Izmerimo koncentracijo zdravila, kaj pa sedaj?

Pogled farmacevta

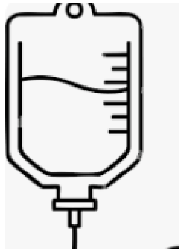
MATEJA SKVARČA, MAG. FARM.

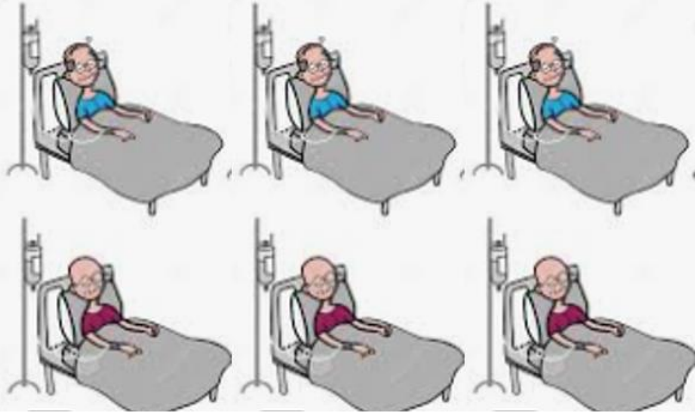
LEKARNA UKCL

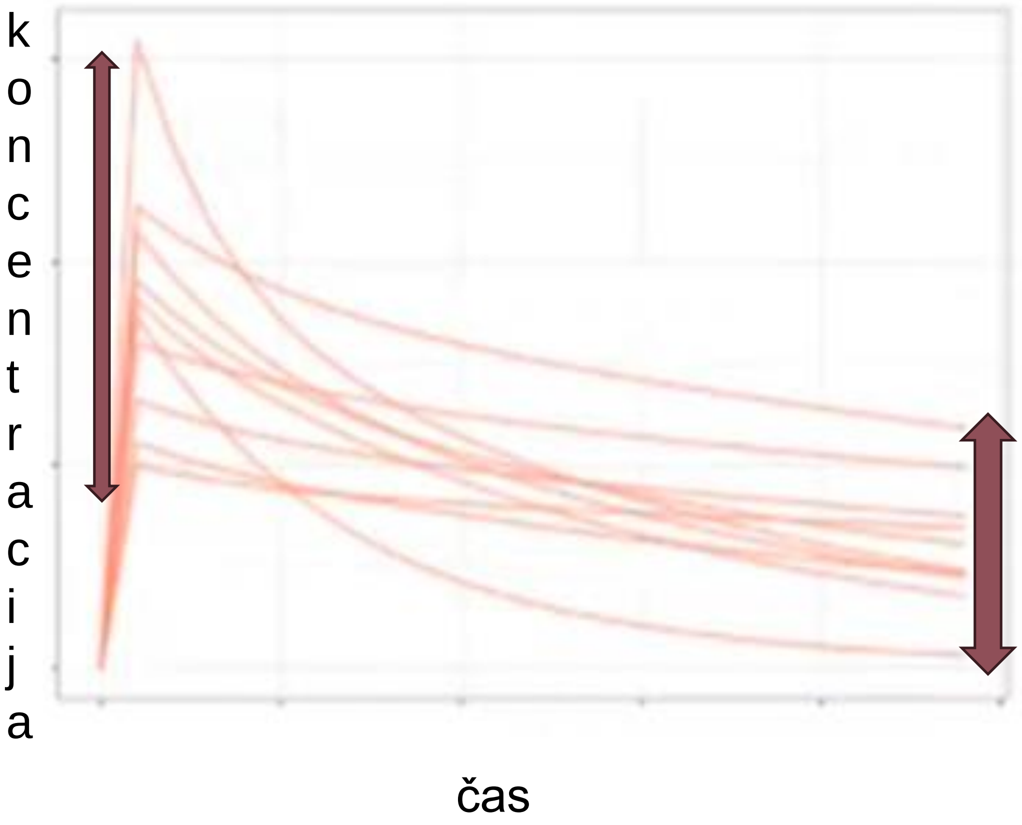
univerzitetni klinični center ljubljana

University Medical Centre Ljubljana

ENAK ODMEREK ZA VSE







TOKSIČNOST IN NEŽELENI UČINKI

VARIABILNOST

NEUSTREZNA UČINKOVITOST
POJAV REZISTENCE

TDM - pri katerih pacientih?

Pri specifični populciji bolnikov (spremenjena FK)

- kritično bolni
- okvara organov (ledvica, jetra..)
- Tx
- debelost
- dializa, ECMO
- zdravljenje okužb (slaba občutljivost na patogene bakterije)
- ...

Personalized Therapy for Mycophenolate: Consensus Report by the International Association of Therapeutic Drug Monitoring and Clinical Toxicology

Stein Bergan, PhD,[1] Mercè Brunet, PharmD, PhD,[2] Dennis A. Hesselink, MD, PhD[3]

Therapeutic Drug Monitoring of Tacrolimus-Personalized Therapy: Second Consensus Report

Mercè Brunet, PharmD, PhD,[1] Teun van Gelder, MD, PhD,[2] Anders Åsberg, PhD,[3] Vincent Haufroid, PharmD, PhD,[4,5] Dennis A. Hesselink, MD, PhD,[6] Loralie Langman, PhD,[7]

CONFERENCE REPORT AND EXPERT PANEL

Antimicrobial therapeutic drug monitoring in critically ill adult patients: a Position Paper

TDM – Katere učinkovine?

- Zdravila z **ozkim terapevtskim oknom** (digoksin, aminoglikozidi)

  - ↓ toksičnost

- Zdravila s **širokim terapevtskim oknom** (betalaktami)

