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The Tetracyclines

JERRY D. SMILACK, M.D.

The tetracyclines, among the first of the antibiotics to become available 50 years ago, remain widely used. Tetracyclines have bacteriostatic activity against a wide variety of pathogens that are responsible for many common and some exotic infections. They are particularly valuable in the treatment of atypical pneumonia syndromes, chlamydial genital infections, rickettsial infection (Rocky Mountain spotted fever, typhus, Q fever), Lyme disease, and ehrlichiosis. On the basis of pharmacokinetic considerations, doxycycline is the preferred agent among the tetra-

cycline congeners. Minocycline may have a limited role in the treatment of methicillin-resistant staphylococcal disease in situations in which an oral antimicrobial agent may be appropriate. The tetracyclines are generally contraindicated during pregnancy and childhood because of their association with dental staining and interference with bone growth. Photosensitivity may occur with some tetracyclines, and several drug and food interactions may limit gastrointestinal absorption.

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Discovered by Duggar¹ 50 years ago, the tetracyclines remain one of the most widely prescribed antibiotic classes in the world. Data collected in 1992 showed that, in the United States, tetracyclines were prescribed by office-based physicians more often than were penicillins, trimethoprim-sulfamethoxazole, ciprofloxacin, or ampicillin; only amoxicillin and erythromycins were prescribed more frequently.² During a 12-month period ending in March 1997, wholesale cost of all tetracycline prescriptions filled in US retail pharmacies totaled almost \$400 million (National Prescription Audit. Unpublished data).

AVAILABLE TETRACYCLINES—SIMILARITIES AND DIFFERENCES

Five tetracyclines are available in the United States (Table 1). The superior pharmacokinetic properties, lesser toxicity, and low cost of doxycycline make it the agent of choice among the tetracyclines. All but demeclocycline are available generically at low cost, although minocycline is considerably more expensive than the other generic tetracyclines. The cost of a course of doxycycline is roughly equivalent to that of tetracycline.

Antimicrobial Activity

The tetracyclines inhibit a wide array of aerobic and anaerobic bacteria, including many rickettsiae, chlamydiae, mycoplasmas, spirochetes, and even some protozoa and mycobacteria.³⁻⁵ These agents are generally bacteriostatic but not bactericidal. Bacterial protein synthesis is

inhibited by reversible binding on the 30 S ribosome and blocking the attachment of transfer RNA to an acceptor site on the messenger RNA ribosomal complex.³

Against certain pathogens, minocycline and doxycycline are more potent than the other tetracycline congeners. Minocycline has excellent in vitro inhibitory activity against both *Staphylococcus aureus* and coagulase-negative staphylococci (for example, *S. epidermidis*), particularly methicillin-resistant *S. aureus* and methicillin-resistant *S. epidermidis* strains.⁶⁻⁸ In one study, all 102 isolates of methicillin-resistant *S. aureus* were inhibited by minocycline concentrations of 2 µg/mL or lower.⁶ A larger study that included 723 *S. aureus* and 1,402 *S. epidermidis* isolates found minocycline susceptibility to be 96% and 98%, respectively.⁷ *Mycobacterium marinum* is susceptible to minocycline, whereas other mycobacteria such as *M. fortuitum* and *M. chelonae* are more susceptible to doxycycline.³

Pharmacokinetic and Pharmacodynamic Considerations

A comparison of pharmacologic properties of the tetracyclines is helpful because certain attributes can be advantageous⁹ (Table 2). Most tetracyclines should be avoided in patients with renal insufficiency; substantial increases in serum levels as a result of diminished renal filtration may lead to hepatotoxicity. In contrast, doxycycline and minocycline are eliminated through the hepatobiliary and gastrointestinal tracts. Doxycycline can be administered without modification in patients with renal failure. Because experience is limited and data concerning pharmacokinetics are conflicting,⁵ minocycline should be avoided in the presence of renal failure.

In light of the long elimination half-lives of doxycycline and minocycline, once- or twice-daily dosing is possible.

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Individual reprints of this article are not available. The entire Symposium on Antimicrobial Agents will be available for purchase as a bound booklet from the *Proceedings* Editorial Office at a later date.

Table 1.—Tetracyclines Available in the United States

Generic name	Trade names	Preparations
Demeclocycline	Declomycin	Oral
Doxycycline	Vibramycin, Doryx, Doxycin, Monodox, and others	Oral and parenteral
Minocycline	Minocin	Oral and parenteral
Oxytetracycline	Terramycin	Oral and parenteral
Tetracycline	Achromycin V, Panmycin, Robitet, Sumycin, Tetracyn, and others	Oral and parenteral

Milk, antacids, iron supplements, and probably other substances with calcium, magnesium, aluminum, and iron decrease tetracycline gastrointestinal absorption considerably and should be ingested at least several hours before or after administration of tetracycline. Although doxycycline and minocycline absorption may be less affected by these divalent and trivalent cations,^{3,9} avoiding administration within 1 to 2 hours after ingestion of interfering food or medication is prudent.

