (prenašalce, encime), ki so vključeni v farmakokinetiko in so povezani z učinkovitostjo in s toksičnostjo

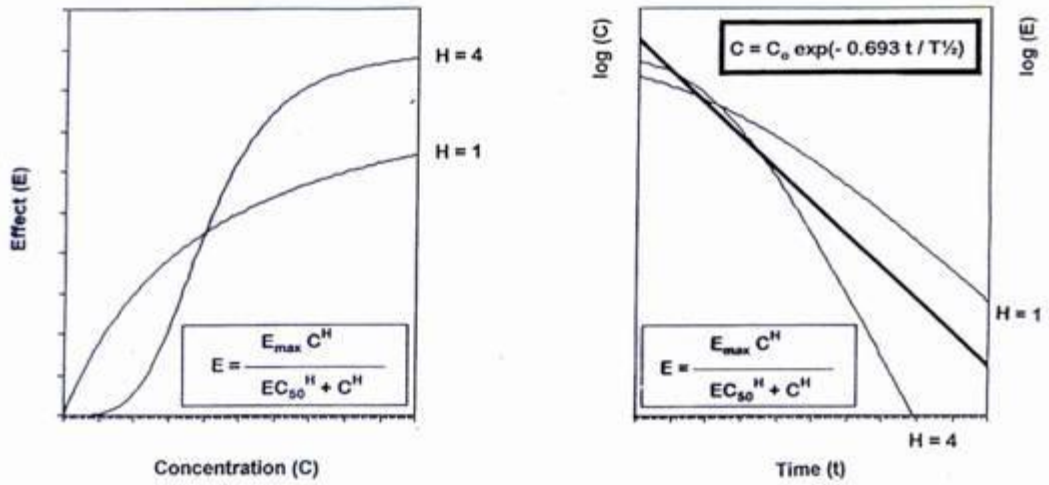


Fig. 1 Effect-concentration correlation and effect-time correlation. Left: the dependence of effect (E) on concentrations (C) is described by the sigmoid E_{max} model. The higher the Hill coefficient, the more sigmoid is the curve. Right: in the most simple case, the logarithm of concentrations (log C) linearly decreases with time. The logarithm of the effect (log E) will decline with time either slower, in parallel or even faster than logarithms of concentrations depending on the EC_{50} value and Hill coefficient.

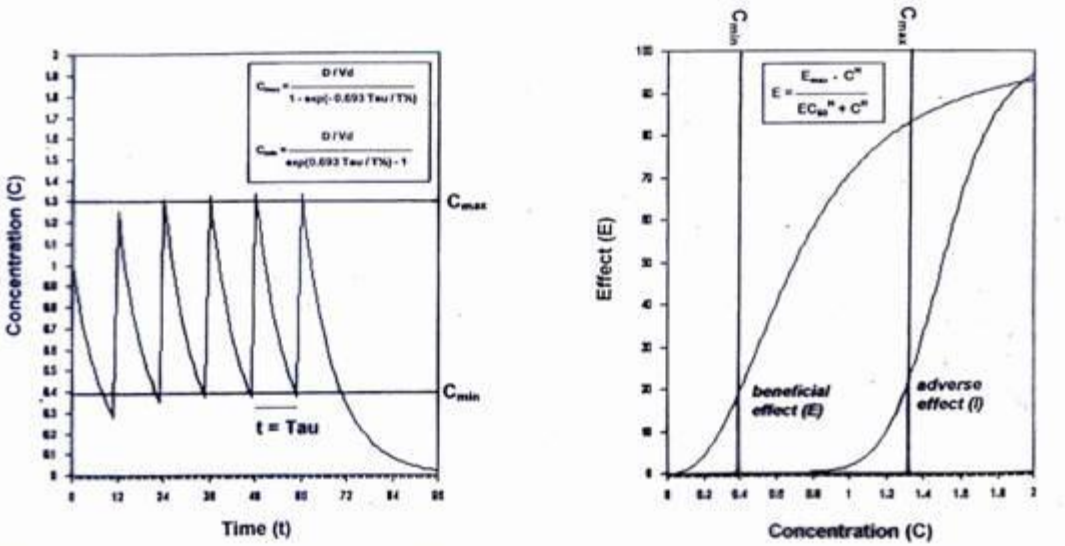


Fig. 2 Pharmacokinetics and pharmacodynamics. Left: following accumulation kinetics, repetitive dosing leads to peak (C_{max}) and trough (C_{min}) levels. Right: according to empirical drug use, dosage is adjusted in such a way that the beneficial effect will just occur at troughs (C_{min}), but the adverse effect will not yet occur at peaks (C_{max}).

