THERAPEUTIC TIPS

Clinically Important Considerations with the Use of Oral Doxycycline

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ABSTRACT

Tetracyclines are the most commonly prescribed oral antibiotics in dermatology. They are used to treat bothcutaneous infections and non-infectious inflammatory disorders, the latter often with chronic therapy. Doxycycline may be favored by some dermatologists over minocycline due to a lower risk of certain adverse reactions, especially some with systemic manifestations. The major adverse events that are more common with doxycycline are gastrointestinal side effects, including pill esophagitis, and phototoxicity. This article reviews practical tips when prescribing oral doxycycline, emphasizing suggestions to optimize therapeutic success and reduce untoward reactions.

INTRODUCTION

Tetracyclines are the most commonly prescribed antibiotics in dermatology in the United States (US).[1] These oral agents, predominantly doxycycline and minocycline, comprise approximately 75% of all antibiotic prescriptions written by dermatologists, with dermatologists accounting for approximately 20% of all tetracyclines prescribed among all physicians in the US.[1-4] Both doxycycline and minocycline are highly lipophilic, which explains their marked skin penetration, with the reasonable scientific assumption that high concentrations are achieved within the lipid-rich pilosebaceous unit.[3] Skin penetration is important for treatment of both cutaneous infections and non-infectious dermatoses, such as acne vulgaris (AV), rosacea, and other inflammatory dermatologic disorders that are treated with tetracycline agents; pilosebaceous unit penetration is important in acne therapy as follicular *Propionibacterium acnes* is one of the therapeutic targets in AV.[2-8] Both doxycycline and minocycline exhibit a broad range of activity against several bacterial organisms relevant to commonly encountered skin conditions, such as *P acnes* (AV) and *Staphylococcus aureus*, including methicillin-resistant strains.[2-5,9] Importantly, tetracyclines also exhibit multiple biologic effects unrelated to their antibiotic activity which appear to play important mechanistic roles in the treatment of common facial inflammatory dermatoses,

such as AV and rosacea, and less common diseases such as bullous pemphigoid and granulomatous disorders.[2,6-8,10,11]

It is important to recognize that although doxycycline and minocycline are within the same general class of antibiotics, namely tetracyclines, there are several clinically relevant differences between these drugs, especially in their potential adverse reaction profiles.[2-5,12] This article specifically reviews clinically relevant considerations when prescribing oral doxycycline, with emphasis on four important practical tips to optimize therapeutic success and avoid adverse sequelae.

Tip #1: Consider the Formulation When Prescribing Oral Doxycycline

Doxycycline is available as either doxycycline hyclate or doxycycline monohydrate, with no clinical evidence of differences in efficacy or safety between the two salts of doxycycline when administered as immediate-release antibiotic-dose formulations .[2,13,14] Enteric-release doxycycline and a specific small-tablet brand doxycycline have been shown to exhibit similar pharmacokinetic profiles, with both demonstrating very similar low rates of potential for gastrointestinal (GI) AEs, such as nausea, abdominal discomfort/pain, and/or vomiting, even in the absence of food.[14] Importantly, however, concurrent administration with food further decreases the risk of GI-related AEs.[14] Enteric-coated doxycycline has been shown to markedly reduce the risk of GI-related AEs compared to a standard brand immediate-release doxycycline formulation.[15] Subantibiotic dose doxycycline, administered as a specific modified-release 40 mg capsule once daily for papulopustular rosacea, was associated with a marked decrease of GI-related AEs as compared to immediate-release doxycycline 100 mg once daily; none of the study subjects receiving subantibiotic dose doxycycline experienced nausea, abdominal discomfort, vomiting, or diarrhea.[16]

Tip #2: Reduce the Potential for "Pill Esophagitis" by Optimizing Patient Education on Proper Administration of Oral Doxycycline

Doxycycline is a leading cause of *pill esophagitis*, which occurs when patients do not properly administer the drug; in many cases this was associated with inadequate patient education.[2,17,18] Esophageal inflammation, erosions, and ulcerations have been described with this entity at all levels within the esophagus. The most commonly associated symptoms are odynophagia, retrosternal pain, and dysphagia.[17,18] In almost all cases, pill esophagitis occurred in patients who reported a history of swallowing their oral doxycycline with only a small amount of water, and taking the medication in a recumbent position, or both.[2,17,18] With proper patient education and compliance, pill esophagitis can be prevented. It is important that patients be instructed to ingest oral doxycycline with a large glass of water, to be in an upright position while ingesting the medication, and to preferably administer during or immediately after a meal.[2,14,17,18]

Tip #3: Consider Potential Dose-Related Phototoxicity and Employ Preventative Measures to Reduce Risk

