EXTENDED REPORT

Short term oral minocycline treatment of meibomianitis

J D Aronowicz, W E Shine, D Oral, J M Vargas, J P McCulley

Br J Ophthalmol 2006;**90**:856–860. doi: 10.1136/bjo.2006.091579

See end of article for
authors' affiliations

Correspondence to:
J P McCulley, MD The
University of Texas
Southwestern Medical
Center, 5323 Harry Hines
Blvd, Dallas, TX 75390-
9057, USA; james.
mcculley@UTsouthwestern.
edu

Accepted for publication
6 April 2006

Aim: To evaluate the clinical impact, aqueous tear parameters, and meibomian gland morphology in patients with primary meibomianitis before, during, and 3 months after a course of oral minocycline.

Methods: 16 patients were prospectively enrolled, 11 male and five female (mean age 69 years old). Each patient received routine clinical evaluations before, after 3 months therapy, and at 6 month study follow up visit. The clinical appearance, tear volume, flow and turnover, evaporation, Schirmer I test, meibomian gland dropout, lissamine green staining, and bacteriology were evaluated.

Results: Improvement was observed in clinical signs of meibomianitis at the second and third visits. Microbial culture findings improved. Decreased aqueous tear volume and flow, and increased evaporation rate range at 35–45% relative humidity (RH) ($p < 0.05$) were also detected. Other related tear parameters did not change. Meibomian gland dropout showed no improvement.

Conclusions: 3 months of oral minocycline resulted in clinical improvements in all meibomianitis signs that persisted for at least 3 months after discontinuation despite decreased aqueous tear volume and flow with increased evaporation (35–45% RH). However, there was improvement in the turbidity of secretions. Short term minocycline therapy probably has efficacy in the management of meibomianitis that extends beyond eradication of bacteria.

Chronic blepharitis is a complex condition that is difficult to eradicate. However, minocycline, a tetracycline analogue, has demonstrated efficacy in treating primary meibomianitis, one type of chronic blepharitis.¹ Minocycline has been recommended as a treatment option for chronic blepharitis because of its high concentration 12 hours post-dose, low renal clearance, long half life, and high level of binding to serum proteins.²

The purpose of this study was to evaluate clinical and bacteriological parameters in patients with primary meibomianitis before initiating treatment with minocycline, after 3 months of treatment, and 3 months after treatment completion.

METHODS

This study was a prospective observational treatment trial.

Selection of patients

Informed consent was obtained in all subjects. Study methods conformed to the Declaration of Helsinki and the institutional review board. Sixteen patients (32 eyes) were enrolled, 11 male and five female with a mean age of 69 years (range 45.6–91.4 years).

Patient inclusion criteria were earlier diagnosis of dry eyes based on referring doctors' assessments and our confirmations at time of referral; symmetrical clinical meibomianitis including signs of inflammation of the posterior lid margin that principally involved the meibomian gland orifice areas as previously described,³ and concomitant symptoms of burning, scratchiness, and foreign body sensation. Exclusion criteria included detection of abnormalities that would interfere with test procedures, antibiotic use, or sensitivity to minocycline or its components.

Treatment protocol

Patients were placed on minocycline 50 mg a day for the first 2 weeks and then 100 mg a day for the next 10 weeks. No other topical medicine or systemic drugs that affect lids or ocular surface were included.

Clinical evaluations

Routine ophthalmological evaluations were performed before beginning treatment, after 3 months on minocycline treatment, and 3 months after completion of the treatment. The following clinical signs were evaluated: thickening of eyelids, lid margin vascularisation, lid margin hyperkeratinisation, presence and type of lid margin debris, meibomian gland orifice extension/obliteration and pouting, visibility of secretion build up within the meibomian gland ducts, appearance of expressed meibomian gland secretions including clarity, turbidity of secretions, meibomian gland secretion expressibility, and the degree of bulbar conjunctival injection. All parameters were graded from 0 to 4; 0 being normal or absence of the sign. The investigator performed all grading of clinical parameters, without reviewing previous examinations but was not masked. No questionnaire was used to address subjective symptoms progress.

