PK/PD of antibiotics
Educational Slide Workshop

- Why is PK/PD important ?
- Who are we ?
- Program of the Workshop

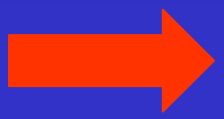
With the support of *Wallonie-Bruxelles-International*

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 20 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 now prediction of success or failure of new antimicrobials**
- **PK/PD may help in preventing the emergence of resistance**

PK/PD since 1989 ...

- Improving the usage of existing drugs
  - aminoglycosides once-daily
  - AUC and fluoroquinolones
  - continuous infusion of β-lactams
- Improving the usage of new drugs
  - registration of new antibiotics
  - definition of optimal doses in reimbursement schemes
- Fighting resistance ...

PK /PD in action in the Regulatory in Europe

EMEA
July 1999

" 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… "

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* Committee for Proprietary Medicinal Products

PK / PD in action in the clinics

Resistance and simple clinical situations ...

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

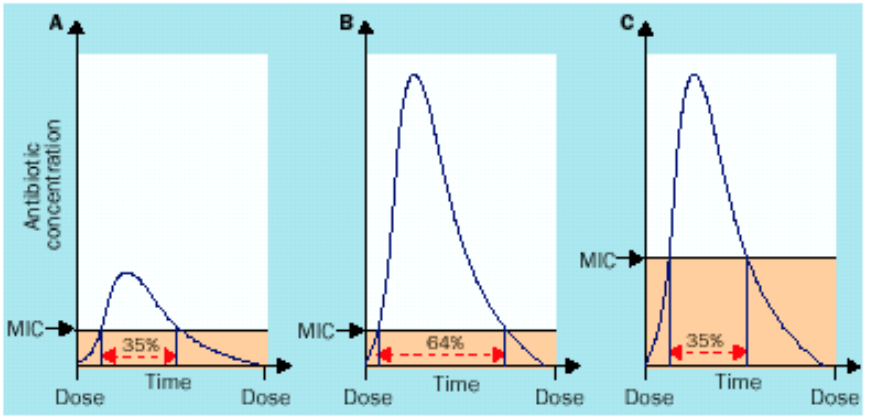

Figure 1. Relation of the free drug concentration at the site of infection to the minimal inhibitory concentration of the drug to the pathogen. (A) A β-lactam drug that achieves concentration above the MIC for <40% of the dosing interval is predicted to have a high rate of failure. (B) Another drug, 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.[2] However, in some recent studies, *H influenzae* was more common than *S pneumoniae* in AOM.[10–12] *S pneumoniae* may be a more virulent pathogen than non-typable *H influenzae* and *M catarrhalis*.[13–18] 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 is this workshop for ?

Education …

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Education ...

We'll try to answer your questions...

But, before we begin, who are we ?

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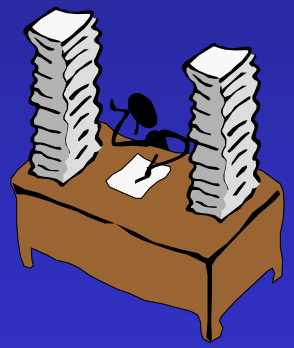
with strong influence from ISAP and ESCMID EUROPEAN SOCIETY OF CLINICAL MICROBIOLOGY AND INFECTIOUS DISEASES PK/PD of Anti-Infectives Study Group

Program, please ...

1. Basic introduction to key microbiological parameters
2. Pharmacokinetics (PK) : the basics
3. Pharmacodynamics (PD)
    - A. the concepts
    - B. the methods
    - C. actual data on the main classes of antibiotics
4. Resistance
    - A. mechanisms and epidemiology
    - B. PK/PD to fight resistance



References

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 ...