24 years of ISAP: Achievements in the PK/PD field

A lecture In Memoriam Bill Craig

Paul M. Tulkens, MD, PhD
Former President of ISAP (1998-2000)

Invited Professor
Cellular and Molecular Pharmacology
Louvain Drug Research Institute
Health Science Sector
Université catholique de Louvain
Brussels, Belgium

ISAP Annual Meeting & post-ICAAC symposium
September 21, 2015, San Diego, CA, USA
Disclosures
(those who paid for our research and talks)

• Research grants
  – Theravance, Astellas, Targanta, Cerexa/Forest, AstraZeneca, Bayer, GSK, Trius, Rib-X, Eumedica
  – Belgian Science Foundation (*F.R.S.-FNRS*), Ministry of Health (*SPF*), and Walloon and Brussels Regions

• Speaking fees
  – Bayer, GSK, Sanofi, Johnson & Johnson, OM-Pharma, AstraZeneca

• Decision-making and consultation bodies
  – General Assembly (current) and steering committee (part) of the European Committee for Antibiotic Susceptibility Testing [EUCAST]
  – European Medicines Agency (external expert)
  – US National Institutes of Health (grant reviewing)
  – Belgian Antibiotic Policy Coordination Committee (BAPCOC)
What shall I talk you about?

From Stockholm 1989 …

W.A. Craig

EMA

lobbying

education

publications

1998

ECCMID 1991

ICAAC 2000

1999

ten clinical practice

lobbying
Disclaimer …

• This is a personal view …, and therefore not that of ISAP…

• I have certainly missed many points and forgotten many of the key actors…

• Most of what I'll show is based on public documents … which means that the reality could be different …

• Thanks to Johan Mouton for the many pictures of ISAP members…
Publications

Often the hard road

But try this!

And you get this

(phenocokinetic* OR pharmacodynamic*) AND (antibiotic* OR antifungal* OR antiviral* )

Results: 1 to 20 of 18850
Publications from 1946 to 2015 *

* PubMed search using (pharmacokinetic* OR pharmacodynamics*) AND (antibiotic* OR antiviral* OR antifungal*)

---

* 20 papers /year


% years

relative specific activity (% papers / % years)

911 papers /year

20 papers /year

---

* 20 papers /year


% years

relative specific activity (% papers / % years)

911 papers /year

20 papers /year

---

* PubMed search using (pharmacokinetic* OR pharmacodynamics*) AND (antibiotic* OR antiviral* OR antifungal*)
Publications from the earliest …

* PubMed search using (pharmacokinetic* OR pharmacodynamics*) AND (antibiotic* OR antiviral* OR antifungal*)
Publications from the earliest …

* PubMed search using (pharmacokinetic* OR pharmacodynamics*) AND (antibiotic* OR antiviral* OR antifungal*)
Publications from the earliest ...

* PubMed search using (pharmacokinetic* OR pharmacodynamics*) AND (antibiotic* OR antiviral* OR antifungal*)

Notes and Abstracts

Prepared by the Committee on Pharmacy and Therapeutics
University of Illinois College of Medicine, Chicago 12

THE ANTIBIOTICS: Pharmacodynamics and Principles of Therapy

1. PENICILLIN AND STREPTOMYCIN

* PubMed search using (pharmacokinetic* OR pharmacodynamics*) AND (antibiotic* OR antiviral* OR antifungal*)
Publications ... to the last ones

**AAC Accepted Manuscript Posted Online 8 September 2015**
Copyright © 2015, American Society for Microbiology. All Rights Reserved.

**Population pharmacokinetics of piperacillin in the early phase of septic shock – does standard dosing result in therapeutic plasma concentrations?**
Kristina Öbrink-Hansen¹#, Rasmus Vestergaard Juul¹, Merete Storgaard³, Marianne Kragh Thomsen⁵, Tore Forsingdal Hardle⁴, Birgitte Brock⁴, Mads Kreilgaard³, Jakob Gjedsted⁶

**AAC Accepted Manuscript Posted Online 8 September 2015**
Copyright © 2015, American Society for Microbiology. All Rights Reserved.

