

# Drivers of resistance

- Antibiotic consumption
  - long duration of treatment
  - inappropriate dosing regimen
  - poor compliance
- Spread of resistance
  - transfer of strains between individuals
  - transfer between strains of genes encoding R
  - co-selection of cross-resistant strains
- Rx failures lead to selection of R clones and promote their spread in the community

# Presentation summary

- Investigation of a new compound
  - definition of optimal dose/dosing regimen
  - prevention of resistance
- Help in the administration of optimal Rx:
  - control of efficacy
  - prevention of toxicity
- Short duration treatment
- Conclusions

# Factors determining which PK/PD parameters predict or contribute to outcome

- Predict outcome:
  - concentration dependence of kill rate
  - bactericidal or static (time dep.) activity
- Contribute to outcome:
  - accumulation in phagocytes
  - ability to induce resistance

# PK/PD parameters predictive of outcome

<u>Time above MIC</u>	<u>AUC/MIC</u>	<u>Peak/MIC</u>
$\beta$ -lactams	Telithromycin	Fluoroquinolones
Erythromycin	Azithromycin	Aminoglycosides
Clarithromycin	Fluoroquinolones	Telithromycin

Drusano and Craig. J Chemother 1997;9:38-44 et al.

Clin Microbiol Infect 1998;4(Suppl2):S27-41

# PK/PD parameters predictive of outcome

Parameter	Time above MIC	AUC/MIC	$C_{\max}/MIC$
correlating with efficacy :			
Examples :	$\beta$ -lactams Erythromycin Clarithromycin	Azithromycin Fluoro- quinolones	Fluor - quinolones Aminoglycosides
Organisms kill :	Time-dependent	Concentration- dependent	Concentration- dependent
Therapeutic goal :	Optimise duration of exposure	Maximise exposure	Maximise exposure

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# Adaptation to PK/PD properties

- Unitary dose and dose intervals
- Risk related to a too low dose:
  - impossibility to reach adequate peak/MIC or AUC/MIC ratios for concentration dependent AB
  - inefficacy of time-dependent AB:  $\text{peak} < \text{MIC}$
  - selection of R bacterial subpopulation
- Risk of a too long interval:
  - bacterial regrowth with a time dep. AB

# In vivo validation

- Peak/MIC:
  - AG >8 (Smith); FQ > 10-12 animals and humans
- AUC/MIC (AUIC)
  - > 125 validated for FQ (Forrest, Bédos),  $\beta$ -lactams and vancomycin (Schentag)
- $t > \text{MIC}$ :
  - 40% of dose interval, validated for pneumococcus in mice (Craig)
- AUC/MIC <100 risk of selection of R to FQ (Thomas)

# Antibiotic combinations

- Schentag, CID, 1998
- AUIC are additive
- Peaks are not additive
- Take into account properties of each drug.
- Each compound should be optimally prescribed

# 1- Development of new compounds (I)

- Prediction of antibacterial effect
- Early preclinical phase
- Study of concentration/effect relationship
- Definition of the predictive parameter(s)
- Simple animal models: thigh/lung models in normal/neutropenic mice. Multiples species/strains.
- Serum levels

## (II)

- Definition of optimal dose/dosing regimen
- Integration of:
  - animal data
  - early phase I PK data; population PK
  - simulation using MIC90s on bacterial species of the spectrum of clinical interest
- Proposed dosing regimen for clinical trials in phase 2 and 3.

# Example of levofloxacin

- PK/PD parameters identical to those of previous FQ (animal models)
- Population PK; definition of a model of clearance in pts with severe infection, after a 500mg dose q 24h (Preston, AAC, 1998). Precision 3%.
- PD: probability of clinical/bacteriological success if  $\text{peak/MIC} > 12$ . Preston, JAMA, 1998. Validation of dosing.

## 2- Clinical relevance

- 2.1. Control of efficacy:
- Main goal: to avoid underdosing
  - use of serum concentrations
- Difficult to treat populations:
  - unstable or difficult to predict PK
  - renal failure
  - acute severe infection
- Choice of sampling times according to AB-PK/PD: peak or trough

## 2.2 Adaptation of dose/dosing

- Control of toxicity (when concentration dependent)
- Dose adaptation
  - renal failure. AB with exclusive/predominant renal excretion and low therapeutic index (AG, glycopeptides). Selection of adequate sampling time (peak, trough)
- Main goals: to avoid underdosing and accumulation.

