MINOCYCLINE DRUG INDUCED LUPUS IN PRIMARY CARE

By

CHRISTIE ANNE KRATOVIL

A project submitted in partial fulfillment of
The requirements for the degree of:

MASTER OF NURSING

WASHINGTON STATE UNIVERSITY
College of Nursing

AUGUST 2010
To the Faculty of Washington State University:

The members of the Committee appointed to examine the project of CHRISTIE ANNE KRATOVL find it satisfactory and recommend that it be accepted.

Renee Hoeksel, PhD, RN, CCRN

Dawn Rondeau, DNP, RN, ACNP, FNP

Lorrie Dawson, PhD, ARNP
MINOCYCLINE DRUG INDUCED LUPUS IN PRIMARY CARE

Abstract

by Christie Anne Kratovil
Washington State University
August 2010

Chair: Renee Hoekse!

Purpose: This article aims to provide the primary care provider with a tool to assist with the use of minocycline for acne vulgaris in the adolescent population in the primary care setting. It provides a comprehensive overview of the pathophysiology of acne vulgaris, the current treatment recommendations for acne vulgaris, and a review of current knowledge on minocycline drug induced lupus (DIL); and concludes with a decision tree to assist in clinical decision making related to prescribing minocycline and the related risk of minocycline DIL. Data sources: data sources included online literature review using PubMed, Cochrane, and CINHAL. The Washington State University Vancouver campus library provided current medical and nursing journals which were reviewed for relevant content. Conclusions: A decision tree for the use in primary care is introduced. This tool will need to be part of future studies to test for efficacy, reliability, and practical implications. Implications for practice: This article provides significant support that minocycline DIL is an often overlooked side effect of the medication and that primary care providers play a pivotal role in the early recognition of minocycline DIL and can impact the morbidity and mortality of this patient population in the future.

ii
# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Signature page</td>
<td>i</td>
</tr>
<tr>
<td>Abstract</td>
<td>ii</td>
</tr>
<tr>
<td>Table of Contents</td>
<td>iii</td>
</tr>
<tr>
<td>Dedication</td>
<td>iv</td>
</tr>
<tr>
<td>Purpose</td>
<td>1</td>
</tr>
<tr>
<td>History of Minocycline</td>
<td>1</td>
</tr>
<tr>
<td>Scope, significance, and Pathophysiology of Acne</td>
<td>3</td>
</tr>
<tr>
<td>Minocycline Drug Induced Lupus</td>
<td>7</td>
</tr>
<tr>
<td>Minocycline Drug Induced Lupus and Laboratory Values</td>
<td>10</td>
</tr>
<tr>
<td>Implications for Clinicians</td>
<td>12</td>
</tr>
<tr>
<td>Conclusion</td>
<td>13</td>
</tr>
<tr>
<td>Appendix A</td>
<td>14</td>
</tr>
<tr>
<td>References</td>
<td>15</td>
</tr>
</tbody>
</table>

*iii*
Dedication

This paper is dedicated to my brother, Matthew Lambdin, who has been living with a chronic case of minocycline drug induced lupus for the past two years now; and to his twin brother Alex Lambdin who has been his quiet and humble supporter throughout this process.
Purpose

The purpose of this paper is to provide the primary care provider with a comprehensive review and update on the use of minocycline for the treatment of acne; and to provide information on the associated risk of minocycline drug induced lupus. This overview will conclude with a tool which can be utilized in primary care and can assist the provider in the following decisions: when to prescribe minocycline for acne, how long to prescribe minocycline for acne, how to monitor the patient on minocycline for acne to ensure their safety and help prevent and minimize the occurrence of drug induced lupus.

History of Minocycline

The class of drugs, tetracyclines was first introduced and became available worldwide by Lederle Laboratories in 1953 (Smith & Leyden, 2005). Tetracyclines are broad spectrum antimicrobial agents (Golstein, Deviere, & Cremer, 1997) and can be further classified as the original and second generation agents. All of the second generation tetracyclines have increased spectrum and incidence of adverse drug reactions, which is linked to accumulation in fatty tissues resulting in a long unpredictable half life (Garner, Eady, Popescu, Newton, & Li Wan Po, 2009).

