Farmacocinética y farmacodinamia aplicada al desarrollo de nuevos fármacos oncológicos

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PK/PD & Drug Development

Model based drug development:

To construct QUANTITATIVE relationships to define and explore key decision criteria

Target ⟷ Drug activity

Drug ⟷ Exposure

Exposure ⟷ Response (biomarker)

Response ⟷ Clinical outcome

PK/PD & Drug Development

- Why is important in Oncology:
  - Generally, drugs have narrow therapeutic ranges
  - Classic anticancer drugs are administered at the maximum tolerated dose
  - Drug exposure in commonly related to the clinical outcome

Safety and efficacy should be optimized for individual patients

PK/PD & Drug Development

- Practical objectives
  - To support optimal treatment to patients
    - Best schedule considering efficacy and toxicity
    - To explain variability
    - Dose individualization
    - Aplication of TDM to anticancer agents
  - To reduce costs
  - To accelerate drug development
  - To support drug approval/discussion with the RAs
  - To support drug label

PK/PD & FDA perspective

- The OCP has recently created a centralized "Pharmacometric Division" to facilitate PK/PD applications:
  - Groups focused on consulting services in IND and NDA review and software development
  - Internal process improvement to increase value of PK/PD
  - Information management architecture design and implementation: The clinical pharmacology module of the CDISC has been completed

PK/PD & Drug Development

- Preclinical:
  - To project the Phase I dose and schedule
  - To establish the conc-effect relationship
  - To identify the region of maximum synergy/antagonism at varying concs of drugs used in combination

PK/PD & Drug Development

- Clinical
  - To define the PK characteristics
  - To calculate and explain PK variability
    - Demographics
    - Renal/liver functions
    - Ethnicity
    - Baseline conditions
  - To relate PK with toxicity and efficacy to optimize and individualize treatment

PK/PD & Regulatory decisions

- Approval
  - Evidence of efectiveness
  - Assess benefit-risk
  - Review targeted safety studies
  - Develop approval criteria
- Designing trials
  - Select dose or exposure range for registration trials
  - Derive optimal sampling schemes

PK/PD & Regulatory decisions

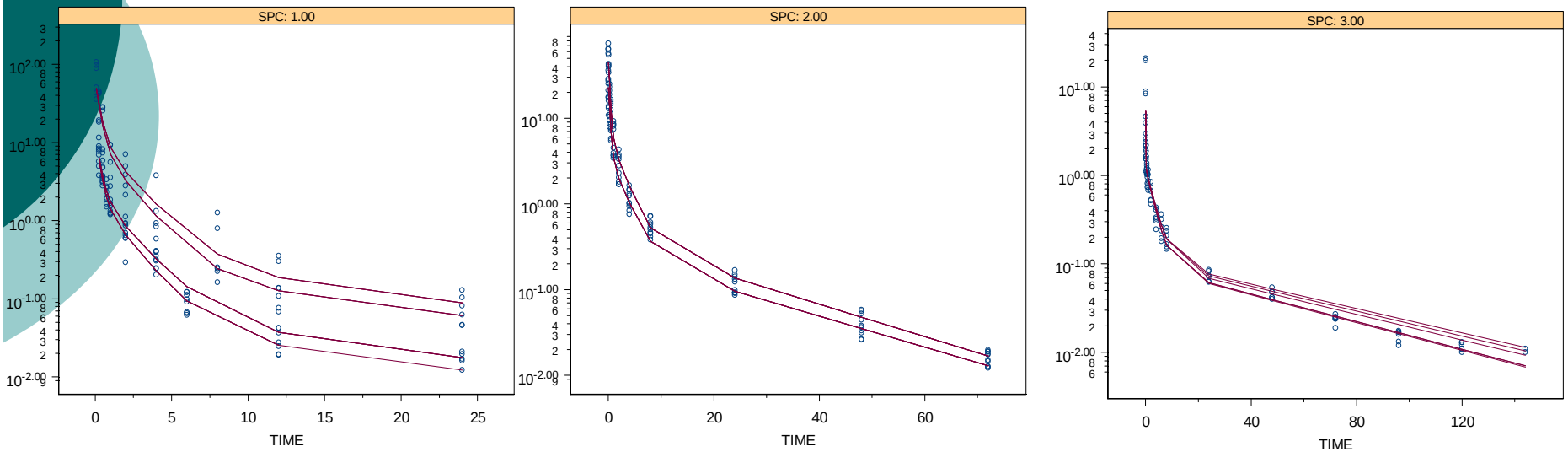
- Labeling
  - Formulate dosing instructions
    - Select dose and regimen
    - Individualize dose
    - Evaluate dosing in special populations (pediatrics, renal impaired)
    - Assess potential for drug interactions
    - Describe time course of effects
  - Provide warnings and precautions

PK/PD & Regulatory decisions

Pivotal: Regulatory decision will not be the same without PM review
Supportive: Regulatory decision is supported by PM review

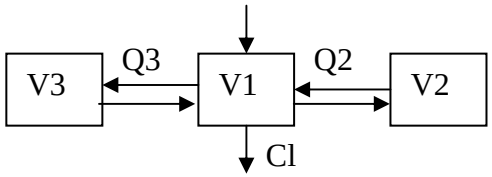
Impact	Approval	Labeling
Pivotal	54%	57%
Supportive	46%	30%
No Contribution	0	14%

Example 1. Allometric scaling



Concentration-time profiles and population predictions in mouse (1), rat (2) and dog (3)