Although the potential for photoxicity associated with oral doxycycline use is well-recognized, a recent systematic review of phototoxicity of doxycycline identified mostly

case reports and only a few studies that shed light on this topic.[19] The potential for phototoxicity is not dependent on gender, age, or duration of therapy, but rather the intensity and duration of ultraviolet light (UV) exposure, with Fitzpatrick skin types I and II exhibiting an enhanced risk.[19,20] Phototoxic skin reactions or photo-onycholysis may occur. The potential for phototoxicity induced by doxycycline appears to be dose-related; one series following patients treated with doxycycline over a 2 year period (N=106) reported phototoxicity in 42% (32/76) of those treated with 200 mg/day and in 20% (6/30) of those treated with 150 mg/day.[21] The reactions did not typically occur during usual daily sun exposure, but rather during periods of much greater UV exposure while on vacation in a sunny climate.[21]

It is important to recognize that tetracycline-related phototoxicity is mediated in the long wavelength of the UVA spectrum (340-400 nm).[19] Sunscreens that absorb UVA light only in the shorter wavelength end of the UVA spectrum, such as oxybenzone (340-360 nm), are inadequate in preventing doxycycline-induced phototoxic reactions.[19,22] It is prudent in patients treated with oral doxycycline to educate them on principles of photoprotection, including the use and periodic re-application of a sunscreen that filters across the entire UVA spectrum, protective clothing, and avoidance of intense mid-day sun exposure whenever possible.[19] Use of oral *Polypodium leucotomos* extract (PLE) to further supplement sunscreen use and other photoprotection measures may further reduce the risk of phototoxic effects; this suggestion is based on theoretical consideration of data supporting the ameliorating effects of PLE after UVA or UVB exposures.[23] For treatment of chronic inflammatory disorders such as AV, it is reasonable to suggest to patients to temporarily discontinue oral doxycycline use over the short duration of a vacation to be spent outdoors in a sunny climate or location of high UV exposure.[21]

Tip #4: Evaluate the Adverse Reaction Profile When Prescribing Oral Doxycycline

The overall safety profile of tetracycline antibiotics is very favorable.[2,4,5,12] The most common potential AEs associated with oral doxycycline use are GI-related AEs, including pill esophagitis, and phototoxicity.[2,5,12,18,18] Both are reasonably preventable as explained above. Doxycycline use has not been associated with some of the potential AEs encountered with utilization of oral minocycline, such as vestibular AEs (eg vertigo, dizziness), cutaneous and/or mucosal hyperpigmentation, and autoimmune reactions (eg hepatitis, drug-induced lupus-like syndrome), the latter being rare but with systemic manifestations; drug hypersensitivity syndrome (drug reaction with eosinophilia and systemic symptoms [DRESS]) has been reported much more commonly with oral minocycline, and appears to be very rare and of negligible risk with oral doxycycline.[2-5,12-14] The rate of acute vestibular AEs associated with oral minocycline use has been shown to be less with use of weight-based dosing (1 mg/kg/day) with a specific extended-release minocycline tablet formulation.[2] Benign intracranial hypertension (pseudotumor cerebri), often presenting with intractable cephalgia, nausea/vomiting, photophobia, and/or diplopia, is a rare side effect that may occur after use of any tetracycline agent, is diagnosed by the presence of papilledema, and warrants early detection and

intervention to reduce the risk of vision loss.[2] When treating papulopustular rosacea with an oral agent, it has been suggested that subantibiotic dose doxycycline (40 mg MR capsule once daily or 20 mg twice daily) be used initially, as there are data demonstrating efficacy comparable to oral doxycycline 100 mg daily with fewer GI-related AEs, and avoidance of antibiotic resistance due to absence of selection pressure.[2,16,24]

SUMMARY

Doxycycline is a commonly prescribed oral antibiotic in dermatology, used for treatment of uncomplicated cutaneous infections, such as those caused by MRSA, and some non-infectious inflammatory dermatoses, such as AV, rosacea, and bullous pemphigoid. Pill esophagitis and phototoxicity are two preventable AEs that can occur with use of oral doxycycline. Ingestion with a large glass of water and food while maintaining an upright position can prevent pill esophagitis. Enteric-coated and a special small tablet formulation of doxycycline are both associated with a low risk of GI-related AEs. Prevention of doxycycline-induced phototoxicity warrants photoprotection measures that includes use of a sunscreen that filters out the full UVA spectrum. Oral doxycycline is essentially devoid of certain side effects associated with oral minocycline use, such as vertigo/dizziness, hyper-pigmentation, drug hypersensitivity syndrome, and autoimmune reactions. Subantibiotic dose doxycycline is a preferred oral therapy choice for papulopustular rosacea due to low potential for AEs and avoidance of antibiotic resistance.

Conflict of Interest: none.

Disclosures: Dr. Del Rosso is a consultant, investigator, and/or speaker for Allergan, Aqua/Almirall, Bayer, BioPharmX, Celgene, Cipher (Innocutis), Cutanea, Dermira, Exeltis, Ferndale, Foamix, Galderma, Genentech, LeoPharma, Novan, Pfizer (Anacor), Pharmaderm, Promius, Regeneron, Sanofi/Genzyme, Sebacia, SunPharma, Taro, Unilever, Valeant (Ortho Dermatologics), and Viamet. This article was developed and written solely by the author. The author did not receive any form of compensation, either directly or indirectly, from any company or agency related to the development, authorship, or publication of this article.

Funding: none.

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