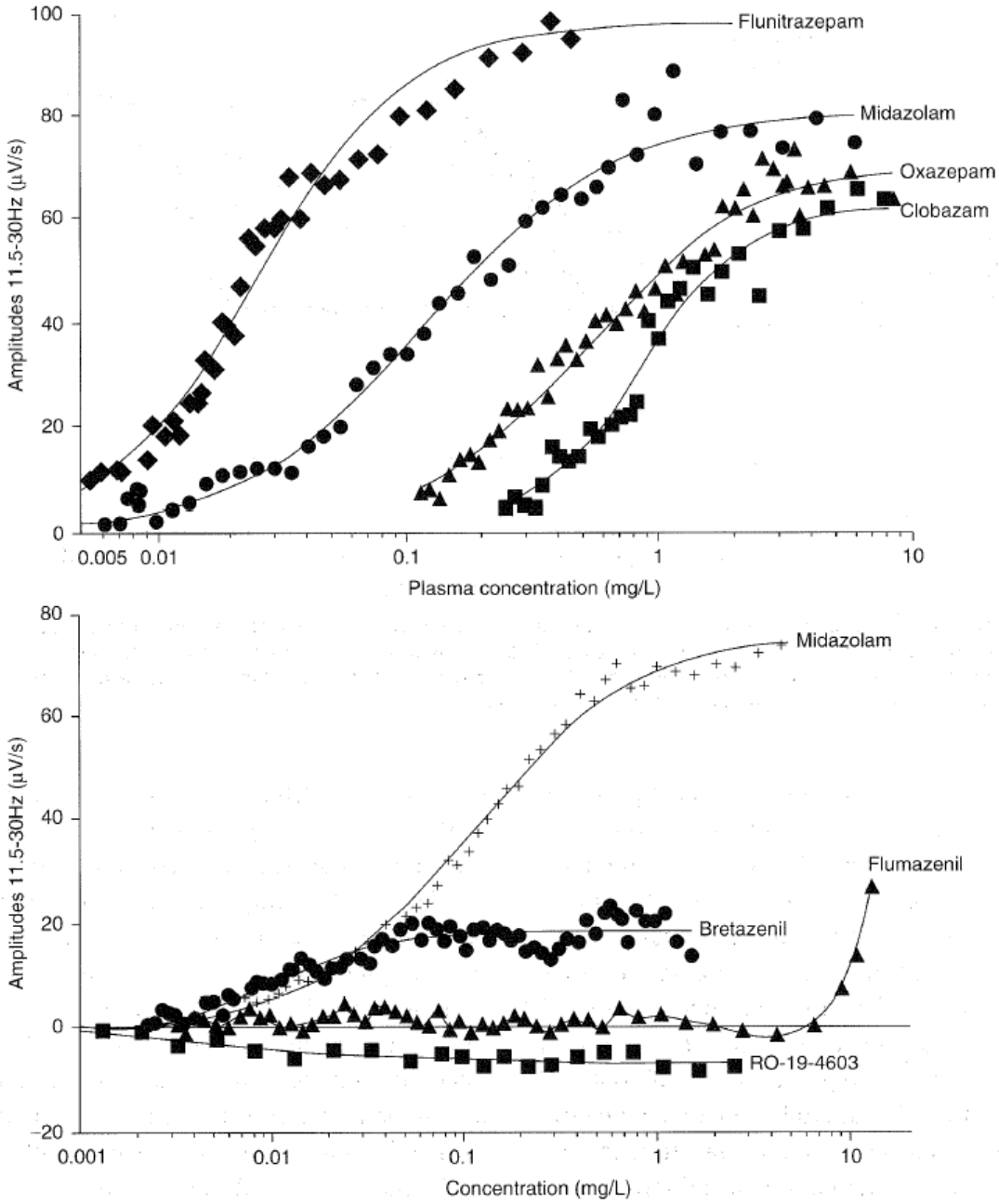
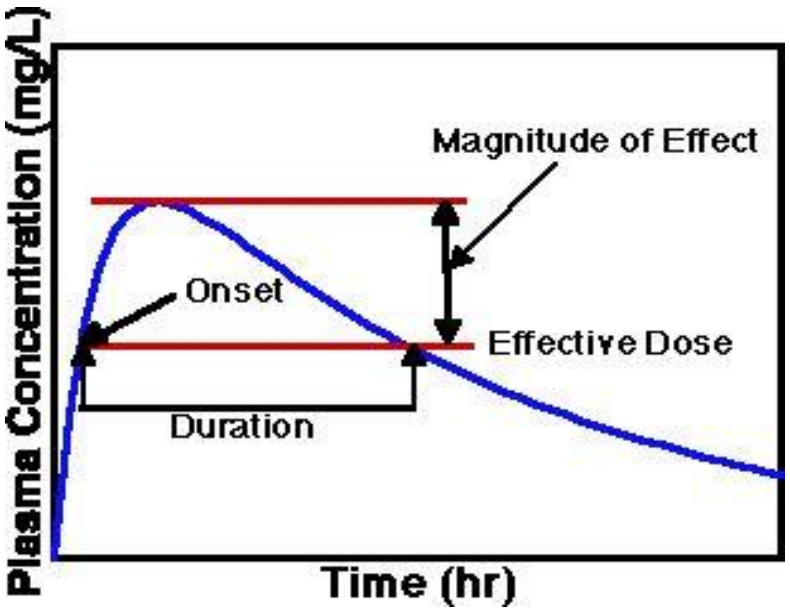