# Examples

- Aminoglycosides: use of PK/PD data:
  - consensus on OD dosing regimen; short Rx
  - Peak/MIC predictive of effect (Kashuba, 1999)
  - AUC and + vanco : predictive of nephrotoxicity (Rybak, AAC, 1999)
  - intervals based on Cr Cl; trough levels (predicted AUC) : <1-2 for gentamicin; < 5-10 for amikacin
  - (no prospective validation)

# Examples

- $\beta$ -lactams:
  - predictive value of trough level of free drug
  - serum levels  $>$  MIC for 40-50% of interval between doses. 100% in severe infections ?
  - Interest of continuous infusion?
  - Risk of underdosing in severe cases (increased  $V_d$  ;Gomez, AAC, 1999)
  - 32% elderly pts with correct dose of imipenem (Ritchie, J Pharm Tech, 1999)

# Examples

- Glycopeptides:
  - time-dependent antibacterial effect; high % PB
  - trough levels  $> 10\text{-}15$  mg/l (total drug) not validated.
  - Controversy around the optimal model (1 or 2 compartments) for the definition of the dose (Leader, Clin Pharmacokinet, 1995)
  - 1 measure of trough at steady state sufficient for vanco (Andres, Ther Drug Monit, 1997)

# Glycopeptides (cont'd)

- Sanchez (JAC, 1999)
- Teicoplanin in children, severe infections
- Three 10 mg/kg doses q 12 h, then OD
- 11% only of the patients had a trough level > 10mg/l
- Strong need of:
  - loading dose
  - control of drug levels to avoid underdosing

### 3. Short duration (sd) therapy

- Shorter than current regimens
- Relationship between AB use and development of bacterial R well established.
- SD may contribute to reduce the quantities of AB delivered in the environment and therefore decrease the risk of selection of R
- while keeping the same efficacy level
- Economical and ecological interests.

# Examples of ecological impact

- Guillemot et al (JAMA,1998):
  - AB Rx > 7d increases the risk of selection of PRSP in children (OR = 3.5, 95% CI 1.3-9.8; OR= 33.5, when combined with the use of underdosed oral penicillins)
- Harbarth et al (Circulation, 2000):
  - AB prophylaxis >48h in CV surgery correlated with increased risk of R GNB or enterococci (OR = 1.6; 95% CI: 1.1-2.6)

# Basic requirements

- Fully susceptible pathogen; no risk of selection of R with the chosen drug
- Cidal AB (or combination): check the dose
- Focus easily accessible to the drug
- No foreign body or abscess
- Patient with normal defenses
- *These conditions make SD-Rx feasible*

# Example of Salmonella infections

- 5d duration Rx with cipro proposed on the basis of: low MICs, SBA, PK properties, efficacy of 10-12 d Rx (Carbon, JID, 1987)
- Since then, numerous studies have validated the SD Rx (DuPont, Drugs, 1993, Limson, Drugs, 1995)
- Possible limitations: R mechanisms-dose ; HIV patients; chronic carriage.

# Discussion of limitations (I)

- Impact of PK: efficacy of 10d Rx: 100% with oflo/cipro; 90 % norflo (Limson)
- Impact of duration: cipro 500 mg BID: 10d:100% efficacy; 6d: 82%, 3d: 67%
- Increased MICs: nalR (0.25-1mg/L) vs nalS (0.03); Rx oflo 200mg BID, 5d:increased time to apyrexia (4.3 vs 7.2); nb of +stools post-Rx (7/17 vs 0/19) (Chinh, AAC, 2000)

# Limitations (II)

- Impact of host defenses:
  - disseminated non-typhi *Salmonella* infections: AIDS defining event. Bacteremia 20 times more frequent in HIV +ve than in non immunocompromised patients (Fernandez-Guerrero, 1997).
  - Relapse rate: 53% without prophylaxis vs 0% if AZT or AB (Salmon-Ceron, 1992)

# Conclusions

- The PK/PD concepts have several applications in human therapy
- Development of new compounds: CPMP, Points to consider (July 2000)
- Optimization of antibiotic therapy
- These concepts should be integrated in general policies of judicious use, to avoid failures and selection of R