Pharmacology

Subject :

Lec no : lec 28

Done By : Hala AL Beshtawe

وَقُل رَّبِّ زِدْنِي عِلْمًا

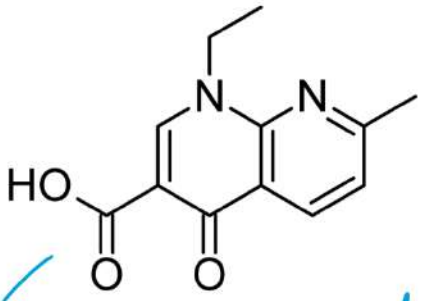
Fluoroquinolones

Quinolones and Folic Acid Antagonists

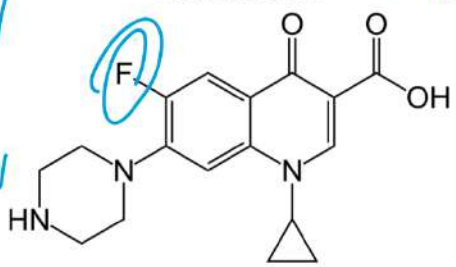
Pharmacology and Toxicology
General Pharmacology
Second Year Medical Students
Tareq Saleh
Faculty of Medicine
The Hashemite University

Textbook: Chapter 31 pp 400-412

Quinolones



Nalidixic acid → original chemical in quinolone family



Ciprofloxacin

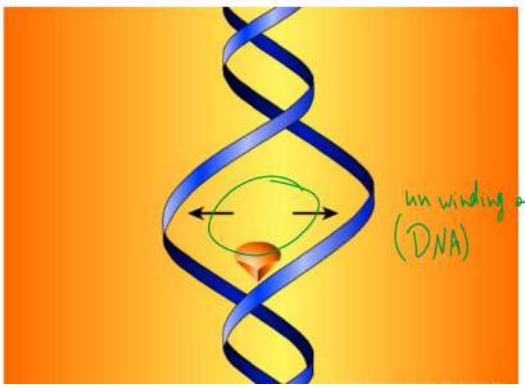
تم اخذ من الفلوروكينولونات

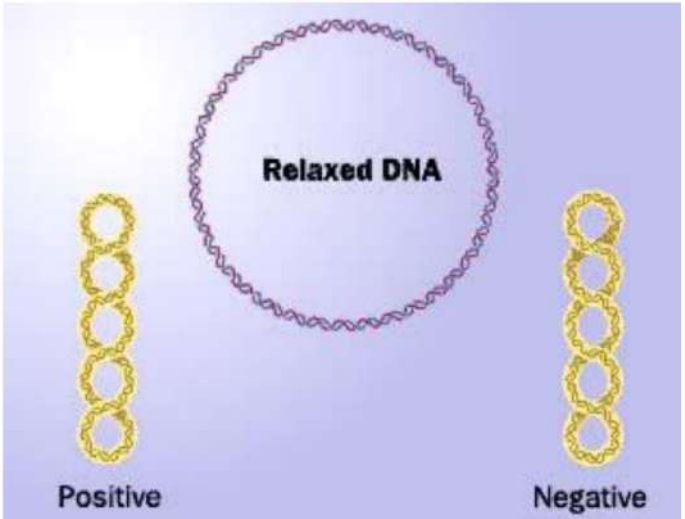
FLUOROQUINOLONES

- *Ciprofloxacin* CIPRO → UTI (التجاري)
- *Levofloxacin* LEVAQUIN
- *Moxifloxacin* AVELOX
- *Nalidixic acid*
- *Norfloxacin* NOROXIN
- *Ofloxacin*