**Augmented renal clearance implies a need for increased amoxicillin/clavulanic acid dosing in critically ill children**
Pieter A.J.G. De Cock,¹,²,³# Joseph F. Standing,⁴,⁵,⁶ Charlotte I.S. Barker,⁴,⁷ Annick de Jaeger,⁵ Evelyn Dhont,⁵ Mieke Carlier,⁴ Alain G. Verstraete,⁵,⁶ Joris R. Delanghe,⁶,⁷ Hugo Robays,⁷ Peter De Paepe⁴

**Journal of Antimicrobial Chemotherapy Advance Access published September 7, 2015**
*J Antimicrob Chemother*
doi:10.1093/jac/dkv233

**A mechanism-based pharmacokinetic/pharmacodynamic model allows prediction of antibiotic killing from MIC values for WT and mutants**
David D. Khan¹*, Pernilla Lagerbäck², Sha Cao², Ulrika Lustig³, Elisabet I. Nielsen¹, Otto Cars², Diarmaid Hughes³, Dan I. Andersson¹ and Lena E. Friberg³

* PubMed search using (pharmacokinetic* OR pharmacodynamics*) AND (antibiotic* OR antiviral* OR antifungal*)
1\textsuperscript{st} series of achievements

- Publishing about pharmacokinetics/pharmacodynamics of antibiotics has become a very popular topic…

- This large amount of scientific data has allowed to characterize the PK/PD parameters of most antibiotics, which is now almost “common knowledge …, was disseminated through workshops, … and is now in most textbooks…”

- But special populations, specific uses, specific targets still need further studies and publications …
Workshops of various kinds

from the personal collection of J.W. Mouton
Workshops of various kinds

from the personal collection of J.W. Mouton
Textbooks

Pharmacokinetics and Pharmacodynamics of Anti-infective Agents

Manjunath P. Pai
Mackenzie L. Cottrell
Angela D.M. Kashuba
Joseph S. Bertino Jr.
Textbooks

Pharmacokinetics and Pharmacodynamics of Anti-Infective Agents

Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases

Figure 19-1 Overview of the pharmacologic and nonpharmacologic factors that m...
Textbooks

Pharmacokinetics and Pharmacodynamics of Anti-infective Agents

19

- Tobramycin
- Ciprofloxacin
- Ticarcillin

Log₁₀ cfu/mL vs Time (hr)

- Control
- 64 MIC
- 16 MIC
- 4 MIC
- 1 MIC
- 1/4 MIC

11/21/2015 ISAP Annual meeting & Post-ICAAC Symposium
Textbooks

Pharmacokinetics and Pharmacodynamics of Anti-infective Agents

Fig. 1. Kill curves of *Pseudomonas aeruginosa* ATCC 27853 with tobramycin and ticarcillin at concentrations one eighth to 64 times MIC. Vertical dashed line estimates number of organisms at 5½ hours.

Textbooks

Pharmacokinetics and Pharmacodynamics of Anti-infective Agents

Manjunath P. Pai
Mackenzie L. Cottrell
Angela D.M. Kashuba
Joseph S. Bertino Jr.

19

Concentration-Dependent Killing Agents
Time-Dependent Killing Agents
Postantibiotic Effect
Higher-Dose Extended-Interval Dosing
Continuous-Infusion and Extended-Infusion Regimens
Dose-Refinement Considerations
# Textbooks

**Antiretroviral Pharmacodynamics**

## Table 19-2: Inhibitory Concentrations and Therapeutic Drug Monitoring (TDM) Recommendations for 14 Commonly Used Antiretroviral and Antiviral Agents

