UNDERSTANDING PHARMACOKINETICS IN VIROLOGY

Antiviral treatment plans may require particular understanding of and attention to pharmacokinetics (PK):[1]

- Rapid viral replication can affect the timing of therapeutic intervention.[1-3]
- PK concepts, such as lag period and clearance rates, become critical with viruses that can replicate without clinical symptoms.[1,4,5]
- The goals of achieving the optimal therapeutic index and maintaining viral suppression can be aided by leveraging the PK concepts below.[1-5]

PHARMACOKINETICS

At its simplest, pharmacokinetics:[4,5]

- Defines the therapeutic goal of reaching and maintaining concentration of a drug such that there is a therapeutic response
- Balances a response with minimum toxicity
  - ▶ Strikes a balance within the “therapeutic index”
- Is governed by four important parameters: Bioavailability; Distribution; Clearance; and Elimination

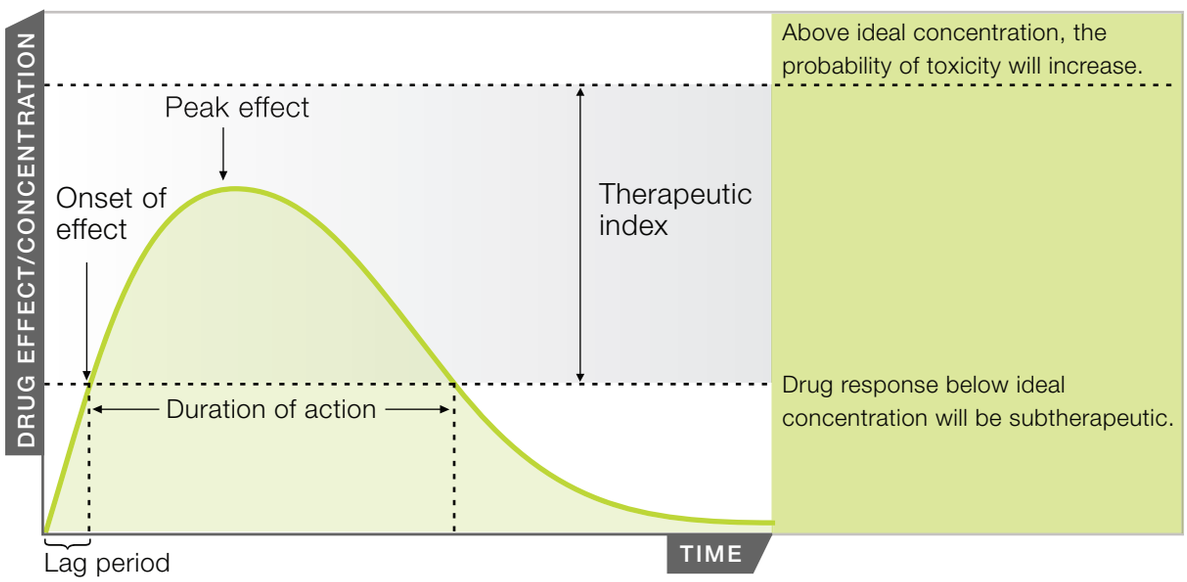
Dosage changes can modulate the drug’s effect by:[4]

- Shifting this response curve
- Increasing or decreasing the “duration of action”

The Area Under the Curve (AUC) can be:[4]

- Used to calculate clearance
- Used as a measure of bioavailability

This simplified graph shows the timing characteristics of these PK concepts:[4]



Adapted from:
Buxton IL, Benet LZ. in Goodman & Gilman's The Pharmacological Basis of Therapeutics.

UTILIZING PHARMACOKINETICS – DESIGNING DOSAGE STRATEGIES

A few examples of PK timing considerations are:[4,5]

- Lag period between dose administration and onset of effect
- Frequency of dosing
- Concentration of drug over a time course

The timing of drug concentration changes are determined by absorption, distribution, clearance and elimination.[4,5]

- Absorption rates can vary (e.g., slow-release formulations)
- Absorption rates affect how much drug is in the plasma and when it's there

Distribution[4,5]

- Relates the amount of drug in the body tissues to the concentration of drug in the systemic circulation[4,5]
- Influenced by a number of biological factors

Clearance is the measure of a body's efficiency of eliminating a drug from systemic circulation. Elimination is the reduction of drug in the body over time.[4,5]

- Clearance estimates are measured using sampling (testing blood levels) during steady-state regimens
- Sampling is done just before the next planned dose
- Blood levels and clearance affect timing of next dose

Simplified Linear PK Process

SUMMARY

Clinical pharmacokinetics provides:[4,5]

- Quantitative relationship between dose and effect
- Information on how to dose to the highest therapeutic effect within the lowest toxicity levels and at the right time intervals

1. Baden LR, Dolin R. Chapter 178. Antiviral Chemotherapy, Excluding Antiretroviral Drugs. In: Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson JL, Loscalzo J, eds. Harrison's Principles of Internal Medicine. 18th ed. New York: McGraw-Hill; 2012.
2. Wang F, Kieff E. Chapter 177. Medical Virology. In: Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson JL, Loscalzo J, eds. Harrison's Principles of Internal Medicine. 18th ed. New York: McGraw-Hill; 2011. http://www.accessmedicine.com/content.aspx?aID=9102816. Accessed November 4, 2011.
3. Levinson W. Chapter 29. Replication. In: Levinson W, ed. Review of Medical Microbiology and Immunology. 11st ed. New York: McGraw-Hill; 2011. http://www.accessmedicine.com/content.aspx?aID=6453915.Accessed November 4, 2011.
4. Buxton IL, Benet LZ. Chapter 2. Pharmacokinetics: The Dynamics of Drug Absorption, Distribution, Metabolism, and Elimination. In: Brunton LL, Chabner BA, Knollmann BC, eds. Goodman & Gilman's The Pharmacological Basis of Therapeutics. 12th ed. New York: McGraw-Hill; 2011. http://www.accessmedicine.com/content.aspx?aID=16658120. Accessed November 8, 2011.
5. Roden DM. Chapter 5. Principles of Clinical Pharmacology. In: Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson JL, Loscalzo J, eds. Harrison's Principles of Internal Medicine. 18th ed. New York: McGraw-Hill; 2012. http://www.accessmedicine.com/content.aspx?aID=9092427. Accessed November 19, 2011.

Genentech
A Member of the Roche Group