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Pharmacokinetic/Pharmacodynamic (PK/PD) Based Approach to Lead Optimization in Discovery Programs

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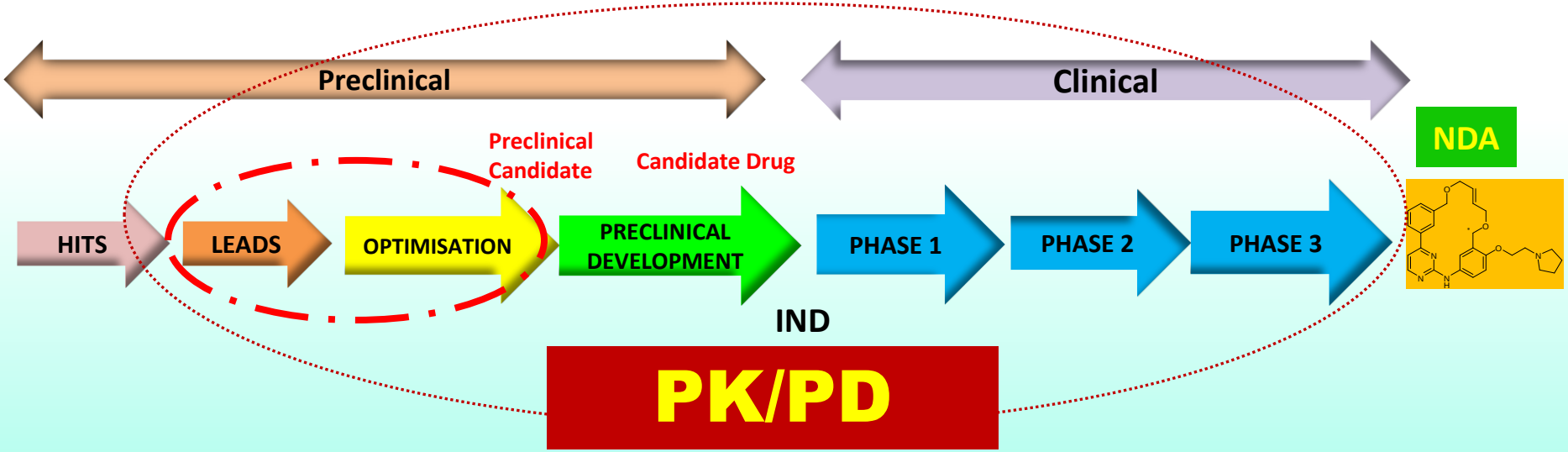
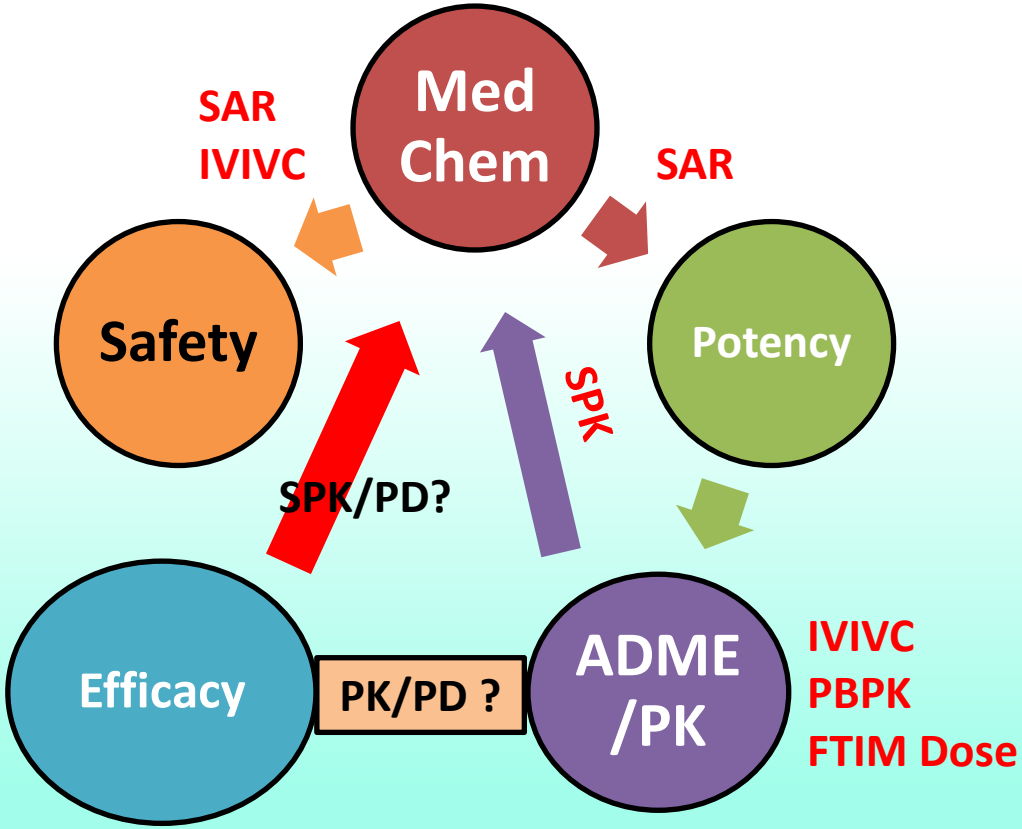
PK/PD in Drug Discovery