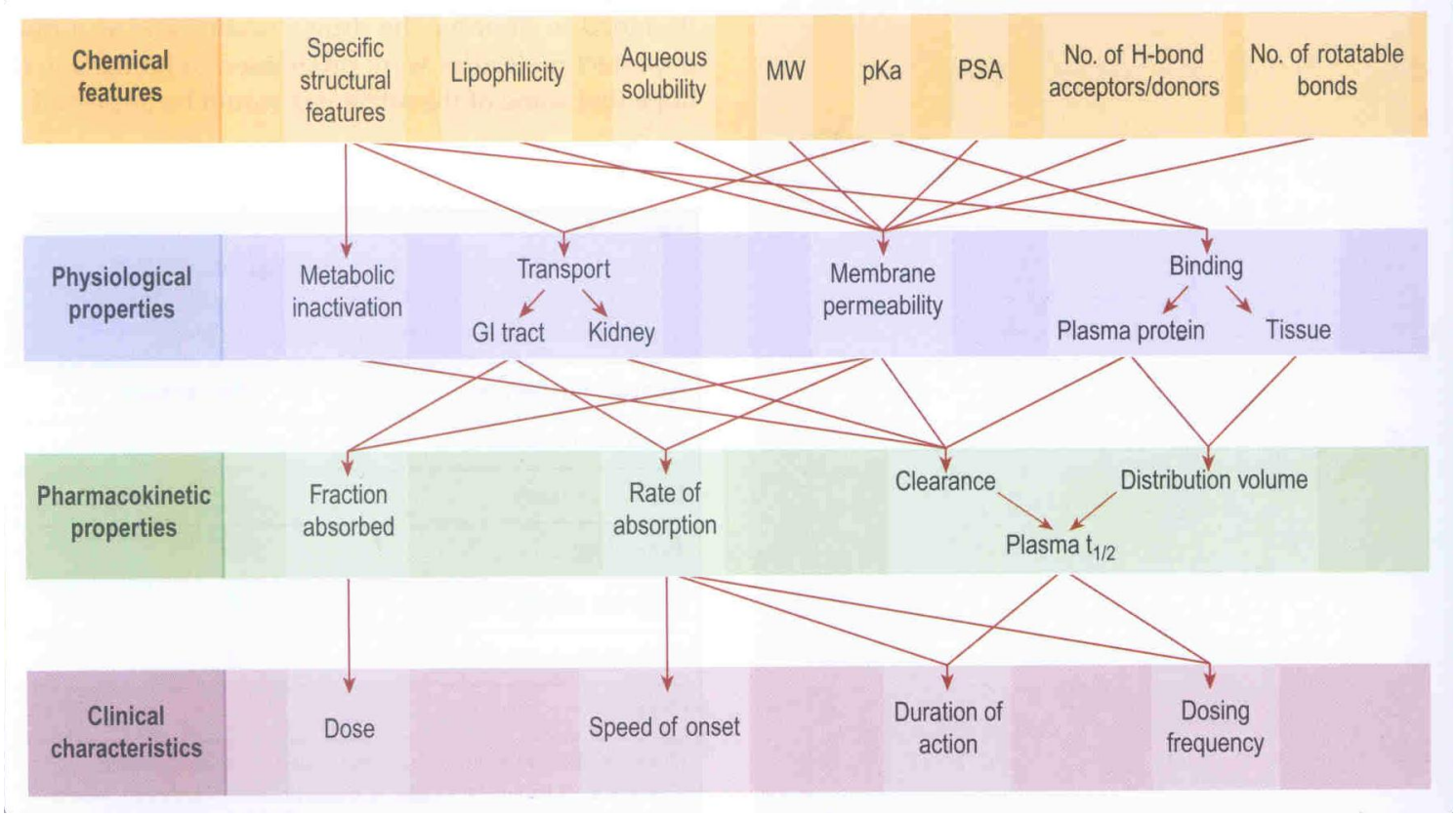


