

# Ten Years After: Where is ISAP?

William A. Craig, M.D.

University of Wisconsin  
Madison, WI

## Birth of ISAP

- 1986-89 Informal discussions
- June 1989 Organizational meeting in Upsala, Sweden after Stockholm Symposium on Dosing of Antimicrobials
- July 1991 Society created at Berlin ICC

## Name of Society

- Initial suggestions developed in Iceland after an opera performance

AIDA - Association for the Improvement of Dosing of Anti-Infectives

OTELLO - Organization for Terminating Every Little Living Organism

- International Society of Anti-Infective Pharmacology (ISAP) chosen in 1990 to emphasize pharmacology as the basic science for activities of the organization

# “Objects and Purposes of the Society”

- To encourage the study and advancement of the science of Pharmacodynamics, Pharmacokinetics and the Dosing of Anti-Infectives

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# Pharmacodynamics before 1991

- Primarily descriptive
  - in vitro and in vivo phenomena (e.g. PAE, PAE-SME, PALE, etc)
  - initial identification of PK/PD parameters in in vitro and animal models
- Application to new dosing regimens for established drugs (e.g. once-daily dosing of aminoglycosides, continuous infusion of beta-lactams)

# Pharmacodynamics in 2001

- Correlation between PK/PD results in animal and in vitro models with outcome in humans with certain classes of drug (e.g. beta-lactams, fluoroquinolones, and aminoglycosides)
- Application in early drug discovery, dosage regimen design for clinical trials, determination of susceptibility breakpoints, guideline development and prevention of resistance.

# Pharmacodynamics in 2001

- Greatest impact with antibacterials where pharmacodynamics is being applied throughout the pharmaceutical industry
- Increasing application to antifungal, antiviral and anti-HIV drugs

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# Activities of ISAP

- Symposia at ICAAC, ECCMID, ICC, ISDA
- Educational workshops at ICAAC and ECCMID
- Workshops and meetings with regulatory agencies in USA and Europe

# Topics of Symposia

- Pharmacodynamics of antivirals, antifungals, new antibacterials, and immunomodulating agents
- Application of pharmacodynamics to: drug discovery and development, susceptibility testing, treatment and prevention of antimicrobial resistance, and antimicrobial toxicity

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# FDA-IDSA Guidelines (1992)

- Minimal comments on pharmacodynamics
- Postantibiotic effect (in vitro and in vivo) - importance for dosing schedule

Clin Infect Dis 15 (Suppl 1):S1-S346, 1992

# Points to Consider (1992)

- Addendum: Dose-response testing
- Use of PK/PD data to select initial dosing regimen believed to be “optimal dose”

# NCCLS Documents (1991-92)

- No mention of pharmacodynamics
- Breakpoints often determined by MIC distributions alone
- Peak levels used for many oral agents

# FDA Modernization Act (1997)

## FDAMA

- Section 112 Expediting study and approval of fast tract drugs
  - PD (surrogate) endpoints
- Section 115 Clinical investigations (single clinical trial)
  - "confirmatory evidence" comprising  
PK & PK/PD

# Developing Antimicrobial Drugs General Considerations (7/98)

## Section VI. Clinical Pharmacology and Biopharmaceutics - added guidance on PK/PD Evaluation of Antimicrobial Drugs

- tool for providing additional level of certainty
  - selection of optimal dosage regimen
- increased utilization - prospectively
- incorporate throughout development
- encourage discussion with the Agency

# PK/PD Parameters

- Correlation with antimicrobial efficacy
  - in vitro models
  - animal models
  - patients
- Other approaches/markers
- More data needed from clinical trials to adequately “validate” parameters/markers

# Pharmacodynamics

Correlation of PK or PK/PD Parameters

-AUC, peak, trough, Peak/MIC, AUC/MIC,  
time above MIC

with

-microbial outcome (eradication, persistence,  
resistance)

-surrogate endpoint (CD4, viral load)

-clinical outcome (cure, improvement, failure)

# PK/PD Applications

- Facilitate early selection of lead drug candidates (e.g. pre-clinical screening)
- Select appropriate dosage regimen (e.g. Phase II/III)
- Better understand clinical/microbiologic outcome (e.g. Phase III)
- More efficient drug development program
- (Facilitate establishment of susceptibility breakpoints)