Instrumentation

Tear volume, flow, and turnover

Background fluorescence was determined before the instillation of 0.5 µl of 0.5% sodium fluorescein onto the ocular surface. Utilising a fluorophotometer (Fluorotron Master, Ocumetrics, Mountain View, CA, USA) eight measurements were taken for each eye to determine tear fluorescence. The first two measurements were done 1 minute apart and subsequent measurements were repeated at 3 minute intervals until completion at 19 minutes.⁴ These data were used to calculate tear volume, tear flow, and tear turnover as previously described.^{5–8}

Tear turnover is a simple percentage change in fluorescein concentration in a given amount of time; there are no units. Tear flow is the amount of tear fluid flowing past the cornea in a given amount of time and expressed as µl/min.⁴ Tear volume refers to the initial tear volume determined by regressing the concentration to time zero, thereby obtaining the decay constant and the concentration at instillation.⁶

Abbreviations: RH, relative humidity

Table 1 Clinical parameters expressed as average group score

Parameters	Visit 1 (n = 32)	Visit 2 (n = 32)	Visit 3 (n = 28)	p Value*
Thickening of eyelids	1.44	0.63	0.69	0.001
Eyelid margin vascularisation	1.44	0.56	0.62	0.04
Eyelid margin hyperkeratinisation	0.25	0	0	<0.001
Eyelid margin debris	1	0.38	0.08	0.001
Meibomian gland orifices extension/obliteration	0.81	0.125	0	0.001
Meibomian gland pouting	0.88	0	0.38	0.007
Visibility of secretion build-up within meibomian gland	1.06	0.56	0.23	0.025
Turbidity of secretion	0.56	0.25	0	0.033
Expressability of meibomian gland secretion	1.88	1.13	0.77	0.807
Bulbar injection	0.56	0.06	0.08	<0.001

n, number of eyes.

All parameters were graded from 0 to 4, 0 being normal or absence of the sign.

*One way ANOVA (comparing visit 1 with visit 3 parameters): Visit 1, baseline;

visit 2, after 3 months of therapy; Visit 3, 3 months after therapy completed.

Neither total staining nor corneal staining improved.

Evaporation

An evaporimeter (Oxdata, Portland, OR, USA) utilised a pump to direct room air through a drying tube (Hammond Drierite, Xenia, OH, USA) into a form fitting goggle, that created a closed environment, and contained a water vapouriser with controlled temperature. Dry air was pumped into the goggle to reduce relative humidity (RH) to 15%, at which time the pump was turned off. The RH within the goggles was allowed to rise. The increase in humidity caused by evaporation from skin or evaporating tears was measured. The process was carried out first with the eye closed and then with it open; the difference was the tear evaporation rate. The area of the interpalpebral ocular surface was used to calculate evaporation per unit area; the image of the area was captured with the use of a digital camera, and was calculated directly with the aid of computer software (Adobe Photoshop, version 6.0.1.2001, Adobe Systems, San Jose, CA, USA)⁸ expressed as $\mu\text{l}/\text{cm}^2/\text{min } 10^{-2}$.

Evaporative volume/total tear volume $\times 100$ (%/min)

Evaporative outflow as a percentage of available tear volume was determined by subtracting the closed eye evaporation (primarily eyelid) from the open eye (primarily tears) evaporation. Thus, the evaporation difference was calculated from changes in RH inside the eye goggles.

Evaporative contribution to total aqueous tear loss

The contribution of tear evaporation to total aqueous tear loss was determined by dividing the evaporative outflow by tear turnover. It is expressed as a percentage.

Meibomian gland dropout

A frame grabber was matched to a Hitachi, KP-F2A progressive scan, near infrared camera mounted on a slit

lamp biomicroscope. The inverted lower eyelid was transilluminated using a muscle light with a small band tip to disperse light, and photographed. The digital picture of the lower lid meibomian glands was further processed, and degree of dropout of individual meibomian lower lid glands was noted. Meibomian gland dropout was calculated based on seven central glands of each lower lid. Each gland was graded proportionately from 0 to 4, 0 meaning no dropout. The score of each of the seven glands was then summed and taken as a percentage of 28 (dropout score/28 $\times 100$), the maximum possible.⁸

Schirmer I test

A Schirmer I was performed without any anaesthetic drops and the tear wetting distance after 5 minutes was measured.