Several additional drug interactions involving the tetracyclines are infrequent but deserve mention.⁹ Anticonvulsants (for example, barbiturates, carbamazepine, and phenytoin) induce hepatic microsomal metabolism of tetracyclines and consequently decrease tetracycline serum concentrations. If given concurrently, cholestyramine and colestipol may bind tetracycline and reduce gastrointestinal absorption. Oral contraceptive efficacy may be decreased with concurrent use of tetracyclines. Potentiation of warfarin-induced anticoagulation with tetracycline use necessitates close monitoring of a patient's prothrombin time.

MAIN INDICATIONS

The tetracyclines are considered the antimicrobial drugs of choice or acceptable alternative agents for a wide variety of infections. Some of the more important uses of the tetracyclines are listed in Table 3. In most situations, any one of the tetracyclines can be selected without concern of a specific antimicrobial advantage of one agent over another. Minocycline is the preferable tetracycline congener for methicillin-resistant staphylococcal therapy when vanco-

mycin is not otherwise considered appropriate.¹² Doxycycline is more active than tetracycline against *Streptococcus pneumoniae*¹³ and may be an acceptable alternative agent in the treatment of pneumococcal pneumonia,¹⁴ but its use should be considered only when high-level penicillin resistance is unlikely.

Certain tetracyclines have been useful in the treatment of several presumably nonmicrobial conditions. Through its inhibition of antidiuretic hormone-induced water reabsorption in the renal tubule and collecting ducts, demeclocycline is indicated for the treatment of the syndrome of inappropriate antidiuretic hormone.⁹ One placebo-controlled, double-blind study demonstrated modest benefit of minocycline in patients with rheumatoid arthritis.¹⁵ Doxycycline may have value in preventing clogging of biliary tract stents.¹⁶ As sclerosing agents, the tetracyclines are useful for the treatment of malignant and other refractory pleural effusions.

TOXICITY AND CONTRAINDICATIONS

Although the tetracyclines are generally well tolerated, certain adverse effects are important, two of which are photosensitivity and discoloration of developing teeth.⁵ Photosensitive reactions can occur in patients taking any of the tetracyclines, although they may be less frequent with doxycycline¹⁷ and minocycline.¹⁸ Tetracycline deposition in bone results in discoloration of primary dentition and may temporarily inhibit bone growth.⁵ The tetracyclines are usually contraindicated during pregnancy and breastfeeding and in children younger than 8 years.

Table 2.—Pharmacologic Characteristics of the Tetracyclines

Drug	Oral absorption (%)	Effect of food on absorption	Elimination half-life (h)	Effect of renal insufficiency on half-life	Primary mode of elimination
Demeclocycline	66	Decreased	10-17	Prolonged	Renal
Doxycycline	90-100	None	12-22	None	Hepatobiliary
Minocycline	90-100	None	11-23	None	Hepatobiliary
Oxytetracycline	58	Decreased	6-10	Prolonged	Renal
Tetracycline	75	Decreased	6-11	Substantially prolonged	Renal

Data from the United States Pharmacopeial Convention.⁹

Table 3.—Major Clinical Conditions for Which Tetracyclines May Be Used*

Respiratory infections
Community-acquired pneumonia in an outpatient setting
Atypical pneumonia (<i>Mycoplasma pneumoniae</i> , <i>Chlamydia pneumoniae</i> , psittacosis)
Acute exacerbations of chronic bronchitis
Legionellosis†
Genital infections
Chlamydia trachomatis (nongonococcal urethritis, pelvic inflammatory disease, epididymitis, prostatitis, lymphogranuloma venereum)
Granuloma inguinale
Syphilis†
Systemic infections
Rickettsiae (Rocky Mountain spotted fever, endemic and epidemic typhus, Q fever)
Brucellosis (in combination with rifampin or streptomycin)
Lyme borreliosis
Ehrlichiosis
Relapsing fever (<i>Borrelia recurrentis</i>)
Vibrio (cholera, <i>V. vulnificus</i> , and <i>V. parahaemolyticus</i>)
Tularemia†
Bacillary angiomatosis (bartonellosis)†
Leptospirosis†
Other (local and systemic) infections
Methicillin-resistant <i>Staphylococcus aureus</i> and <i>S. epidermidis</i> † (minocycline) when vancomycin or other agents are not considered appropriate
<i>Pasteurella multocida</i> †
<i>Mycobacterium marinum</i> †
Helicobacter pylori (in combination with bismuth subsalicylate and metronidazole or clarithromycin)
<i>Yersinia pestis</i> †
Other conditions
Acne vulgaris
Prophylaxis
Mefloquine-resistant <i>Plasmodium falciparum</i> malaria

*Tetracyclines are the drug of choice for the infections that are in boldface.

†Infections for which a tetracycline is an acceptable alternative to standard agents.

Data from references 3, 5, and 9 through 11.