Data were fitted to a 3 comparment model



$$Cl = 0.932WT^{0.9}1.2^{Sex}$$

$$V1 = 1.01WT^{0.882}$$

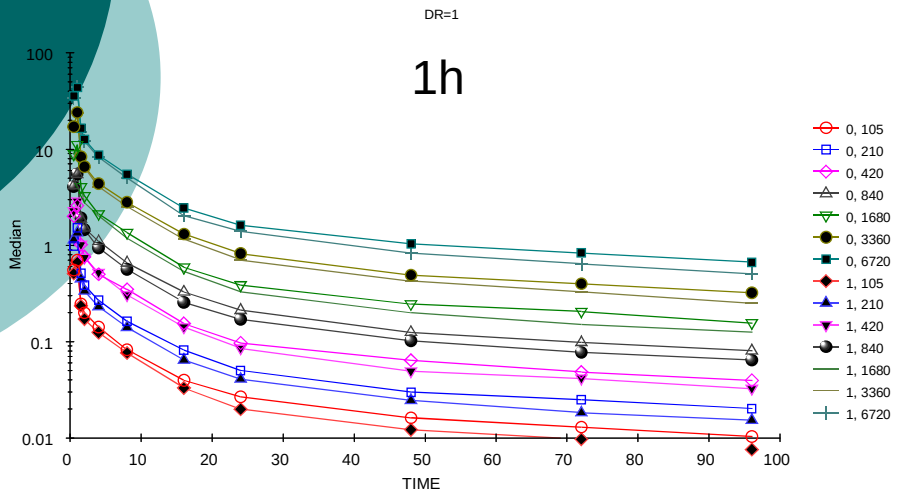
$$Q2 = 434WT^{1.16}fu^{1.59}$$

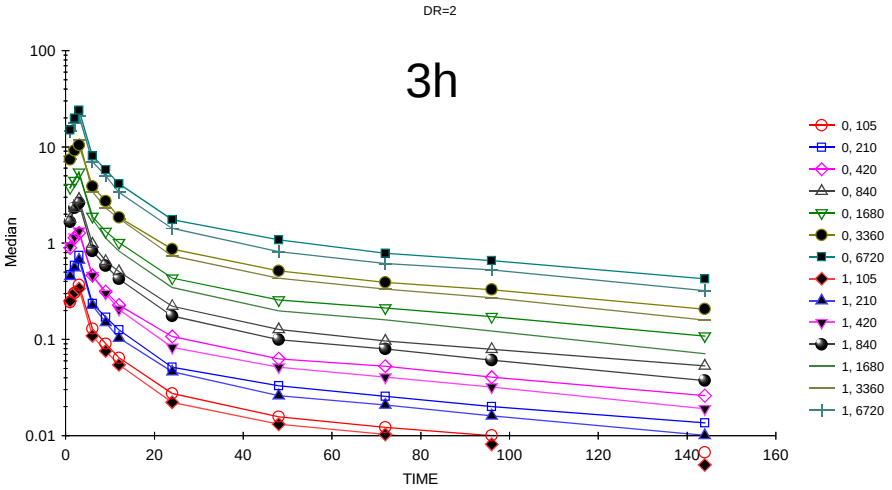
$$V2 = 2.34WT^{1.07}$$

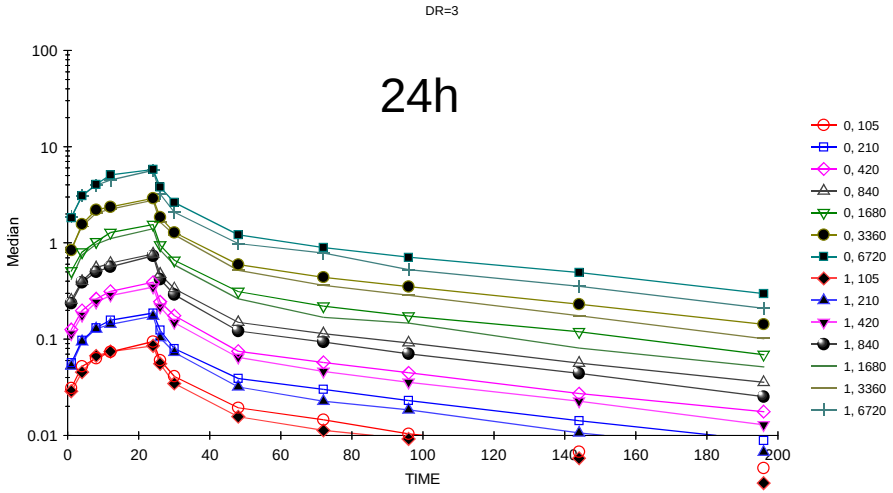
$$Q3 = 0.9WT^{1.34}BrW^{-0.312}$$

$$V3 = 9.84WT^{1.15}$$

Example 1. Allometric scaling



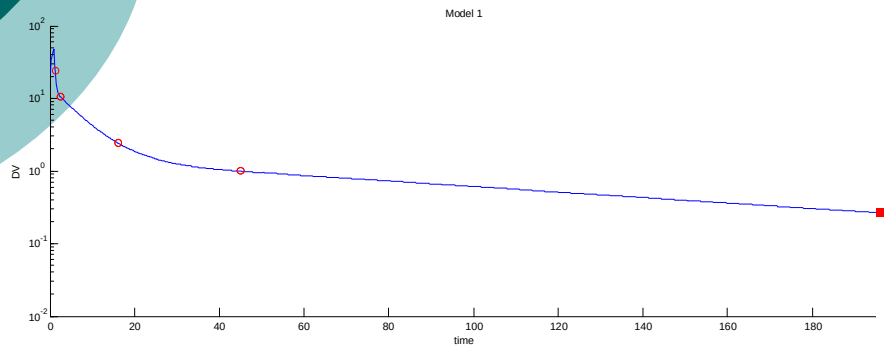




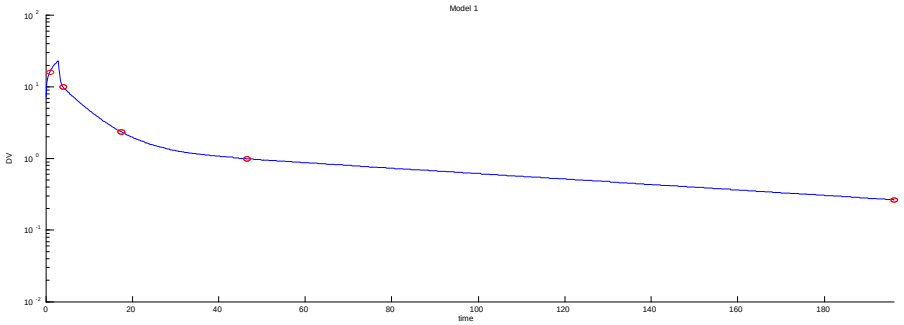
Simulation of PK curves for 7 different dose levels infused in 1, 3 and 24 hours.

Example 1. Allometric scaling

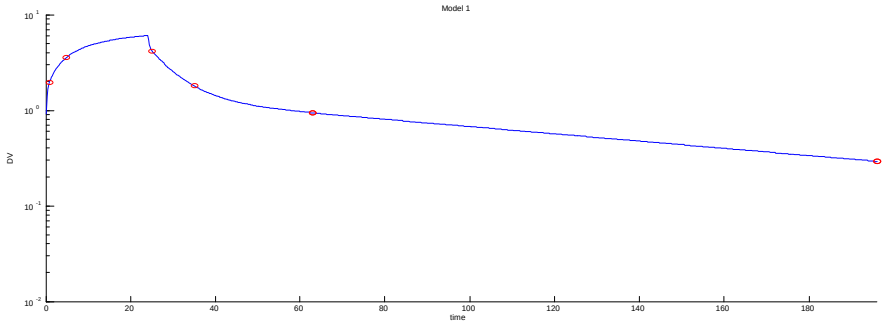
PopEd (Uppsala University) was used to estimate the optimal sample times in infusions of 1, 3 and 24 h for a dose of 6720 ug.



Infusion 1h. Tiempos: 0, 1.3, 2.5, 16, 45 y 196 h.