The first second generation agents doxycycline (introduced in 1967) and minocycline (introduced in 1972) were advertised with easier dosing schedules and being more readily absorbed with food (Smith & Leyden, 2005). Minocycline is also more commonly prescribed because of its increased lipid solubility; however because of this it has a half life between 16-18
hours and can be detected in urine up to 180 hours after the last dose (Garner et al., 2005). Common side effects of the second generation tetracyclines are gastrointestinal symptoms, central nervous system effects, pigmentation changes, pediatric tooth discoloration, and candidiasis (Smith & Leyden, 2005). Minocycline is commonly used for the treatment of many disorders including Lyme disease, rheumatoid arthritis, reactive arthritis, and acne (Smith & Leyden, 2005). Minocycline was originally introduced for the treatment of acne, and has become “one of the most commonly used treatments for acne, prescribed for an estimated 15.2 million pediatric patients in the United States annually” (El-Hallak et al., 2008, p. 314). Approximately 65% of minocycline prescriptions written in the US are for the treatment of acne (Garner et al., 2005). Minocycline side effects include: gastrointestinal symptoms, vestibular dysfunction, headache, visual disturbance, memory disturbance, poor concentration, urticaria, photosensitivity, vaginal candidiasis, pigmentation of all major organs, serum sickness syndrome, and drug induced lupus (DIL) (O’Dell et al., 1999). Prevalence of these side effects are commonly reported as minimal; however, one of the rarest and most serious, DIL is estimated at a rate of 15,000-20,000 reported cases per year (Sarzi-Puttini, Atzeni, Capsoni, Lubrano, & Doria, 2005).

Minocycline is marketed under the names of Dynacin (available in 50, 75, and 100mg tablets), Minocin capsules (available in 50mg or 100mg), and Solodyn 1mg/kg/day (available in 45mg, 90mg, and 135mg) when used for the treatment of acne (Roebuck, 2006). Minocycline is prescribed at a usual dosage range of 50-200mg in once daily or twice daily dosing (Layton, Buchanan, & Courtenay, 2006, Roebuck, 2006).
Scope, Significance, and Pathophysiology of Acne

Acne is a complex disorder consisting of abnormalities in processes performed regularly by the skin. Acne is the most common dermatological illness affecting over 50 million Americans and 80% of adolescents (Ramos-e-Silva & Carneiro, 2009, Roebuck, 2006). Eighty five percent of the population between the ages of 15 and 24 is affected by acne (Roebuck, 2006). Acne is more persistent in females but more severe in males (Roebuck, 2006). Acne has no gender, race, or ethnic prevalence (Dipiro et al., 2008); however darker skinned individuals are at more risk for post inflammatory hyperpigmentation, hypertrophic, and keloid scars (Roebuck, 2006). The complications from acne include both physical concerns such as permanent scarring, and also present a significant psychological risk. Psychological effects include lowered self esteem, social inhibition, anxiety, depression, as well as scarring from acne contributing as an established risk factor for suicide in males (Gollnick, 2003). Furthermore, the patient’s concept of body image when affected by acne does not necessarily correlate with the clinical severity of acne (Layton et al., 2006).

Acne consists of variable skin lesions which are categorized as non-inflammatory: closed comedones and open comedones, and inflammatory: papules, pustules, and nodules (Roebuck, 2006). Closed comedones, more commonly termed whiteheads are the result of a follicle which is blocked, sebum then begins to build and a comedone forms (Gollnick, 2003). Open comedones, more commonly termed blackheads, are the result of a follicle filled with desquamated keratinous cells and sebum but have an open dilated surface visible on the skin (Gollnick, 2003). Papules are seen as solid raised lesions and are caused by a deeper
inflammatory reaction of the skin (Gollnick, 2003). A pustule is a small raised lesion that is filled with pus; it is the result of a superficial closed comedone (Gollnick, 2003). A nodule is also called a pseudocyst and is a large abscess which can coalesce under the skin and cause sinus tracts; nodules can leave severe scarring after they heal (Gollnick, 2003).

Acne is treated by breaking the disorder into levels of severity and treating these separate levels. These general levels are divided into mild, moderate, and severe. Mild acne is generally defined as closed and open comedones with no inflammatory involvement and is treated with a topical retinoid which is chosen by the provider based on risk of adverse effects, lifestyle, and realistic price for the patient (Layton et al., 2006). The topical retinoids include adapalene gel or cream, isotretinoin gel, and tretinoin gel or cream. Other topical therapies can also be used including benzoyl peroxide, azelaic acid, and topical antibiotics (Layton et al., 2006). There are several studies available that show topical therapy works better synergistically, or with more than one of the agents working together (Layton et al., 2006).