Ocular surface staining

Lissamine green vital staining was performed before any instrumentation and again at the end of each visit. Staining score was based on the van Bijsterveld system.^{9, 10}

Microbiology

Separate lid and conjunctival microflora cultures of each eye were taken with a calcium alginate swab dipped in 0.9% salt solution. After streaking the swab on the different plates (blood agar, chocolate agar, and reduced brucella blood agar), it was placed into a tube of thioglycolate as previously described.¹¹ Cultures were reported as no growth or positive for *Staphylococcus aureus*, *Staph epidermidis*, or *Staph saccharolyticus*. The growth was not quantified. Results represent percentage of lids or conjunctivae with positive cultures.

Table 2 Results of bacterial cultures from lids and conjunctivae at three study visits

	Visit 1 (%)	Visit 2 (%)	Visit 3 (%)
Lids (n = 16 patients)			
<i>Staph aureus</i>	31.25	12.5	6.25
<i>Staph epidermidis</i>	87.5	87.5	75
<i>Staph saccharolyticus (anaerobes)</i>	56.25	31.25	18.75
No growth	0	12.5	12.5
Conjunctivae (n = 16 patients)			
<i>Staph aureus</i>	25	6.25	6.25
<i>Staph epidermidis</i>	25	31.25	12.5
<i>Staph saccharolyticus (anaerobes)</i>	25	6.25	6.25
No growth	50	56.25	68.75

Data analysis

Statistics

Both eyes were included as individual data points. Average scores for clinical parameters were determined for each of the three visits. Bacterial culture data are expressed as percentage of positive lids and conjunctivae at each visit. The tear analyses were averaged (SD).

One way ANOVA and Dunn's one way analysis of variance by rank test were used to analyse and compare baseline, end of 3 month therapy, and 3 months post therapy time points (Sigmastat and Excel).

RESULTS

Clinical population

All 16 originally enrolled subjects returned for the visit at the end of oral minocycline therapy. Thus, 32 eyes were studied at each of the first two visits. Fourteen patients completed the final visit evaluation. Two subjects did not return for the final visit because of family obligations. They reported that clinical improvement persisted. None of the patients reported toxicity or side effects during the trial period.

Clinical signs

Clinical parameters were expressed as average group scores (table 1) based on grading. Improvement was observed in all clinical signs at the second visit as oral therapy was completed and third visit 3 months post-therapy compared to the initial visit before treatment was begun.

Thickening of the eyelid margins and eyelid margin vascularisation (table 1) improved with treatment ($p = 0.001$, $p = 0.04$ respectively); this was maintained 3 months after cessation of treatment. Eye lid margin hyperkeratinisation improved by the second visit, and was maintained at the third visit ($p < 0.001$). Eyelids margin debris was present in 56% at the first visit, 31% at the second visit, and only 8% at the third visit ($p = 0.001$). The most common debris was scurf.

The meibomian gland orifice extension/obliteration was present at the first visit in 50% of eyes, and improved progressively by the second (13%) and third (0%) visits ($p < 0.001$). Meibomian gland pouting (that is, inflammation) was present at the first visit in 100% of eyes but disappeared in all patients after 3 months of treatment. However, after 3 months without minocycline therapy, 31% of eyes had pouting despite significant improvement ($p = 0.007$).

Visibility and secretion build-up within the main ducts of meibomian glands was present in 69% of eyes (average score was 1.06) at the first visit; these signs improved at the second (44%) and third (23%) visits ($p = 0.025$).

Turbid secretions were present in 56% of eyes at the first visit, 25% at the second, and none at third visits. ($p = 0.033$) The meibomian gland secretion expressibility also continued improving on treatment and after 3 months without it. Eighty one per cent of eyes presented difficult expressibility at the first visit, 73% at the second, and 54% at the third visits. Bulbar conjunctival injection diminished from the scores at baseline (31%) to visits 2 (6%) and 3 (8%).