  - ↓ subterapevtske koncentracije

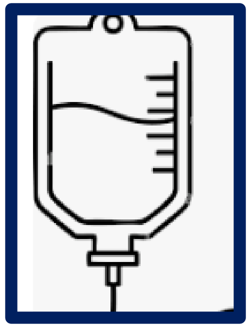
- Zdravila s kompleksno, nelinearno FK

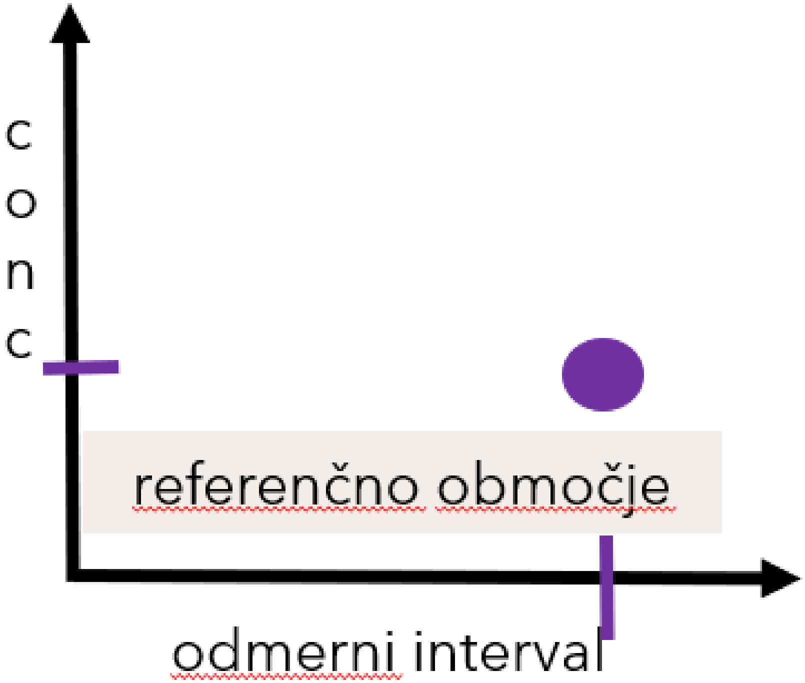
  - npr. vorikonazol, fenitoin

- Interakcije med zdravili

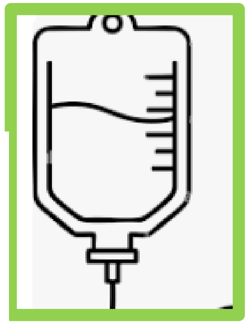
DEFINIRANA PK/PD
ODMEREK –
IZPOSTAVLJENOST -
UČINEK/TOKSIČNOST

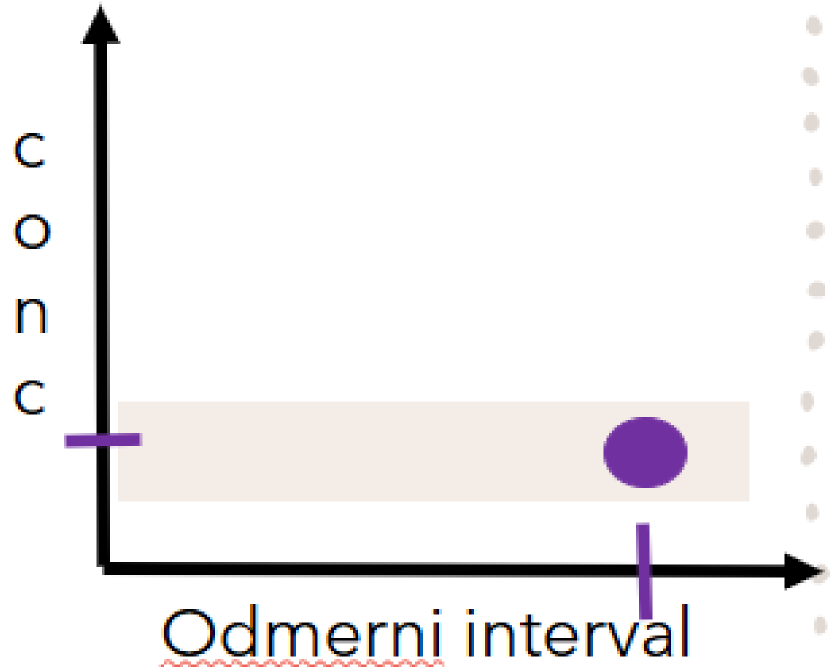
KLASIČNI TDM





Standardni odmerek
Navodila (SmPC)
Smernice
Emprično





Izkušnje
Nomogrami
Algoritmi za odmerjanje
Izračuni
Poizkušanje

ČAS JEMANJA VZORCA

Šele v **stacionarnem stanju** (Css):

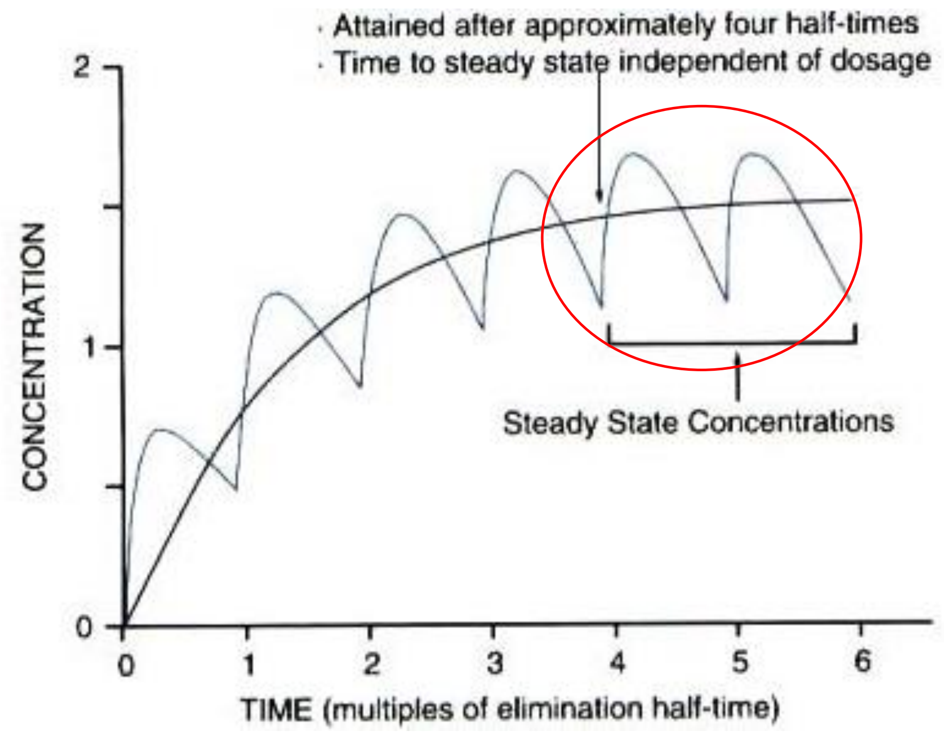
- sepsa (*hitrost je življenje*)
- zdravila z dolgim razpolovinim časom (npr. izavukonazol)

Dejanski Cmin?