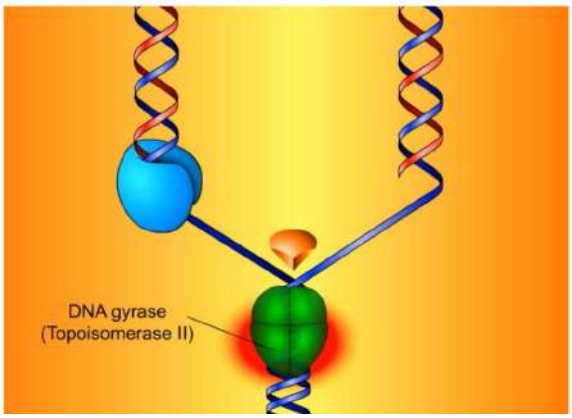
DNA Supercoiling

DNA Helicase





DNA Gyrase



Quinolones, Folic Acid Antagonists, and Urinary Tract Antiseptics

31

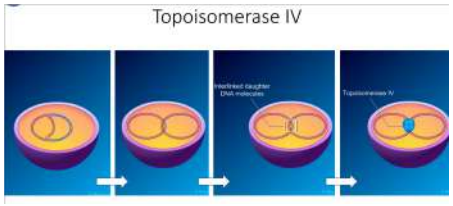
Kenneth P. Klinker and Joseph Pardo

I. FLUOROQUINOLONES

Discovery of quinolone antimicrobials led to the development of numerous compounds utilized in clinical practice. Following synthesis of *nalidixic acid* in the early 1960s, continued modification of the quinolone nucleus expanded the spectrum of activity, improved pharmacokinetics, and stabilized compounds against common mechanisms of resistance. Due to these enhancements, quinolone antimicrobials were rapidly integrated into human and agricultural medicine. Unfortunately, overuse resulted in rising rates of resistance in gram-negative and gram-positive organisms, increased frequency of Clostridium difficile infections, and identification of numerous untoward adverse effects. Consequently, these agents have been relegated to second-line options for various indications. This chapter reviews key characteristics of fluoroquinolones and their role in therapy. The fluoroquinolones and other antibiotics discussed in this chapter are listed in Figure 31.1.

A. Mechanism of action

Most bacterial species maintain two distinct type II topoisomerases that assist with deoxyribonucleic acid (DNA) replication, DNA gyrase, and topoisomerase IV. DNA gyrase is responsible for reducing torsional stress ahead of replicating forks by breaking double-strand DNA and introducing negative supercoils. Topoisomerase IV assists in separating daughter chromosomes once replication is completed. Following cell wall entry through porin channels, fluoroquinolones bind to these enzymes and interfere with DNA ligation. This interference increases the number of permanent chromosomal breaks, triggering cell lysis. In general, fluoroquinolones have different targets for gram-negative (DNA gyrase) and gram-positive organisms (topoisomerase IV), resulting in rapid cell death.



FLUOROQUINOLONES
Ciprofloxacin CIPRO
Delafloxacin BAXDELA
Gemifloxacin FACTIVE
Levofloxacin LEVAQUIN
Moxifloxacin AVELOX, MOXEZA, VIGAMOX
Ofloxacin GENERIC ONLY
INHIBITORS OF FOLATE SYNTHESIS
Mafenide SULFAMYLON
Silver sulfadiazine SILVADENE, SSD, THERMAZENE
Sulfadiazine GENERIC ONLY
Sulfasalazine AZULFIDINE
INHIBITORS OF FOLATE REDUCTION
Pyrimethamine DARAPRIM
Trimethoprim PRIMSOL, TRIMPEX
COMBINATION OF INHIBITORS OF FOLATE SYNTHESIS AND REDUCTION
Cotrimoxazole (trimethoprim + sulfamethoxazole) BACTRIM, SEPTRA
URINARY TRACT ANTISEPTICS
Methenamine HIPREX, UREX
Nitrofurantoin MACROBID, MACRODANTIN

Figure 31.1
Summary of drugs described in this chapter.