Lissamine green ocular surface staining

Ocular surface vital staining (1.95 (SD 2.07)) at baseline did not improve following treatment (visit 2) and after cessation of treatment (visit 3). Neither total staining nor corneal staining improved.

Microbiology

Although microbiology (table 2) findings were not statistically significant ($p > 0.05$), there was a trend that correlated with the clinical and symptom improvement. The most

Table 3 Aqueous tear parameters and meibography

	Volume (μ l)	Flow (μ l/min)	Turnover (%/min)	Schirmer's (mm)	Evaporation		Evap contribution to total aqueous tear loss = evap outflow/turnover $\times 100\%$ (%)	Dropout (%)
					Evap 25%–35% RH† (μ l/cm ² /min 10 ⁻²)	Evap 35%–45% RH† (μ l/cm ² /min 10 ⁻²)		
First visit								
Mean	2.05	0.22	12.56	17.83	0.056	0.034	48.09	29.62
SD	2.02	0.20	6.19	9.06	0.032	0.022	27.32	21.46
Second visit								
Mean	0.804*	0.11*	14.82	14.22	0.054	0.084*	49.98	30.28
SD	0.65	0.09	7.43	6.72	0.031	0.042	26.37	24.68
Third visit								
Mean	0.995*	0.12*	14.72	16.12	0.053	0.033†	44.05	24.14
SD	0.91	0.11	7.38	6.71	0.026	0.019	27.96	16.92

*Compared to first visit $p < 0.05$.

†Compared to second visit $p < 0.05$.
‡Relative humidity.

common bacteria were *Staph epidermidis* followed by *Staph aureus* and *Staph saccharolitycus*.

Staph aureus was present at the first visit in the lids of 31% and 25% of the conjunctivae of the eyes, decreasing its presence in the second (lids 13%, conjunctiva 6%) and third visits (6% in both). *Staph saccharolitycus* was present in 56% of lids and 25% of conjunctivas and progressively decreased to 31% in the lids and 6% in conjunctiva at the second and 19% and 6% respectively at the third visit. *Staph epidermidis* was present in the lids (88%) in the first and second visit, decreasing slightly at the third visit (75%) and, in the conjunctiva, was present in 25% at the first visit, 31% at the second, and 13% at the third visit.

The conjunctival cultures had no growth of 50%, 56%, and 69% for the first, second, and third visits, respectively. Similarly, no growth for lid specimens was 0%, 13%, and 13% for the same visits.

Aqueous tear measurements

Tear volume and flow showed decreases in values at both visits 2 and 3 (table 3). By Dunn's one way analysis of variance, the decreases in tear volume and flow were significant ($p < 0.05$). Despite corresponding decreases in tear volume and tear flow, tear turnover increased at visits 2 and 3, but did not reach statistical significance. Tear turnover showed an increase at the second and third visits compared to the first visit. However, this trend was not statistically significant.

Evaporation rate (25–35% RH) and evaporation contribution to total aqueous tear loss did not change at different visits (table 3).

In contrast, evaporation rate at 35–45% RH increased at the second visit and returned to the initial value at the third visit. The results at visit 2 were statistically significant in comparison to either visit 1 or visit 3 ($p < 0.05$).

Schirmer test

The schirmer results (table 3) were not statistically significant and were within the normal ranges at the three visits.

Meibography

The meibomian gland dropout did not show improvement over the duration of the study ($p > 0.05$) (table 3).

DISCUSSION

We have demonstrated clinical benefits from oral minocycline treatment of meibomianitis that persist for at least three additional months following 3 months of therapy. The antimicrobial effect of tetracycline analogues (for example, minocycline) (table 2) has previously been observed by Shine *et al.*,¹ Dougherty *et al.*,¹² and Ta *et al.*¹³ These studies have demonstrated a decrease of *Staph aureus* and *Staph epidermidis* when patients were taking tetracycline analogues that persisted up to 3 months after completion of therapy. This study confirms those observations. Our investigative group also previously demonstrated that tetracycline causes significant decreases in lipase production of both sensitive and resistant strains of *Staph epidermidis* without concomitant decreases in bacterial growth. In contrast, there were parallel decreases in lipase production and inhibition of growth of sensitive and resistant strains of *Staph aureus*.¹² Together with this clinical study, it is clear that minocycline provides benefits in addition to antimicrobial activity in the successful management of meibomianitis. The combination of multiple clinical parameters, microbiology data, and aqueous tear studies supports the clinical efficacy of pulsed oral minocycline therapy for significant meibomianitis.

