

# Pharmacokinetic Basis of Dose Fractionation in Anti-infective Pharmacology

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Dose fractionation (DF) is an experimental method used to identify the pharmacokinetic/pharmacodynamic (PK/PD) index of an anti-bacterial molecule. Two non-compartmental PK parameters  $C_{max}$  and AUC, in addition to time above a threshold concentration and in vitro potency (e.g. MIC) are the basis for determining the PK/PD index that best describes the pharmacodynamics of the molecule. PK/PD index and magnitude are used to assess the probability of attainment of target through phase 1, 2, 3 clinical trials which ultimately help in defining optimum dose and regimen in patients. The objective of DF is to decrease the correlation between the three PK/PD indices so that the index best associated with efficacy is clearly identified. The requirement of DF is that the molecule should show linear PK in the dose range studied. The PK basis for DF is illustrated with DQ5, an antibacterial molecule with MIC = 1  $\mu\text{g/ml}$  on a pathogen. DQ5 shows linear PK between 1 and 10 mg/kg oral doses.

## Oral PK parameters of DQ5 in mice @ 10 mg/kg

1 <sup>o</sup> Parameter	Estimate
V/F [ml/kg]	1392.5
$K_a$ [ $\text{h}^{-1}$ ]	1.413
$K_e$ [ $\text{h}^{-1}$ ]	0.200
2 <sup>o</sup> Parameter	Estimate
AUC [ $\mu\text{g}\cdot\text{h/ml}$ ]	35.9
$t_{1/2, K_a}$ [h]	0.49
$t_{1/2, K_e}$ [h]	3.47
CL/F [ml/h/kg]	278.5
$T_{max}$ [h]	1.61
$C_{max}$ [ $\mu\text{g/h}$ ]	5.20

## PK parameters of DQ5 in mice when 10 mg/kg given as 1, 2, 3 & 4 equally divided doses in 24 h

Dose [mg/kg]	Regimen	AUC [ $\mu\text{g}\cdot\text{h/ml}$ ]	$C_{max}$ [ $\mu\text{g/ml}$ ]
10	1 dose	35.9	5.2
5	2 doses	35.9	2.6
3.3	3 doses	35.9	1.72
2.5	4 doses	35.9	1.3

AUC is the same for 10 mg/kg when administered as 1,2,3,4 equally divided doses.  $C_{max}$  decreases with increasing dose frequency

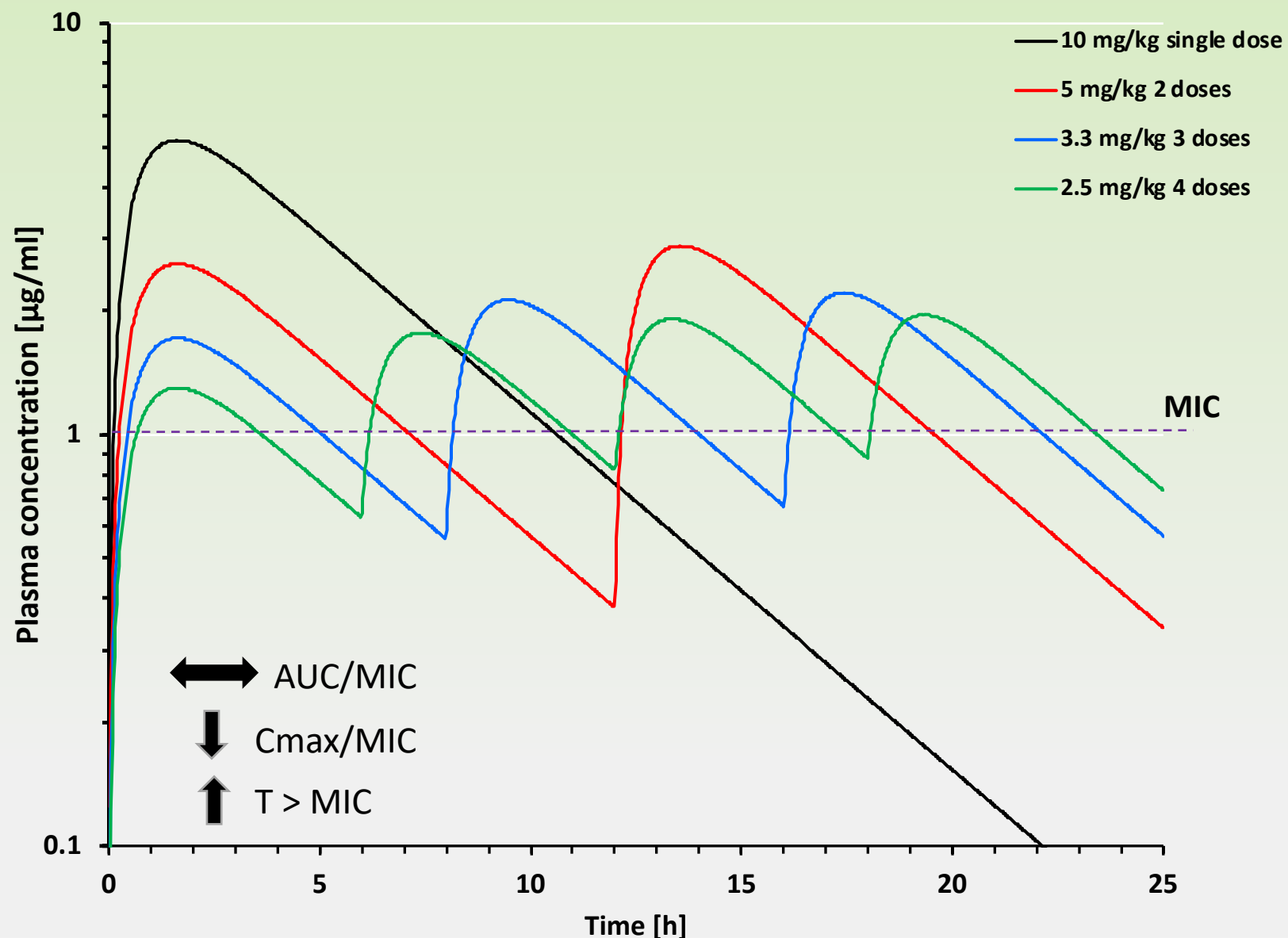
PK/PD ratios of DQ5 estimated for total dose 10 mg/kg administered as 1, 2, 3, 4 equally divided doses

## Magnitude of PK/PD indices of DQ5 following DF of TD = 10 mg/kg

Dose [mg/kg]	Regimen	AUC/MIC	$C_{max}/MIC$	$t > MIC$ [h]
10	1 dose	35.9	5.2	10.5
5	2 doses	35.9	2.6	14.5
3.3	3 doses	35.9	1.72	17
2.5	4 doses	35.9	1.3	19.5

When a TD of 10 mg/kg is fractionated, the magnitude of AUC/MIC is the same for all the doses,  $C_{max}/MIC$  decreases,  $t > MIC$  increases with increasing dose frequency

## Principle of Dose Fractionation : DQ5 total dose 10 mg/kg fractionated in infected mice



By fractionating several total doses, the PK/PD index that best describes the efficacy of an antibacterial agent can be identified. DF is simple when dosing interval is greater than  $t_{1/2}$  of molecule (accumulation does not occur). However if dosing interval is lesser than  $t_{1/2}$ , accumulation can occur with differing peak concentrations within a dosing regimen, and this has to be factored when performing DF analysis.