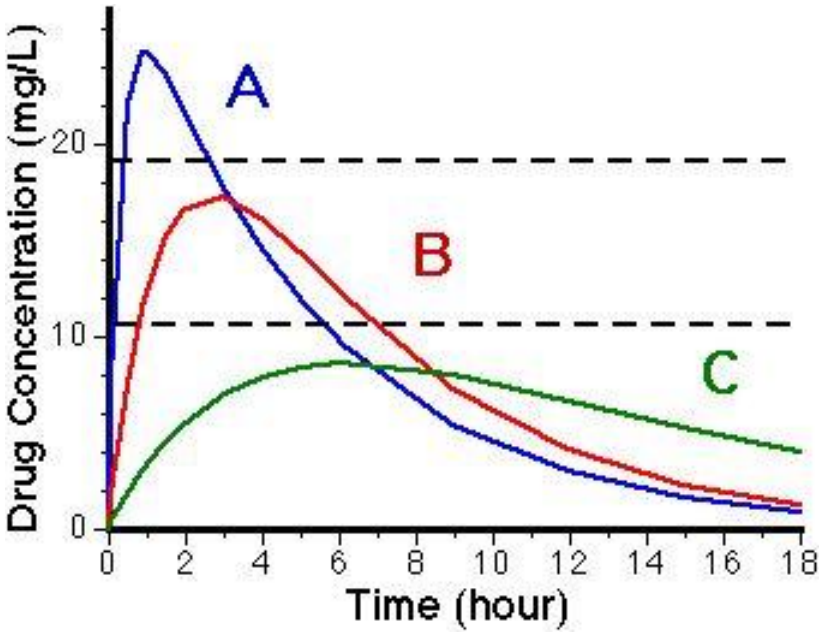
Fig. 3. Estimation of the potency and intrinsic activity of benzodiazepines in vivo on the basis of concenctrations rather than dose in preclinical studies. In chronically instrumented rats the time course of the EEG effect is determined in conjuction with plasma concentrations. By pharmacokinetic-pharmacodynamic modelling, individual concentration-effect relationships are derived. The upper panel shows the difference in potency between flunitrazepam, midazolam, oxazepamand clobazam; the lower panel shows the difference in activity between midazolam, bretazeil, flumazenil and RO 19-4603.[24,25]



