Pharmaco Kinetic and Dynamic (PK/PD) Approach to Antibiotic Therapy

Introduction

1. **Pharmacokinetics (PK)** is concerned with **the time course of antimicrobial concentrations in the body**
2. P**harmacodyamics (PD)** is concerned with **the relationship between those concentrations and the antimicrobial effect.**

Antibiotic dosing regimens have traditionally been determined by PK parameters only. However, PD plays an equal, if not more important, role. With increasing antimicrobial resistance, PD becomes even more important because these parameters may be used to design dosing regimens which counteract or at least help prevent resistance.

Discussion

The primary measure of antibiotic activity is the minimum inhibitory concentration (MIC). The **MIC** is the lowest concentration of an antibiotic that completely inhibits the growth of a microorganism in vitro.

While the MIC is a good indicator of the potency of an antibiotic, it indicates nothing about the time course of antimicrobial activity.

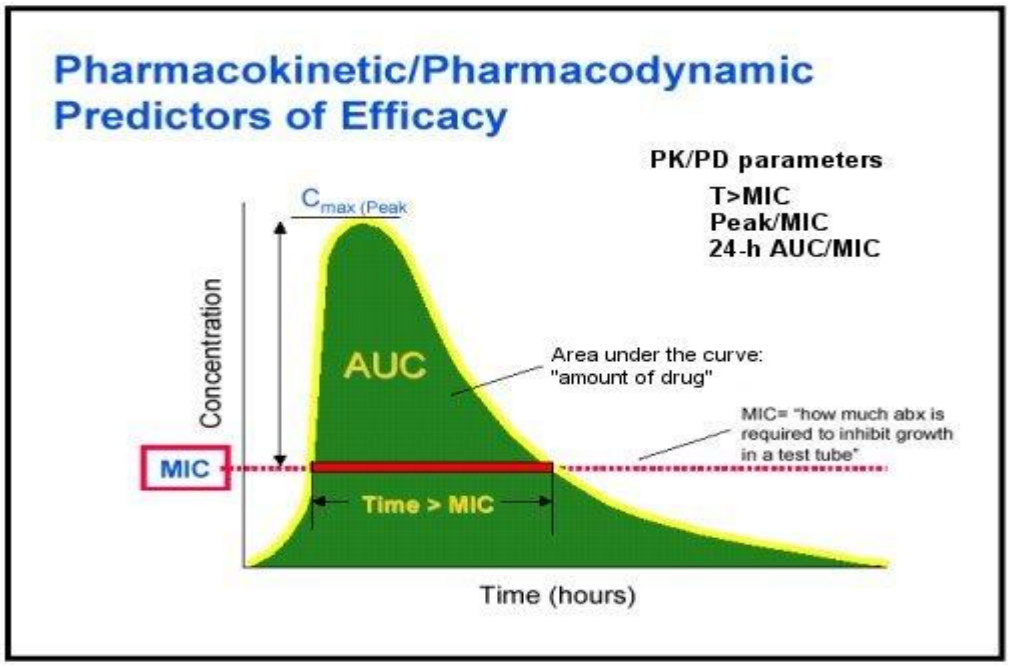
PK parameters quantify the serum level time course of an antibiotic.
The three pharmacokinetic parameters that are most important for evaluating antibiotic efficacy are

a. **peak serum level (Cmax)**
b. **trough level (Cmin)**
c. **Area Under the serum concentration time Curve (AUC)**

While these parameters quantify the serum level time course, they do not describe the killing activity of an antibiotic.

Integrating the PK parameters with the MIC gives us three PK/PD parameters which quantify the activity of an antibiotic: 1. **Peak/MIC ratio** 2. **T>MIC** 3. **24h-AUC/MIC ratio**

- The Peak/MIC ratio is the Cpeak max divided by the MIC
- The T>MIC (time above MIC) is the percentage of a dosage interval in which the serum level exceeds the MIC
- The 24h-AUC/MIC ratio is determined by dividing the 24-hour-AUC by the MIC.



Antimicrobial Parameters

The three pharmacodyamic properties of antibiotics that best describe killing activity are

1. **time-dependence**
2. **concentration-dependence**
3. **persistent effects**

The rate of microbial killing is determined by either
- the length of time necessary to kill (time-dependent), or
- the effect of increasing concentrations (concentration-dependent).
- Persistent effects include the **Post-Antibiotic Effect (PAE)**. PAE is the persistent suppression of bacterial growth **following** antibiotic exposure.

