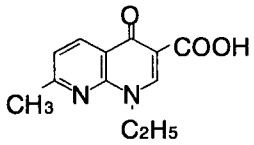
Strategic Development of Quinolones

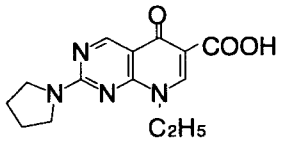
- History of discovery of quinolones
- Therapeutic contribution and medical needs
- Parameters for "Go" or "No Go" decision
- Development strategy
- Indications and clinical study design
- Guidelines for evaluation of antibacterial drugs
- Worldwide development of sparfloxacin

Discovery of Quinolones (1)

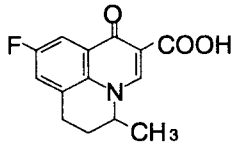
Nalidixic Acid Analogues



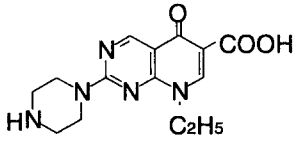
Nalidixic Acid (1961)



Piromidic Acid (1965)



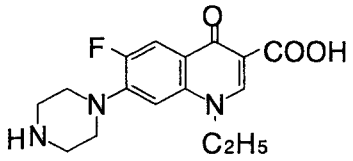
Flumequine (1972)



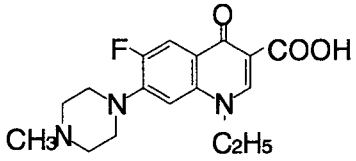
Pipemidic Acid (1972)

Discovery of Quinolones (2)

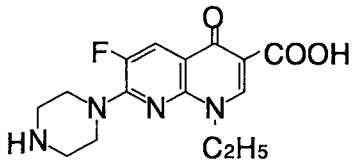
1st Generation of Fluoroquinolones



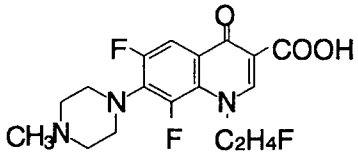
Norfloxacin (1977)



Pefloxacin (1977)



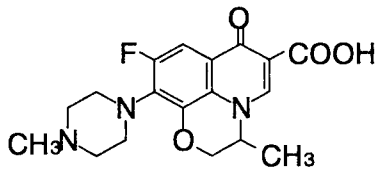
Enoxacin (1978)



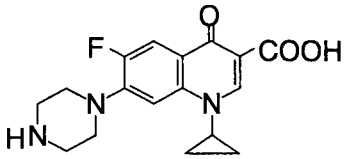
Fleroxacin (1980)

Discovery of Quinolones (3)

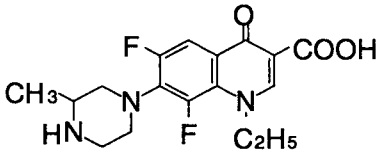
New Findings in Chemical Structure



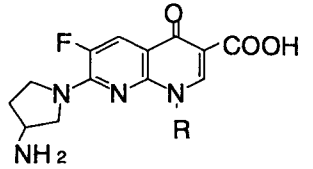
Ofloxacin (1981)



Ciprofloxacin (1981)



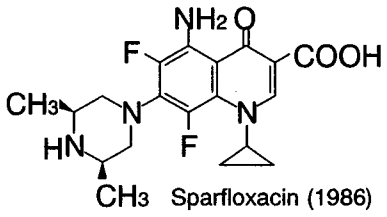
Lomefloxacin (1983)



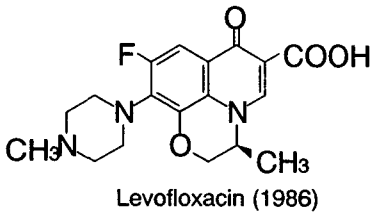
AT2468 (1979) R = C_2H_5

Tosufloxacin (1982) R =

Discovery of Quinolones (4)
Arrival of Newer Fluoroquinolones



Sparfloxacin (1986)



Levofloxacin (1986)

Therapeutic Contribution

- UTI: cystitis
  - standard first line therapy
- STD: gonococcal urethritis
  - standard first line therapy
  - single oral-dose treatment
- RTI: acute exacerbation of chronic bronchitis
  - reduction in risk of hospitalization
  - remedy for pseudomonal infection

Medical Needs (1)

- Novel antibiotics in general
  - can be used as empirical treatment
    - cover at least main causative pathogens
  - do not generate problems of bacterial resistance.
    - prevent development of cross-resistance
  - have an improved safety profile
    - clear class effect adverse reactions
  - improve patients' QOL
    - reduction in dose and duration of treatment

Medical Needs (2)

- Novel quinolones can be used
  - as an alternative tostandard drugs for treatment of pneumococcal pneumonia
  - empirically for treatment of RTI
  - for moderate cases of RTI
  - for pseudomonal infections
  - for pediatric infections
  - with a once-daily dose

Weak Points to Overcome

- Relatively low activity against S. pneumoniae
  - Most quinolones not recommended as a first choice for the treatment of pneumonia
- Interaction with anti-inflammatory agents
  - CNS adverse reactions are a main concern
- Interaction with theophylline
  - Theophylline is very often prescribed for patients with AECB