Effect as a function of time. From a graph such as this we can see the relationship between drug concentration and drug effect. If a drug has to reach an effective concentration at a target site this will be reflected as a required blood concentration.

Lastnosti učinkovine in organizma, ki vplivajo na klinično učinkovitost zdravil





Plasma concentration time curves for three theoretical formulations with different ka values. The plasma concentrations achieved can be controlled by the rate of drug absorption. As shown product A would be toxic. A smaller dose, or a slower formulation should be considered. Formulation B appears to be effective in the dose and formulation used. The dosage form C appears to be too slow and thereby ineffective. If it is a drug requiring a sustained effect this formulation may be more useful at a higher dose or after repeated doses.

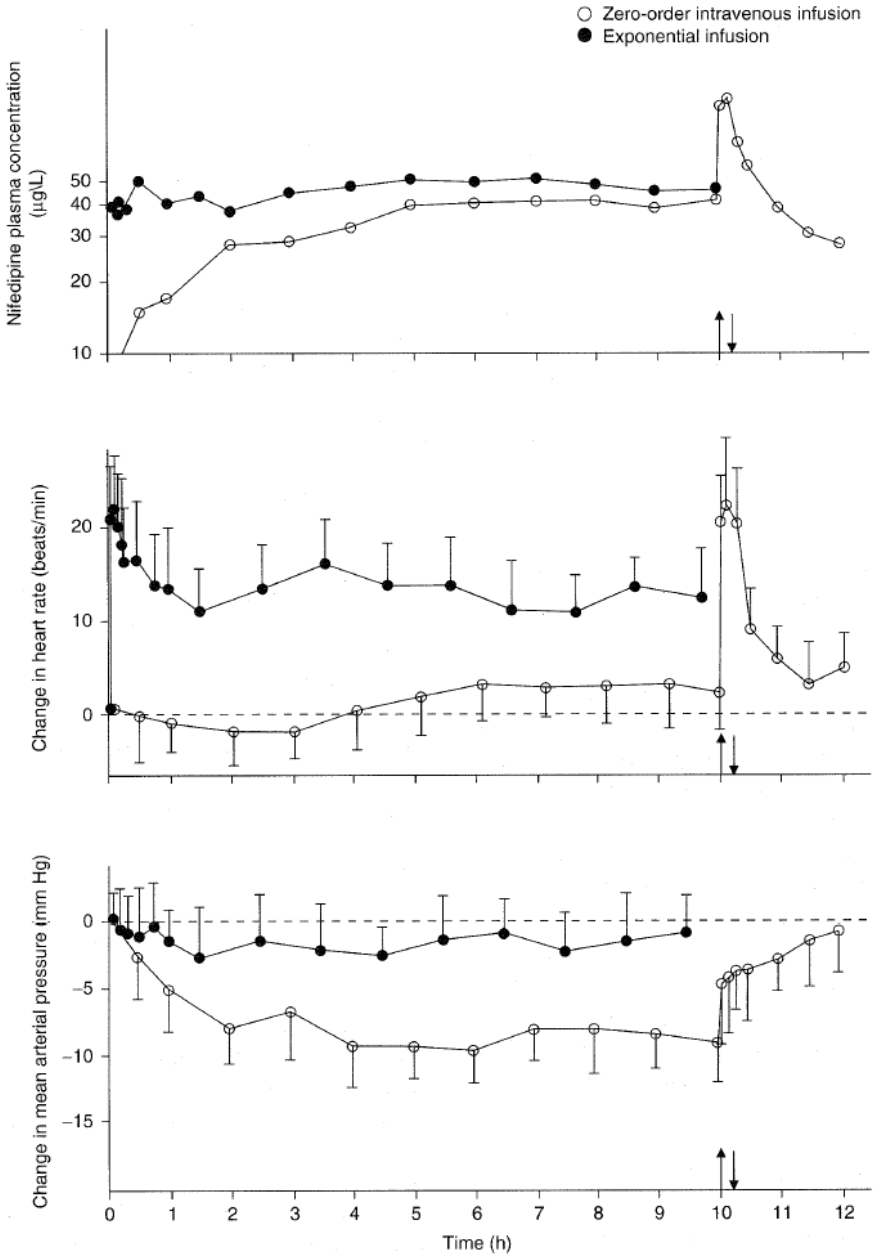


Fig. 2. The influence of the rate of change in plasma concentration on the haemodynamic effect of nifedipine was determined in healthy volunteers. The upper panel shows the plasma concentration-time profile in an individual upon administration as zero-order intravenous infusion at a rate of 1.3 mg/h and by an exponential infusion resulting in the rapid rise of plasma concentration. The middle and lower panels show the effects on heart rate and mean arterial pressure, respectively. Upon rapid infusion an increase in heart rate and attenuated effect on mean arterial pressure are observed. However, upon slow infusion there is no increase in heart rate and a consistent decrease in blood pressure. This observation has been the basis for the development of the osmotically powered sustained release tablets of nifedipine (from Kleinbloesem et al. [22] with permission).

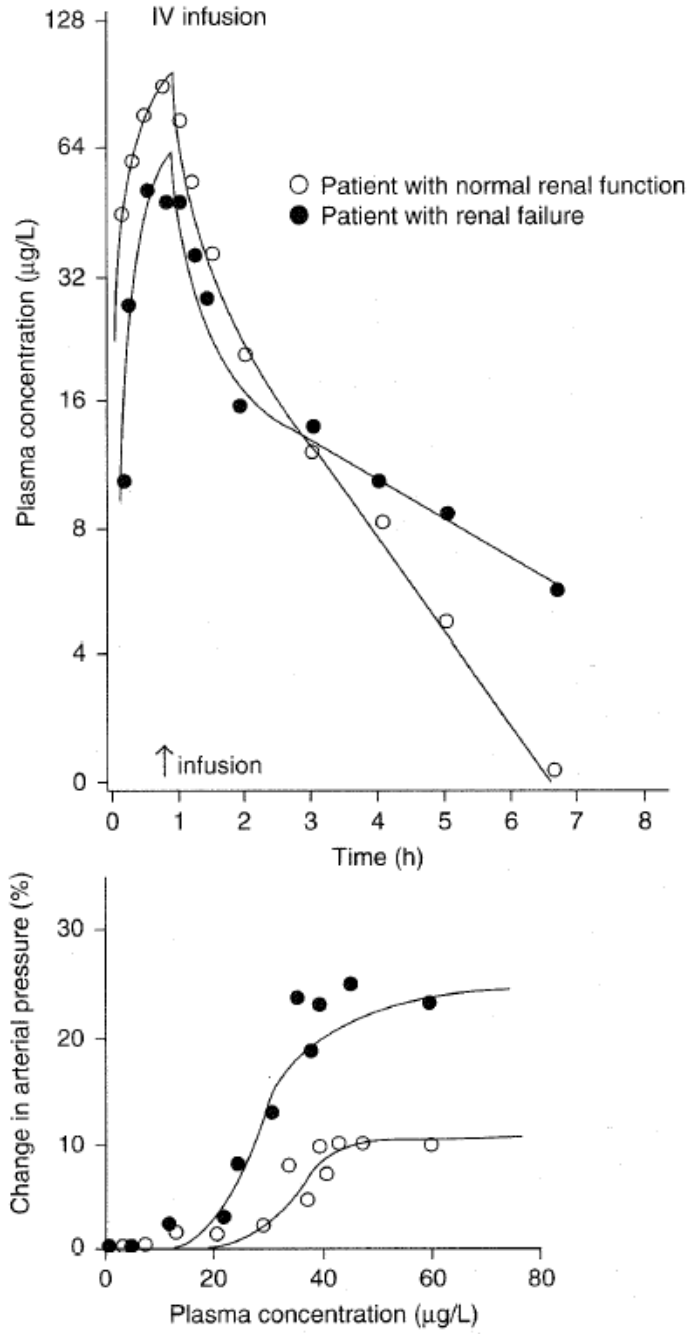


Fig. 5. Interindividual variability in the pharmacokinetics and pharmacodynamics of nifedipine in patients with different degrees of renal impairment. The pharmacokinetics and the concentration-effect relationships for the decrease in mean arterial pressure are shown in a representative patient with a normal renal function and a patient with renal failure. Only minor differences in pharmacokinetics were observed; the pharmacodynamics on the other hand were markedly different. In patients with an impaired renal function the maximum effect is significantly larger (from Kleinbloesem et al.,[31] with permission).

