Q17 September 2009
Explain the difference and clinical relevance, between zero and first order kinetics. Give an example that is relevant to Intensive Care practice.

First order kinetics

- Constant fraction of drug in the body is eliminated per unit time
- This is because elimination pathways (e.g. metabolising enzymes) are usually not saturated
- Clearance = Rate of elimination/Concentration of drug (c)
- Clearance for a particular drug remains constant over the whole range of drug concentrations encountered clinically
- Therefore if clearance is constant, the rate of elimination is directly proportional to the drug concentration
- Absolute rate of elimination of the drug is a linear function of its plasma concentration; whereas plasma concentration vs. time is an exponential decay graph

Zero order kinetics

- Constant amount of drug is eliminated per unit time
- Occurs when elimination pathways become saturated
- Clearance varies with the concentration of the drug
- Clearance = $V_m/K_m + c$
    - V_m is the maximal rate of elimination
    - K_m is the concentration at which half the maximal rate of elimination is reached (i.e. concentration at which 50% of V_m is reached)
- At concentrations high relative to K_m, the elimination rate is almost independent of concentration
- If dosing rate exceeds elimination capacity, the concentration will keep rising as long as dosing continues
- Drugs with a target concentration greater than K_m have a narrow therapeutic window and a variable half-life; therefore need therapeutic monitoring

Clinical relevance

- In first order kinetics, some drugs are cleared very readily by the organ of elimination:
    - Elimination depends primarily on the rate of drug delivery to the organ (i.e. high extraction ratio)
- Phenytoin
    - Metabolism becomes saturated in the therapeutic concentration range
    - Changes to zero order kinetics
    - Half-life varies from 7-42 hours
    - Requires dose monitoring