

Tetracyclines: History and Current Formulation Review From a Dermatology Perspective

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Tetracycline antibiotics, a class that includes the titular antibiotic as well as doxycycline, minocycline, and others, have long been a reliable treatment of both infectious and non-infectious conditions. There are now many options within the tetracycline class, and even distinguishing between monohydrate and hyclate salts can be obscure. This discussion aims to provide an overview of the various forms of tetracyclines available and their current uses within dermatology.

Tetracyclines are bacteriostatic and work by binding to the 30s subunit of bacterial ribosomes and inhibiting the binding of charged tRNA to the receptor on the mRNA-charged ribosome complex.¹ It is now known that tetracyclines not only exert an antimicrobial effect but can be utilized for their anti-inflammatory effects as well. These anti-inflammatory mechanisms of action occur through the inhibition of inducible prostaglandin expression, inhibition of excessive collagenase activity, decrease in lymphoproliferative responses within phagocytic and metabolic functions, and alterations in the alternative complement pathway.^{2,3,4} As a lipophilic substance, they accumulate to high concentrations within the pilosebaceous unit, thereby exerting their anti-microbial and anti-inflammatory effects against *Propionibacterium acnes*.⁵

Tetracyclines are effective against various gram positive, gram negative, aerobic, anaerobic, protozoan, spirochetal, and mycobacterial organisms.³ In addition to the treatment of acne vulgaris, they are used in the treatment of other dermatologic conditions including rosacea, perioral dermatitis,

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folliculitis decalvans, hidradenitis suppurativa, Lyme disease, Rocky Mountain spotted fever, cutaneous anthrax, bullous pemphigoid, and Chlamydial infections.^{3,5}

Tetracyclines are essentially absorbed completely after oral intake. They are absorbed and bound to plasma proteins at varying degrees, depending on their formulation. After being processed and concentrated in the liver, they are excreted in the urine and feces.⁶

HISTORY

Since the initial use of tetracycline in 1952, doxycycline in 1967, and minocycline in 1972, tetracyclines have improved greatly in both efficacy and tolerability.⁷ Recent studies have demonstrated the use of subantimicrobial doses of tetracyclines for the treatment of acne vulgaris and rosacea, while still successfully reducing inflammation and preventing the emergence of resistance.⁷ For example, in clinical trials, doxycycline hyclate 20mg twice daily has been proven effective for the treatment of acne vulgaris, rosacea, and periodontitis.^{4,8,9} This confirmation

of the effectiveness of subantimicrobial dosing has led to additional formulations of tetracyclines including doxycycline monohydrate, Oracea (ER doxycycline), Periostat, and Solodyn (ER minocycline).

DOXYCYCLINE HYCLATE VS. DOXYCYCLINE MONOHYDRATE

Doxycycline was initially approved at antimicrobial doses of 50mg-100mg twice daily.¹⁰ Now, doxycycline hyclate and monohydrate can be prescribed at various subantimicrobial doses. Doxycycline hyclate and doxycycline monohydrate are two different salt forms of the same active drug. Doxycycline hyclate is very water soluble, while doxycycline monohydrate is only slightly water soluble. This difference is only important during the manufacturing of the drug, however; once both salt forms are absorbed, they both become the same active form of doxycycline.

Skidmore, et al. conducted a multi-center, double-blind, randomized, placebo-controlled study to evaluate only the anti-inflammatory effects of doxycycline hyclate in the treatment of acne by using subantimicrobial dosing. This study included 41 adult patients with moderate acne that were assigned to either a group who received a subantimicrobial dose of doxycycline hyclate twice daily for six months or who received placebo for six months. Topical or other antibiotic treatments were not permitted. At the study's end point, there was a 52.3 percent reduction in comedones and inflammatory lesions in the doxycycline hyclate group, compared to a 17.5 percent reduction in the placebo group. Of note, there was not a significant difference in the composition of the normal skin flora between groups, and there was not a strong correlation between resistance to doxycycline and resistance to other antibiotics tested. Adverse effects in the treatment group included influenza in three patients, headache in three patients, rash in two patients, and gastrointestinal bleeding in one patient, which could not be directly related to treatment.⁴