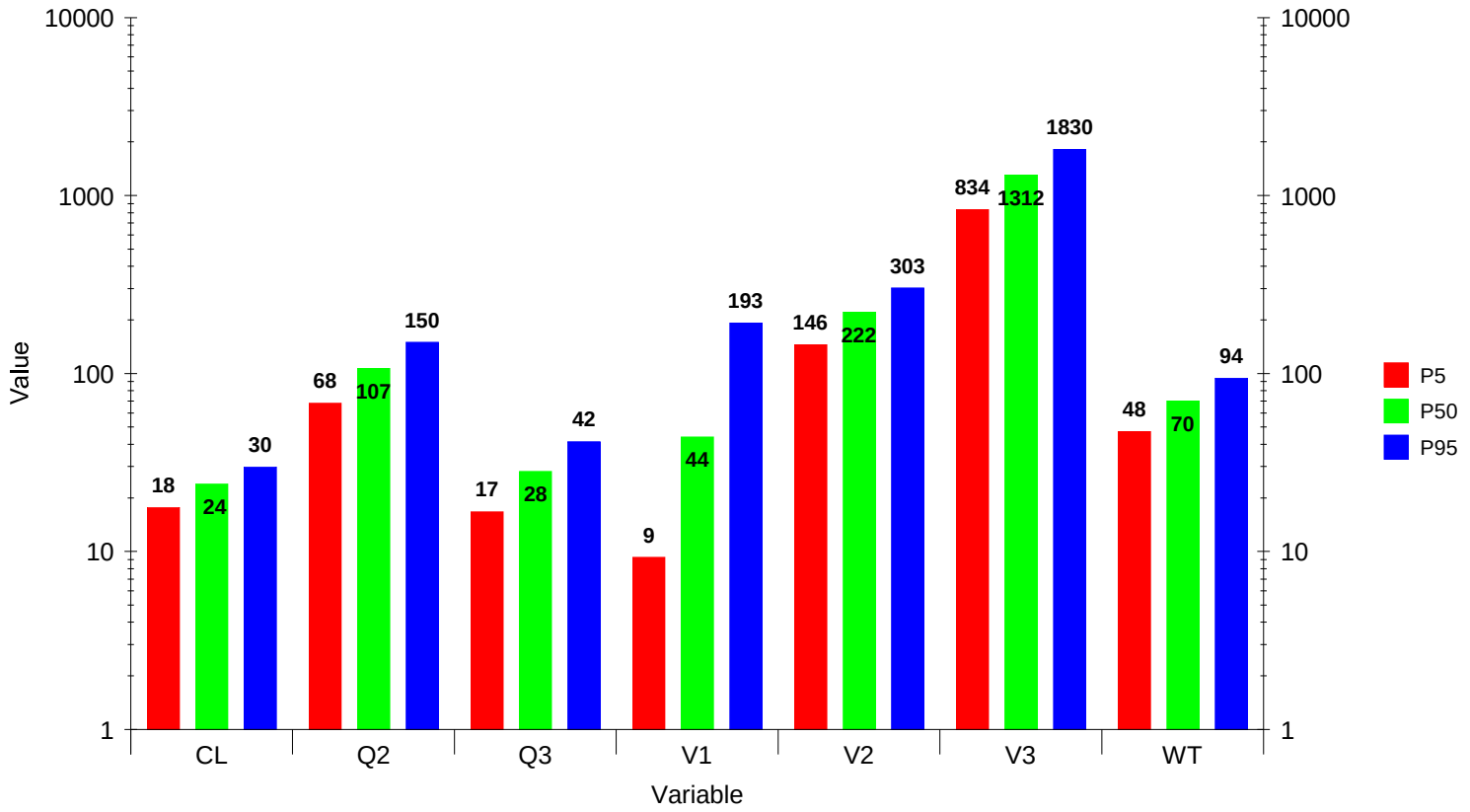


Infusion 3h. Tiempos: 0, 1, 4.2, 17.5, 46.5 y 196 h.