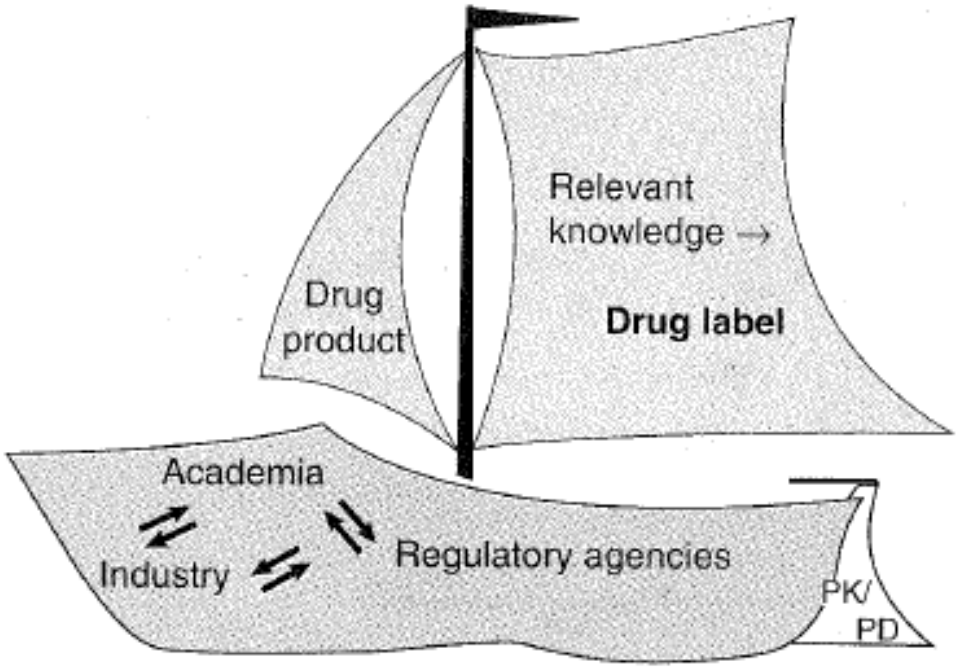


Fig. 6. The 'wooden shoe' paradigm illustrating the relevance of pharmacokinetics-pharmacodynamics in drug development. The 2 sails represent the principal components of a drug, the drug product (hardware) and the drug label (software). The latter contains the relevant information for actual use in clinical practice. Pharmacokinetics-pharmacodynamics is the steering mechanism throughout the drug development process to obtain the information relevant to be put into the label. Collaboration between industry, academia and regulatory agencies is necessary to achieve this.

Načrtovanje režimov odmerjanja risperidona

Risperidon je atipičen antipsihotik:

- **z encimom CYP2D6 se presnavlja v aktivni 9-OH-risperidon (glavni metabolit),**
- **razmerje med plazemskimi koncentracijami risperidona in 9-OH-risperidona je zelo različno med posamezniki.**
- **povezava med plazemskimi koncentracijami aktivne oblike risperidona (RISP + 9-OH-RISP) in antipsihotičnim delovanjem je šibka.**
- **ekstrapiramidne motnje gibanja (parkinsonizem, nemir, distonija, tardivna diskinezije) so glavni neželeni učinki terapije z risperidonom. Pogosteje se pojavijo pri odmerkih višjih od 4 mg/dan.**
- **Uvajanje terapije z risperidonom je postopno (titriranje odmerka).**