Moderate acne is generally defined as open and closed comedones with the addition of some papules and pustules, the risk of significant scarring, and the risk of psychological conditions. Moderate acne is also defined by treatment failure with topical medications (Layton et al., 2006). The treatment of moderate acne includes systemic therapy along with continued topical therapy. Systemic therapy available for moderate acne includes the tetracyclines: oxytetracycline, erythromycin, minocycline, doxycycline, and lymecycline. Hormonal therapy is an alternative treatment used in female patients which is thought to work by decreasing the amount of androgens and has proven to be effective regardless of measurable androgen levels.
Oxytetracycline is prescribed at a dosage of 1 gram a day and must be taken 30 minutes before meals for absorption purposes (Layton et al., 2006). Erythromycin is used for acne in pregnancy due to its safety profile as well as in children younger than 12, but is not used often in the general population due to an increased resistance to *Propionibacterium acnes* (P. acnes) (Layton et al., 2006). Of the second generation tetracyclines available, minocycline has been shown to be more effective for therapy resistant acne due to its increased anti-inflammatory effects; however, because the adverse effects of minocycline are more serious than doxycycline and lymecycline, minocycline should only be used after one of the other second generation tetracyclines have been attempted (Layton et al., 2006). One of the marketed advantages of minocycline is that it is unaffected by absorption factors; however, a study conducted in 1985 concluded that food in the stomach decreased the absorption of minocycline anywhere from 2-51% (Garner et al., 2005).

Severe acne is generally defined as open and closed comedones, with the addition of inflamed pustule, papular, and nodular lesions which have the risk of significant scarring and the risk of psychological factors (Garner et al., 2005). This level of acne only has one recommended treatment and should only be commenced if all other treatment options have failed and the acne is causing the patient significant impairment in their daily life with a high risk of permanent physical and psychological effects and scarring. At this point oral isotretinoin which is extremely teratogenic and has a high risk of multiple serious adverse effects is used. Because of this, recommended dosage is started low at 0.5mg/kg/day and continued or increased cautiously. The patient is usually required to follow a pregnancy prevention plan, and monitoring includes...
regular checks of liver enzymes and lipids at least every three months (Layton et al., 2006).

Acne has four different primary causes that include: increased sebum production, blockage of the follicular duct due to abnormal sloughing of the keratinocytes, bacterial growth and colonization of Propionibacterium acnes (P.acnes), and the inflammatory process and immune response (Layton et al., 2006, Dipiro et al., 2008). The tetracycline antibiotics work in two of these pathways, by reducing the colonization of P.acnes as well as having an anti-inflammatory effect that is independent of the antimicrobial properties (Roebuck, 2006). P.acnes is the usual target of the antibacterial treatment of acne because it is the prime bacterium. P.acnes is a normal bacterium of the skin which increases at puberty, usually significantly by late adolescence and is seen mainly in areas of the skin with increased sebaceous glands such as the face (Gollnick, 2003). The increase in P.acnes is concurrent with an increase in sebum production implying sebum may influence the growth rate of P.acnes (Gollnick, 2003). “P.acnes produces an extracellular lipase that hydrolyses sebum triglycerides to glycerol, used by the organism as a growth substrate, and free fatty acids, which have pro-inflammatory and comogenic properties” (Gollnick, 2003, p. 1585). Prolonged use of antibiotics has been shown to increase the development of resistant strains of P.acnes; the recommendation is to limit antibiotic therapy to three months (Leyden et al., 2006). Inflammation is linked to IL-1α levels up to 1000 times higher have been measured in acne lesions when compared to other skin tissues, as well as the pro-inflammatory cytokine TNFα (Gollnick, 2003). The inflammatory process is very complicated and many different hypotheses have been postulated to explain the exact process.
Minocycline Drug Induced Lupus