Infusion 24h. Tiempos: 0, 1, 5, 25, 35, 63 y 196 h

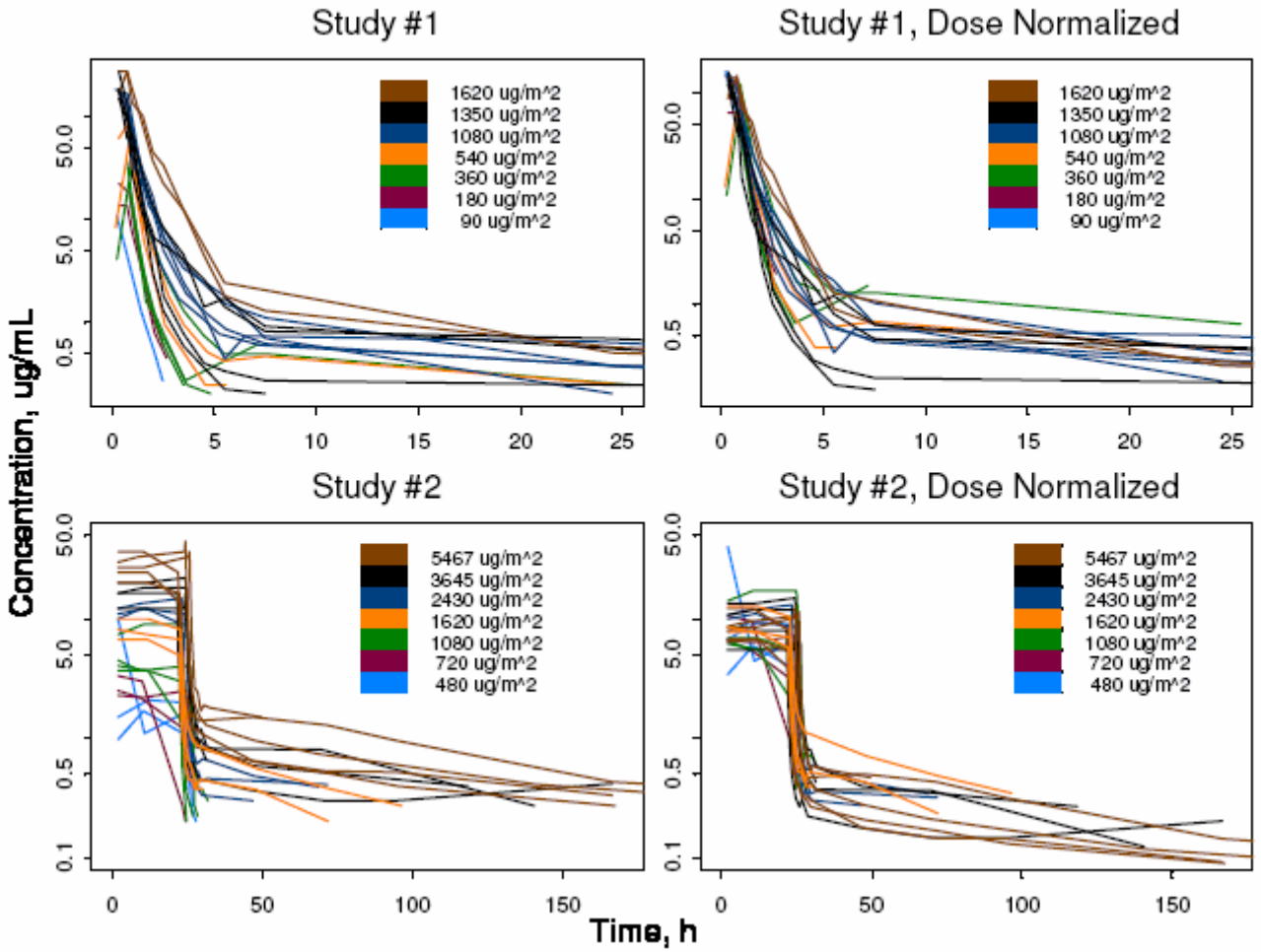
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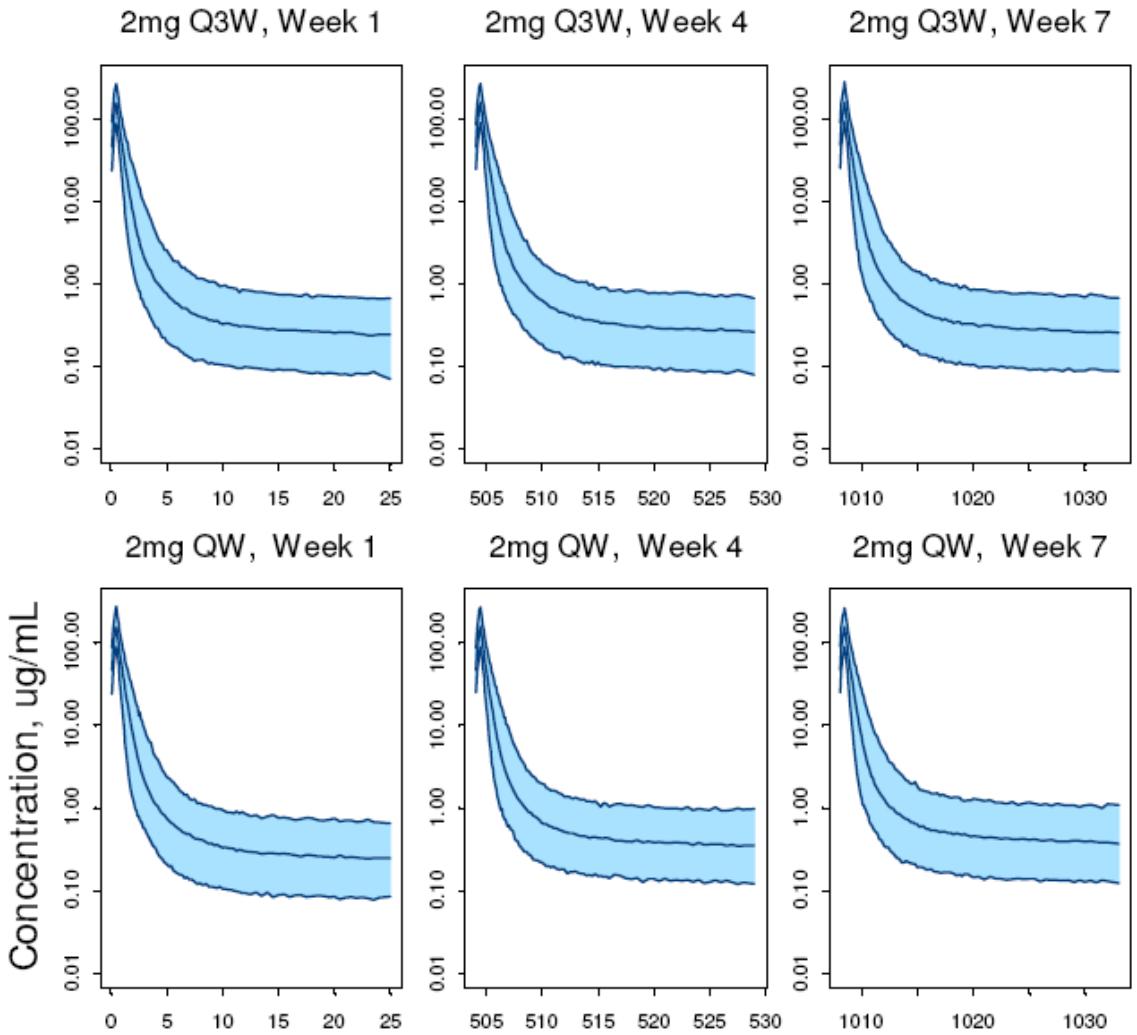
Percentiles 5, 50 and 95 of parameters in simulated human population. CL, Q2, Q3 in L/h, V1 to V3 in L, and WT in Kg.

Example 2. Regulatory waiver for a single agent weekly study

Raw and normalized time course of the plasma concentrations of PM02734 after 0.5h (upper pannel) and 24h (lower pannel).