Klinična raziskava

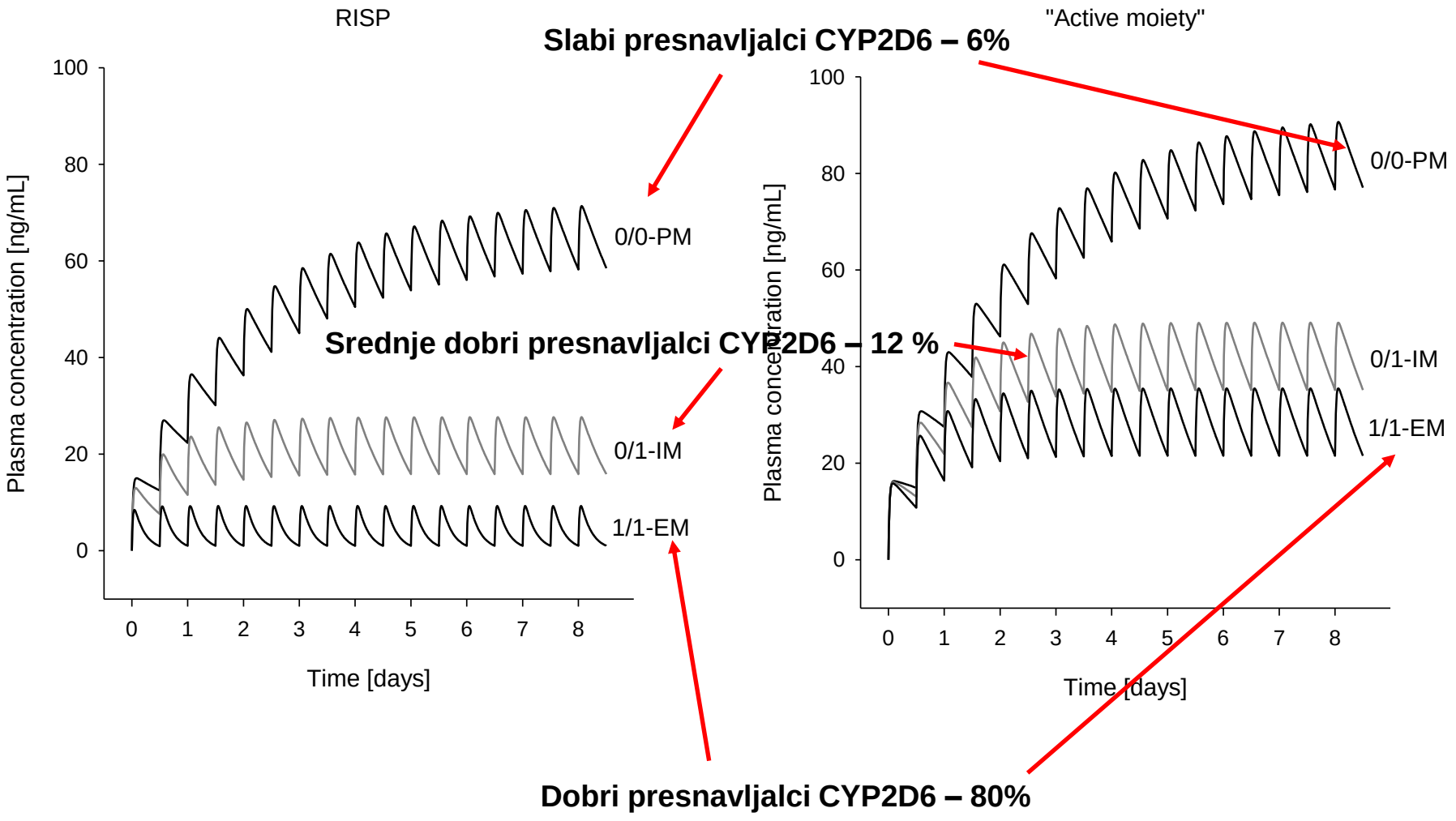
Potek raziskave:

- **50 hospitaliziranih bolnikov v akutni fazi zdravljenja shizofrenije (UKC Maribor).**
- **8. dan terapije so odvzeli 2 krvna vzorca in ocenili stopnjo ekstrapiramidnih motenj gibanja (SAS, BARS, AIMS).**

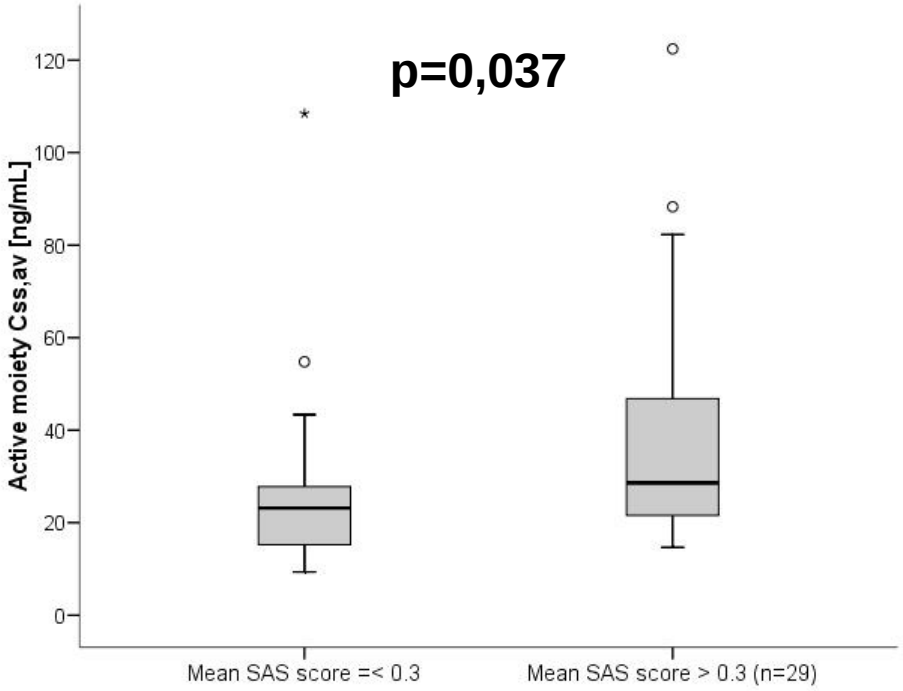
Cilj raziskave:

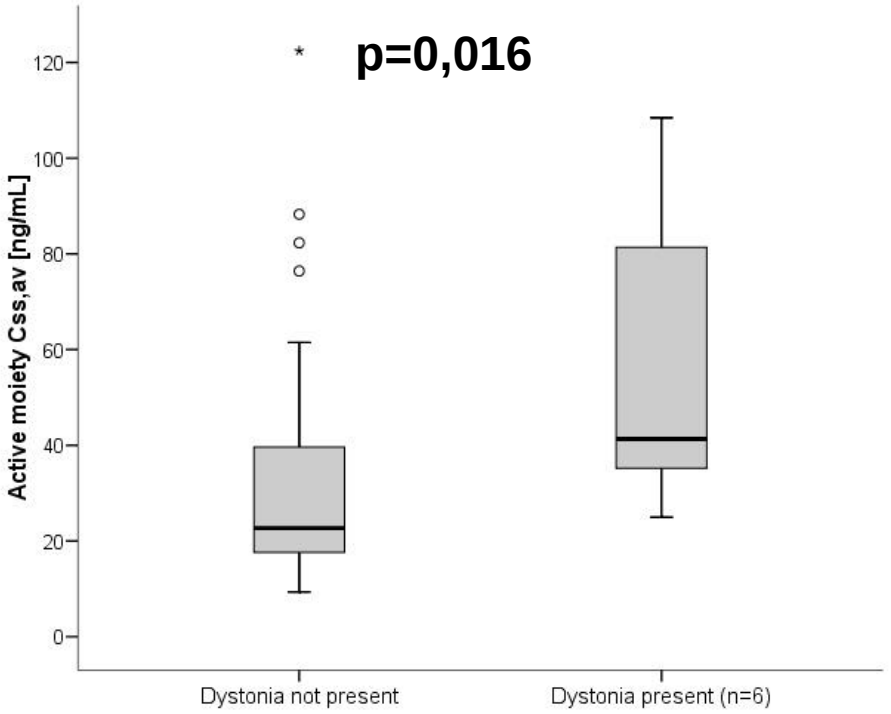
- **opredeliti vpliv aktivnosti CYP2D6 (genetski polimorfizem) na interindividualno variabilnost v metabolizmu risperidona,**
- **ugotoviti povezavo med FK risperidona in pojavnostjo neželenih učinkov (ekstrapiramidne motnje gibanja),**
- **predlagati individualizacijo režima odmerjanja risperidona pri bolnikih v akutni fazi shizofrenije.**

Vpliv genotipa *CYP2D6* na plazemske koncentracije risperidona in aktivne oblike



Povezava FK risperidona s pojavnostjo ekstrapiramidnih motenj gibanja





Bolniki, ki so izkazovali klinične znake parkinsonizma ali akutne distonije, so imeli višje plazemske koncentracije aktivne oblike risperidona.

Sklep

Bolniki, z manjšo aktivnostjo CYP2D6, so imeli višje plazemske koncentracije aktivne oblike risperidona.

Bolniki s kliničnimi znaki parkinsonizma ali akutne distonije, so imeli višje plazemske koncentracije aktivne oblike risperidona.

Bolnike v akutni fazi shizofrenije, ki so slabi ali srednji presnavljalci substratov za CYP2D6, je smiselno zdraviti z nižjimi začetnimi odmerki risperidona.

FARMAKOKINETIČNE RAZISKAVE PRI *ODKRITJU IN RAZVOJU* NOVIH ZDRAVIL

Faza odkritja (Drug Discovery):

- **farmakokinetično rešetanje (early ADMET)**

Namen: definirati spojino vodnico

Ugotavljanje absorpcije, distribucije, metabolizma, ekskrecije in toksičnosti z *in silico, in vitro* in *in vivo* poskusi

Faza razvoja (Drug Development):

- **predklinične farmakokinetične raziskave**

Namen: podpora farmakodinamičnim raziskavam, podpora toksikološkim raziskavam, napoved farmakokinetike pri človeku, rešetanje dostavnih sistemov/načinov aplikacije

Ugotavljanje absorpcije, distribucije, metabolizma in ekskrecije na različnih živalskih vrstah

- **klinične farmakokinetične raziskave**

Namen: podpora raziskavam varnosti in učinkovitosti

Ugotavljanje absorpcije, distribucije, metabolizma, ekskrecije, toksičnosti ter odnosa odmerek – varnost in učinkovitost na zdravih ljudeh in bolnikih po različnih načinih aplikacije