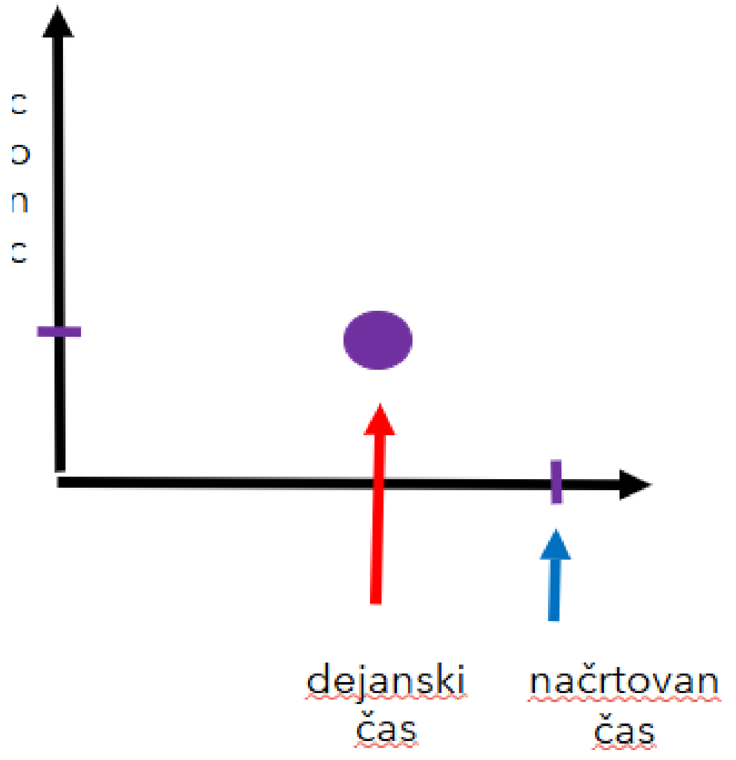
- načrtovan čas odvzema Cmin

vs.

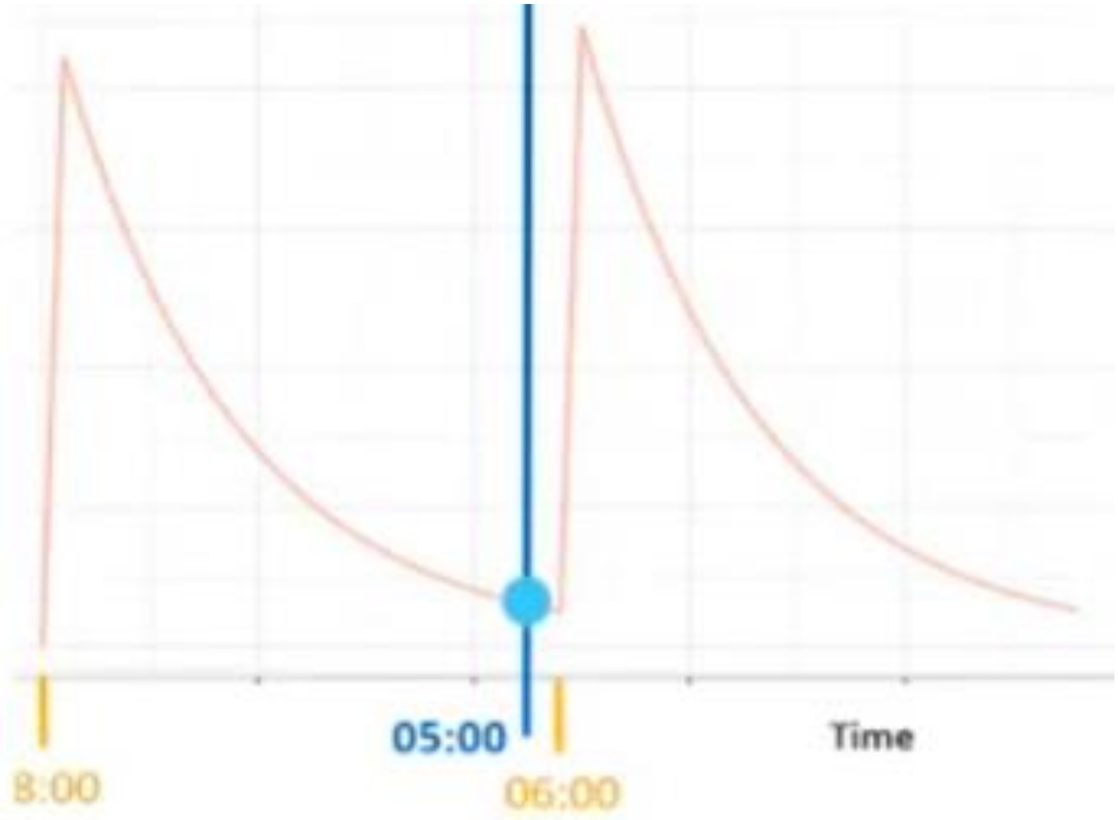
- dejanski čas odvzema Cmin



Wanigasinghe, Jithangi. (2016). Epilepsy and your child A guide to parents.