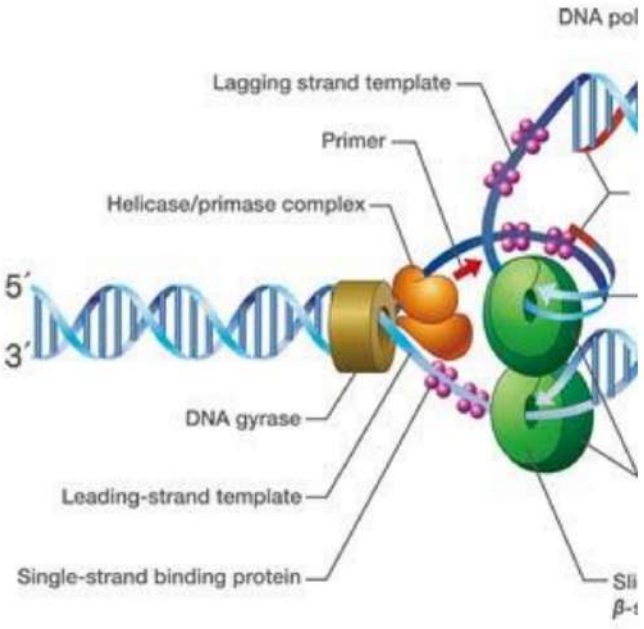
Quinolones

Mechanism of action

- Inhibit ligation step of bacterial DNA gyrase and bacterial topoisomerase IV

-Inhibition of gyrase: increases the number of permanent chromosomal breaks

-Inhibition of topo IV: interferes with the separation of newly replicated DNA



Quinolones

Antibacterial spectrum

- Bactericidal
- Time-dependent killing
- Effective against gram-negative (including E.coli and Pseudomonas), atypical, gram-positive (strep), mycobacteria….
- Levofloxacin: excellent activity against *S. pneumoniae*

B. Antimicrobial spectrum

Fluoroquinolones are bactericidal and exhibit area-under-the-curve/minimum inhibitory concentration (AUC/MIC)-dependent killing. A major facet of their development centered on improving microbiologic coverage. Modifications to the quinolone nucleus steadily improved topoisomerase inhibitory activity and facilitated bacterial cell wall penetration. These changes enhanced activity against a variety of pathogens including aerobic gram-negative and gram-positive organisms, atypical organisms (for example, Chlamydia, Legionella, and Mycoplasma spp.), and anaerobes. Based on the impact of these structural changes, fluoroquinolones are often classified according to spectrum of activity.

First-generation compounds (for example, *nalidixic acid*) were narrow spectrum agents with activity against aerobic gram-negative bacilli, mostly Enterobacteriaceae. Second-generation compounds (for example, *ciprofloxacin*) exhibit improved intracellular penetration and broadened coverage, which includes Enterobacteriaceae, Pseudomonas aeruginosa, Haemophilus influenzae, Neisseria spp., Chlamydia spp., and Legionella spp. Third-generation compounds (for example, *levofloxacin*) maintain the bacterial spectrum of second-generation agents, with improved activity against Streptococcus spp., including S. pneumoniae, *methicillin*-susceptible Staphylococcus aureus, Stenotrophomonas maltophilia, and Mycobacterium spp. Fourth-generation compounds (*moxifloxacin*, *gemifloxacin*, and *delafloxacin*) have enhanced gram-positive activity, including Staphylococcus and Streptococcus spp. *Delafloxacin* has activity against *methicillin*-resistant Staphylococcus aureus (MRSA) and Enterococcus faecalis. Further, *delafloxacin* and *moxifloxacin* have activity against Bacteroides fragilis and Prevotella spp., while maintaining activity against Enterobacteriaceae and Haemophilus influenzae. From this group, only *delafloxacin* has activity against Pseudomonas aeruginosa. Lastly, these agents maintain atypical coverage, with *moxifloxacin* and *delafloxacin* showing activity against Mycobacteria spp. Common therapeutic applications of fluoroquinolones are shown in Figure 31.2.