Lead Optimization Process



Lead:

- **How is PK related to Efficacy?**
- **Optimum PK = Optimum Efficacy?**
- **Quantitation of PK/PD**
  - ❑ **Dose?**
  - ❑ **Frequency?**
  - ❑ **Duration?**

Intrinsic Pharmacodynamics

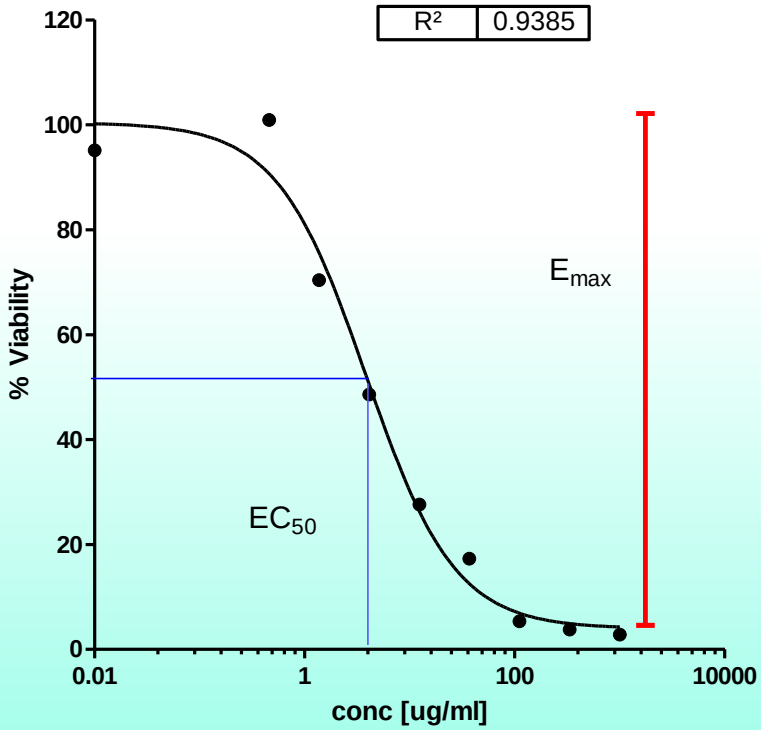
In vitro

- ❑ Enzyme/receptor
- ❑ Cells

Intrinsic Efficacy [E_{max}]

$$E = \frac{E_{max} \cdot C_{ss}^{N}}{C_{50\%}^{ss\,N} + C_{ss}^{N}}$$

Potency [EC_{50}]



In vivo

1. What dose?

✓ **Dose (PK) response**

2. What frequency?

✓ **Time course of response**

3. Duration of dosing to achieve maximum effect?

✓ **Based on 1 and 2**

E_{max} and EC_{50} *in vivo*

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TUBERCULOSIS: DISCOVERY OF ANTI-TB COMPOUNDS

Murine Model : Tuberculosis

M. Tuberculosis [H37Rv]

Aerosol infection

4 week post infection

Treatment : 3 - 4 weeks

Termination: lungs homogenized, plated

Bacteria/lung (3 weeks)

PK/PD Based Evaluation of compounds

- ❑ **SOC Drugs - Rifampicin, INH : PK/PD = AUC/MIC**
- ❑ **Four Fluoroquinolones**
  - **Analogues**