<table>
<thead>
<tr>
<th>ANTIRETROVIRAL OR ANTVIRAL AGENT</th>
<th>$EC_{50}$</th>
<th>TDM RECOMMENDATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atazanavir</td>
<td>2.62-5.28 nM</td>
<td>$C_{trough}$ 150 ng/mL</td>
</tr>
<tr>
<td>Darunavir</td>
<td>1-5 nM</td>
<td>$C_{trough}$ Not established</td>
</tr>
<tr>
<td>Lopinavir</td>
<td>17-100 nM</td>
<td>$C_{trough}$ 1000 ng/mL</td>
</tr>
<tr>
<td>Ritonavir</td>
<td>60 nM-1040 nM</td>
<td>$C_{trough}$</td>
</tr>
<tr>
<td>Nelfinavir</td>
<td>6.14-25.9 nM</td>
<td>$C_{trough}$ 800 ng/mL</td>
</tr>
<tr>
<td>Nevirapine</td>
<td>8.94-34.14 nM</td>
<td>$C_{trough}$ 3000 ng/mL</td>
</tr>
<tr>
<td>Indinavir</td>
<td>0.31-1.73 nM</td>
<td>$C_{trough}$ 1000 ng/mL</td>
</tr>
<tr>
<td>NVP</td>
<td>0.13-0.73 nM</td>
<td>Not established</td>
</tr>
<tr>
<td>Raltegravir</td>
<td>5-12 nM</td>
<td>$C_{trough}$ Not established</td>
</tr>
<tr>
<td>Elvitegravir</td>
<td>32 nM</td>
<td>$C_{trough}$ Not established</td>
</tr>
<tr>
<td>Telaprevir</td>
<td>1100 nM</td>
<td>$C_{trough}$ Not established</td>
</tr>
<tr>
<td>Boceprevir</td>
<td>480 nM</td>
<td>$C_{trough}$ Not established</td>
</tr>
<tr>
<td>Foscarnet</td>
<td>151-155 μM</td>
<td>$C_{max}$ 500-800 μM</td>
</tr>
<tr>
<td>Valacyclovir</td>
<td>HSV-1 0.09-60 μM</td>
<td>$C_{max}$ Not established</td>
</tr>
<tr>
<td></td>
<td>HSV-2 0.53-48 μM</td>
<td>$C_{max}$ Not established</td>
</tr>
</tbody>
</table>
And books…
What do we know today about determinants of activity of most antibiotics…

- **β-lactams antibiotics** are essentially time-dependent … and frequent administration (or even continuous infusion) is the way to go…
What do we know today about determinants of activity of most antibiotics

- **β-lactams antibiotics** are essentially time-dependent … and frequent administration (or even continuous infusion) is the way to go…

> MINIREVIEW

Continuous Infusion of β-Lactam Antibiotics

WILLIAM A. CRAIG¹,²,³* AND STEVEN C. EBERT³,⁴

Department of Medicine¹ and School of Pharmacy, ³ University of Wisconsin, Madison, Wisconsin 53792;
Department of Medicine, William S. Middleton Memorial Veterans Hospital, Madison, Wisconsin 53705²; and Department of Pharmacy, Meriter Hospital, Madison, Wisconsin 53715⁴

- But monitoring may be essential as serum levels are largely unpredictable…
What do we know today about determinants of activity of most antibiotics

- **β-lactams antibiotics** are essentially time-dependent … and frequent administration (or even continuous infusion) is the way to go…

- But monitoring may be essential as serum levels are largely unpredictable…

What do we know today about determinants of activity of most antibiotics

- **β-lactams antibiotics** are essentially time-dependent … and frequent administration (or even continuous infusion) is the way to go…

  *MINIREVIEW*

  Continuous Infusion of β-Lactam Antibiotics

  WILLIAM A. CRAIG¹,²,³* AND STEVEN C. EBERT³,⁴

  Department of Medicine¹ and School of Pharmacy, ³ University of Wisconsin, Madison, Wisconsin 53792; Department of Medicine, William S. Middleton Memorial Veterans Hospital, Madison, Wisconsin 53705²; and Department of Pharmacy, Meriter Hospital, Madison, Wisconsin 53715⁴

- But monitoring may be essential as serum levels are largely unpredictable…

- And we may discuss what is the necessary $C_s$/MIC ratio (or $C_{min}$ ?)
What do we know today about determinants of activity of most antibiotics

- **β-lactams antibiotics** are essentially time-dependent … and frequent administration (or even continuous infusion) is the way to go…

- But monitoring may be essential as serum levels are largely unpredictable…

- And we may discuss what is the necessary C<sub>s</sub>/MIC ratio (or C<sub>min</sub>?)

