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Review article

On the prescribing of oral doxycycline or minocycline by UK optometrists as part of management of chronic Meibomian Gland Dysfunction (MGD)

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ABSTRACT

Purpose: To review the special pharmacology of tetracycline antibiotics as anti-inflammatory drugs for treatment of obstructive Meibomian gland disease (MGD)
Methods: PubMed was used as principal resource for articles, regardless of language, on doxycycline and minocycline with key interests being on their serum and tissue pharmacokinetics and their use in clinical studies as part of management of MGD.
Results: With oral dosing of between 50 and 200 mg, peak blood levels of these antibiotics have been reported to be predictably dose-dependent at between 1 and 5 microgram/mL, with human tear film levels not being detectable with 100 mg dosing of doxycycline but levels of 0.2 microgram/mL with 200 mg minocycline. That these two tetracycline antibiotics reach the conjunctiva is indicated by conjunctival pigmentary changes due to photosensitization after very long term use. Based the reported use in a range of clinical studies on MGD, dosing with these two antibiotics for MGD is likely to be useful at relatively low doses (e.g. 100 mg for doxycycline or 50 mg for minocycline, either at once or twice daily depending on severity at presentation and previous history) continued for 2 to 3 months, with the expected outcome being small-to-substantial decreases in abnormal appearance of the glands (from −4 to −89%) and increases in tear film stability (from 21 to 273%).
Conclusions: Oral doxycycline and minocycline have predictable pharmacokinetics and have been reported to improve Meibomian gland dysfunction over a few months of use.

1. Introduction

The Meibomian glands of the marginal zone of both eyelids normally provide the necessary oily secretions to support a stable tear film, but inflammation and blockage of the glands and/or their orifices can lead to a spectrum of common complaints resembling dry eye [1–9]. The chronic manifestation of the condition is generally referred to nowadays as Meibomian Gland Dysfunction (MGD), but older terms include meibomianitis or sometimes simply as a chronic form of (posterior) blepharitis. With abnormal function of the Meibomian gland being associated with development of dry eye, a 'Meibomian keratoconjunctivitis' or 'Meibomian keratitis' may also be described.

The glands, long since recognized to contain unusual lipid content [9,10], are of a holocrine type, i.e. the complete contents are secreted, with the synthesised and assembled wax/oil droplets in the intra-glandular acini being transformed into an emulsion in the glandular ducts prior to secretion [9]. This process is illustrated in Fig. 1 showing numerous acini with round electron-translucent lipid (oil droplet) inclusions on one side of the image, a small strip of adjacent connective tissue and then a zone (on the right hand size of the image) of amorphous material that is considered to be the emulsified contents of the acini presumably just ready for secretion (Fig. 1). With chronic inflammation, the normal secretion-related events of the glands are impaired or completely blocked with the emulsified material having very different characteristics (leading to inspissation of the secretions).

Overall, while the aetiology of MGD (and related dry eye conditions) is not well understood, there are both inflammation and infection-related issues according to the systemic condition associated with MGD. While acne (vulgaris) is an inflammatory disease affecting the hair follicles of the skin and associated with *Propionibacterium* sp, inflammation of the eyelid margins can be associated with a secondary response to toxins liberated by *Staphylococcus* sp

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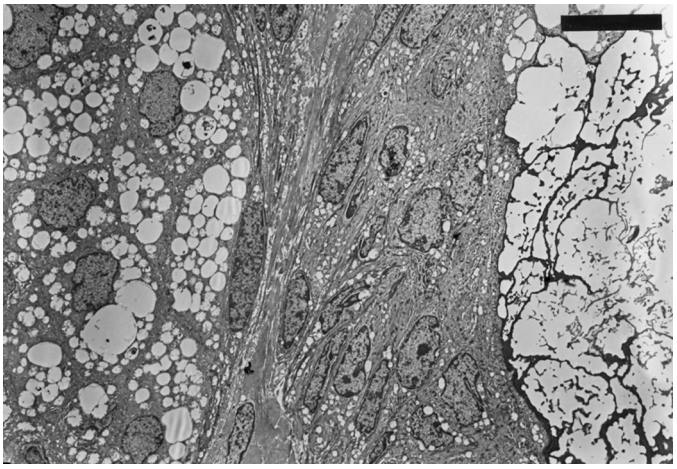

Fig. 1. Lower magnification (× 1400 original, scale bar = 11 μm) transmission electron microscopy (TEM) image taken from close to the Meibomian orifices of the upper eyelid of a young adult rabbit. The lipid inclusions produced by the Meibomianocytes in the acini in the left hand side of the micrograph can be seen to have a range of sizes indicating a process of progressive coalescence and blending together of the lipids. Across the right hand side of the image, this process of emulsification appears to be complete and the material ready for secretion into an adjacent duct leading to the orifice.

[11]. Treatment of MGD has three broad aims, namely to overcome the inflammation, restore active gland secretion (including removal of blockage of the orifices) and to manage the dry eye-related condition. Since MGD may be associated with systemic diseases such as (acne) rosacea [8], perhaps with the condition being classified as ocular rosacea (subtype 4 for rosacea) [12], part of the management of the MGD can include treating the systemic condition [2,8,12].