Jayaram et al. Antimicrobial Agents And Chemotherapy, July 2003, p. 2118–2124

Potency, PK : Fluoroquinolones

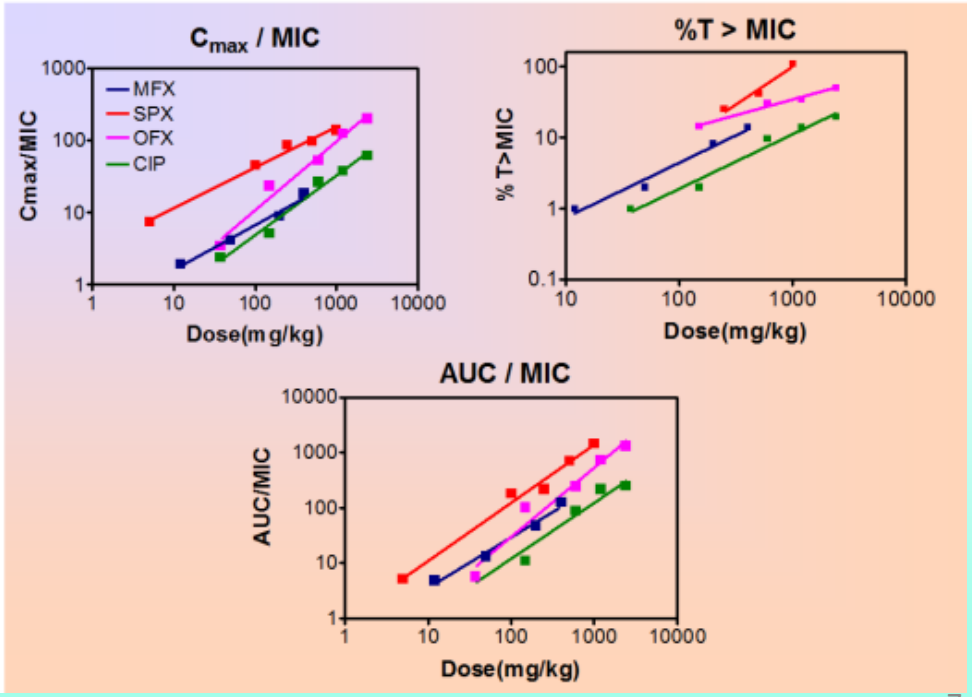
- Moxifloxacin (MFX)
- Sparfloxacin (SPX)
- Ofloxacin (OFX)
- Ciprofloxacin (CIP)

MINIMUM INHIBITORY CONC [mg/L]

	Mfx	Spx	Ofx	Cip
Broth	0.5	0.1	0.5	0.5
Serum	0.5	0.2	0.5	0.5
Intracellular	1.0	0.5	2.0	4.0