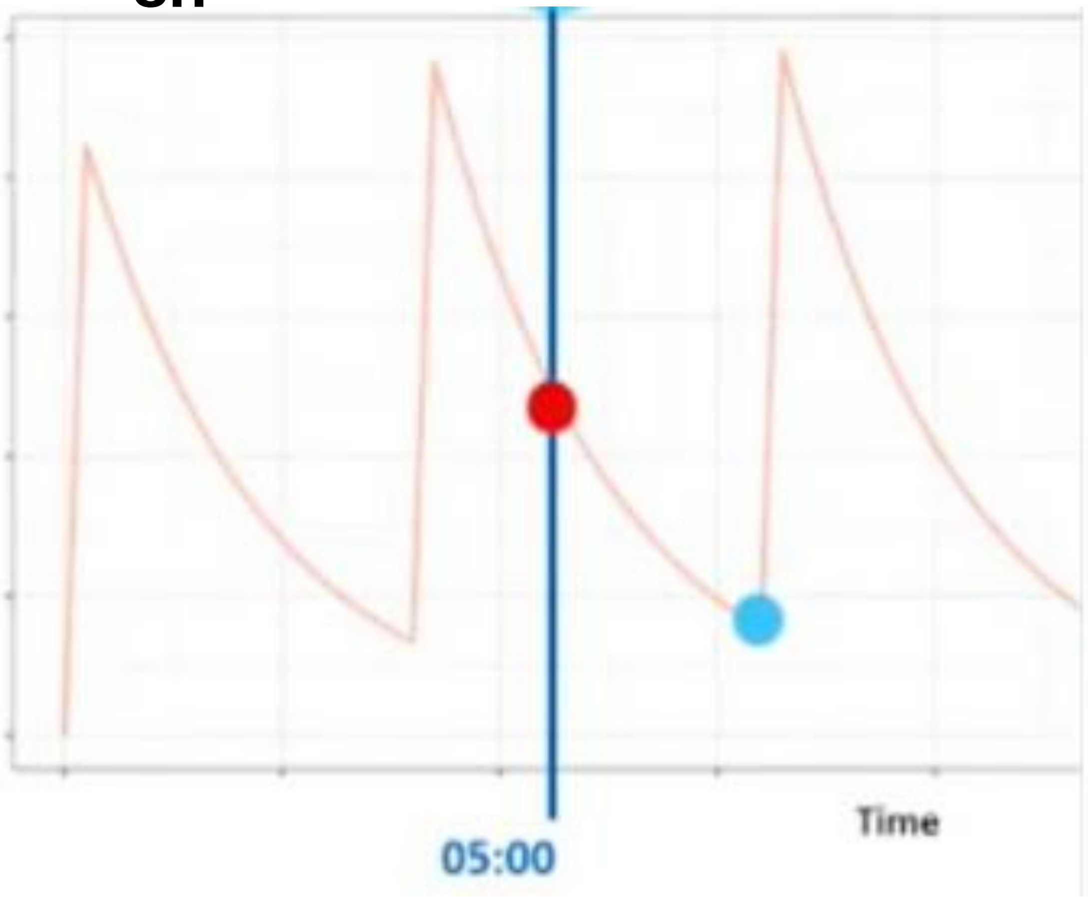


12 h



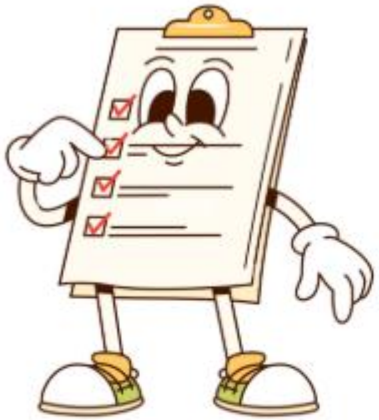
Cmin

8h



Cmin ?

Natančno beleženje in dokumentiranje

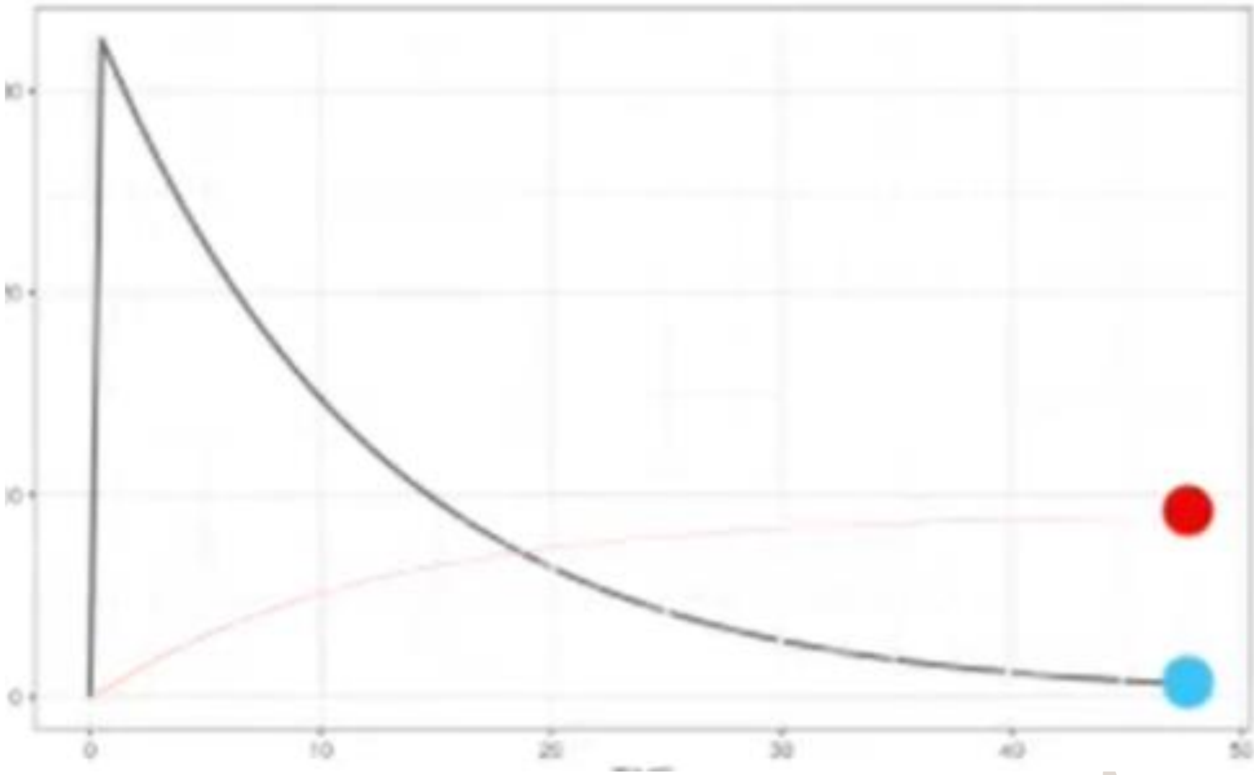


Točenga časa, ne samo planiranega:

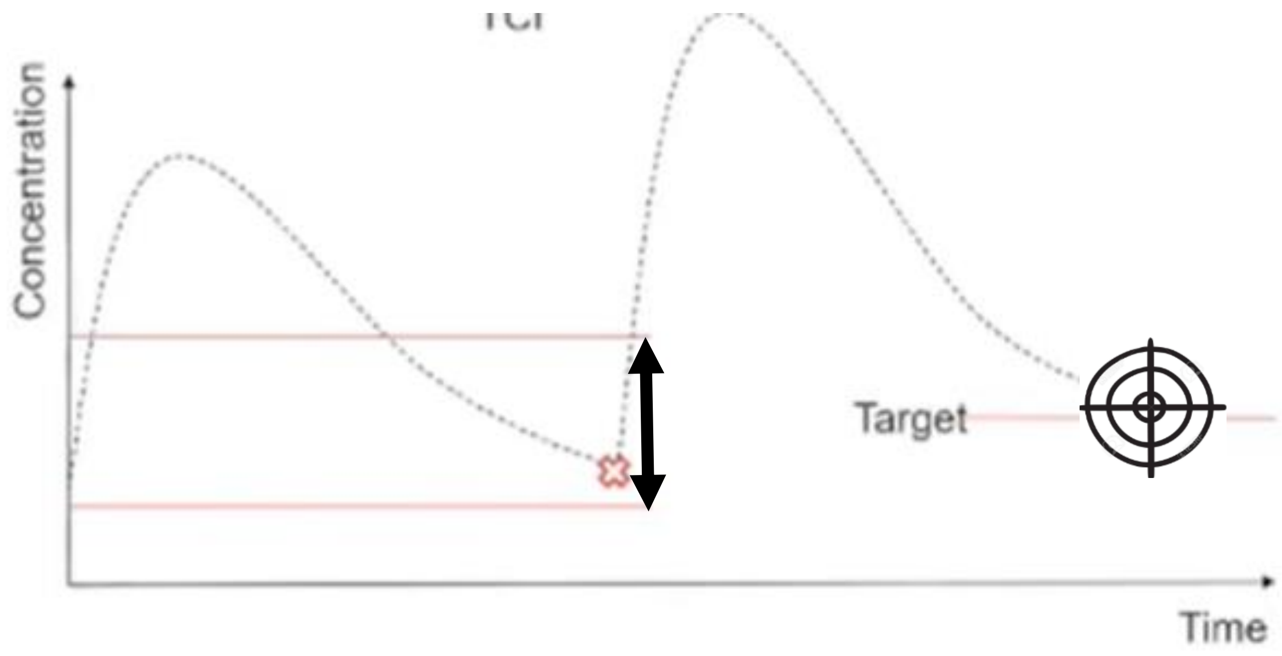
- odvzema vzorca
- aplikacije odmerka zdravila

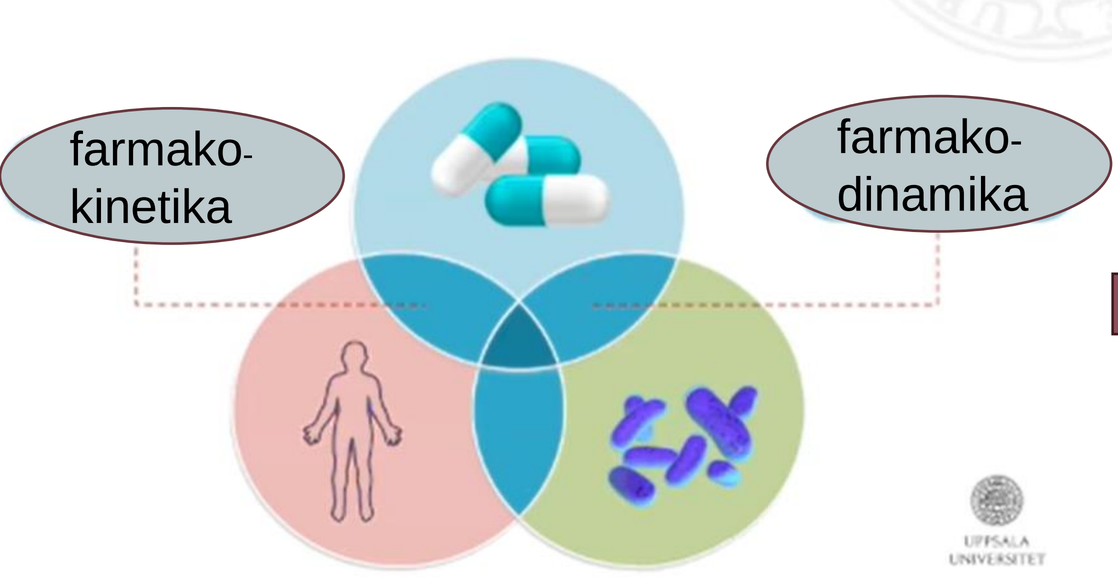
Točnega podatka o :

- odmerku, odmernem intervalu in času aplikacije zdravila (intermitenta infuzija vs. kontinuirana infuzija)



CILJNE VREDNOSTI ZDRAVLJENJA (*»target«*)





PK/PD indeks učinkovitosti

Cmin – Ali obstajajo boljše tarče?

- AUC
- Cmax
- T>MIK
- …..

Cmin ⟷ AUC

<u>Vankomicin</u>

- nova priporočila:

Odmerjanje glede na AUC

↓ nefrotoksičnost

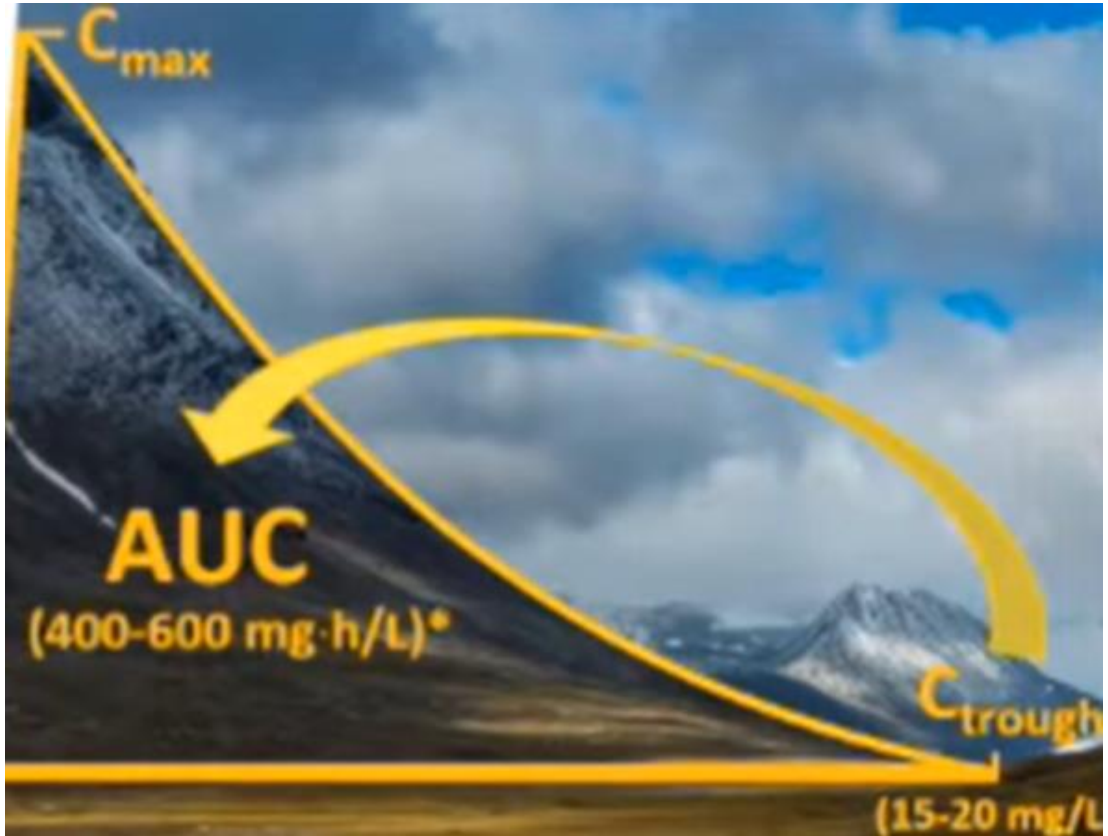
PK/PD = AUC/MIK = 400 – 600

(MIK≤ 1)

