Asian PK/PD Educational Workshop

Welcome

- Why is PK/PD important?
- Who are we?
- Programme of the Workshop
PK / PD of antiinfectives: where do we come from?

The basics:

• anti-infective drug usage has long been irrational or not scientifically based on a pharmacodynamic point of view
  • search for low doses for fear of toxicity
  • “errors” in drug dosages at registration
  • misunderstanding of “optimal schedules”

• pharmacokinetics was mostly used to establish “drug presence” rather than to correlate dosing with efficacy

pharmacodynamics of antiinfective drugs was largely “terra incognita” 10 years ago
PK/PD of antiinfectives: what has been done?

Over the last 10 years, three major concepts have emerged and proven useful:

• Dose-effect relationships are not the same for all anti-infectives
  • Beta-lactams or glycopeptides vs fluoroquinolones or aminoglycosides

• Integration of PK/PD within pre-clinical and early clinical development allows prediction of success or failure of new antimicrobials

• PK/PD may help in preventing the emergence of resistance
How did it start?
How did it start?

A bunch of good guys met in Stockholm in 1989...
What did they think all about?

- population pharmacokinetics
- tissue concentrations
- efficacy/toxicity ratios
- postantibiotic effect
- AUIC and fluoroquinolones
- and β-lactam infusion
- once-daily dosing of aminoglycosides
- once-daily dosing of aminoglycosides
1991 : Creation of the International Society of Antiinfective Pharmacology

- incorporated in 1993 (Australia, now USA)
- 108 members worldwide
  (40% US, 40% Europe, 20% elsewhere)
  - academy
  - industry
- 11 independent symposia
- 11 co-sponsored symposia (ICAAC, ECCMID, …)
- 3 discussion symposia with Regulators
- 8 public educational workshops

http://www.isap.org
PK/PD since 1989 ...

1994 ... : organization of sessions on pharmacodynamics at the major international meetings (ICAAC, ECCMID, etc…)

1995 ... : Introduction of PK/PD considerations in the drug development and registration process ...

1998 ... : PK/PD considerations introduced in clinical investigations and daily clinical activities ...

now .... : PK/PD considerations begin to be used to define optimal reimbursement schemes in some European countries …
PK/PD in action in the Regulatory in the USA

PK/PD - Potential Benefits

- Facilitate Early Selection of Lead Drug Candidate (e.g., Pre-Clinical Screening)
- Select Appropriate Dosage Regimen (e.g., Phase 1/2)
- Better Understand Clinical / Microbiological Outcome (e.g., Phase 3)
- More Efficient Drug Development Program

July 1998

http://www.fda.gov/cder/present/anti-infective798/biopharm/index.htm
PK /PD in action in the Regulatory in the USA

FDA November 2002

IDSA/PhRma/FDA Working Group Meeting
November 19-20, 2002

- Agenda
- Minutes Day 1 and Day 2

IDSA/PhRma/FDA Working Group Mtg. Presentations:

2. Drug Development for Resistant Pathogens by Francis P. Tally, M.D.
3. Developing Drugs for the Treatment of Infections due to Resistant Pathogens by Edward Cox, M.D., M.P.H.
4. Use of PK/PD to Facilitate Development of Drugs for Treatment of Resistant Pathogens by William A. Craig, M.D.
5. Use of PK/PD to Facilitate Development of Drugs for Treatment of Resistant Pathogens by James A. Poupard, Ph.D.
6. Exposure-Response: Application to Antimicrobial Drug Development by Philip Colangelo,

http://www.fda.gov/cder/present/anti-infective798/biopharm/index.htm
"Inadequate dosing of antibiotics is probably an important reason for misuse and subsequent risk of resistance.

A recommendation on proper dosing regimens for different infections would be an important part of a comprehensive strategy.

The possibility of approving a dose recommendation based on pharmacokinetic and pharmacodynamic considerations will be further investigated in one of the CPMP* working parties…"

* Committee for Proprietary Medicinal Products
Publications of the EMEA ...

The European Agency for the Evaluation of Medicinal Products

25 March 1999
EMEA/9880/99, Rev. 1

EMEA Discussion Paper on Antimicrobial Resistance

London, 27 July 2000
CPMP/EWP/2655/99

POINTS TO CONSIDER ON PHARMACOKINETICS AND PHARMACODYNAMICS IN THE DEVELOPMENT OF ANTIBACTERIAL MEDICINAL PRODUCTS
PK / PD in action for science and clinics

Some achievements:

• once-daily dosing of aminoglycosides
  registration or reregistration in several countries
  • amikacin, netilmicin (from bid to qd)
  • isepamicin (registered essentially for qd dosing)

• 24h AUC / MIC and $C_{\text{max}} / \text{MIC}$ ratios used as guides
  for phase II / III trials, for treatment optimization
  and for registration of new antimicrobials
  • moxifloxacin
  • telithromycin

• continuous infusion of beta-lactams brought to
  clinical trials
PK / PD in action for science and clinics

Publications ...