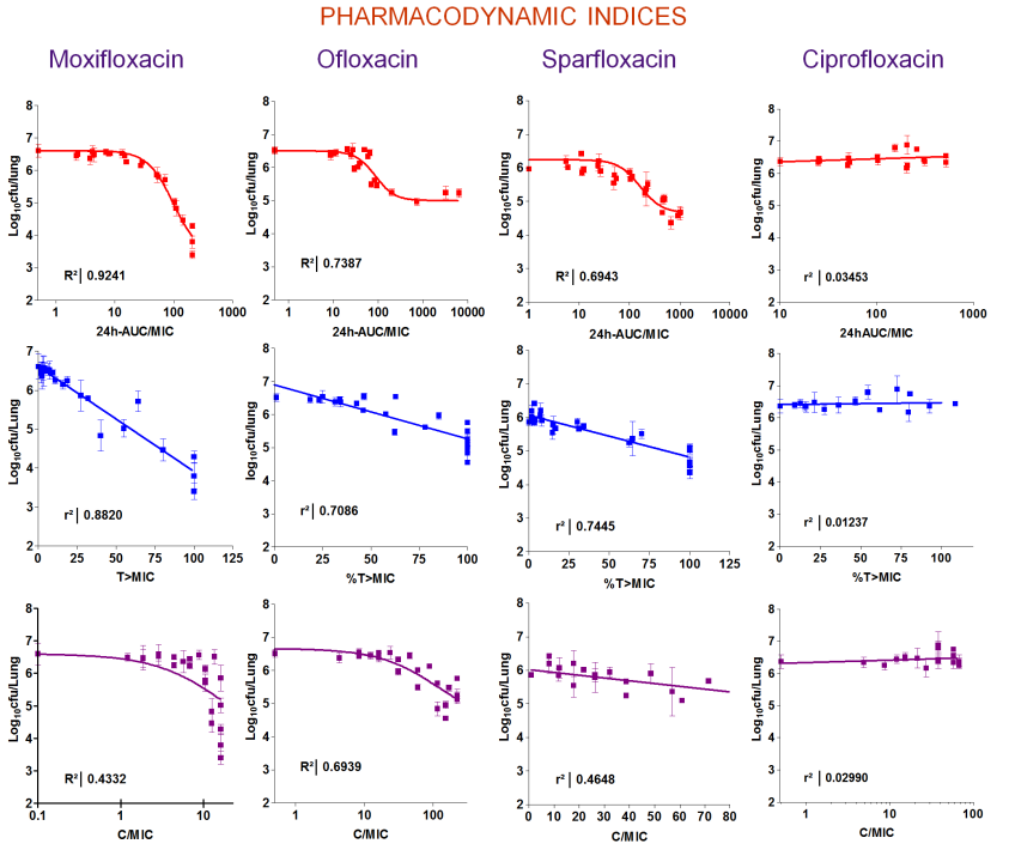
Oral Plasma PK in Mice

DOSE PROPORTIONALITY



Shandil et al Antimicrobial Agents And Chemotherapy, Feb. 2007, p. 576–582

PK/PD Relationships



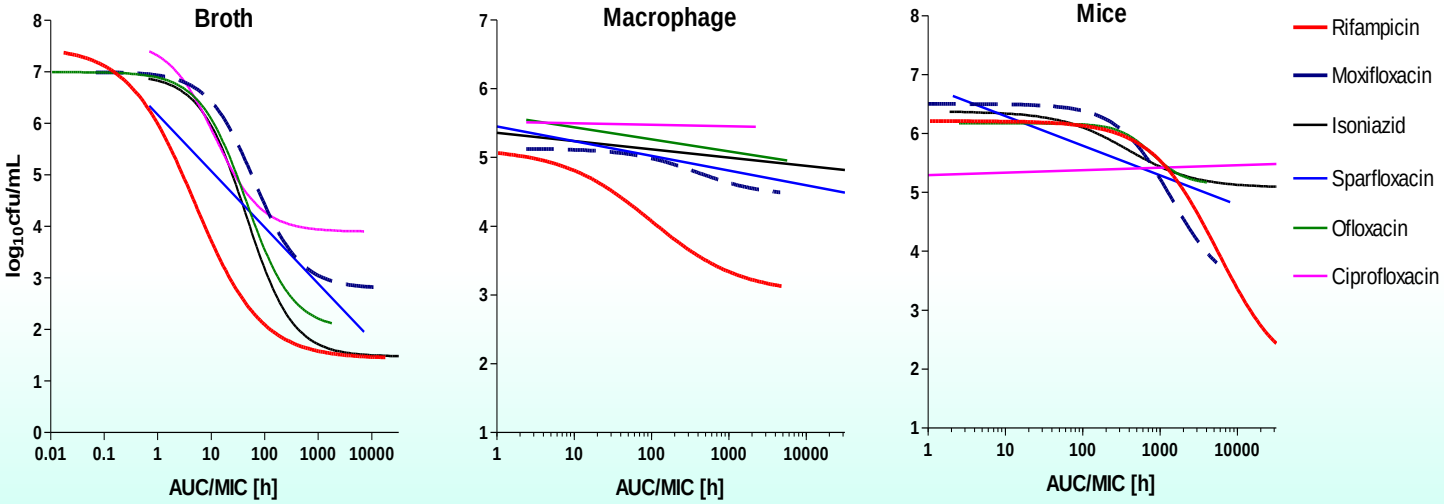
In vivo Bactericidal Effect

	E_{max}	EC_{50} - AUC_{24}/MIC
MFX	3.2	97.2
OFX	1.5	87.7
SPX	1.3	164.5
CIP	0	nd

- ❑ **AUC/MIC correlated with Efficacy**
- ❑ **Different Efficacies**
- ❑ **Similar Potencies**

Shandil et al Antimicrobial Agents And Chemotherapy, Feb. 2007, p. 576–582

In vitro-in vivo Pharmacodynamic Correlations



Learning from Fluoroquinolones:

