Pharmacokinetics and pharmacodynamics of peptide and protein drugs

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Learning outcomes

- Overview of PK/PD
- PK: elimination of protein therapeutics
- PK: distribution of protein therapeutics
- PD: models for protein therapeutics
- PD/PK link models
Receptor theory

1878 Langley – Ehrlich 1909
"PK – PD"

- What do these terms mean?
  - PK is what the body does to the drug
  - PD is what the drug does to the body
Figure 2  Physiological scheme of pharmacokinetic and pharmacodynamic processes.
Filgrastim: dual mechanism of elimination

- **Renal clearance:**
  - Rapid excretion via the kidneys
  - Dependent on kidney function

- **Neutrophil-mediated clearance:**
  - Internalisation and degradation of the G-CSF / receptor-complexes in the cell
  - Dependent of neutrophil count

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**Pharmacokinetics in nephrectomised rats**
Filgrastim 100 μg/kg

- Control (n = 4)
- Nephrectomised (n = 3)

G-CSF, granulocyte-colony stimulating factor
Properties of pegylation

Properties of PEG

- Enhanced water solubility
- Physiologically inert
- Well tolerated, no immunogenecity
- Mainly neutrophil-mediated degradation
- Self-regulating via ANC

CH₃O

H

Ethylenglycol

Possible advantages of pegylation (PEG)

- Novel mechanism of elimination
- Enhanced molecular volume
- Changed PK
  - Renal clearance marginal
  - Mainly neutrophil-mediated degradation
- Self-regulating via ANC

PK, pharmacokinetics; ANC, absolute neutrophil count

Luxon BA. From Research to Practice. 2001;3:3-9
Biological properties unchanged by PEG

- **Proliferation assays**
  - Similar stimulation of G-CSF–dependent cells

- **Receptor binding**
  - Comparable competitive binding affinity towards the G-CSF receptor

- **Neutrophil Response**
  - Dose-response relationship with regard to the rise of neutrophils

- **Functional studies of neutrophils**
  - No differences in release of superoxide and phagocytosis of *E. coli*

Pegfilgrastim = pegylated filgrastim

Filgrastim

Pegfilgrastim

- Helical bundle
- N-terminal End
- Polyethylenglycol (PEG)

18,800 Daltons

Molecular weight

Renal

Primary pathway of elimination

Daily

administration

39,000 Daltons

Via neutrophils

1x / CT-cycle
Pegfilgrastim: neutrophil-mediated elimination

**Pharmacokinetics: nephrectomised rats**

**Filgrastim 100 µg/kg**
- Control (n = 4)
- Nephrectomised (n = 3)

**Pegfilgrastim 100 µg/kg**
- Control (n = 4)
- Nephrectomised (n = 4)

**Concentration in plasma (µg/L)**

- Rapid decrease of plasma concentration
  - → Daily administration

- **Renal clearance**

- **Neutrophil-mediated clearance**

- **Longer half-life**
  - → Gavage only 1x/CT-cycle

Data on file, Amgen
Self-regulation by Pegfilgrastim

PK: distribution of protein therapeutics

- IV darbepoetin alfa (n = 11)
- IV r-HuEPO (n = 10)

Graph showing baseline-corrected serum concentration (ng/ml) over time after injection (hours).
Indirect-direct effects

**Pharmacokinetics**

Dose $\rightarrow$ Conc. vs. time

**Pharmacodynamics**

Conc. $\rightarrow$ Effect

**PK/PD**

Dose $\rightarrow$ Effect vs. time
PK/PD link model

Central compartment

Peripheral compartment

PD: models for protein therapeutics
Indirect effect models
PK/PD link model
DR- and CR-curves are useful predictors for clinical trials

Self-regulation by Pegfilgrastim

Where does this fit into?
Scaling techniques are used for interspecies prediction of PK curves.
Conclusion slide

• Overview on PK/PD
  – What does PK/PD mean for drug/body?
• PK: elimination of protein therapeutics
  – To degrade or not degrade… that is…
• PK: distribution of protein therapeutics
  – Binding to the plasma proteins or what?
• PD: models for protein therapeutics
• PD/PK link models
  – Dry matters