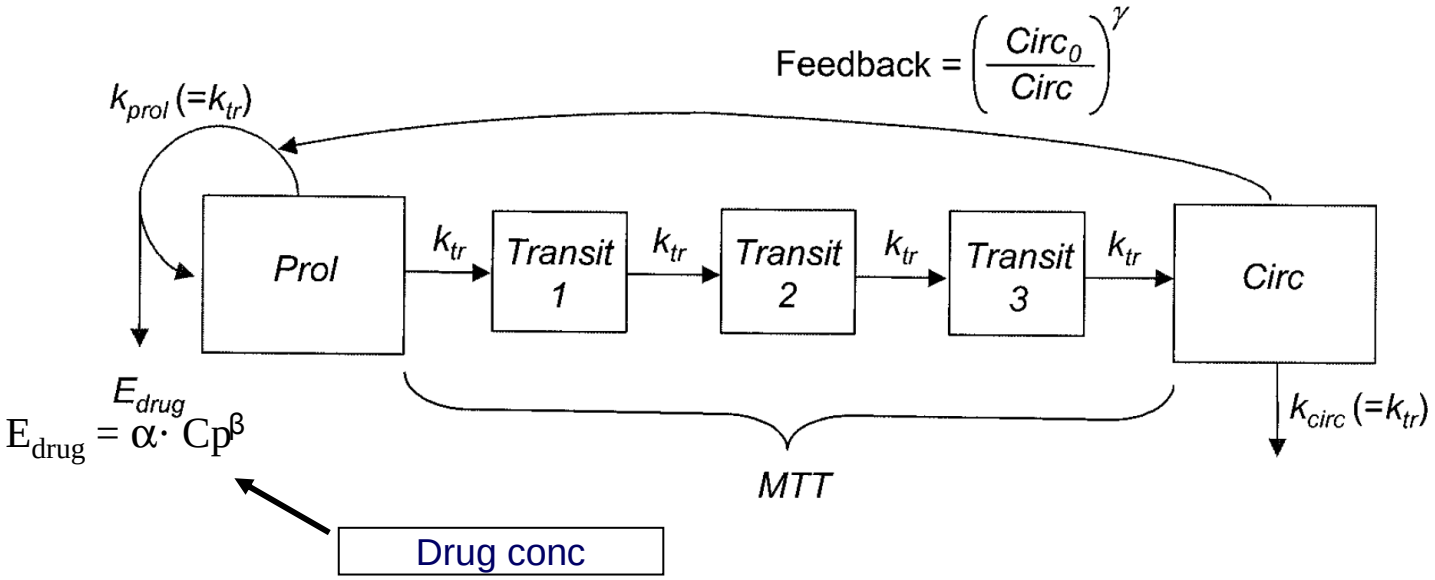


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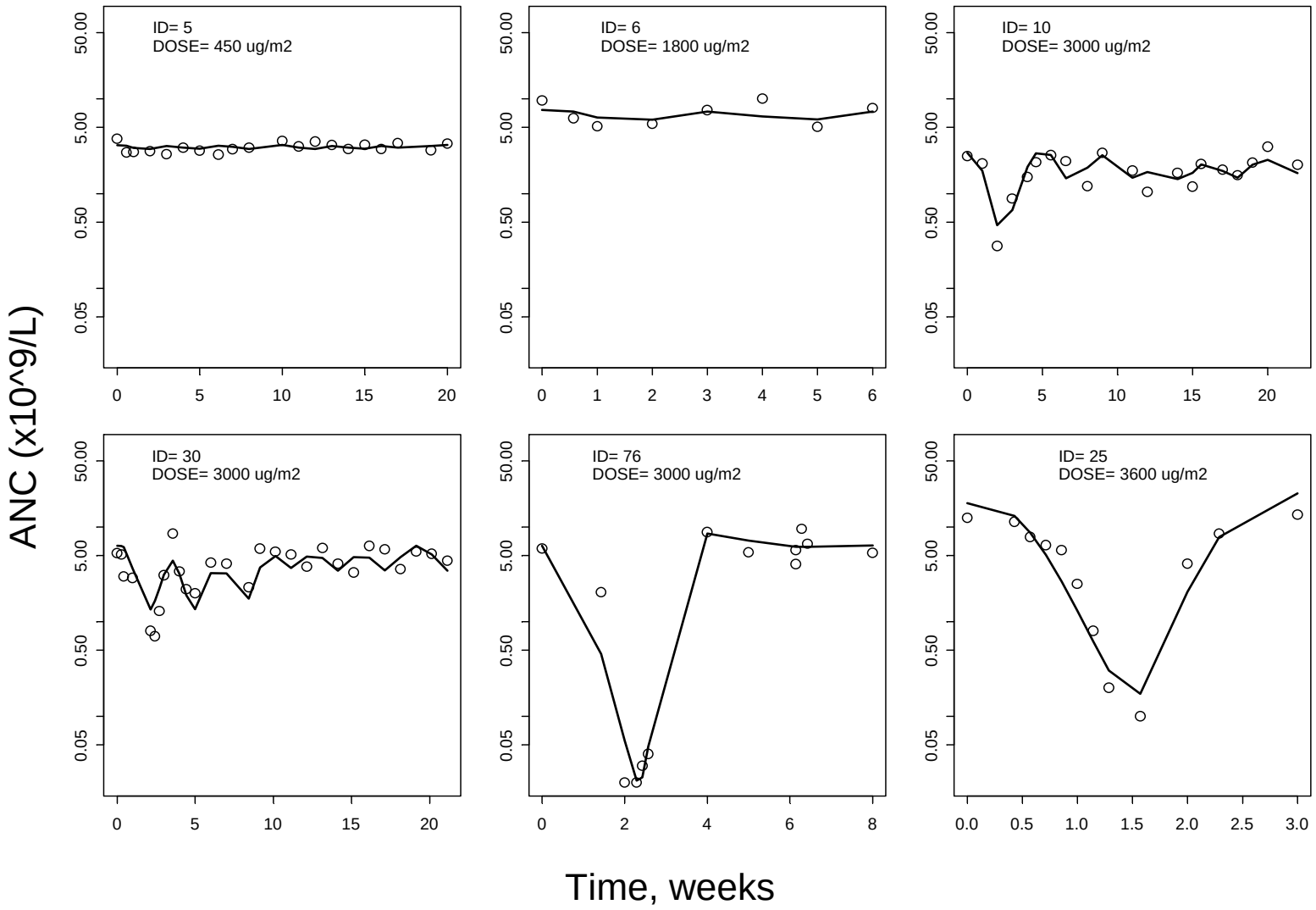


Example 3. Neutropenia

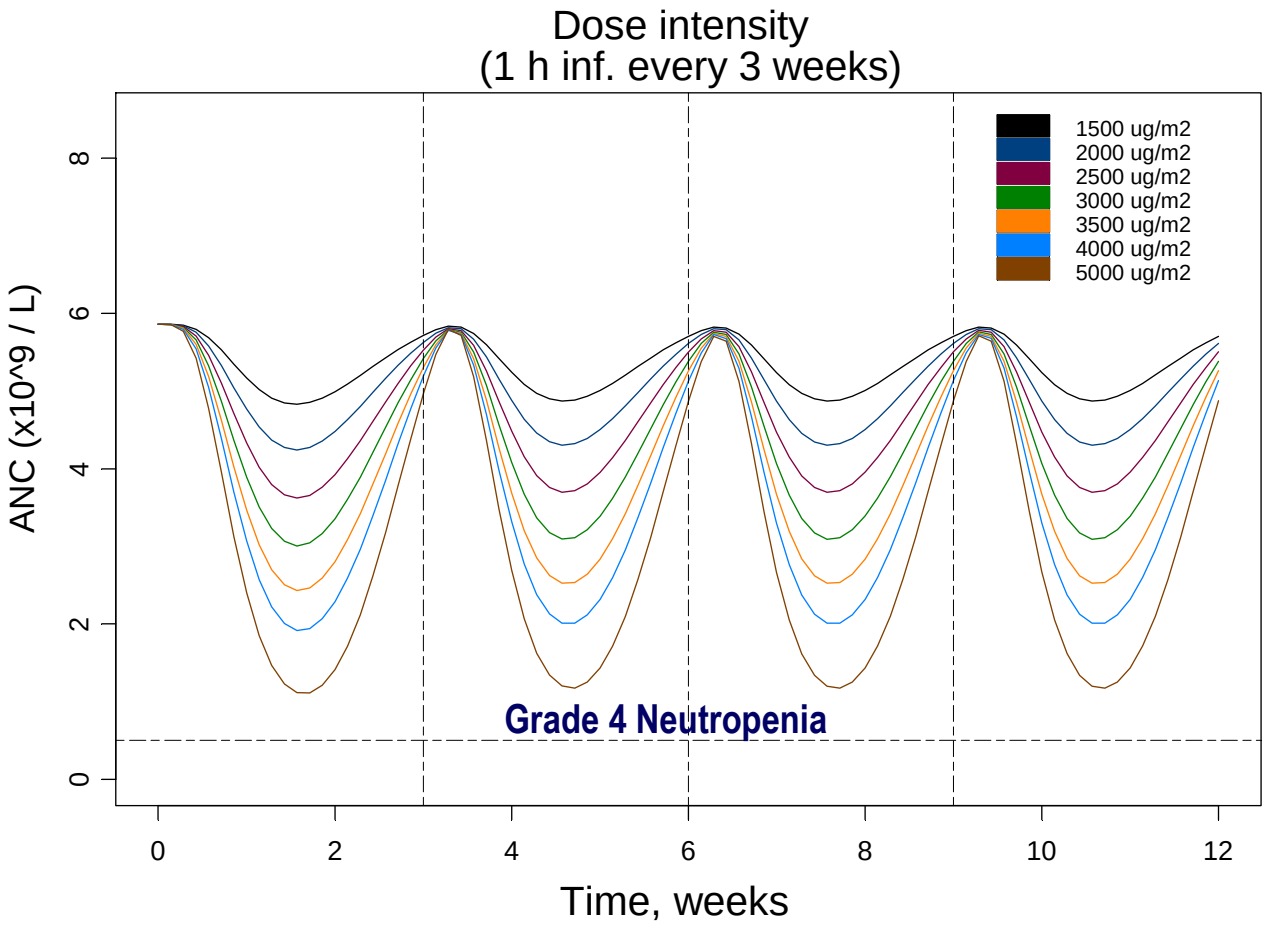
- Classic approach: Drug exposure is related to neutrophils nadir.
- What is lost: time course and neutropenia duration, directly related with the risk of infection.
- POP-PK/PD models can explain and predict the grade and length of the neutropenia, and evaluate different schedules regarding dose intensity, dose density and length of infusions.



