Quinolones : A Comprehensive Review

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Am Fam Physician 2002;65:455-64.

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Quinolones - Mechanism of Action

- Inhibition of DNA gyrase
  - Formation of quinolone-DNA gyrase complex →induced cleavage of DNA
  - Primary target of quinolones in Gram-negative bacteria.
- Inhibition of type IV topoisomerase → G(+) bacteria
  - Primary target of quinolones in Gram-positive bacteria.

Quinolones - Pharmacokinetics

- Concentration-dependent bacterial killing
  - 殺菌效力與抗生素的尖峰濃度(Cmax)成正比
  - Postantibiotic effect about 1 ~ 2 hours
- 口服吸收好
  - quinolones chelate with cations (Al, Mg, Ca, Fe)
- Elimination half-lives → 1.5 to 16 hours
- majority of quinolones are excreted renally
  - sparfloxacin, moxifloxacin and trovafloxacin are excreted hepatically.

Quinolones – Tissue penetration

- Conc > serum
  - Stool
  - bile
  - prostatic tissue
  - lung tissue
  - Neutrophils
  - Macrophages
  - kidney
- Cons < serum
  - prostatic fluid
  - saliva
  - Bone
  - CSF

Antimicrobial Activity

G (-)

G (+)

Quinolone generations	Microbiologic activity	Administration and characteristics
First generation Nalidixic acid (NegGram) Cinoxacin (Cinobac)	Enterobacteriaceae	Oral administration Low serum and tissue drug concentrations Narrow gram-negative coverage
Second generation Class I Lomefloxacin (Maxaquin) Norfloxacin (Noroxin) Enoxacin (Penetrex)	Enterobacteriaceae	Oral administration Low serum and tissue drug concentrations Improved gram-negative coverage compared with first-generation quinolones Limited gram-positive coverage
Class II Ofloxacin (Floxin) Ciprofloxacin (Cipro)	Enterobacteriaceae, atypical pathogens; *Pseudomonas aeruginosa* (ciprofloxacin only)	Oral and intravenous administration Higher serum, tissue, and intracellular drug concentrations compared with class I agents Coverage of atypical pathogens
Third generation Levofloxacin (Levaquin) Sparfloxacin (Zagam)* Gatifloxacin (Tequin) Moxifloxacin (Avelox)	Enterobacteriaceae, atypical pathogens, streptococci	Oral and intravenous administration Similar to class II second-generation quinolones but with modest streptococcal coverage Increased hepatic metabolism (sparfloxacin and moxifloxacin)
Fourth generation Trovafloxacin (Trovan)*	Enterobacteriaceae, *P aeruginosa* (reduced or absent), atypical pathogens, methicillin-susceptible *Staphylococcus aureus*, streptococci, anaerobes	Oral and intravenous administration Similar to third-generation quinolones but with improved gram-positive coverage and added anaerobic coverage

Sparfloxacin and trovafloxacin have significant nonrenal elimination pathways → 不要用於治療UTI

Therapeutic Uses of Quinolones

- **Genitourinary Infections**
  - Complicated UTI
    - stones, obstructive uropathies, catheter related infections.
    - ciprofloxacin, lomefloxacin, levofloxacin, and gatifloxacin have higher renal clearance and greater renal concentration
    - *P. aeruginosa* → Failure rates : 20 %
- **Prostatitis**
  - excellent penetration into prostatic tissue
  - 4 ~ 6 weeks → eradication rates 67 to 91 %.
    - Treatment failures: shorter treatment courses and less susceptible bacteria(*P. aeruginosa* and Enterococcus species)
  - 1st line: Levofloxacin
    - Ciprofloxacin 用於 pseudomonal and enterococcal prostatitis

Therapeutic Uses of Quinolones

- **Respiratory Diseases**
  - Acute bacterial sinusitis → 不建議用quinolone為第一線用藥，因可能產生抗藥性。
  - Acute bronchitis
  - Community-acquired pneumonia
    - General ward :
      - macrolide + extended-spectrum cephalosporin
      - beta-lactam/beta lactamase inhibitor + macrolide
      - fluoroquinolone
    - ICU:
      - macrolide or a fluoroquinolone + extended-spectrum cephalosporin or a beta-lactam/betalactamase inhibitor

Therapeutic Uses of Quinolones

- **Respiratory Diseases**
  - Moxifloxacin and gatifloxacin have been shown to have superior in vitro activity against pneumococci.
  - ciprofloxacin and trovafloxacin have been studied most extensively in the treatment of nosocomial pneumonia.
    - Ciprofloxacin has been found to be comparable in efficacy to imipenem-cilastatin in mechanically ventilated patients
    - Fluoroquinolone monotherapymay worsen the increasing problem of antibiotic resistance in the nosocomial setting.