SUBANTIMICROBIAL DOSE DOXYCYCLINE

Oracea and Periostat are two branded formulations of subantimicrobial doxycycline. Periostat was the first FDA-approved subantimicrobial dose formulation of doxycycline. It was approved in 1998 for the treatment of adult periodontitis.⁴ It is proposed that twice daily subantimicrobial dose (20mg) of Periostat works by inhibiting metalloproteinases MMP-8, MMP-13, MMP-9, interleukin 1B, and tumor necrosis factor, thereby decreasing the immune response.¹¹

Periostat is now available in a generic formulation. It is currently used to improve tooth attachment and prevent

gum inflammation and breakdown. As its formulation is a submicrobial dose, Periostat has a low side effect profile and high tolerability.¹²

Oracea is a once daily 40mg capsule consisting of 30mg immediate release beads and 10mg of delayed release beads of doxycycline monohydrate. It is recommended that Oracea be taken in the morning, on an empty stomach.¹³ A multicenter, double-blind, 16-week, Phase III study including 537 patients evaluated the use of Oracea for the treatment of rosacea. At the end of the four-month study period, there was a 9.4 percent reduction in lesion count from baseline in the Oracea group, compared to a 4.3 percent reduction in the placebo group. Of note, there was not a significant improvement in erythema in the Oracea group compared to the placebo group.¹³

IMMEDIATE RELEASE MINOCYCLINE AND EXTENDED RELEASE MINOCYCLINE

Minocycline increased in use for the treatment of acne after studies showed that its longer half life (15-25 hours), lower risk for resistance, fewer GI side effects, and less influence of dairy intake on its effect make it a more optimal choice for the battle against *P. acnes*.^{3,14} However, the use of minocycline has been associated with an increased risk of adverse effects including dizziness and drug-induced lupus. These adverse effects have been associated with the use of immediate release minocycline hydrochloride 100mg twice daily, the usual dosing when treating acne vulgaris.^{7,10,15} The development of extended release minocycline allows for a less rapid rise in serum levels and a lower maximum concentration, thereby potentially reducing the risk of systemic side effects associated with higher serum levels of minocycline.¹⁶

One study found that 1mg/kg dosing of ER minocycline showed statistically significant improvements in acne and was associated with a similar adverse effect risk as placebo.¹⁷ Fleisher, et al. studied patients with moderate to severe acne and demonstrated a 32.9 percent change in acne lesion count from baseline with patients taking 0.75-1.5mg/kg of ER minocycline compared to a 22.1 percent change in the placebo group after 84 days of treatment.¹⁴ Mild severity side effects of headache, nausea, fatigue, dizziness, and pruritus were similar between the ER minocycline and placebo groups. However, more severe side effects of pruritus, urticaria, rash, aggravated acne, and fatigue led to discontinuation of 20 patients within the study group. Within the study conducted by Stewart et al, 16 participants withdrew from treatment secondary to adverse drug effects. Two subjects had a positive ANA but were asymptomatic.¹⁴ There are currently dosage options of 55, 65, 80, 105, and 115mg tablets available for ER minocycline.

TABLE 1: SUMMARY OF BRANDS, FORMULATION, DOSAGES, AND APPROVED INDICATIONS

Brand Name, formulation	Dosage	Approved indications
Acticlate, doxycycline hyclate	75mg, 150mg tablets	Acne, rickettsial infections, STIs, respiratory infections, ophthalmic infections, anthrax, malaria prophylaxis ³²
Doryx, delayed release doxycycline hyclate	200mg tablets	Acne, Chlamydia
Oracea, immediate and delayed release doxycycline monohydrate	40mg once daily	Rosacea
Periostat	20mg doxycycline hyclate tablets	Chronic periodontitis
Monodox	75mg, 100mg capsules	Acne, various gram negative and gram positive infections ³²
Solodyn, extended release minocycline hydrochloride	55mg, 65mg, 80mg, 105mg, 115mg tablets	Acne

SIDE EFFECTS AND CONTRAINDICATIONS

The most common side effect of tetracyclines is gastrointestinal upset, which can generally be prevented by eating a meal and drinking water when taking the drug.³ However, this only holds true for doxycycline and minocycline, as the absorption of tetracycline is significantly decreased by the intake of food. There is also risk for esophageal erosion and oral candidiasis with any of the class. Drinking a glass of water when taking the medication can help prevent esophagitis and possible erosion, and should be emphasized to patients; additionally, patients should be cautioned to avoid lying down shortly after taking tetracyclines for the same reason.³ Patients should be advised to maintain strict sun protection while taking tetracyclines, as they increase photosensitivity. Frost, et al. found that photosensitivity is much less severe with minocycline than with doxycycline, as none of the patients taking minocycline experienced an increase in sun burn or paresthesias, but 11 of 15 patients experienced these side effects taking doxycycline.¹⁸