Hepatotoxicity, specifically acute fatty necrosis, may occur in pregnant women and in patients with renal impairment, as well as in those receiving high-dose tetracycline therapy.⁹

Esophageal ulceration has been reported with use of doxycycline but can be minimized with adequate fluid intake when a capsule or tablet is given orally.¹⁹⁻²¹ Certain vestibular side effects, including dizziness, ataxia, and vertigo, occur in association with minocycline use, but the reported frequency varies widely.¹⁸ Minocycline use has been associated with skin and mucous membrane pigmentation.⁹ Blue or blue-black oral pigmentation was seen in

10% of patients taking minocycline for at least 1 year; the rate increased to 20% after 4 years of continuous use.²²

Infrequent or relatively minor side effects associated with tetracycline treatment include gastrointestinal intolerance, diarrhea, and fungal superinfection.⁹ Lupuslike symptoms associated with minocycline therapy have recently been emphasized.²³ Pseudotumor cerebri is an extremely rare adverse effect of tetracycline use. Nephrogenic diabetes insipidus may result from demeclocycline therapy.

REFERENCES

1. Duggar BM. Aureomycin: product of continuing search for new antibiotics. *Ann N Y Acad Sci* 1948;51:177-181.
2. McCaig LF, Hughes JM. Trends in antimicrobial drug prescribing among office-based physicians in the United States [published erratum appears in *JAMA* 1998;279:434]. *JAMA* 1995;273:214-219.
3. Williams DN. Tetracyclines. In: Gorbach SL, Bartlett JG, Blacklow NR, editors. *Infectious Diseases*. 2nd ed. Philadelphia: Saunders; 1998. pp 227-231.
4. Smilack JD, Wilson WR, Cockerill FR III. Tetracyclines, chloramphenicol, erythromycin, clindamycin, and metronidazole. *Mayo Clin Proc* 1991;66:1270-1280.
5. Kucers A, Crowe SM, Grayson ML, Hoy JF. *The Use of Antibiotics: A Clinical Review of Antibacterial, Antifungal and Antiviral Drugs*. 5th ed. Oxford (England): Butterworth-Heinemann; 1997. pp 719-762.
6. Qadri SM, Halim M, Ueno Y, Saldin H. Susceptibility of methicillin-resistant *Staphylococcus aureus* to minocycline and other antimicrobials. *Chemotherapy* 1994;40:26-29.
7. Yuk JH, Dignani MC, Harris RL, Bradshaw MW, Williams TW Jr. Minocycline as an alternative antistaphylococcal agent [letter]. *Rev Infect Dis* 1991;13:1023-1024.
8. Archer GL, Climo MW. Antimicrobial susceptibility of coagulase-negative staphylococci. *Antimicrob Agents Chemother* 1994;38:2231-2237.
9. USP DI: *Drug Information for the Health Care Professional*. Vol 1. 13th ed. Rockville (MD): US Pharmacopeial Convention; 1993. pp 2610-2620.
10. The choice of antibacterial drugs [published erratum appears in *Med Lett Drugs Ther* 1998;40:54]. *Med Lett Drugs Ther* 1998;40:33-42.
11. Advice for travelers. *Med Lett Drugs Ther* 1996;38:17-20.
12. Lewis S, Lewis B. Minocycline therapy of resistant *Staphylococcus aureus* infections [abstract]. *Infect Control Hosp Epidemiol* 1993;14:423.
13. Shea KW, Cunha BA, Ueno Y, Abumustafa F, Qadri SM. Doxycycline activity against *Streptococcus pneumoniae* [letter]. *Chest* 1995;108:1775-1776.
14. Bartlett JG, Breiman RF, Mandell LA, File TM Jr. Community-acquired pneumonia in adults: guidelines for management. *Clin Infect Dis* 1998;26:811-838.
15. Tilley BC, Alarcon GS, Heyse SP, Trentham DE, Neuner R, Kaplan DA, et al (MIRA Trial Group). Minocycline in rheumatoid arthritis: a 48-week, double-blind, placebo-controlled trial. *Ann Intern Med* 1995;122:81-89.
16. Smit JM, Out MM, Groen AK, Huibregtse K, Jansen PL, van Marle J, et al. A placebo-controlled study on the efficacy of aspirin and doxycycline in preventing clogging of biliary endoprotheses. *Gastrointest Endosc* 1989;35:485-489.
17. Cunha BA. New uses for older antibiotics: the 'rediscovery' of four beneficial and cost-effective antimicrobials. *Postgrad Med* 1997 Apr;101:68-70; 73-74; 79-80.
18. Allen JC. Minocycline. *Ann Intern Med* 1976;85:482-487.
19. Lanza FL. Esophageal ulceration produced by doxycycline: review of the literature and comparison of the injury from doxycycline hyclate and hydrochloride with that from doxycycline monohydrate. *Curr Ther Res Clin Exp* 1988;44:475-484.
20. Schneider R. Doxycycline esophageal ulcers. *Am J Dig Dis* 1977;22:805-807.
21. Shiff AD. Doxycycline-induced esophageal ulcers in physicians [letter]. *JAMA* 1986;256:1893.
22. Eisen D. Minocycline-induced oral hyperpigmentation [letter]. *Lancet* 1997;349:400.
23. Singer SJ, Piazza-Hepp TD, Girardi LS, Moledina NR. Lupuslike reaction associated with minocycline [letter]. *JAMA* 1997;277:295-296.