# PK/PD Applications

- Optimal dosing to reduce the risk of resistance
- Optimal dosing to reduce the risk of toxicity
- Improved dose recommendations to prescribing physicians

# PK/PD Applications

- To reduce number of clinical cases for indication against certain pathogens (penicillin-resistant pneumococci)
- Not yet to reduce clinical trials from 2 to 1, even though this is possible with FDAMA

# CPMP (European Regulatory): Points to Consider on PK and PD in the Development of Antibacterial Medicinal Products - 1999

- “CPMP..... Recommends that the PK/PD relationships for an antibacterial medicinal product should be investigated during the development process”
- “CPMP recommends that emergence of resistance be an integral part of investigation of the PK/PD outcome relationship to better understand the role of dosing to contain antimicrobial resistance”

# CPMP (European Regulatory): Points to Consider on PK and PD in the Development of Antibacterial Medicinal Products - 1999

- “However, the CPMP does not believe that current information would support the use of preclinical information on the PK/PD relationships to significantly reduce the scope and content of the phase III development program”
- “There may be areas in which detailed study of PK/PD relationships might potentially impact the clinical program - special populations, rare pathogens, certain types of infections”

# PK/PD Parameters with Beta-Lactams

- Time above MIC is the major determinant of efficacy in animal models
- 24-hr AUC/MIC and time above MIC have both been shown to be predictive of efficacy in humans (very limited number of dosing regimens)
- Consensus ?????

# PK/PD Parameters with Fluoroquinolones

- 24-hr AUC/MIC major determinant of efficacy in animal models
- Peak/MIC, 24-hr AUC/MIC, and time above MIC all shown to be predictive of efficacy in humans (very limited number of dosing regimens)
- Consensus ?????

# PK/PD Parameters and Levofloxacin

<u>Parameter</u>	<u>Estimate</u>	<u>P-Value</u>
Peak/MIC	0.148	<0.001
Time > MIC	0.040	<0.001
AUC/MIC	0.011	0.006

Preston et al JAMA 1998: 279:125-129.

# PK/PD Parameters with Fluoroquinolones

- Magnitude of 24-hr AUC/MIC required for efficacy of gram-negative bacilli and *Streptococcus pneumoniae*?
- Is magnitude of PK/PD parameter in ELF (Epithelial lining fluid) important for lower respiratory infections
- Consensus???

# Pharmacodynamics and Regulatory Organizations

- Regulatory organizations have shown considerable interest in pharmacodynamics over the past few years
- FDA has started to use pharmacodynamics as “confirmatory evidence” in the approval process
- Consensus and further validation in clinical trials is needed to increase acceptance of pharmacodynamic concepts by regulatory organizations

# Factors to Consider when Establishing Breakpoints (NCCLS)-M23 Document

- Population distributions of MICs
- Known resistance mechanisms
- Relationship between MICs and clinical and bacteriologic outcome in clinical trials
- Pharmacodynamics - PK/PD parameter correlating with efficacy; magnitude with proposed breakpoints & comparison with other drugs in same class

Pharmacodynamic and Old and New (Jan 2000)  
 NCCLS Susceptibility Breakpoints for Various  
 Oral  $\beta$ -Lactams with *Streptococcus pneumoniae*

<b>Drug</b>	<b>Old Breakpoint</b>	<b>PD Breakpoint (T&gt;MIC &gt;40%)</b>	<b>New Breakpoint</b>
<b>Amoxicillin</b>	<b>0.5</b>	<b>2</b>	<b>2</b>
<b>Cefaclor</b>	<b>-</b>	<b>0.5</b>	<b>1</b>
<b>Cefuroxime</b>	<b>0.5</b>	<b>1</b>	<b>1</b>
<b>Cefprozil</b>	<b>-</b>	<b>1-2</b>	<b>2</b>
<b>Cefpodoxime</b>	<b>-</b>	<b>0.5</b>	<b>0.5</b>
<b>Cefixime</b>	<b>-</b>	<b>0.5</b>	<b>-</b>

# “Objects and Purposes of the Society”

- To encourage research and training by way of grants from the funds of the Society

# Tasks for the Future

- Get involved in writing and publishing consensus statements
- Look for and emphasize the similarity of results by different techniques and approaches rather than the differences
- Prepare basic and advanced pharmacodynamics courses for certification for ID fellows, ID pharmacists, microbiologists and others

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