Tetracyclines

Jonathan G. Ma | Amir Elhassan | Alan David Kaye | D'andra J. Davis

Uses

- Administered PO (most common), IV (fewer side effects), IM (rare, painful), topically (eyes only).
- Original broad-spectrum antibiotic with activity against gram-positive and gram-negative bacteria; species of *Chlamydia, Rickettsia, and Mycoplasma* (in adults); some protozoa. One of few agents active against organisms without cell walls. Resistance is increasing worldwide.
- Secondary uses: Alternative drugs in the treatment of syphilis, treatment of respiratory infections caused by susceptible organisms, prophylaxis against infection in chronic bronchitis, treatment of leptospirosis, and in the treatment of acne.
- Selective uses:
  - Tetracycline for treatment of GI ulcers caused by *Helicobacter pylori*
  - Doxycycline for Lyme disease, prevention of malaria, and treatment of amebiasis
  - Minocycline for meningococcal carriers
  - Demeclocycline for management of pts with ADH-secreting tumors
- Usage in USA is about 20 million doses per y.

Perioperative Risks

- IV tetracycline frequently leads to thrombophlebitis, lessens efficacy of oral contraceptives.
- Decrease dose with age.
- Decrease dose in those with poor renal/hepatic function, because tetracycline accumulates in such pts and can lead to hepatic toxicity (instead, in pts with renal dysfunction, use doxycycline, which has an unchanged elimination half-life in such pts).
- Barbiturates may lower the half-life β; tetracycline will increase cone of digoxin or warfarin. Pts may exhibit GI distress, even *Clostridium difficile* colitis.

Worry About

- Tetracycline (especially first-generation) is absorbed poorly if given within 3 h of divalent or trivalent cations (Ca^{2+}, Al^{3+}, Mg^{2+}, Fe^{2+}, Bi^{3+}).
- Possibility of tetracycline-resistant bacterial enteritis as well as GI distress limits the oral doses of these antibiotics.
- Doxycycline should be administered only PO or IV.

Overview/Pharmacology

- Two generations: First (e.g., tetracycline) and second (e.g., doxycycline, minocycline).
- Classified as bacteriostatic (newest ones are possibly bactericidal).
- First-generation half-life β is 6–12 h; excreted in urine and feces.
- Second-generation drugs are more lipophilic, greater V_d, recirculation, half-life β 16–18 h; >90% of doxycycline is excreted in feces; safe for anephric pts.
- Adjust dose with age and for pts with impaired renal/hepatic function.
- After PO administration, drugs taken up in duodenum (especially first-generation drugs); peak level 2 h; IV peak level 1 h.

Drug Class/Mechanism of Action/Usual Dose

- Original broad-spectrum antibiotic.
- Effective against *Rickettsia, Mycoplasma, Chlamydia, Borrelia*, spirochetes, some fungi
- Local irritant (in sclerotherapy).
- Normal dose impairs bacterial protein synthesis; binds via a Mg^{2+} bridge to single active site of 30 S subunit of bacterial ribosome; prevents binding of aminoacyl tRNA to the mRNA-ribosome complex. Without this codon-anticodon interaction, formation of peptide chains cannot proceed.
- Inhibit collagenase (osteoarthritis), tumor-induced angiogenesis (chemotherapy)
- Usual dose: Doxycycline 100 mg PO twice daily.

Assessment Points

System	Effect	Assessment by Hx	Test
HEENT	Children: Brown teeth; risk greatest from second trimester to age 8 y		
CV	Frequently causes thrombophlebitis decrease Tumor-mediated angiogenesis		
HEPAT	Rare toxicity, especially with higher doses, IV route, or in pregnancy; usually reversible with drug cessation	Hepatitis	LFTs
GI	Irritation, distress, especially when given PO, higher doses may lead to superinfection (with *S. aureus or C. difficile*) Disturbances in the normal flora may lead to candidiasis (oral and vaginal)	Mild N/V, severe colitis	
HEME	May inhibit/suppress antibody production, leukotaxis, complement system		
GU	May aggravate uremia in susceptible pts; crosses placenta, excreted in breast milk		BUN
CNS	Penetrates CNS; may increase ICP during therapy, especially in infants Doxycycline and minocycline: Vestibular problems (dizziness and vertigo), especially in women; reversible	Vision change, headache Dizziness, nausea	
DERM	Phototoxic skin reaction, especially with first-generation drugs		
MS	Retards bone growth in preemies, decreases collagenase in joints		

Key References: Chopra I, Hawkey PM, Hinton M: Tetracyclines, molecular and clinical aspects, *J Antimicrob Chemother* 29(3):245–277, 1992; Stoelting RK: *Pharmacology and physiology in anesthetic practice*, Philadelphia, 2006, Lippincott-Raven; Trevor AJ, Katzung BG, Masters SB: *Katzung & Trevor's review of pharmacology*, New York, 2007, McGraw-Hill Medical.

Perioperative Implications

Preoperative Concerns

- May increase digoxin levels, higher prothrombin time if pt is on warfarin

Possible Drug Interactions

- Methoxyflurane, tetracycline may lead to renal failure
- Barbiturates may lower half-life of β.

Reversal

- May augment nondepolarizing NM blocker.

Novel Therapies—Potential Nonantibiotic Indications

- Minocycline found to be cytoprotective; may have protective role in cardiovascular pathology and activity against myocardial ischemia-reperfusion injury.
- Reduces tolerance to morphine; can reduce symptoms of allodynia and hyperalgesia.
  - Neuroprotective properties in neurogenerative diseases associated with glial activation thought critical in neuropathic pain.
  - Neuroprotective in cerebral ischemia, spinal cord injury, Parkinson disease, Huntington disease, and Alzheimer disease.
  - Minocycline shown to inhibit sevoflurane-induced apoptosis, inflammation, amyloid accumulation.
  - Minocycline may alleviate postop cognitive impairment.
- Tetracyclines have been used successfully for pleurodesis.

Anticipated Problems/Concerns

- Although resistance is rising, tetracyclines remain useful antibiotics, with nonantibiotic indications increasing.
- Contraindicated in pregnancy and childhood.