

Loading Dose and Maintenance Dose in Therapy

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In critical care medicine, the goal is to deliver therapeutic drug concentrations rapidly in blood and then maintain therapeutic concentrations for extended durations for optimum therapeutic outcome. Oral dosing has the disadvantage of not being able to rapidly achieve therapeutic concentrations in blood due to delay in absorption and bioavailability issues. IV infusion to reach steady state concentrations can take time depending on the elimination half-life of drug. A combination of IV loading dose and maintenance dose (IV/oral) can meet this specific objective.

The requirement for an antibiotic is to maintain 0.25 - 0.5 µg/ml concentration for a period of 4 h to rapidly control infection. Given its PK parameters, MTD is 5000 µg/kg, how can one design a dose and regimen to achieve this goal?

PK Parameters

Parameter	Estimate
B t _{1/2} (h)	2.984
C _{max} (ug/ml)	26.225
V ₁ (ml/kg)	1143.93
CL (ml/h/kg)	1209.72
V _{ss} (ml/kg)	3962.25
V ₂ (ml/kg)	2818.32
CLD2 (ml/h/kg)	2135.71

Steady state concentration is determined by dosing rate and systemic clearance

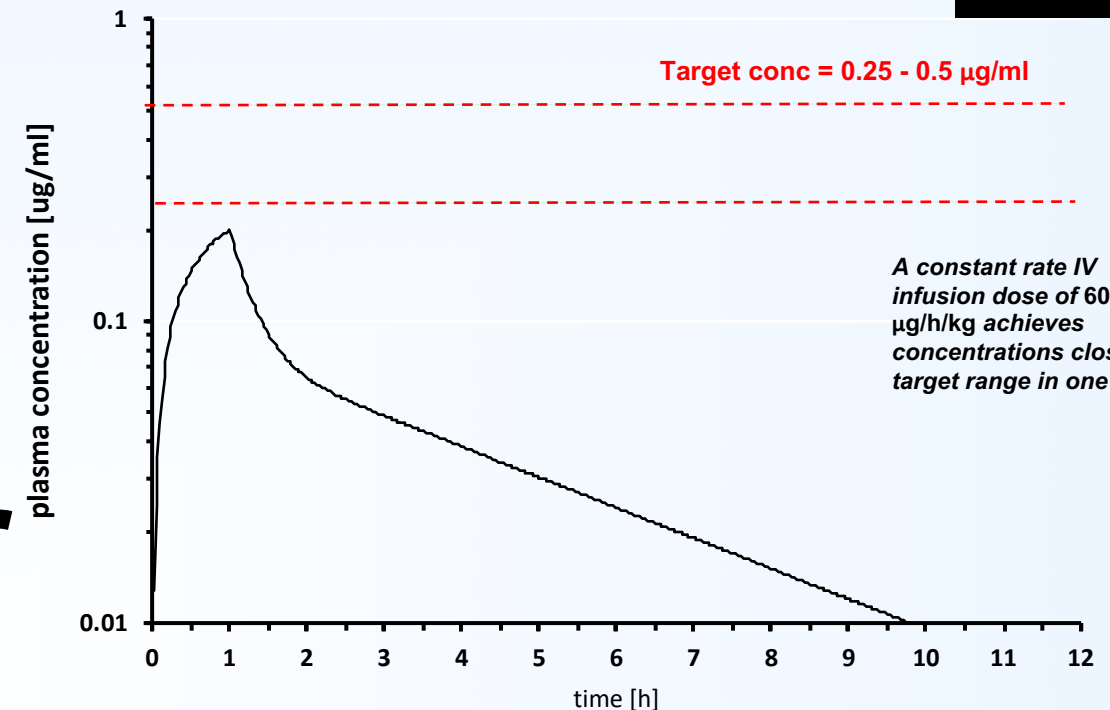
$$C_{ss} = \frac{\text{Dosing rate}}{\text{Clearance}}$$

$$\begin{aligned}\text{Dosing rate} &= C_{ss} * \text{Clearance} \\ &= 0.5 \mu\text{g/ml} * 1209 \text{ ml/h/kg} \\ &= 604.5 \mu\text{g/h/kg}\end{aligned}$$