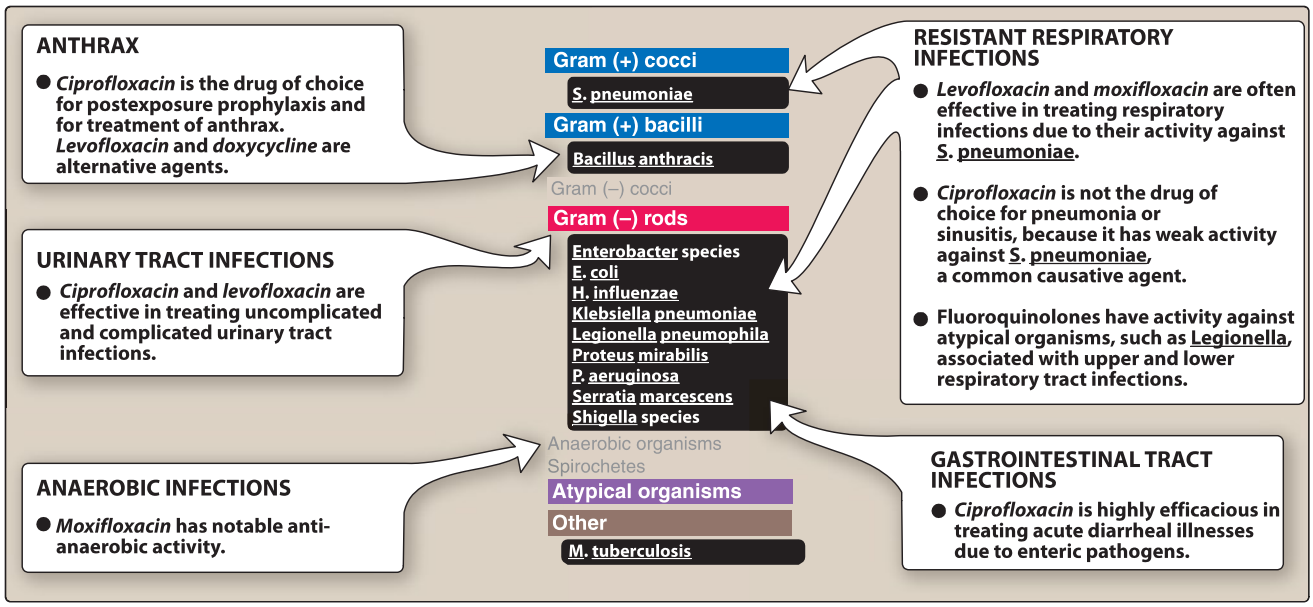


Figure 31.2
Typical therapeutic applications of fluoroquinolones.

Quinolones

Antibacterial spectrum

- **First-generation (nonfluorinated): nalidixic acid**

-narrow-spectrum → the old once + doesn't cover that many bacterial species

- **Second-generation: ciprofloxacin and norfloxacin**

-gram-negative (pseudomonas, H.influenzae) and atypical

- **Third-generation: levofloxacin**

-gram-negative, atypical and gram-positive (including S. pneumoniae and MSSA)

- **Fourth-generation: moxifloxacin, Gemifloxacin, delafloxacin**

-enhanced gram-positive effects including staph and strep + coverage of gram-negative Enterobacteriaceae

-Homework: Which fourth-generation fluoroquinolone is effective against MRSA?

Delafloxacin has activity against methicillin esistant Staphylococcus aureus (MRSA) and Enterococcus fae alis. Further, delafloxacin and moxifloxacin have activity against Bacteroides fragilis and Prevotella spp

Examples of Clinically Useful Fluoroquinolones

Ciprofloxacin

- Effective against gram-negative including P. aeruginosa
- Clinical indications:

1. Gastroenteritis e.g., traveler's diarrhea
2. Typhoid fever → Caused by salmonela typhy
3. Anthrax (drug of choice) prevent the post exposure prophylaxis
4. Urinary tract infections

(high dose for pseudomonal infections)

Levofloxacin

- Similar to cipro but also effective against gram-positive (strep not staph) → (UTI) بعالج مش
- Clinical indications:

First-line therapy for community acquired-pneumonia → Caused by streptococcus pneumoniae

Examples of Clinically Useful Fluoroquinolones

4th Generation

Moxifloxacin → Same as levofloxacin

- Effective against gram-negative, S. pneumonia and mycobacterium (TB)
- Clinical indications:

1. For community-acquired but not nosocomial pneumonia (weak against pseudomonas)
2. Second-line for TB

Community acquired

* we don't prefer it to treat hospital acquired pneumoniae → Caused by multi drug resestant bacteria
MRSA → No
Pseudomonas → weak

Fluoroquinolones and UTIs

ciprofloxacin → used to treat severe UTI } effective لكن بعض against UTI
↳ we don't use it for acute uncomplecated cystitis }

"Fluoroquinolones (eg, ofloxacin, ciprofloxacin, levofloxacin) are highly effective in UTIs, but these agents have a propensity for causing collateral damage and should be reserved for important uses other than acute uncomplicated cystitis. IDSA guidelines recommend that fluoroquinolones be used as second-line agents for acute uncomplicated cystitis and as first-line oral therapy for complicated cystitis".

International Clinical Practice Guidelines for the Treatment of Acute Uncomplicated Cystitis and Pyelonephritis in Women: A 2010 Update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases

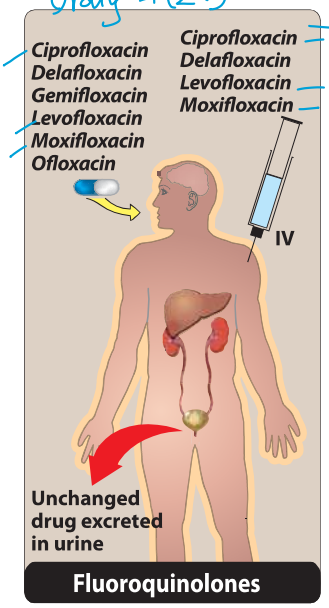
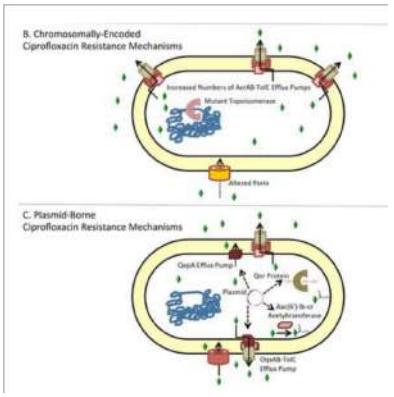