For skin-related (acne) conditions, treatment can be with appropriate systemic antibacterial drugs, along with topical (skin) antibacterial drugs and antiseptics. It has long been recognized, however, that the doses needed for some of these antibiotics to manage the inflammation associated with rosacea were below the minimum inhibitory concentrations (MIC) that would be expected to simply counter an infection [13–16]. While current medical and pharmaceutical directories and pharmaceutical information sources (at least in the UK) do not obviously include an indication for the use of certain antibiotics for the management of MGD, an 'off-label' use has evolved over many years for some of the tetracycline antibiotics as part of the management of this condition. A similar scenario has developed for treating ocular rosacea in the USA with such off-label use but, for example, approved by FDA [14]. Recent guidelines from the American Academy of Ophthalmology also note the use of 'oral tetracyclines' for management of moderate-to-severe MGD [4].

The goal of this review is to consider this special and longer term use of two of these orally-administered tetracycline antibiotics as part of the treatment of the inflammation associated with chronic MGD, along with briefly noting the other aspects of the management and prescribing of these drugs. Their use is included under current legislation that allows Independent Prescriber (IP) optometrists (in the UK) to 'prescribe any licensed medicine for ocular conditions affecting the eye and the tissues surrounding the eye . . .' (except controlled drugs or medicines for parenteral administration) [17], although a case can be made that co-management of these patients with a GP or dermatologist could be a good option.

2. The tetracycline antibiotics – their pharmacology

There are a number of drugs in the class 'tetracyclines' including tetracycline itself, initially isolated in 1947 from the *Streptomyces aureofaciens* [15]. However, while chlortetracycline, usually in ointment form as Aureomycin®, was once widely used as a topical ocular antibiotic including for blepharitis [18], the two tetracyclines of major interest for management of chronic blepharitis are in fact semi-synthetic derivatives. These are doxycycline and minocycline, both of which have numerous and widespread indications as systemic antibiotics for bacteria-associated infections such as acne, certain types of upper respiratory or urinary tract or periodontal infections, as well as *Chlamydia* infections. Doxycycline is also indicated for 'ophthalmic infections' [19], which will include those due to susceptible strains of *Staphylococcus, Haemophilus* and *Chlamydia*.

The antibiotic action of the tetracyclines is exerted via the (bacterial) ribosomes to block binding of incoming amino acyl-tRNA molecules required for the assembly of peptide chains, and so inhibits protein synthesis for susceptible bacteria. The tetracyclines, at clinically used doses, can be expected to exert bacteriostatic effects. MIC values are similar for both doxycycline and minocycline against *Staphylococccus aureus* with values of around 0.1 to 1 μg/mL [15,20,21], while for susceptible *Propionibacterium* sp, MIC values have been reported as closer to 2 μg/mL for doxycycline and perhaps half this value for minocycline [22].

These levels of tetracyclines are typically realized in the blood (as based on serum measurements at different times after oral administration) at around 2 to 4 h after ingestion. The tetracyclines can form strong complexes with a wide range of divalent cations, and while a Mg^{2+}-dependent association with ribosomes is part of their antibiotic actions, high levels of divalent cations can also reduce the bioavailability of tetracyclines, e.g. they can bind to divalent cations rather than being unbound and be readily available for systemic absorption [23]. Changes in serum divalent cations can also occur following ingestion of sources rich in these elements (milk, certain foodstuffs etc.) but the net effect on doxycycline or minocycline (as opposed to tetracycline itself) appears to be smaller [23–27]. For this reason, there are no obvious recommendations (e.g. in UK pharmaceutical listings) that the oral administration of doxycycline and minocycline should be undertaken in any special way, although some might still recommend that water rather than milk (for example) should be used as an aid to swallowing capsules of doxycycline [25].

As well as a traditional antibiotic action, it has repeatedly been reported that the use of lower doses (compared to what might be needed to achieve antibacterial effects) of doxycycline and minocycline can be very effective in the management of acne-type conditions [14,28–32]; in short, these daily doses for acne can be a quarter to one half those administered for 'infections'. This is not to say that the effective anti-inflammatory doses, *per se*, are necessarily always lower since, for example, they have been stated to be between 3 to 10 μg/mL for upper respiratory tract [33]. It can be concluded, however, that an anti-inflammatory effect can apparently be achieved in acne with administration of lower doses. This conclusion is, in part, based on measurements that can be made in various cell types of anti-inflammatory actions of these tetracyclines.

Along with measurements of serum levels of these tetracyclines (see later) it is also possible to assess other characteristics of the blood. These include certain anti-inflammatory activities associated with neutrophils, where modest oral dosing (e.g. 100 twice daily for 2 days) with doxycycline has been reported to slightly reduce (by c. 20%) the activities of what are collectively known as 'matrix metalloproteinase' or MMP activities [34]. Similar partial reductions in tear film, corneal or conjunctival MMP activities have also been reported following oral administration of doxycycline in humans [35,36] and mice [37], as well as in isolated human white blood cells [34], in cultured human corneal epithelial cells [38], and cultured human conjunctival fibroblasts [39]. Doxycycline