Therapeutic Uses of Quinolones

- **Sexually Transmitted Diseases**
  - PID is a polymicrobial infection
    - ofloxacin plus metronidazole
    - ofloxacin plus cefoxitin
    - ciprofloxacin plus clindamycin
      - Fluoroquinolone monotherapy is incomplete
- Gastroenteritis
  - Ciprofloxacin and ofloxacin are the agents of choice for treatment of enteric typhoid fever
  - Norfloxacin is superior to trimethoprim-sulfamethoxazole and doxycycline in the treatment of *Vibrio cholerae* infection

Quinolones – Adverse Events

TABLE 2
Adverse Effects of Quinolones*

Gastrointestinal: nausea, vomiting, diarrhea, abdominal pain
CNS: headache, dizziness, drowsiness, confusion, insomnia, fatigue, malaise, depression, somnolence, seizures, vertigo, lightheadedness, restlessness, tremor
Dermatologic: rash, photosensitivity reactions, pruritus
Other: QTc prolongation, hepatotoxicity, abnormal or bitter taste, tendon rupture

Because quinolones have been associated with arthropathy and chondrotoxicity in immature animals, they are not recommended for use in children and adolescents younger than 18 years of age, or in pregnant or breastfeeding women.

Quinolones - Drug Interactions

TABLE 3
Potential Interactions Between Quinolones and Other Drugs

Any quinolone*
Decreased absorption of quinolones if didanosine (Videx) or multivalent cations are administered concomitantly or less than two hours before or after a quinolone.†
May increase anticoagulant effects of warfarin (Coumadin)‡
May increase caffeine levels§
May increase cyclosporine (Sandimmune) levels§
May increase theophylline levels§
May prolong QTc if used concomitantly with antiarrhythmics (e.g., class IA and III agents) or with cisapride (Propulsid)‖
May increase risk of CNS stimulation and convulsions if used concomitantly with nonsteroidal anti-inflammatory drugs
May lead to hypoglycemia and/or hyperglycemia if used concomitantly with antidiabetic agents (oral hypoglycemics or insulin)¶

Gatifloxacin (Tequin)
Increased serum digoxin (Lanoxin) levels#

Trovafloxacin (Trovan)
Decreased absorption if used concomitantly with sodium citrate and citric acid oral solution (Bicitra)
Decreased effect of orally administered trovafloxacin if used concomitantly with intravenously administered morphine

Applications of Fluoroquinolones in Biologic Warfare

Specific fluoroquinolones are indicated for prophylaxis or treatment of anthrax, cholera, plague, brucellosis, and tularemia.

TABLE 4
Selected Potential Biologic Pathogens: Postexposure Prophylaxis and Treatment

Pathogen	*Postexposure prophylaxis*	*Treatment*
Bacillus anthracis (anthrax)	Agent of choice: ciprofloxacin (Cipro)* Alternative: doxycycline (Vibramycin)	Agents of choice: ciprofloxacin, doxycycline Alternative if organisms are penicillin sensitive: penicillin G
Vibrio cholerae (cholera)	Not available	Agents of choice: oral rehydration therapy, tetracycline, doxycycline, ciprofloxacin, norfloxacin (Noroxin)
Yersinia pestis (plague)	Agents of choice: doxycycline, ciprofloxacin Alternative: tetracycline	Agents of choice: streptomycin, gentamicin, ciprofloxacin Alternative: doxycycline
Brucella melitensis (brucellosis)	Agents of choice: doxycycline plus rifampin (Rifadin)	Agents of choice: doxycycline plus rifampin Alternative: ofloxacin (Floxin) plus rifampin
Francisella tularensis (tularemia)	Agent of choice: doxycycline Alternatives: tetracycline, ciprofloxacin	Agent of choice: streptomycin Alternatives: gentamicin, ciprofloxacin

Thank for your attention !