Figure 31.3
Administration and fate of the fluoroquinolones.



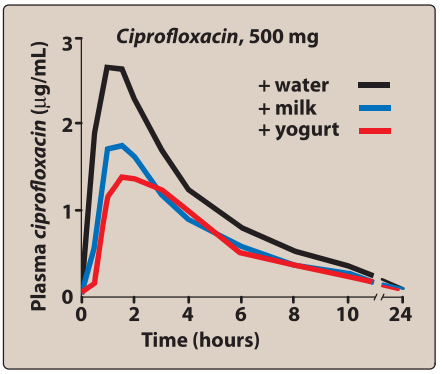


Figure 31.4
Effect of dietary calcium on the absorption of *ciprofloxacin*.

C. Resistance

Numerous mechanisms of fluoroquinolone resistance exist in clinical pathogens. High-level fluoroquinolone resistance is primarily driven by chromosomal mutations within topoisomerases, although decreased entry, efflux systems, and modifying enzymes play a role. Mechanisms responsible for resistance include the following:

1. **Altered target binding:** Mutations in bacterial genes encoding DNA gyrase or topoisomerase IV (for example, gyrA or parC) alter target site structure and reduce binding efficiency of fluoroquinolones.

2. **Decreased accumulation:** Reduced intracellular concentration is linked to 1) a reduction in membrane permeability or 2) efflux pumps. Alterations in membrane permeability are mediated through a reduction in outer membrane porin proteins, thus limiting drug access to topoisomerases. Efflux pumps actively remove fluoroquinolones from the cell.

3. **Fluoroquinolone degradation:** An aminoglycoside acetyltransferase variant can acetylate fluoroquinolones, rendering them inactive.

D. Pharmacokinetics

1. **Absorption:** Fluoroquinolones are well absorbed after oral administration, with *levofloxacin* and *moxifloxacin* having a bioavailability that exceeds 90% (Figure 31.3). Ingestion of fluoroquinolones with *sucralfate*, aluminum- or magnesium-containing antacids, or dietary supplements containing iron or zinc can reduce the absorption. Calcium and other divalent cations also interfere with the absorption of these agents (Figure 31.4).

2. **Distribution:** Binding to plasma proteins ranges from 20% to 84%. Fluoroquinolones distribute well into all tissues and body fluids. Concentrations are high in bone, urine (except *moxifloxacin*), kidney, prostatic tissue (but not prostatic fluid), and lungs as compared to serum. Penetration into cerebrospinal fluid is good, and these agents may be considered in certain central nervous system (CNS) infections. Accumulation in macrophages and polymorphonuclear leukocytes results in activity against intracellular organisms such as Listeria, Chlamydia, and Mycobacterium.

3. **Elimination:** Most fluoroquinolones are excreted renally. Therefore, dosage adjustments are needed in renal dysfunction. *Moxifloxacin* is metabolized primarily by the liver, and while there is some renal excretion, no dose adjustment is required for renal impairment (see Figure 31.3).

E. Adverse reactions

In general, fluoroquinolones are well tolerated (Figure 31.5). Common adverse effects leading to discontinuation are nausea, vomiting, headache, and dizziness. These agents carry boxed warnings for tendinitis, tendon rupture, peripheral neuropathy, and CNS effects