Moderate acne is a common problem among adolescents and therefore will be a common diagnosis requiring treatment within a primary care office visit. Minocycline is one of the commonly used medications for moderate acne with one of the most severe side effects being drug induced lupus. “Autoimmunity develops when there is dysregulation of one or more components of the normal immune response” (Dedeoglu, 2009, p. 547). Currently, more than 90 different medications have been identified in drug induced autoimmunity (DIA) (Dedeoglu, 2009). Causes of DIA are thought to be multifactorial and complex with a combination of genetic, epigenetic, and environmental factors (Dedeoglu, 2009) working together to trigger a complex response, which is seen in various signs and symptoms grouped together in a predictable pattern. DIA is a broad term and is traditionally broken into separate sub categories such as drug induced hepatitis, lupus, arthritis, and vasculitis. In some medications, including minocycline, there is significant overlap of these disorders implying these separate disorders may be describing different parts of a single process which occurs as a reaction to a specific medication (Dedeoglu, 2009). The first case of recognized drug induced lupus (DIL) was in the 1950s associated with hydralazine and sulphadiazine (Dedeoglu, 2009). Common features seen in patients with DIL are arthralgia (90%), myalgia (50%), malaise, fever, plueritis, pericarditis, mild leukopenia, thrombocytopenia, anemia, and anorexia (Dedeoglu, 2009). Other symptoms that are sometimes seen include hepatitis, serositis, and lymphadenopathy. Vasculitis is seen in some cases and signifies a more chronic and serious form of DIL (Dedeoglu, 2009).
Formal diagnostic criterion have not been established for the diagnosis of DIL; the most thorough criteria found include: treatment of one month or longer with a medication known to cause DIL; common symptom profile of arthralgias, myalgias, malaise, fever, serositis laboratory profile including anti-histone antibodies (with preference of IgG anti H2A-H2B DNA) with no other antinuclear antibody specificities, and symptom improvement within days to weeks of discontinuation of the suspected medication (Sarzi-Puttini et al., 2005). A last diagnostic criterion was rechallenging with the suspected agent which should cause reoccurrence of similar symptoms, however due to ethical reasons this is usually not done (Sarzi-Puttini et al., 2005). Minocycline DIL is challenging to recognize in the clinical setting due to slow onset requiring anywhere from 3 days to 6 years to develop with mild, vague symptoms that worsen progressively over time if the offending agent is not stopped (Dedeoglu, 2009, Sarzi-Puttini et al., 2005, Ahmed, Kelsey, & Shariff, 2007). A cumulative dose of the medication causing DIL usually needs to be reached; for minocycline the highest risk is in patients with a cumulative dose of over 50000mg (Dedeoglu, 2009). When applied to the usual dosage of minocycline for the treatment of acne at a dose of 100mg per day, the 50000mg mark is reached after approximately 17.8 months of treatment; at the 200mg per day dose, the 50000mg mark is reached after approximately 9 months.

There is an 8.5 fold increased risk of DIL with the use of minocycline in comparison with doxycycline, oxytetracycline, and tetracycline having a combined risk of 1.7 fold (Porter & Harrison, 2003). Minocycline DIL has a female to male ratio of 5:1, which differs from other forms of DIL, possibly due to the population of patients who are placed on minocycline for
treatment of acne (Sarzi-Puttini et al., 2005, Porter & Harrison, 2003). Hepatic involvement in
minocycline DIL is common; other complications include dermatological findings, lung disease,
pleurisy, and peripheral neuropathy (Porter & Harrison, 2003).

There are no significant risk factors or known triggers for DIL. However, there is
significant research available on systemic lupus erythematosus and risk factors. A genetic
component was first discovered in the 1970s, since then it has become known that 10-20% of
SLE patients have an affected first degree relative. This is a more significant genetic link than
seen in other well researched autoimmune disorders such as Grave's disease, multiple sclerosis,
psoriasis, type one diabetes, and rheumatoid arthritis (Kaiser & Criswell, 2010). The
monozygotic twin rate of SLE is also very high, at 24-57%; however, this leaves a large
percentage of monozygotic twins who do not develop SLE, implying there are also other factors.
There are a few known environmental triggers to SLE including smoking and the Epstein-Barr
virus (Kaiser & Criswell, 2010). DIL is linked to an environmental trigger which is the specific
medication. There have been no identified genetic links however; due to the similarities in
presentation between SLE and DIL it leads this author to question the link between DIL and the
possibility of unidentified genetic markers and the patient population who experience DIL. This
issue also raises the question of whether DIL is truly a drug reaction or a true autoimmune
disorder that has been triggered in the case of chronic DIL. For example, a case study was found
in which a patient suffering from minocycline DIL had a brother with SLE, supporting the
possibility of DIL being a currently inactive autoimmune disorder. This further raises the
question as why DIL in most cases resolves with treatment and time whereas SLE is a chronic
condition for a lifetime. DIL has different courses or subcategories which involve systemic DIL and cutaneous DIL and are caused by different drugs suggesting immune pathways are involved depending on the specific drug and the specific reaction (Dedeoglu, 2009). More research is needed to answer these questions.