ASHP REPORT

Therapeutic monitoring of vancomycin for serious methicillin-resistant *Staphylococcus aureus* infections: A revised consensus guideline and review by the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society, and the Society of Infectious Diseases Pharmacists

Rybak MJ, et al. Clin Infect Dis 2020 Sept 12;71(6):1361-1364



Rybak MJ et al;Am J Health Syst Pharm 2020 May 19;77(11):835-864.

Učinkovitost - toksičnost ⟷ Cmax - Cmin

Aminoglikozidi (gentamicin, amikacin, tobramicin) - 2 meritvi

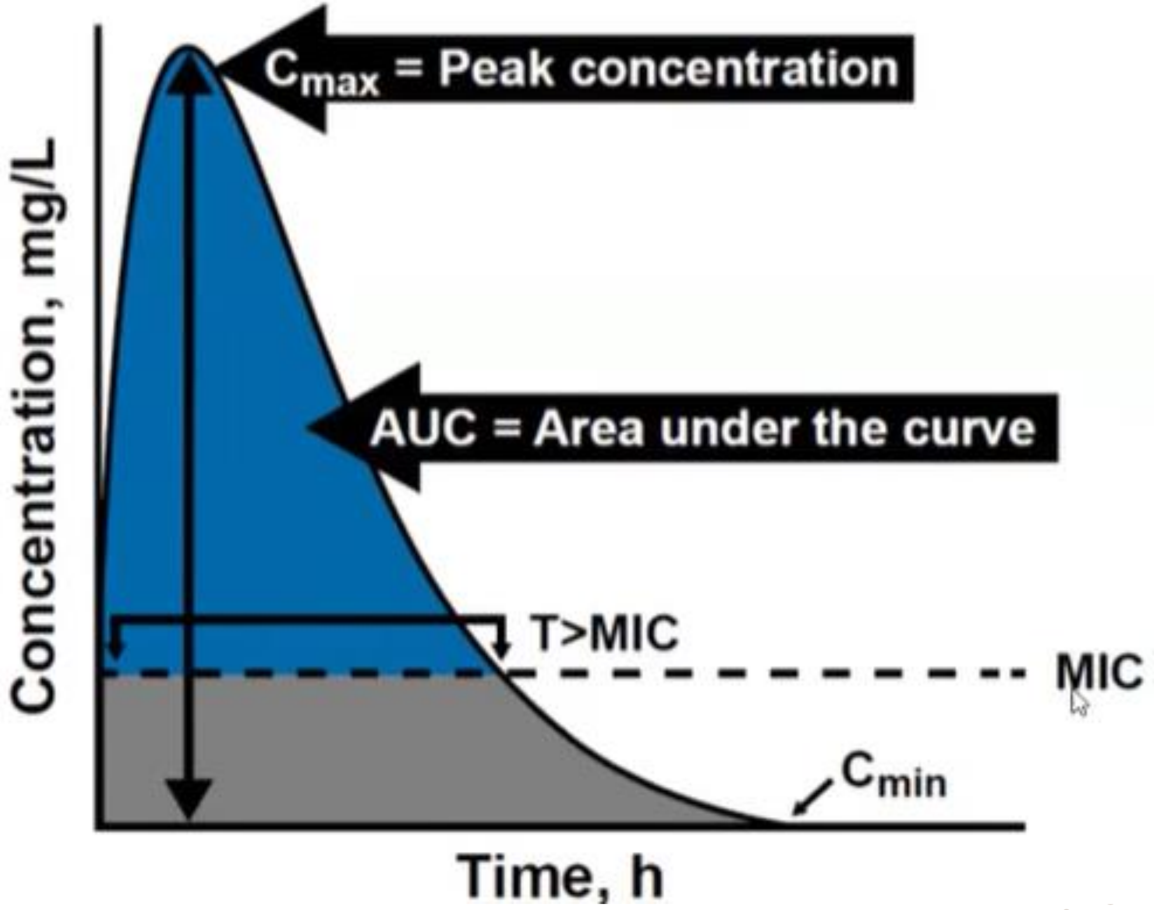
- učinkovitost :

  Cmax = 8 – 10 > MIK oz.

  AUC/MIK >120;

- varnost:

  Cmin



PK/PD indeks učinkovitosti

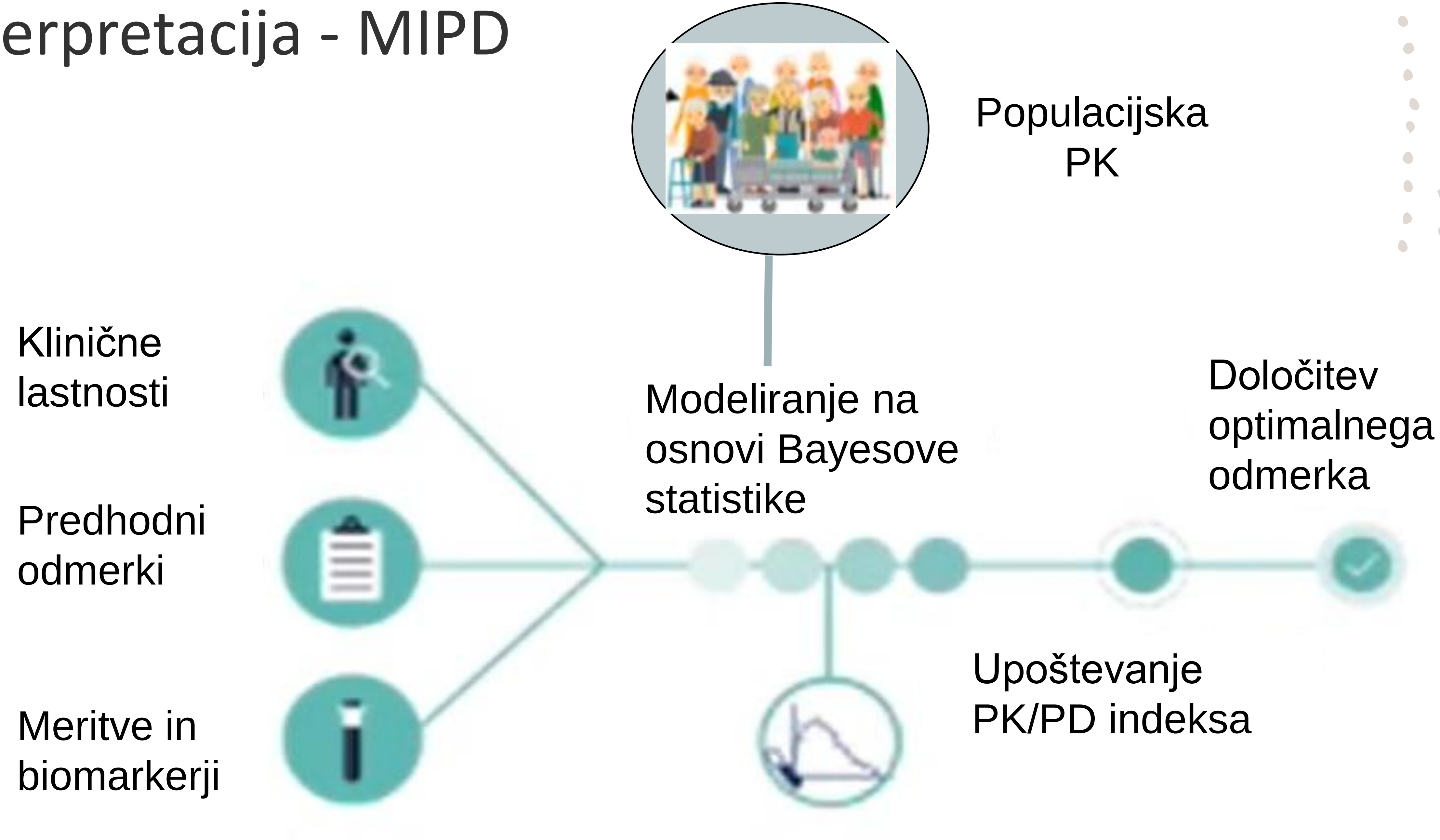
Betalaktami - PK/PD = % T > MIK

- MIK odvisen od bakterije
- Od resnosti okužbe - 45 – 100% T > MIK
- Kritično bolni **100 % T > do 4x MIK**

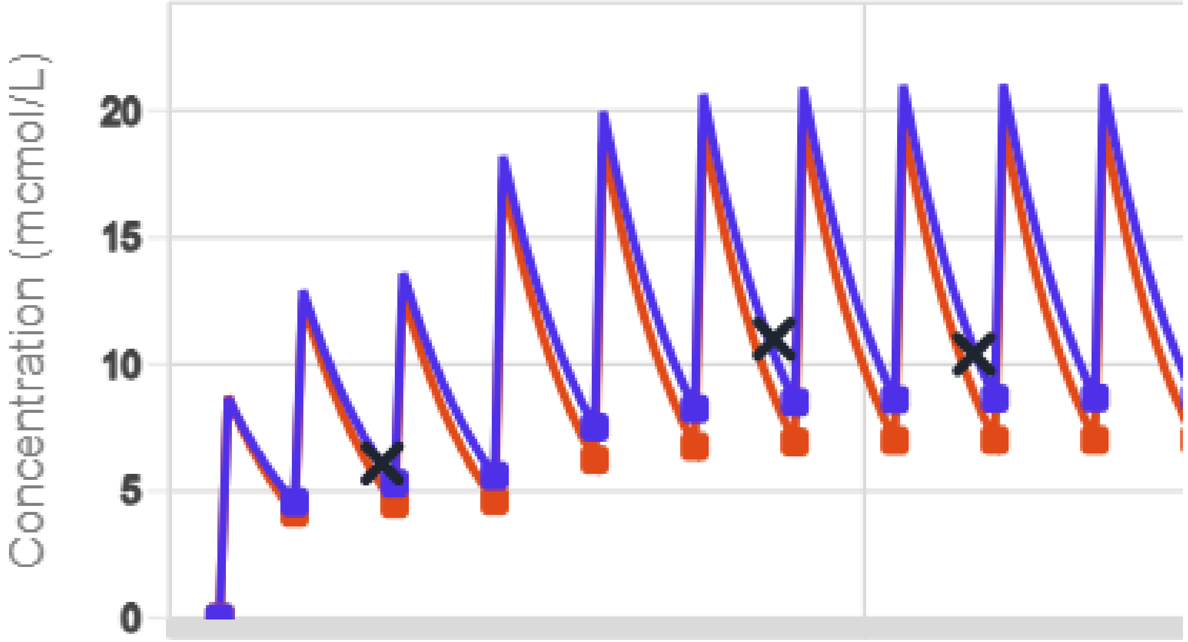
Busulfan - PK/PD = kumulativen AUC

4-dnevni kumulativni AUC = 75 -100 mg*h/L

Interpretacija - MIPD



DoseMe - VANKOMICIN



PK Parameters

	Individual	Population
Vd:	74.41 L	73.5 L
Vd_{ss}:	74.41 L	73.5 L
CL:	5.99 L/h	6.83 L/h
Terminal T1/2:	8.61 h	7.46 h
Ke:	0.0805 /h	0.0929 /h