Example 3. Neutropenia

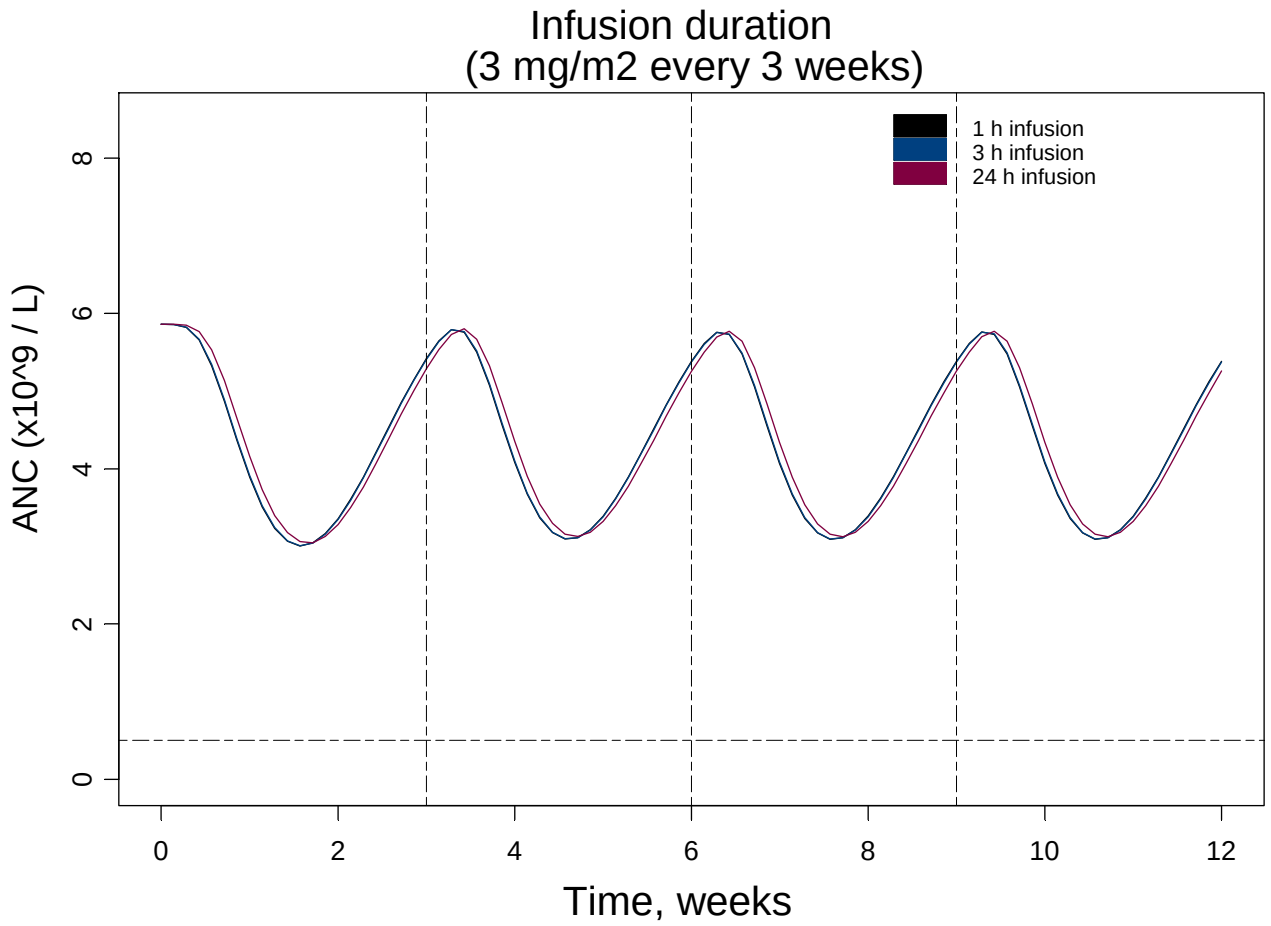


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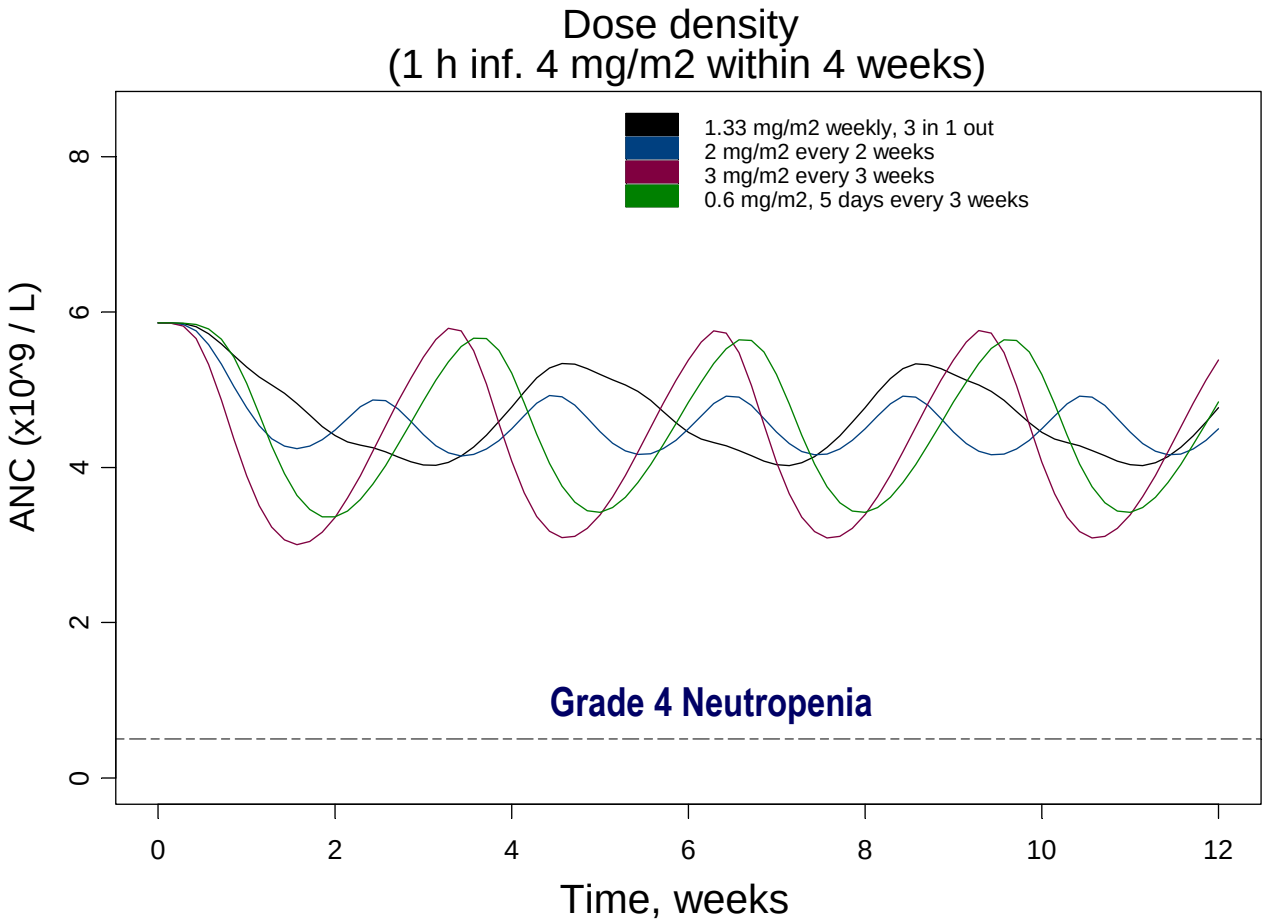
Drug exposure and neutrophils time course is not