---

Fig. 10.2  Relationship between concentration of ceftazidime (a) and meropenem (b) and kill rate. The relationship follows a Hill type model with a relatively steep curve; the difference between no effect (growth, here displayed as a negative kill rate) and maximum effect is within 2–3 twofold dilutions. The maximum kill rate is attained at around 4×MIC. Figure modified from Mouton and Vinks (2005b, 2007). Reproduced from Mouton JW, Vinks AA. Pharmacokinetic/pharmacodynamic modelling of antibacterials in vitro and in vivo using bacterial growth and kill kinetics; the minimum inhibitory concentration versus stationary concentration. Clin Pharmacokinet. 2005;44(2):201–10 with permission from Adis (© Springer International Publishing AG [2005]. All rights reserved
What do we know today about determinants of activity of most antibiotics

- **aminoglycosides** are concentration-dependent and need to be given once-daily both for increased efficacy and possible reduction of toxicity

---


**Review**

**Determinants of efficacy and toxicity of aminoglycosides**

H. Mattie*, W. A. Craig§ and J. C. Pechère⊗

*University Hospital, Department of Infectious Diseases, Bldg 1, C5-P, PO Box 9600, 2300 RC Leiden, The Netherlands; §William S. Middleton Memorial Veterans’ Hospital, 2500 Overlook Terrace, Madison WI 53705, USA; ⊗Department of Microbiology, Centre Médicale Universitaire, 9, Avenue de Champel, 1211 Geneva, Switzerland
What do we know today about determinants of activity of most antibiotics

- aminoglycosides are concentration-dependent and need to be given once-daily both for increased efficacy and possible reduction of toxicity.
What do we know today about determinants of activity of most antibiotics

- **aminoglycosides** are concentration-dependent and need to be given once-daily both for increased efficacy and possible reduction of toxicity.
What do we know today about determinants of activity of most antibiotics

• **fluoroquinolones** need to reach a sufficient AUC24h/MIC ratio (125 ?) to be effective against Gram-negative bacteria

Pharmacodynamics of Intravenous Ciprofloxacin in Seriously Ill Patients

ALAN FORREST, DAVID E. NIX, CHARLES H. BALLOW, THOMAS F. GOSS,
MARY C. BIRMINGHAM, AND JEROME J. SCHENTAG*

Center for Clinical Pharmacy Research, School of Pharmacy, State University of New York at Buffalo,
Buffalo, New York 14260, and The Clinical Pharmacokinetics Laboratory,
Millard Fillmore Hospital, Buffalo, New York 14209-1194

Received 19 February 1992/Accepted 5 February 1993
What do we know today about determinants of activity of most antibiotics

- **fluoroquinolones** need to reach a sufficient AUC24h/MIC ratio (125 ?) to be effective against Gram-negative bacteria.

---

**Pharmacodynamics of Serum Antibiotics**

ALAN FORREST, DAVID E. KAYSER, MARY C. BIRMBARD

Center for Clinical Pharmacy Research
Buffalo, New York 14260

Received 19 January 1993

**FIG. 5.** Time (days of therapy) to bacterial eradication versus AUIC illustrated by a time-to-event (survival) plot. Shown is the day of therapy versus the percent patients remaining culture positive on that day. The three AUIC groups differed significantly ($P < 0.005$).
Today, every new antibiotic is PK/PD assessed.

In Vivo Pharmacokinetics and Pharmacodynamics of the Lantibiotic NAI-107 in a Neutropenic Murine Thigh Infection Model

Alexander J. Lepak, Karen Marchillo, William A. Craig, David R. Andes

Department of Medicine, University of Wisconsin School of Medicine and Public Health, Madison, Wisconsin, USA; Department of Medical Microbiology and Immunology, University of Wisconsin, Madison, Wisconsin, USA; William S. Middleton Memorial VA Hospital, Madison, Wisconsin, USA

Today, every new antibiotic is PK/PD assessed...

**In Vivo Pharmacokinetics and Pharmacodynamics of NAI-107 in a Neutropenic Murine TSS Model**

Alexander J. Lepak, Karen Marchillo, William A. Craig, David R. Atkinson

Department of Medicine, University of Wisconsin School of Medicine and Public Health Immunology, University of Wisconsin, Madison, Wisconsin, USA; William S. Middleton Memorial Veterans Hospital, Madison, Wisconsin, USA.