Simulation suggests ~ 0.2 µg/ml is achieved at 1 h by infusing drug for 1 h at 604.5 µg/kg

1 h constant rate infusion dose to achieve target concentration

IV infusion

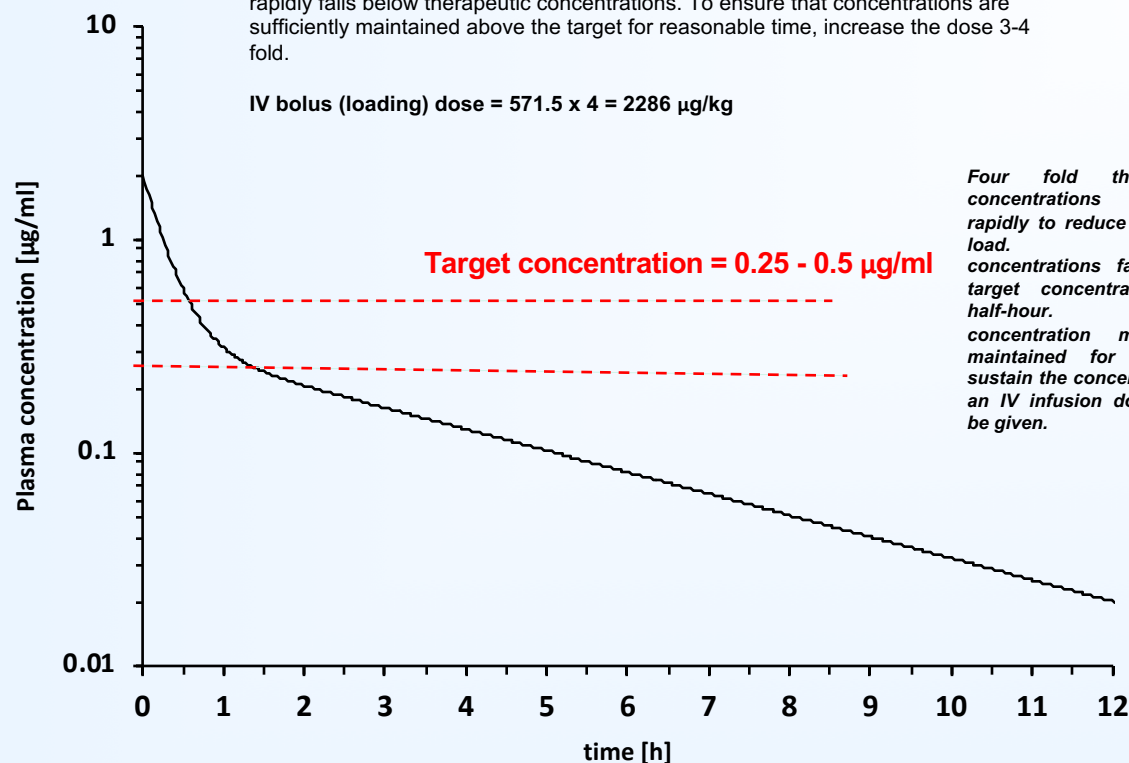


$$\begin{aligned}\text{Dose} &= V_c \times \text{target Concentration} \\ &= 1143 \text{ ml/kg} \times 0.5 \mu\text{g/ml} \\ &= 571.5 \mu\text{g/kg}\end{aligned}$$

IV Bolus dose

Following an IV bolus dose the target concentration will be achieved rapidly but also rapidly falls below therapeutic concentrations. To ensure that concentrations are sufficiently maintained above the target for reasonable time, increase the dose 3-4 fold.

$$\text{IV bolus (loading) dose} = 571.5 \times 4 = 2286 \mu\text{g/kg}$$



Loading dose (2286 ug/kg)+ Maintenance dose (604.5 ug/h/kg) for 4 h to maintain steady state concentrations

IV Loading + Maintenance Dose