Calculated by DoseMeRx

Dose mg	Infusion hours	Interval hours	Doses No.
1500	1	12	6

AUC24 mg.h/L	Peak mcmol/L	Trough mcmol/L
501.01	20.64	8.87

DoseMe – BUSULFAN iv

Individualized Dose Recommendation

Total Cumulative AUC target: 80 mg.h/L

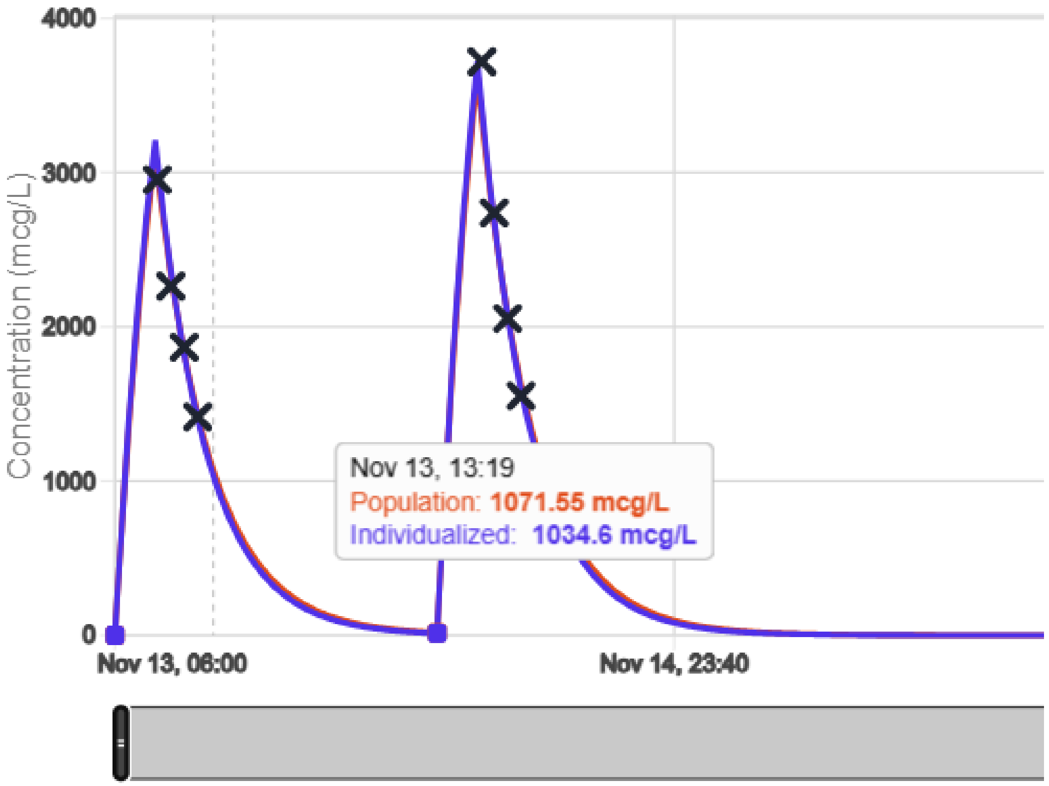
Dose mg	Infusion hours	Interval hours	Doses No.	Regimen days
269	3	24	2	2

Predicted Outcomes

Calculated by DoseMeRx

Cumulative AUC96 mg.h/L
79.98

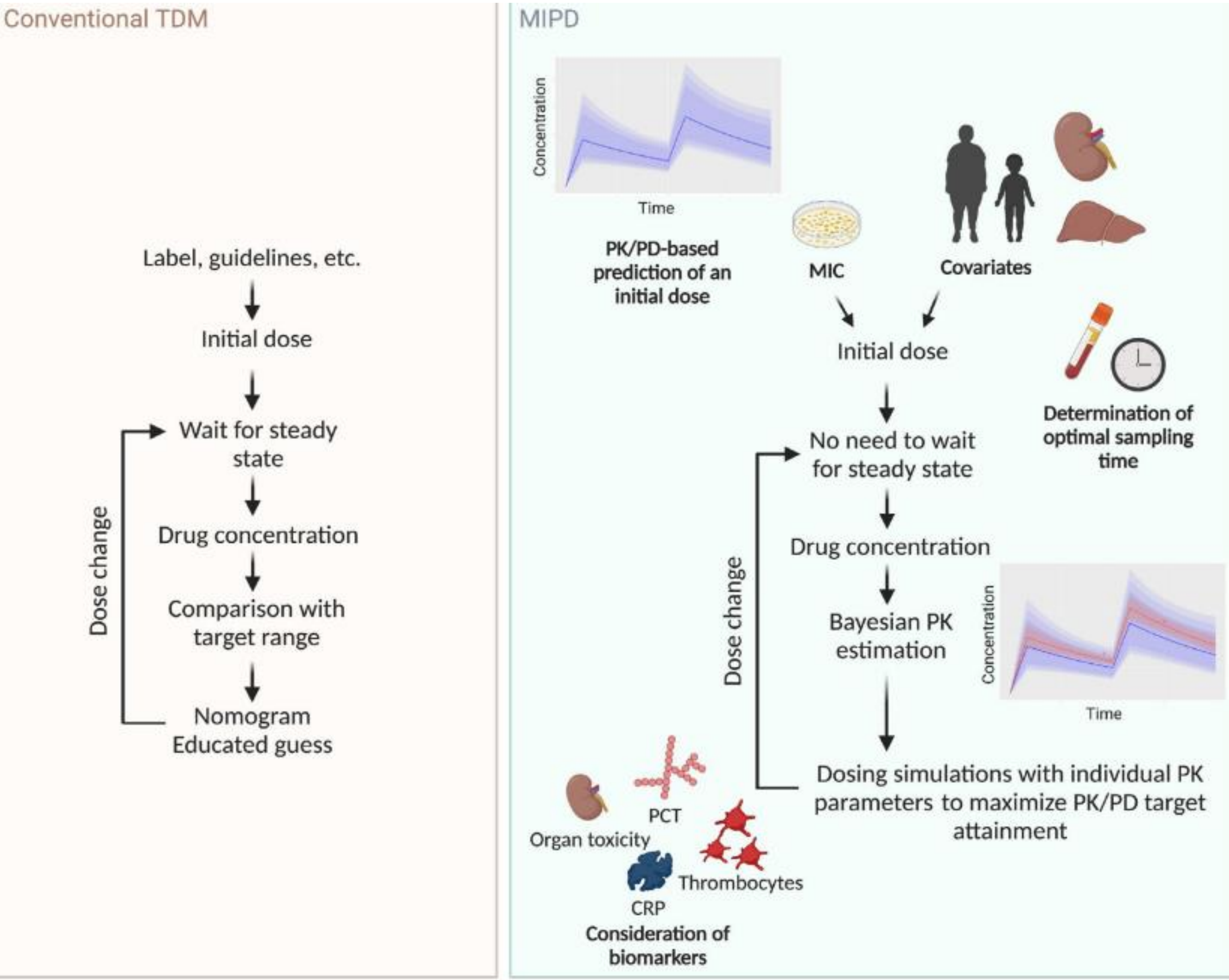
Dosing Profile



PK Parameters

	Individual	Population
Vd:	49.27 L	51.36 L
Vd_{ss}:	49.27 L	51.36 L
CL:	12.87 L/h	12.72 L/h
$K_{elimination}$:	0.2612 /h	0.2476 /h
Terminal $T_{1/2}$:	2.65 h	2.8 h

Klasični TDM vs. MIPD



Wicha SG et al., Clin Pharmacol Therapy. 2021 Apr;109(4):928-941

Prednosti:

❖izračun začetnega učinkovitega odmerka

❖meritev koncentracije pred dosego stacionarnega stanja

❖časovno neodvisno jemanje vzorca

❖že ena sama meritev lahko ustrezno oceni celotno FK krivuljo in izračun FK parametrov