*FIG 4* Impact of pharmacodynamic regression of the *in vivo* dose fractionation study with NAI-107 against *S. aureus* ATCC 25923. Each symbol represents the mean and standard deviation from four thighs. The dose data are expressed as either the $C_{\text{max}}$/MIC (A), the AUC/MIC (B), or the percentage of time drug concentrations exceeded the MIC over the dosing period (C) (% time above MIC). The $R^2$ represents the coefficient of determination. The $ED_{50}$ represents the PD index associated with 50% of the maximal effect ($E_{\text{max}}$), and $N$ is the slope of the relationship or the Hill coefficient. The line drawn through the data points is the best fit line based upon the sigmoid $E_{\text{max}}$ formula. The horizontal dashed line at 0 represents the burden of organisms in the thighs of mice at the start of therapy. Data points below the line represent killing and points above the line represent growth.

once again, an AUC/MIC-dependent antibiotic...
2\textsuperscript{d} series of achievements

- Integrating PK/PD in the processes of drug registration and in breakpoint settings
2\textsuperscript{nd} series of achievements

- Integrating PK/PD in the processes of drug registration and in breakpoint settings

Model-Based Drug Development Today

<table>
<thead>
<tr>
<th>Preclinical</th>
<th>IND</th>
<th>Clinical</th>
<th>NDA</th>
<th>Post-Approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemistry models</td>
<td>Dosing</td>
<td>SAR safety alerts</td>
<td>Signal confirmation (6 mo. safety review)</td>
<td></td>
</tr>
<tr>
<td>Exposure models</td>
<td>Dose ranging</td>
<td>ADME prediction</td>
<td>PK/PD Bridging</td>
<td></td>
</tr>
<tr>
<td>Biology Models</td>
<td>Dose escalation</td>
<td>DDI</td>
<td>Pediatrics</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Human PK/PD Prediction</td>
<td>PK/PD</td>
<td>Elderly</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Study endpoints</td>
<td>Biomarkers</td>
<td>Dosage forms</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Disease progression</td>
<td>Biomarkers</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Most modeling in regulatory review is currently exposure-based and done using sponsor data, supplemented as needed with basic information on disease processes, drug properties, and patient populations.

2\textsuperscript{d} series of achievements

- Integrating PK/PD in the processes of drug registration and in breakpoint settings

2\textsuperscript{d} series of achievements

- Integrating PK/PD in the processes of drug registration and in breakpoint settings
2\textsuperscript{d} series of achievements

• Integrating PK/PD in the processes of drug registration and in breakpoint settings

Concept Paper on revision of the points to consider on pharmacokinetics and pharmacodynamics in the development of antibacterial medicinal products (CHMP/EWP/2655/99) and conversion to a CHMP guideline
Fig. 2.6  Change in $\log_{10}$ CFUs/thigh over 24 h for various Enterobacteriaceae following treatment with multiple fluoroquinolones in neutropenic mice. Redrawn from data in Andes and Craig (2002)
Breakpoint setting...

Fig. 2.6 Change in $\log_{10}$ CFUs/thigh over 24 h for various Enterobacteriaceae following treatment with multiple fluoroquinolones in neutropenic mice. Redrawn from data in Andes and Craig (2002).

![Change in log_{10} CFUs/thigh over 24 h](image)

Fig. 3.2 Relationship between $\%T>MIC$ and MIC for various dosing regimens of ceftobiprole. Illustrated is the close relationship between target MIC (usually the clinical breakpoint) and the dosing regimen. Adapted from Mouton et al. (2004).
Use of Preclinical Data for Selection of a Phase II/III Dose for Evernimicin and Identification of a Preclinical MIC Breakpoint

G. L. DRUSANO,1* S. L. PRESTON,1 C. HARDALO,2 R. HARE,2 C. BANFIELD,2 D. ANDES,3 O. VESGA,3 AND W. A. CRAIG3

Division of Clinical Pharmacology, Albany Medical College, Albany, New York1; Schering Plough Research Institute, Kenilworth, New Jersey2; and Division of Clinical Pharmacology, University of Wisconsin, Madison, Wisconsin3

Received 22 November 1999/Returned for modification 26 April 2000/Accepted 1 September 2000
FIG. 4. Fractional attainment of the 90% $E_{\text{max}}$ target for *S. pneumoniae* for the 6-mg/kg dose (●) and the 9-mg/kg dose (▲). The interval MIC distribution information is included (■).
Fig. 3.4  Summary of the process of setting PK/PD breakpoints by EUCAST (Mouton et al. 2012)
Where are we?
What do we need to do now?*

• cover "old antibiotics"
  – low interest from Regulatory bodies and NO interest from drug companies...