Several studies have described the beneficial effects of minocycline and other tetracycline derivatives (for example, doxycycline) in the treatment of chronic blepharitis.^{1 2 12 14}

The aqueous tear parameters—tear volume and tear flow—showed a statistically significant decrease on treatment that was maintained for at least 3 months after treatment cessation. Thus, there was a decrease in the aqueous tear production that occurred along with clinical improvement. Mathers and colleagues have studied tear volume and tear flow in normal subjects by decades of life.¹⁵ Our population, with an average age of 69, appears to have had excessive tear volume and tear flow initially in association with active meibomianitis. After minocycline therapy, the values decreased to the expected levels for their age group. The Schirmer test results were unchanged over the course of the study and within normal limits. We were unable to detect a decrease in aqueous tear evaporation as would have been predicted on the basis of current hypotheses regarding the aetiology of dry eye states. There was an unexpected increase in the evaporation rate as the RH increased from 35% to 45% at visit 2. At visit 3 the evaporation rate was once again similar to the pretreatment value. At this point it is not possible to assign a role for evaporation in either meibomianitis or its therapy with oral minocycline.

Decrease in bacterial flora producing lipolytic exoenzymes^{1 13} and inhibition of lipases production¹² with resultant decrease in meibomian lipid breakdown products¹ may contribute to widespread improvement in clinical parameters in this meibomianitis population.

The use of minocycline improved clinical parameters, microbiology, and tear volume and flow for at least 3 months beyond the 3 months of therapy. No safety issues were seen in the current study. The safety issues encountered in long term oral antibiotic therapy including minocycline are well known. Recently, a new possible complication was detected as antibiotic use was more common in breast cancer patients, especially with long treatment durations.¹⁶

The management of meibomianitis patients with short term oral minocycline for a 3 month period appears to be efficacious for extended periods of at least 3 months of therapy, and may have greater safety than prolonged, sustained courses.

The authors recognise that this is an open trial and that the use of both eyes of each patient in the analyses may cause some bias. However, we did additional analyses using single eyes from each subject and saw the same results. Despite some issues raised by study design, important results are evident, especially that the treatment effect persists at least 3 months beyond the trial. This provides solid basis for a trial comparing different treatments lengths and the determination of condition free status intervals.

ACKNOWLEDGEMENTS

Supported in part by NIH grants EY12430, EY016664, and an unrestricted grant from Research to Prevent Blindness, Inc.

Authors' affiliations

J D Aronowicz, W E Shine, D Oral, J M Vargas, J P McCulley, Department of Ophthalmology, The University of Texas Southwestern Medical Center at Dallas, Dallas, TX, USA

The authors have no proprietary interest in any product or concept discussed in this paper.

REFERENCES

- Shine WE, McCulley JP, Pandya AG. Minocycline effect on meibomian gland lipids in meibomianitis patients. *Exp Eye Res* 2003;**76**:417–20.
- Hoeprich PD, Warshawer DM. Entry of four tetracyclines into saliva and tears. *Antimicrob Agents Chemother* 1974;**3**:330–6.