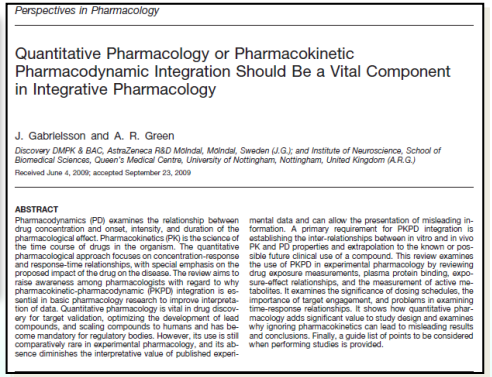
- ❑ **Plasma PK + intracellular kill predictive of efficacy**
- ❑ **E_{max} different but EC_{50} similar for members of same class**

Conclusions:

- ❑ **Design analogues based only on MIC, intracellular potency and PK**
- ❑ **All compounds need not be tested in lengthy animal model: Quicker turnaround**
- ❑ **PK/PD approach saves time and resources for optimization phase**

Advantages of Intrinsic Pharmacodynamics

- **Rank order compounds based on Intrinsic Efficacy - E_{max}, EC_{50}**
  - ➢ **Factors PK and PD properties of compound**
  - ➢ **Best PK ≠ Best Efficacy?**



Perspectives in Pharmacology

Quantitative Pharmacology or Pharmacokinetic Pharmacodynamic Integration Should Be a Vital Component in Integrative Pharmacology

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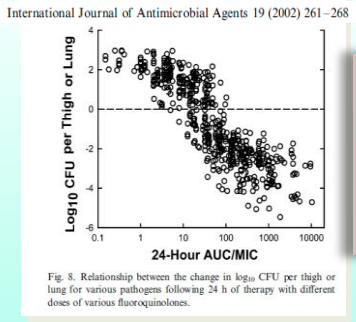
ABSTRACT

Pharmacodynamics (PD) examines the relationship between drug concentration and onset, intensity, and duration of the pharmacological effect. Pharmacokinetics (PK) is the science of the time course of drugs in the organism. The quantitative pharmacological approach focuses on concentration-response and response-time relationships, with special emphasis on the proposed impact of the drug on the disease. The review aims to raise awareness among pharmacologists with regard to why pharmacokinetic-pharmacodynamic (PKPD) integration is essential in basic pharmacology research to improve interpretation of data. Quantitative pharmacology is vital in drug discovery for target validation, optimizing the development of lead compounds, and scaling compounds to humans and has become mandatory for regulatory bodies. However, its use is still comparatively rare in experimental pharmacology, and its absence diminishes the interpretative value of published experimental data and can allow the presentation of misleading information. A primary requirement for PKPD integration is establishing the inter-relationships between in vitro and in vivo PK and PD properties and extrapolation to the known or possible future clinical use of a compound. This review examines the use of PKPD in experimental pharmacology by reviewing drug exposure measurements, plasma protein binding, exposure-effect relationships, and the measurement of active metabolites. It examines the significance of dosing schedules, the importance of target engagement, and problems in examining time-response relationships. It shows how quantitative pharmacology adds significant value to study design and examines why ignoring pharmacokinetics can lead to misleading results and conclusions. Finally, a guide list of points to be considered when performing studies is provided.

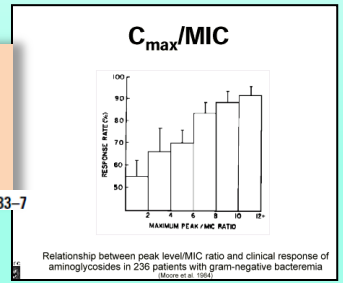


International Journal of Antimicrobial Agents 19 (2002) 261–268

Fig. 8. Relationship between the change in $\log_{10}$ CFU per thigh or lung for various pathogens following 24 h of therapy with different doses of various fluoroquinolones.

- **Predicting effect of subsequent compounds [LO phase] based on PK & Potency**
  - ➢ **compounds from same class act on same target**
  - ➢ **Useful for long term efficacy models**

- **Scalability of PK/PD to Humans**
  - ➢ **Set Exposure and Dose needed to achieve maximum efficacy in the Clinic**



C_{max}/MIC

Relationship between peak level/MIC ratio and clinical response of aminoglycosides in 236 patients with gram-negative bacteremia (Moore et al. 1984)

Clinical Infectious Diseases 2001; 33(Suppl 3):S233–7

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