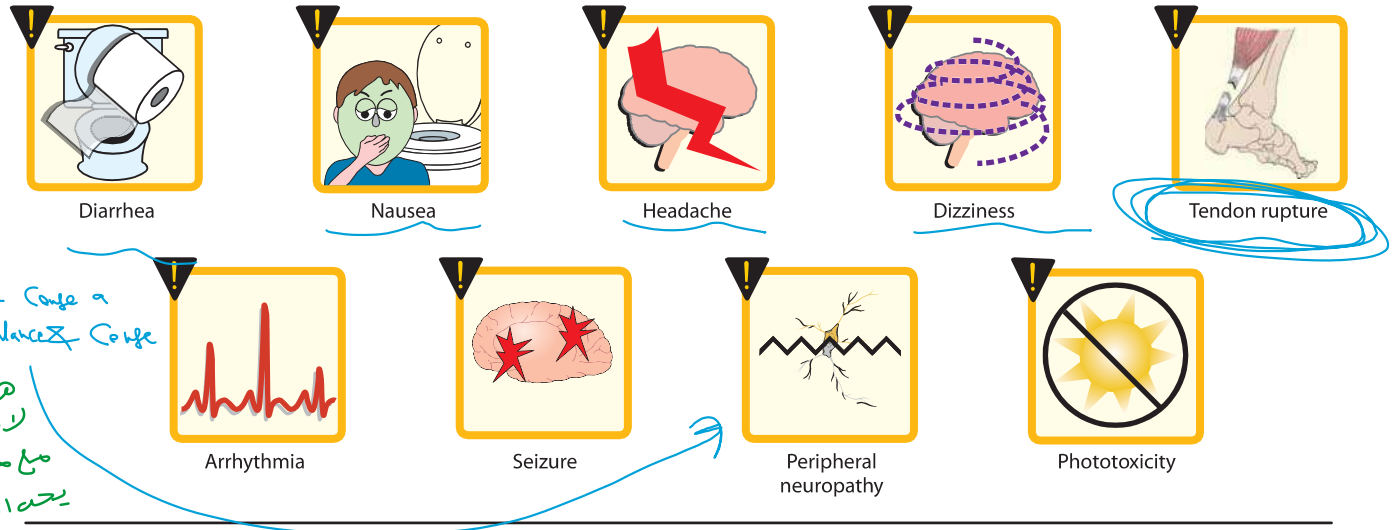


Figure 31.5
Some adverse reactions to fluoroquinolones.

(hallucinations, anxiety, insomnia, confusion, and seizures). Patients taking fluoroquinolones are at risk for phototoxicity resulting in exaggerated sunburn reactions. Patients should use sunscreen and avoid excessive exposure to ultraviolet (UV) light. Arthropathy is uncommon, but arthralgia and arthritis are reported with fluoroquinolone use in pediatric patients. Use in the pediatric population should be limited to distinct clinical scenarios (for example, cystic fibrosis exacerbation). Hepatotoxicity or blood glucose disturbances (usually in diabetic patients receiving oral hypoglycemic agents or insulin) have been observed. Identification of any of these events should result in prompt removal of the agent. Fluoroquinolones may prolong the QT_c interval, and these agents should be avoided in patients predisposed to arrhythmias or taking medication associated with QT prolongation. *Ciprofloxacin* inhibits P450 1A2- and 3A4-mediated metabolism. Serum concentrations of medications such as *theophylline*, *tizanidine*, *warfarin*, *ropinirole*, *duloxetine*, *caffeine*, *sildenafil*, and *zolpidem* may be increased (Figure 31.6).

Drug-drug interaction
- Cipro can inhibit metabolism of theophylline, others
- Quinolones can raise serum warfarin

F. Examples of clinically useful fluoroquinolones

Due to increasing resistance and boxed warnings, fluoroquinolones should be used with caution in select circumstances. They may be considered in patients who do not tolerate other agents (for example, severe beta-lactam allergies) or as definitive therapy once susceptibilities are available. Listed below are potential indications for these agents.

1. **Ciprofloxacin:** *Ciprofloxacin* [SIP-roe-FLOX-a-sin] has good activity against gram-negative bacilli, including P. aeruginosa. *Ciprofloxacin* is used in the treatment of traveler's diarrhea, typhoid fever, and anthrax. It is a second-line agent for infections arising from intra-abdominal, lung, skin, or urine sources. Of note, high-dose therapy should be employed when treating Pseudomonas infections.

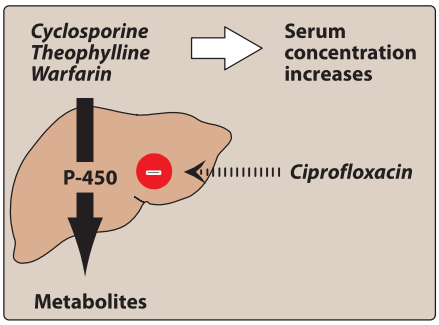


Figure 31.6
Drug interactions with *ciprofloxacin*.