Nonlinear Pharmacokinetics & Capacity Dependent Clearance

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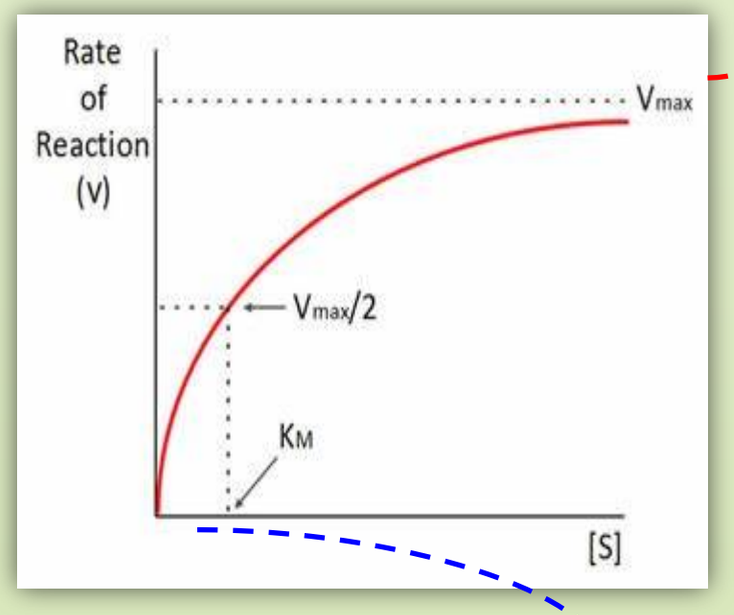
Dose Quantics

Clearance (CL) relates the rate of elimination of a molecule with its concentration in vivo. Many small molecules are cleared by enzymatic (metabolism) and transporter based mechanisms. Consequently, molecules cleared by these mechanisms tend to display Michaelis-Menten (MM) or saturable (capacity dependent) kinetics. When concentrations are much below Km, CL is constant (V_{max}/K_m), exposures increase linearly with dose. When concentrations are much higher than K_m, CL is saturated, exposures increase non-linearly with dose. This behavior can be distinguished when concentration and time are plotted on log-linear scale. This has implications in understanding dose-exposure-response relationships in pharmacology and toxicology.

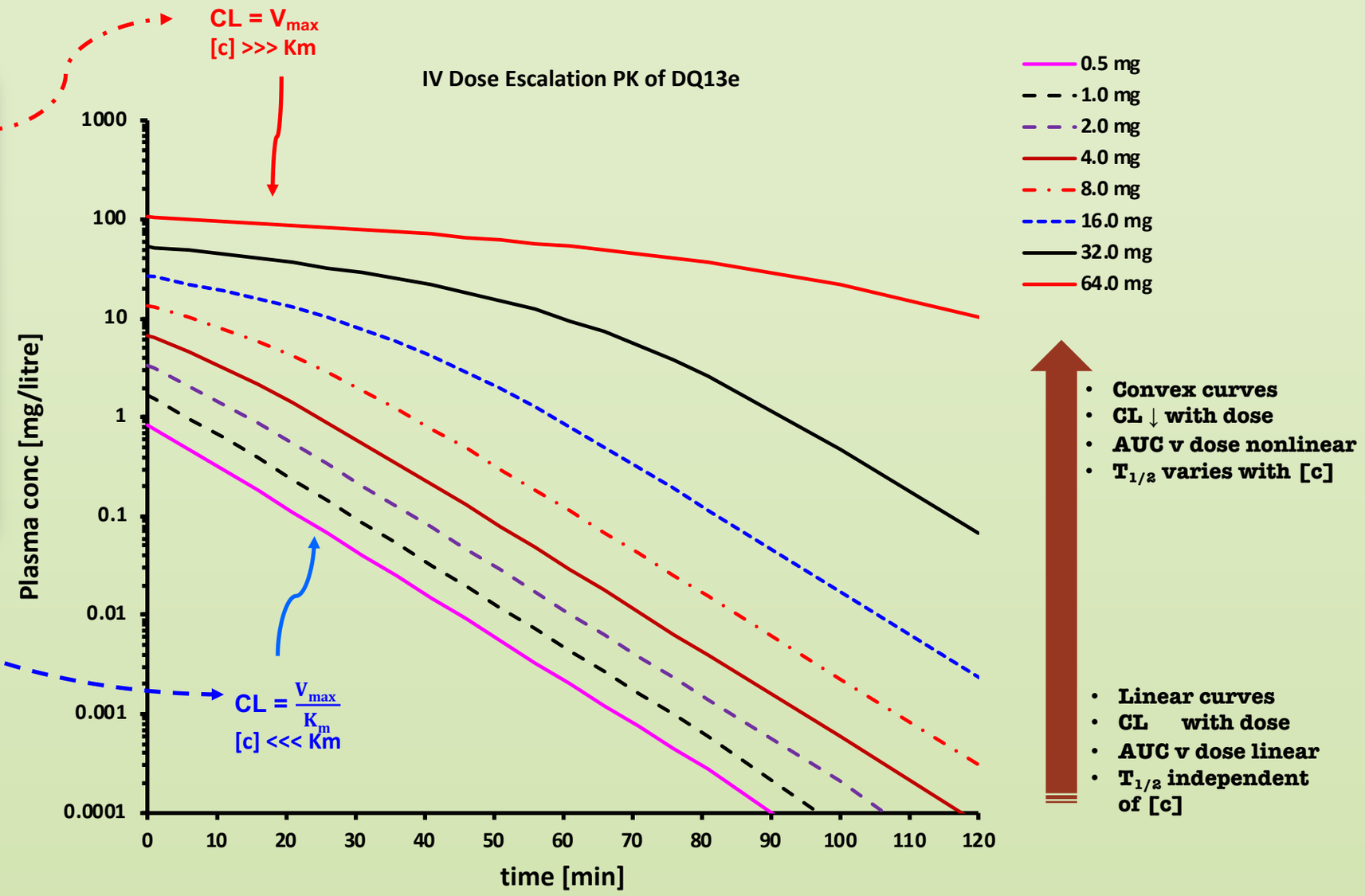


Rate of elimination

$(dc/dt) = - k * c$

$$k = - \frac{CL}{V}$$

$$CL = [\frac{V_{max}}{K_m + C}] * c$$



Gabrielsson J & Weiner D. Pharmacokinetic and Pharmacodynamic data analysis: Concepts & Applications. 3rd ed. Swedish Pharmaceutical Press