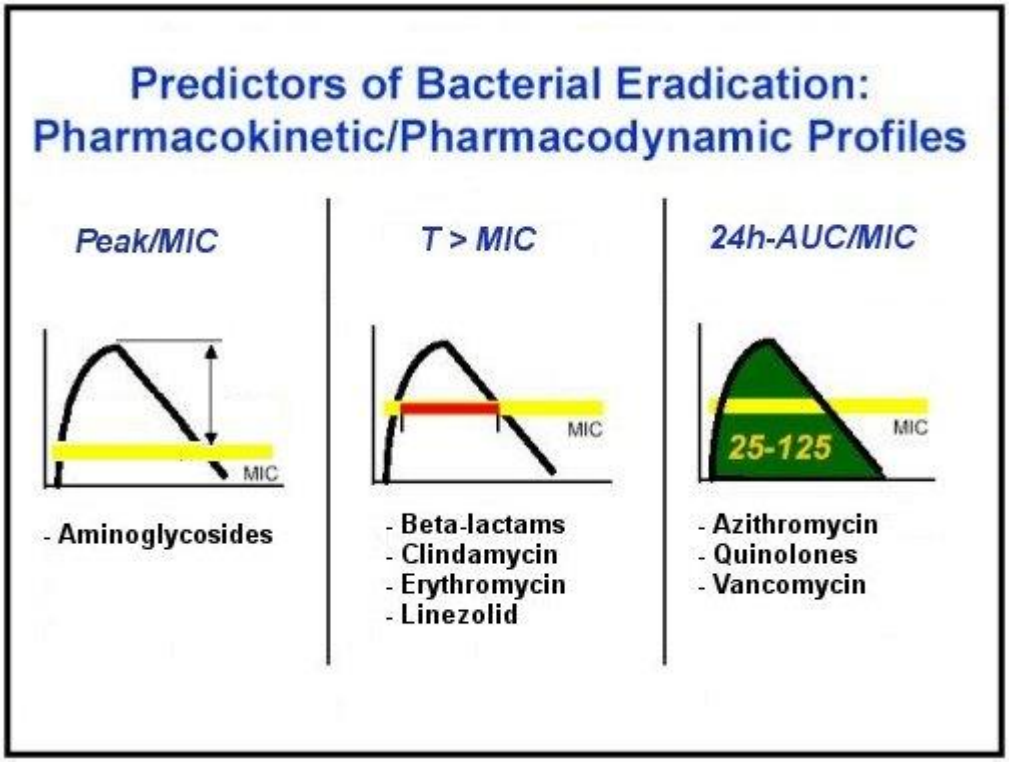
Using these parameters, antibiotics can be divided into 3 broad categories:

Pattern of Activity	**Antibiotics**	**Goal of Therapy**	**PK/PD Parameter**
Concentration-dependent killing and Prolonged persistent effects (PAE)	Aminoglycosides Daptomycin Fluoroquinolones Ketolides	Maximise concentrations	24h-AUC/MIC Peak/MIC
Time-dependent killing and Minimal persistent effects	Carbapenems Cephalosporins Erythromycin Linezolid Penicillins	Maximise duration of exposure	T>MIC
Time-dependent killing and Moderate to prolonged persistent effects.	Azithromycin Clindamycin Oxazolidinones Tetracyclines Vancomycin	Maximise amount of drug	24h-AUC/MIC

For c**oncentration-dependent** antibiotics (aminoglycosides, fluoroquinolones, daptomycin and the ketolides), the ideal dosing regimen would **maximise concentration**, because the higher the concentration, the more extensive and the faster is the degree of killing. Therefore**, the 24h-AUC/MIC ratio, and the Peak/MIC ratio are important predictors of antibiotic efficacy**. For aminoglycosides (e.g. gentamicin), aim for a **Peak/MIC ratio of at least 8-10 to optimise efficacy and prevent resistance.** (NB toxicity issues to those people being treated are measured by trough levels). The ideal 24h-AUC/MIC ratio for FQ's varies widely in the literature.

Time-dependent antibiotics (beta-lactams, clindamycin, erythromcyin, and linezolid) demonstrate the complete opposite properties. The ideal dosing regimen for these antibiotics maximises the **duration** of exposure. The T>MIC is the parameter that best correlates with efficacy. For beta-lactams and erythromycin, maximum killing is seen when the time above MIC is at least 70% of the dosing interval.