• individualized therapy
  – follow the path ...

• toxicodynamics
  – we may do better but mechanisms are complex ....

• prevention of resistance
  – this may be the real challenge

* personal views
Old antibiotics ?

[Image of two people waving from an old vintage car]
Old antibiotics?

ESCMIID Conference on Reviving Old Antibiotics

Optimisation of therapy in Gram-negative infections
Old antibiotics?

do you need help?
Individualized therapy

6 Population Pharmacokinetic–Pharmacodynamic (PK/PD) Modeling…

Fig. 6.5 Schematic representation of the target-controlled model-based individualized dosing strategy. A clinical pharmacokinetics program with a patient-specific population model describing absorption, distribution, and elimination of the antibiotic in relation to patient-specific parameters is used. Patient data and desired target concentrations are entered into the system. Next, a model-based loading dose and maintenance regimen required to optimally achieve the target concentrations is determined. This regimen is administered to the patient and subsequent concentration measurement(s) are used as feedback to check target attainment and update the model and/or design a new dosing regimen, if required. PK pharmacokinetics, PD pharmacodynamics, PG pharmacogenetics
Clinical Vignette 12.1: TDM of Vancomycin Administered by Continuous Infusion

A 21-year-old student has developed subacute meningitis and peritonitis in the presence of a ventriculoperitoneal shunt that was placed for hydrocephaly that developed following removal of a brain tumor. He has a fever of 38.9 °C, headache, and severe abdominal pain.

His length is 187 cm and his weight is 67 kg. The cerebrospinal fluid (CSF) WBC count is $>2.0 \times 10^9$/ml and the Gram stain shows Gram positive cocci in clusters.

Empirical therapy with vancomycin is started at a loading dose of 15 mg/kg and a daily dose of 30 mg/kg/day by i.v. continuous infusion (CI). In practice, two syringes of 1 g are administered over 12 h with an infusion pump. Both *S. aureus* MSSA (MIC 1 μg/mL) and coagulase-negative staphylococci (MIC 2 μg/mL) are cultured from the CSF. The shunt is removed and a ventricular external drain is placed. Vancomycin 10 mg is given once intraventricularly.

A vancomycin serum level on Day 3 is 15 μg/mL. The daily CI vancomycin dose is increased to 2,250 mg (two syringes of 1,225 mg) and in the subsequent days target serum levels of 20 μg/mL are reached.

Because of the CI, each serum level sample is a correct one, regardless of the time of sampling, and adjustments of dosing are easily achieved in this neurosurgical department.
Toxicodynamics

The aminoglycosides revisited ....

FIG. 1. (A) Curve of probability of development of aminoglycoside nephrotoxicity for patients receiving the drug on a twice-daily basis as estimated by multivariate logistic regression analysis. The probability rises as a function of increasing daily exposure to aminoglycoside, as indexed to the AUC. Concurrent vancomycin use provides a marked increase in the probability of nephrotoxicity for equivalent exposure to aminoglycosides, as indexed to the daily AUC. (B) Once-daily administration shifts the curves of probability of nephrotoxicity as influenced by daily aminoglycoside AUC to the right.
Toxicodynamics

The oxazolidinones visited ....

![Graph showing the relationship between Linezolid $C_{\text{min}}$ (mg/L) and the probability of platelet reduction > 30%.]