1. Ibrahim KH, Hoyde LB, Ross G, Gunderson B, Wright DH, Rotschafer JC.
   Microbiologic effectiveness of time- or concentration-based dosing strategies in Streptococcus pneumoniae.
   PMID: 12493174 [PubMed - in process]
PK / PD in action for science and clinics

Resistance ...

[PubMed search results for "pharmacodynamic* and antibiotic* and resistance"]

Items 1-20 of 239
PK / PD in action for science and clinics

Bacterial eradication in the treatment of otitis media

Ron Dagan and Eugene Leibovitz

Drugs differ in their ability to eradicate various pathogens from the middle-ear cavity during acute otitis media (AOM), and these differences clearly affect clinical outcome. Outcome is derived from differences in the association between concentrations of the drugs at the site of infection and the antimicrobial effect (termed pharmacodynamics). These differences are even more marked in the present era of antimicrobial resistance. However, since AOM is a self-limiting disease in most cases, difference in clinical outcome is more difficult to ascertain than that of bacteriological outcome, which is measured within 3–5 days. A favourable clinical outcome regardless of the bacteriological effect of the drug can result in false optimism when less-effective antibiotic drugs are used. Inappropriate study design and manipulation of clinical results add to this confusion. In this review we attempt to highlight the evidence regarding bacteriological response to antibiotics in AOM and to draw attention to potential flaws that may mislead clinicians.

Lancet Infect Dis 2002; 2: 593–604

Figure 1. Relation of the free drug concentration at the site of infection to the minimal inhibitory concentration of the drug to the pathogen. (A) A β-lactam drug that achieves concentration above the MIC for ~40% of the dosing interval is predicted to have a high rate of failure. (B) Another drug, if administered against the same organisms as in curve A, will show a high rate of eradication, since its concentration at the site of infection exceeds 40–50% of the dosing interval. (C) By increasing the MIC, the pathogen that was easily eradicated under the condition presented in curve B will not be eradicated if the concentrations of the same drug as in curve B does not exceed 40% of the dosing interval.

Exudates worldwide and causes roughly 40% of episodes of otitis media. However, in some recent studies, *H influenzae* was more common than *S pneumoniae* in AOM. *S pneumoniae* may be a more virulent pathogen than non-typable *H influenzae* and *M catarrhalis*. Altogether, *S pneumoniae* and non-typable *H influenzae* constitute in most studies more than 80% of all AOM pathogens, and thus bacterial eradication of these two organisms is the key...
So, why have we agreed to come here?

Please, be interactive and DO ask questions

Education ...

Education ...

Education ...

We'll try to answer ...
But, before we begin, who are we?

Michael R. Jacobs, MD, PhD
Professor of Pathology and Medicine,
Case Western Reserve University, Cleveland, Ohio, USA
Director of Clinical Microbiology
University Hospitals of Cleveland, Cleveland, Ohio, USA

Paul M. Tulkens, MD, PhD
Professor of Pharmacology and Drug Development
Department of Pharmaceutical Sciences
Catholic University of Louvain, Brussels, Belgium
Where the hell could Belgium be?
Paul M. Tulkens and PK/PD ...

- **Scientific activities**
  - toxicology of aminoglycosides
  - intracellular infection
  - introducing new modes of AB administration to the clinics

- **Belgian and EU Regulatory activities**
  - Adviser to the Registration Commission (for AB)
  - Member of the National Commission for Drug Reimbursement
  - Member of the National Committee for the Coordination of the Antibiotic Policy

- **International activities**
  - Founding member and Past-President of ISAP
  - Editorial Board of Antimicrobial Agents and Chemotherapy

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- the once-a-day concept (1985-1990)
  - present AB
  - new derivatives

- $\beta$-lactams by continuous infusion

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GSK Asian PK/PD workshop -- Taipei, Taiwan, January 10th, 1-20
Programme, please ...

Morning sessions:

- Basic introduction to microbiological parameters
  M. Jacobs

- The general concepts of pharmacokinetics
  P.M. Tulkens

- Pharmacokinetics as applied to animal and in vitro models
  M. Jacobs

- The general concepts of pharmacodynamics
  P. M. Tulkens

What you always wished to know but never dared to ask because it seemed so basic ...

... and did not know how to begin with all that stuff ...
Programme, please ...

Afternoon sessions:

- Pharmacodynamics as applied to animal models, or how to discover PK/PD parameters [P.M. Tulkens]
- PK/PD models for selected antibiotics [M. Jacobs]
- New approaches in PK/PD (drug transport, intracellular infections, difficult-to-reach areas) [P.M. Tulkens]
- Regulatory aspects and Population-based approaches [M. Jacobs]
- Resistance and PK/PD [P.M. Tulkens]
- Applications to practical situations (RTI as an example) [M. Jacobs]

How to (really) go from basic science to your daily (and future !!) activities