Time-dependent and prolonged PAE antibiotics (vancomycin, tetracyclines, azithromycin, and the dalfopristin-quinupristin combination) have mixed properties, they have time-dependent killing and moderate persistent effects. The ideal dosing regimen for these antibiotics maximises the **amount** of drug received. Therefore, the 24h-AUC/MIC ratio is the parameter that correlates with efficacy. For vancomycin, a 24h-AUC/MIC ratio of at least 125 is necessary (some researchers recommend a ratio of 400 or more for problem microbes).



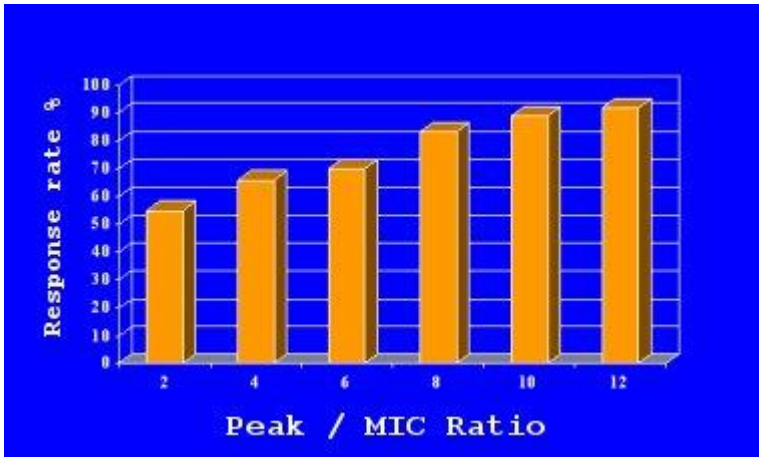
Outcome studies:

Aminoglycoside concentration dependent Pharmacodynamics in Vivo

Initial serum peak level	**Died**	**Survived**
< 5mcg/ml	**21%**	**79%**
>= 5mcg/ml	**2%**	**98%**

i.e. increasing aminoglycoside concentration peak maximises efficacy. Moore et al, J Infect Dis 149: 443, 1984

Aminoglycoside concentration dependent Pharmacodynamics in Vivo



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Vancomycin Outcome vs **24h-AUC/MIC** ratio

24h-AUC/MIC ratio	**Satisfactory**	**Unsatisfactory**
< 125	4 (**50%**)	4
> 125	71 (**97%**)	2

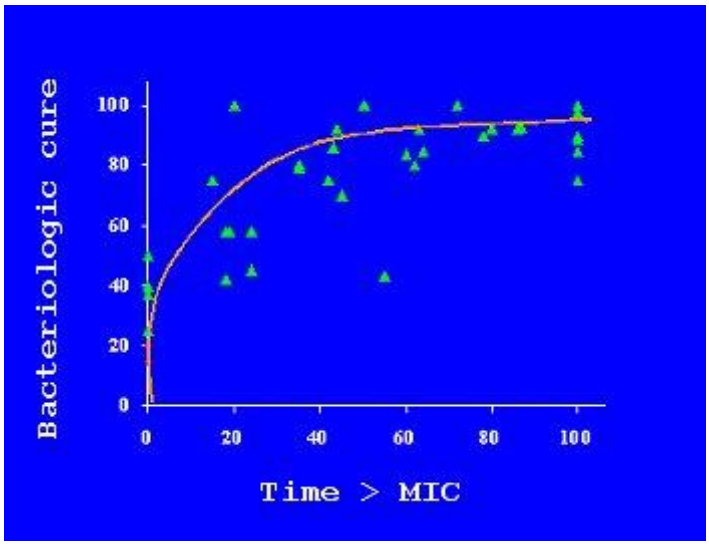
Hyatt et al, Clin Pharmacokinet 28: 143, 1995

Fluoroquinolone Pharmacodynamics vs S. pneumoniae

24h-AUC/MIC ratio	**Microbiological Response**
< 33.7	(**64%**)
> 33.7	(**100%**)

Ambrose et al, Antimicrob Agents Chemo 10: 2793, 2001

Pharmacodynamics of Beta-Lactams and Macrolides in Otitis Media



Craig et al, Ped Infect Dis 15: 255, 1996

Conclusion

PK dosing has shown us that one dose is not appropriate for all patients.

Pharmacodynamics shows us that one target level is not appropriate for all patients. We need to evaluate both the serum level data and the MIC, taking into consideration the PD properties of the antimicrobial.

Numerous outcome studies have shown that class-appropriate PK/PD parameters are excellent predictors of antibiotic efficacy.

References http://www.rxkinetics.com/antibiotic_pk_pd.html (edited)

Ben Harris, Infection Prevention & Control, Canterbury Southern Community Laboratories **June 2015**