**Fig. 16.13** Linezolid $C_{\text{min}}$ and logistic regression model for thrombocytopenia (Pea et al. 2012), reproduced with permission. The symbols refer to the $C_{\text{min}}$ observed over time in each patient with (top) or without (bottom) thrombocytopenia. The continuous line represents the result of the logistic regression model. The vertical broken line identifies the $C_{\text{min}}$ value predicting 50% probability of thrombocytopenia.
Toxicodynamics

The oxazolidinones visited ….in much more details….

Clinical Population Pharmacokinetics and Toxicodynamics of Linezolid

Lauren M. Boak, a*, Craig R. Rayner, a,b M. Lindsay Grayson, c,d David L. Paterson, c* Denis Spelman, f Sharmila Khumra, c,h Blair Capitano, e* Alan Forrest, g Jian Li, a Roger L. Nation, a Jurgen B. Bulitta, a,g,h

Drug Delivery, Disposition and Dynamics, Monash Institute of Pharmaceutical Sciences, Monash University (Parkville campus), Parkville, Australia a; d3 Medicine LLC, Parsippany, New Jersey, USA b; Department of Medicine, Austin Hospital, Melbourne, Australia c; Department of Epidemiology and Preventive Medicine, Monash University, Melbourne, Australia d; University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania, USA e; Department of Infectious Diseases, Alfred Hospital and Monash University, Melbourne, Australia f; School of Pharmacy and Pharmaceutical Sciences, SUNY at Buffalo, Buffalo, New York, USA g; Centre for Medicine Use and Safety, Monash University (Parkville campus), Parkville, Australia h

Toxicodynamics

The oxazolidinones visited ....in much more details....

FIG 1 Structure of the final mechanism-based population pharmacokinetic/toxicodynamic model. The pharmacokinetic model is comprised of three absorption lag compartments, a gut compartment, and a central compartment. One series of 15 transit compartments was used to describe platelet precursor cells in the bone marrow, and another series of 15 transit compartments to describe platelets in the circulating pool. Platelets displayed a feedback effect on the synthesis of platelet precursor cells. A lack of platelets in the circulating pool compared to the platelet count at steady state caused a stimulation of platelet precursor synthesis, and an excess of platelets in the circulating pool caused an inhibition of platelet precursor synthesis.
Toxicodynamics

The oxazolidinones visited ....in much more details....

**FIG 4** Simulated probabilities for nadir platelet counts below $100 \times 10^9$/liter for various normal and front-loaded linezolid dosage regimens when mean baselines were as indicated.

The oxazolidinones visited ....in much more details....
Resistance

The saga of the fluoroquinolones and shutting down resistance...

Figure 3. Ability of a dose of drug to attain an area under the curve (AUC):MIC ratio of 87 (the target ratio for eradication of the pathogen) is affected by the distribution of the drug's clearance in the population and by the MIC of the pathogen. The fractional target attainment for 10,000 simulated subjects is displayed as a function of MIC values for levofloxacin (750 mg intravenous once daily, A) and for ciprofloxacin (400 mg iv every 8 h, B). In addition, the fraction of isolates at a specific MIC value for levofloxacin is displayed for Pseudomonas aeruginosa and Enterobacter cloacae. For ciprofloxacin, these data are provided for P. aeruginosa. This allows placing the target-attainment fractions in perspective. The drug dose will be expected to perform better if the fraction of isolates is high, whereby the MIC values give a high level of target attainment. The pharmacokinetic data used for the analysis in panel B are from Forrest et al. [19].

Drusano et al. The Journal of Infectious Diseases 2004; 189:1590–7

Well, you did it, did you not?

my simple interpretation is that the breakpoint should be <<< the CLSI breakpoint...
To finish

- We were helped by technical developments

Fig. 5.21  Hollow fiber model by Zinner et al. (1981)
To finish

- modelling population PK with difficult antibiotics
- sparse sampling
- monitoring and adjusting
- prevention of resistance
- and many other achievements
But who did it?

but hey were many others....

The right team, folks
Two examples of people who should not have died...

In Memoriam: William A. Craig

Dr. Craig was renowned as a clinician-scholar in the fields of antimicrobial therapy and infectious disease. His early work on quantifying the relationship between antimicrobial dosing and treatment effect led to the development of the field of antimicrobial pharmacodynamics.

He died from infectious complications of anticancer therapy.
I forgot many important points…

but ask questions…