SWOT for Quinolones (in terms of RTI)

Strengths	**Opportunities**
activity against Gram (-)	empirical therapy
PK profile	improved QOL
Threats	**Weaknesses**
resistance development	activity against S. pneumoniae
image of UTI drugs	ADRs & interaction

Etiology in Adults: pneumonia

- Gram (+)
  - **S. pneumonia**: increase in penicillin resistant strains
- Gram (-)
  - **H. influenzae**: Beta-lactamase (+) strains
  - M. catarrhalis, K. pneumoniae
- Atypical pathogens
  - **M. pneumoniae**: increasing
  - C. pneumoniae, L. pneumophilia

Development of Resistance

- Penicillin resistant S. pneumoniae
- Beta-lactam resistant H. influenzae
- Beta-lactamase-producing M. catarrhalis
- Quinolone resistant P. aeruginosa
- MRSA

Benefit/Risk Assessment

- Patients and the medical community
  - QOL: shorter treatment, oral and once daily dosage
  - Safer drugs
  - Reduction in payment
- Regulatory Authorities
  - Necessity of new drugs
  - Balance in efficacy and safety
  - Differences compared to existing drugs
  - Benefits for patients and the medical community

Cost/Benefit Analysis

- By society
  - Contribution to health care
  - Cost effectiveness: comparison with the standard therapy
- By the company
  - Expansion of business
  - Costs of raw materials and manufacturing
  - Costs of quality control and logistics

Making Decision for Development

"Go" if most of the following elements are positive

- **Patent**: coverage of the product, area and duration
- **Efficacy**: antibacterial activity & spectrum
- **PK Profile**: ADME
- **Safety**: balance of class effects and other side effects
- **Marketing**: cost, sales price, competitors
- **Society**: social security, government policy

Development Strategy

- Targeted area
  - worldwide or domestic
- Starting clinical development
  - First step: which countries
- How to develop
  - Self-/co-development or licensing
- Indication(s)
  - wide indication/focused indication

List of Clinical Studies

- Phase I: tolerance, dose response
- Clinical Pharmacology: ADME & interactions
- Early Phase II: several open studies
- Late Phase II: dose finding studies (?)
- Phase III: double blind studies and strategical open studies
- Phase IIIb: enhancement of efficacy and safety

Clinical Study Design

- Diseases: RTI (pneumonia, AECB, sinusitis)
- Dosage: dose and duration of treatment
- Study design: double-blind/open?
- Comparator: standard therapy regardless of class of drugs/standard quinolone?
- Evaluation: endpoints (primary and secondary) for evaluating efficacy
- Statistical analysis: superiority/equivalence

Guidelines for Evaluation

- **US**
  - FDA (1977), *IDSA*/FDA guidelines (1992)
  - FDA "Points to Consider" (1992)
  - FDA draft "Guidance for Industry" (1997)
- **Europe**
  - BSAC (UK)(1989)/WHO (1986)
  - *ESCMID* guidelines in (1993)
- **Japan**
  - MHW first guidelines (1982), draft update (1987)
  - MHW draft new guidelines (1997)

Clinical Isolate Investigation

- Determination of MIC distribution with respect to causative pathogens
- Development of resistance by periodical survey
- Continuous monitoring through an established network

Worldwide Development of Sparfloxacin

- 1986: discovery/patent
- 1987: IND/Phase I in Japan (Dainippon)
- 1989: Phase I in EC (Rhone D.P.C. Europe)
- 1991: Phase I in US (Warner-Lambert)
- 1992: Phase III in US (Rhone-Poulenc Rorer)
- 1993: approval in Japan
- 1994: approval in France, UK
- 1994: clinical studies in Korea (Sam-A)
- 1995: approval in Korea
- 1996: approval in US

Claims According to Area/Medical Needs

Case of sparfloxacin

	Japan	EC	US
Indications (planned)	wide range	RTI, STD, UTI	RTI, UTI, SSSI
(claimed)	wide range	RTI, (STD)	RTI
Administration	qd or bid	qd	qd
Dose	100-300 mg	100 mg*:AECB 200 mg*:Pn., Si.	200 mg *
Duration of treatment	not specified	5 days & 10 days	11 days
Tablets	100 & 150 mg	200 mg	200 mg

*; loading dose (double) on Day 1

RTI: pneumonia, AECB, sinusitis

Safety class effects of quinolones

- Central nervous system: interaction with non-steroid anti-inflammatory drugs
- Interaction with theophylline: difficulties of concomitant use
- Photosensitivity: manageable but requires caution
- Tendinitis: many reports in France (pefloxacin)
- Temafloxacin syndrome: hematological effects

Conclusion

- In addition to targeting and selecting candidates, designing a good strategy for the clinical development of new antibacterial agents is a key issue.
- This strategy must be based on objective viewpoints and precise, with particular emphasis on scientific aspects, medical needs, regulatory affairs, marketing, and economics, taking into account not only the domestic situation but also international trends and needs.