This should not discount the side effects specific to minocycline, which some may call more severe and less predictable compared to those of doxycycline. Side effects associated with minocycline include: dizziness, lightheadedness, ataxia, tinnitus, brown discoloration of sclera and nails, blue or black discoloration of sclera or gingiva, pseudotumor cerebri, and autoimmune hepatitis. The brownish discoloration of sclera, nails, and scars is generally reversible, whereas the blue or black discoloring of gingiva tends to be permanent.^{3,14,19} A rat

model of minocycline pigmentation demonstrated that co-administration of ascorbic acid (vitamin C) totally prevented pigmentation; to our knowledge, this has not been studied in humans.²⁰ Stewart, et al. noted that vestibular events including dizziness and vertigo were most common in the first five days of treatment. Therefore it may be helpful to advise patients about these possible side effects when starting treatment but encourage them that it is probable they will eventually resolve.

Additional serious side effects of minocycline include the risk for serum sickness reactions, hypersensitivity reactions, and drug-induced lupus. Through both retrospective studies and a review of previous studies, Knowles, et al., identified 17 hypersensitivity reactions, seven serum sickness reactions, and 25 drug-induced lupus cases.¹⁴ The onset of drug-induced lupus is generally not until two years of minocycline use. Therefore, it has been recommended that physicians with patients taking minocycline for an extended duration should monitor antinuclear antibodies.¹⁴ Although somewhat controversial, there is a risk for failure of oral contraceptives in women taking minocycline, prompting the recommendation that patients should use a second form of contraception when taking minocycline.^{21,22}

Importantly, tetracyclines should not be given to children under the age of eight (barring serious illness without other viable options) as they can cause permanent discoloration of teeth and prevent bone growth. Accordingly, tetracyclines are contraindicated in pregnancy (category D) and breastfeeding due to their interference with bone formation.^{21,22}

DOXYCYCLINE VS. MINOCYCLINE IN TREATMENT OF ACNE

Doxycycline and minocycline are both four-ring structures but differ at positions five and seven for doxycycline, and position six for minocycline, when compared to their predecessor tetracycline.²³ There have been various studies comparing the efficacy and safety profiles of doxycycline and minocycline. Laux, et al. conducted a randomized, comparative study including 50 patients receiving either a once daily dose of 50mg doxycycline or once daily dose of 50mg minocycline. After three months of treatment, “cure or improvement was found in 22 percent in the doxycycline group and 18 percent in the group of patients treated with minocycline.”²⁴ These results were not significantly different statistically, thereby concluding similar efficacy against acne. Other studies comparing doxycycline and minocycline treatment for three months have yielded similar efficacy results between both treatments.^{25,26,27}

Overall clinicians seem to vary on their preference for doxycycline vs. minocycline. There seems to be more recent evidence to support the superiority of efficacy in treating acne with minocycline versus doxycycline, but with this comes an increase in risk for more severe side effects, such as elevated ANA and ANCA.^{28,23} Additionally, with more predictable and somewhat more limited side effects, paired with probable comparable effectiveness for acne, doxycycline remains a very reasonable first choice.²³

Cost continues to be a complex and dynamic consideration. Generally, generic formulations are more affordable for patients, cheaper for the healthcare system, and usually have better insurance coverage.^{29,30} Recently, however, increasing generic prices and a preponderance of high-deductible insurance plans has made some of the branded formulations with their accompanying rebate programs much more attractive for certain patients.³¹

CONCLUSION: A SAFE AND USEFUL OPTION

Tetracyclines remain a useful and generally safe treatment option for a number of skin conditions, infectious, inflammatory, or both. When choosing which tetracycline to use, the clinician must weigh the severity of the disease, strength of data on clinical effect, risk for side effects specific to the patient, cost (including type of insurance), and dosing; all of which can be factors in medication adherence. The newer extended release and subantimicrobial formulations of doxycycline and minocycline have decreased risk for adverse side effects while still demonstrating clinical effect, and thus may be worth consideration. Looking forward, even with increased pressure to avoid antibiotic overuse, this incredibly useful class is likely here to stay for quite some time in dermatology. ■

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