- 3 McCulley JP, Dougherty JM, Deneau DG. Classification of chronic blepharitis. *Ophthalmology* 1982;**89**:1173-80.
- 4 Best JA van, Benitez del Castillo JM, Coulangeon L-M. Measurement of basal tear turnover using a standardized protocol European concerted action on ocular fluorimetry. *Graefes Arch Clin Exp Ophthalmol* 1995;**233**:1-7.
- 5 Mathers WD, Lane JA, Sutphin JE, et al. Model for ocular tear film function. *Cornea* 1996;**15**:110-19.
- 6 Mathers WD, Daley TE. Tear flow and evaporation in patients with and without dry eye. *Ophthalmology* 1996;**103**:664-9.
- 7 Eter N, Gobbels M. A new technique for tear film fluorophotometry. *Br J Ophthalmol* 2002;**86**:616-19.
- 8 McCulley JP, Shine WE, Aronowicz J, et al. Presumed hyposecretory/hyperevaporative KCS: tear characteristics. *Trans Am Ophthalmol Soc* 2003;**101**:141-52.
- 9 Van Bijsterveld OP. Diagnostic test in the sicca syndrome. *Arch Ophthalmol* 1969;**82**:10-14.
- 10 Foulks GN. Challenges and pitfalls in clinical trials of treatments for dry eye. *The Ocular Surface* 2003;**1**:20-30.
- 11 Dougherty JM, McCulley JP. Comparative bacteriology of chronic blepharitis. *Br J Ophthalmol* 1984;**68**:524-8.
- 12 Dougherty JM, McCulley JP, Silvany RE, et al. The role of tetracycline in chronic blepharitis. *Invest Ophthalmol Vis Sci* 1991;**32**:2970-5.
- 13 Ta CN, Shine WE, McCulley JP, et al. Effects of minocycline on the ocular flora of patients with acne rosacea or seborrheic blepharitis. *Cornea* 2003;**22**:545-8.
- 14 Gulbenkian A, Myers J, Freis D. Hamster flank organ hydrolase and lipase activity. *J Invest Dermatol* 1980;**75**:289-92.
- 15 Mathers WD, Lane JA, Zimmerman MB. Tear film changes associated with normal aging. *Cornea* 1996;**15**(3):229-34.
- 16 Velicer CM, Heckbert SR, Lampe JW, et al. Antibiotic use in relation to the risk of breast cancer. *JAMA* 2004;**291**:827-35.

Clinical Evidence—Call for contributors

Clinical Evidence is a regularly updated evidence-based journal available worldwide both as a paper version and on the internet. *Clinical Evidence* needs to recruit a number of new contributors. Contributors are healthcare professionals or epidemiologists with experience in evidence-based medicine and the ability to write in a concise and structured way.

Areas for which we are currently seeking contributors:

- Pregnancy and childbirth
- Endocrine disorders
- Palliative care
- Tropical diseases

We are also looking for contributors for existing topics. For full details on what these topics are please visit www.clinicalevidence.com/ceweb/contribute/index.jsp

However, we are always looking for others, so do not let this list discourage you.

Being a contributor involves:

- Selecting from a validated, screened search (performed by in-house Information Specialists) epidemiologically sound studies for inclusion.
- Documenting your decisions about which studies to include on an inclusion and exclusion form, which we keep on file.
- Writing the text to a highly structured template (about 1500-3000 words), using evidence from the final studies chosen, within 8-10 weeks of receiving the literature search.
- Working with *Clinical Evidence* editors to ensure that the final text meets epidemiological and style standards.
- Updating the text every 12 months using any new, sound evidence that becomes available. The *Clinical Evidence* in-house team will conduct the searches for contributors; your task is simply to filter out high quality studies and incorporate them in the existing text.

If you would like to become a contributor for *Clinical Evidence* or require more information about what this involves please send your contact details and a copy of your CV, clearly stating the clinical area you are interested in, to CECommissioning@bmjgroup.com.

Call for peer reviewers

Clinical Evidence also needs to recruit a number of new peer reviewers specifically with an interest in the clinical areas stated above, and also others related to general practice. Peer reviewers are healthcare professionals or epidemiologists with experience in evidence-based medicine. As a peer reviewer you would be asked for your views on the clinical relevance, validity, and accessibility of specific topics within the journal, and their usefulness to the intended audience (international generalists and healthcare professionals, possibly with limited statistical knowledge). Topics are usually 1500-3000 words in length and we would ask you to review between 2-5 topics per year. The peer review process takes place throughout the year, and out turnaround time for each review is ideally 10-14 days.

If you are interested in becoming a peer reviewer for *Clinical Evidence*, please complete the peer review questionnaire at www.clinicalevidence.com/ceweb/contribute/peerreviewer.jsp