lineal. Reducing the dose results in a more than proportional increase in neutrophils nadir.

Example 3. Neutropenia



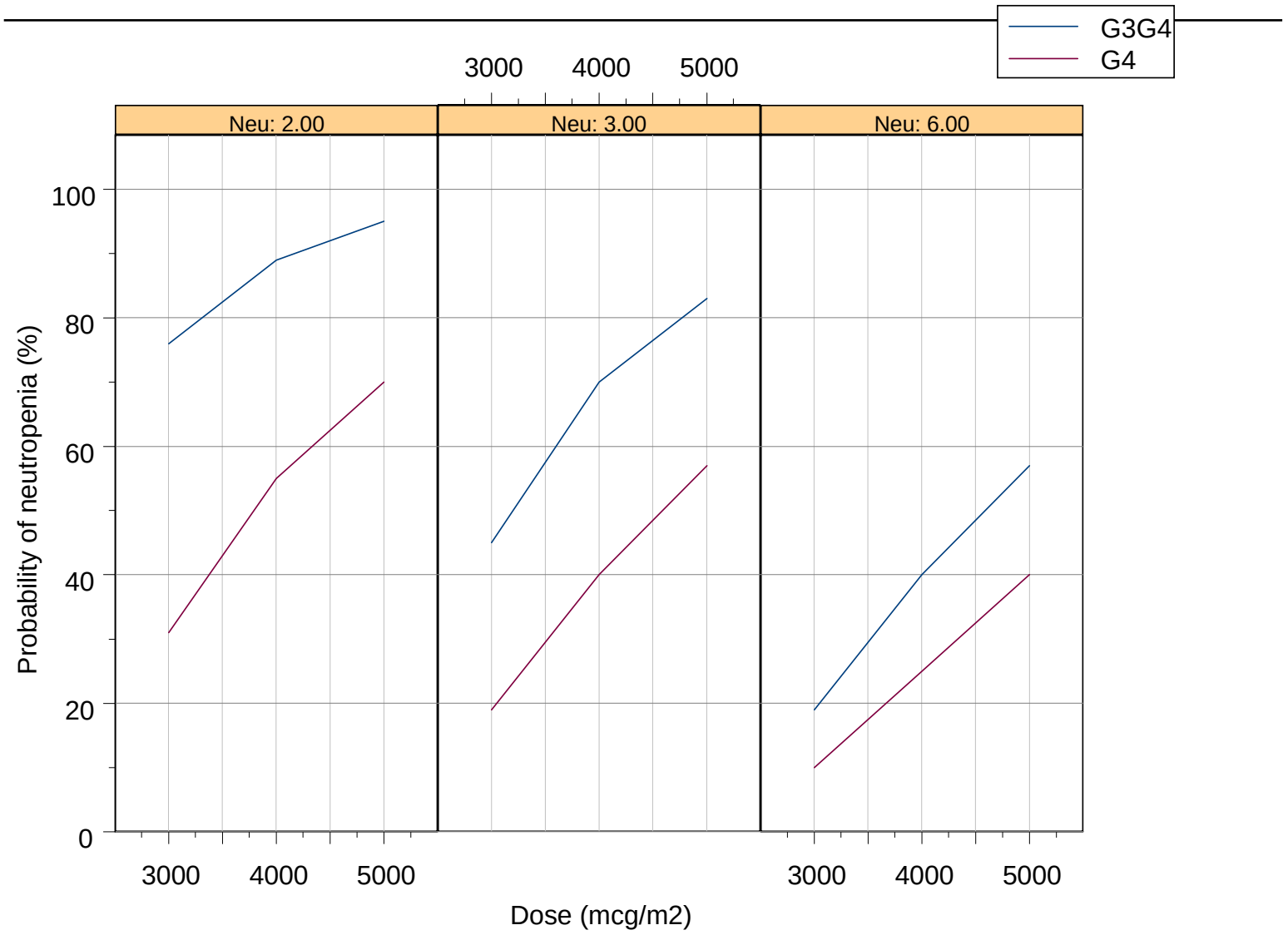
Length of infusions has a negligible impact on neutropenia

