Antimicrobial PK/PD Predictions

Considering PK Relative to MIC Works

David Andes
University of Wisconsin
Why do we conduct PK-PD infection models?
Improving the Probability of Positive Outcome
What do we do?
Tie Drug Potency to Antimicrobial Exposure = Pharmacodynamics

MIC = minimum inhibitory concentration; AUC = area under the curve; T = time
In vivo PK/PD Work Horse (Mouse)

- Murine thigh and lung models
  - Mimics soft tissue/sepsis and pneumonia, respectively
  - Neutropenic
  - Organism burden primary endpoint
  - Supports growth of most bacteria
  - Multiple drug administration routes
  - Large group of comparator antibacterial agents
  - Outcomes correlated with treatment success in patients
  - Useful for trial dosing regimen selection and susceptibility breakpoint development
Typical Study Design

Immunosuppress D-4, D-1

Organism Preparation D-1, H-12

Infect, 100 µl thigh
50 µl lung

Antibiotic Therapy

-2 hr

Pharmacodynamic Analysis

Bacterial Burden Assessment
How do we define the PK/PD target?

Dose Level
Nonlinear regression and
Hill equation to estimate
Emax (difference from
untreated control), P_{50}
(dose giving 50% of
Emax) and slope (N) of
the dose-response
relationship

\[ \Delta \text{CFU} = \frac{(\text{Emax}) \cdot \text{Dose}^N}{\text{Dose}^N + P_{50}^N} \]

Introduce additional isolates, preferably with MIC variation
Does MIC Help Define the PK/PD Target
Impact of MIC Variation on the PK/PD Target

MIC (mg/L)

0.008 0.03 0.12 0.5 2 8

T>MIC (%)

0 10 20 30 40 50

- Cephalosporins
- Penicillins
- Carbapenems

N=65, >1000 X MIC range

MIC Variability
Impact of Resistance and ESBL Production

N=20 organisms, 4 cephalosporins

MIC is Helpful for Defining the PK/PD Target - EXCEPT
Impact of Organism Fitness

Strain 1 SD 2.9
Strain 2 SD 35
Control 1 0.98 log
Control 2 2.18 log

Less than 1 log Δ in growth
= 10-fold Δ in PD target
Murine infection model PK/PD can be used to forecast effective regimens in patients
Despite:

- Different doses (mg/kg)
- Faster half-life in small animals

BUT:

- Drug target is in the organism and NOT the host
- Exposure relative to MIC is the determinant
PK-PD INFECTION MODELS
Do They Forecast Success?

• Relationship between the regulatory approval and the probability of pre-clinical PK-PD target attainment
  o The study period was December 1996 through 2011

• Indications included community- and hospital-acquired pneumonia
  o For CAP, *S. pneumoniae* was the index pathogen
  o For HAP, the index pathogen was antibiotic spectrum dependent
  o 14 antibiotics that gained regulatory approval and 6 that failed to gain approval

- Cefditoren
- Ceftarolene
- Ceftobiprole
- Daptomycin
- Doripenem
- Ertaopenem
- Faropenem
- Garenoxacin
- Gatifloxacin
- Gemifloxacin
- Levofloxacine
- Linezolid
- Moxifloxacin
- Televanine
- Teillithromycin
- Tigecycline
- Trovafloxcin
PK-PD INFECTION MODELS

Do They Forecast Success?

The Answer: Yes! The probability of regulatory approval increases with the probability of PK-PD target attainment.

Note: PK-PD target was net-bacterial stasis in neutropenic mice for CAP agents and 1-2 log_{10} unit reduction in bacterial burden for HAP agents.
THANK YOU

Serum Drug Concentration

Peak:MIC

AUC:MIC Ratio

Time Above MIC

Time

“It all started with a mouse.” AND AN MIC
- Walt Disney and Bill Craig