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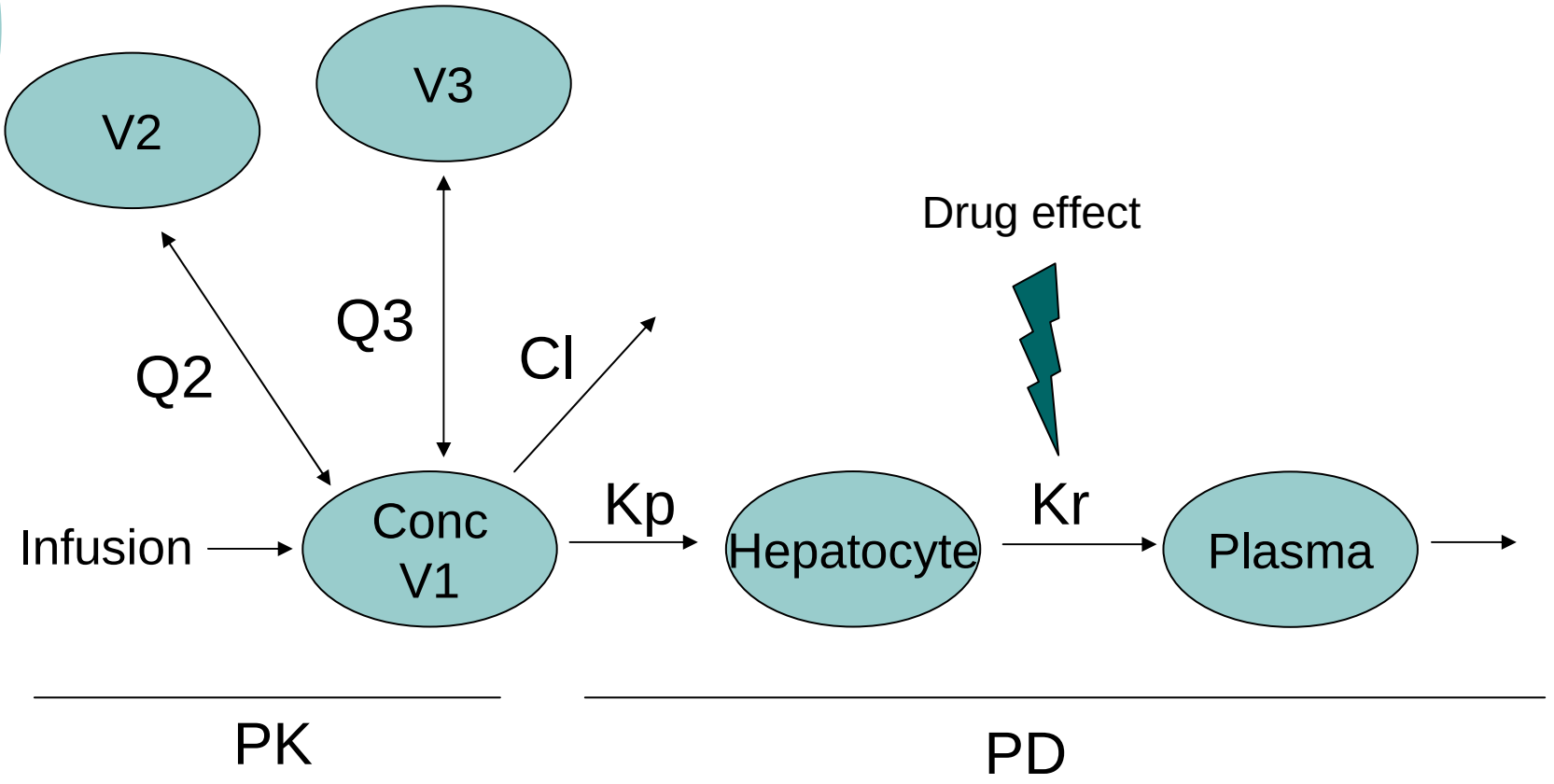


For a fixed cumulative dose, the severity of neutropenia can be reduced by using schedules with more frequent doses. Higher doses at prolonged intervals result in a more severe neutropenia.

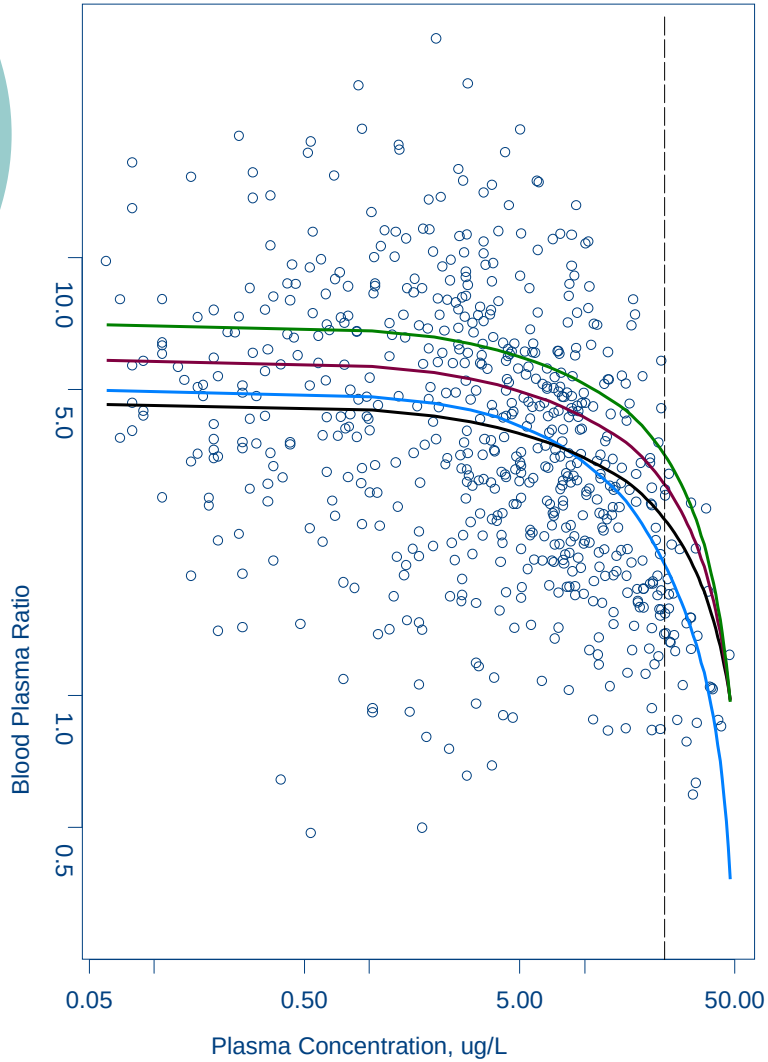
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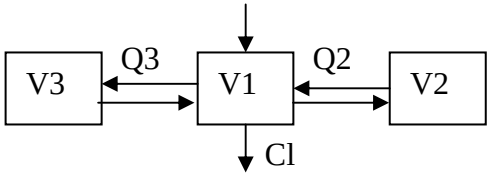


Example 4. Transaminase increase



Example 5. Binding to red blood cells





$$Cs = Cp(1 - HTCO) + \frac{B_{max} \cdot HTCO \cdot Cp}{C_{50} + Cp}$$

Example 5. Binding to red blood cells