Minocycline Drug Induced Lupus and Laboratory Values

As a clinician, it is important to analyze the laboratory data that would support a diagnosis of minocycline DIL. Usual laboratory findings include elevated ANA, CRP, ESR, and negative antibodies to dsDNA, and negative antihistone antibodies but exceptions to these general guidelines have been documented (Porter & Harrison, 2003). Almost all clinically significant cases of DIL are seen in patients who have a positive ANA at baseline, and 82.2% of minocycline DIL cases present with a positive ANA (Dedeoglu, 2009, Sarzi-Puttini et al., 2005). Antinuclear antibody (ANA) is performed in patients to rule out connective tissue diseases (Fischbach & Dunning III, 2009). ANA may be positive in elderly people and other healthy people; however, if the result of the ANA is positive then allow a titer of the specimen. A normal titer is an ANA<1:60 (Fischbach & Dunning III, 2009). A positive ANA with a significant titer can be seen in a patient on minocycline and does not necessitate withdrawing the drug if the patient has no signs or symptoms and otherwise normal blood work results (Dedeoglu, 2009). A C-reactive protein (CRP) can also be seen. CRP is a measure of a protein which appears in the blood when the body is reacting to an inflammatory process and is negative in healthy individuals (Fischbach & Dunning III, 2009). Erythrocyte sedimentation (ESR) is “the rate at which erythrocytes settle out of anticoagulated blood in 1 hour” (Fischbach & Dunning III,
2009, p.110). The erythrocytes become heavier when they clump together, which happens in inflammatory and necrotic processes causing the rate at which they settle to increase which is measured as an increased ESR (Fischbach & Dunning III, 2009). The ESR in minocycline DIL is often elevated because of the inflammatory nature of the disorder. A positive antihistone antibody has been termed the "hallmark" of DIL, but this is less commonly seen in minocycline DIL (Dedeoglu, 2009).

DIL and SLE are most distinguishable by the confirmation of a medication that is a culprit and symptom improvement with discontinuation as well as DIL usually having negative findings of antidoouble stranded DNA antibodies (dsDNA) whereas this is a commonly positive finding in SLE (Dedeoglu, 2009). The dsDNA is a test done specifically for lupus, if the result to this test is negative it helps to distinguish minocycline DIL from SLE (John Hopkins Arthritis Center, 2010).

Patients with minocycline DIL often have liver involvement which can be organized into three categories: fatty liver degeneration which occurs within days to weeks; allergic idiosyncratic damage which occurs within days to weeks; and, autoimmune hepatitis which takes time to develop and causes a more chronic condition (Sarzi-Puttini et al., 2005). A baseline liver panel should also be performed in these patients. Due to the liver involvement, hepatic transaminases have been concluded to be positive in about one third of the reported cases of minocycline DIL (Sarzi-Puttini et al., 2005). To rule out the possibility of liver enzyme elevation caused by another illness, tests for hepatitis A, B, C, and cytomegalovirus should also be done.
(Porter & Harrison, 2003). Because of the presenting clinical symptoms Epstein-Barr virus, ELISA and rheumatoid factor have also been drawn post therapy in some of the case studies that were reviewed after symptoms of DIL developed (Porter & Harrison, 2003).

Another less common complication of minocycline DIL is vasculitis. There is a test called antinuetrophil cytoplasmic antibodies (ANCA) which are separated into two types, cANCA and pANCA. These two different immunoflourescent stains produce different patterns when staining the nuetrophils; pANCA is found in patients with vasculitis (Porter & Harrison, 2003). In some cases, a patient with minocycline DIL may have a positive pANCA implying vasculitis and a more serious chronic course of minocycline DIL (Porter & Harrison, 2003).

The treatment of minocycline DIL should be handled by referral to a specialist, either a rheumatologist or hepatologist or both depending on how the disorder has affected the individual. The recovery course is usually short with little complication, but there have been chronic courses as well as fatalities reported in the literature (Porter & Harrison, 2003, Garner et al., 2005).

Implications for Clinicians

All of the information presented can seem overwhelming to sort through; especially since there are no available tools or methods of organization for the provider. Therefore, the object of this article was to create a decision tree (see appendix A) to assist the primary care provider with the choice of safely using minocycline for the treatment of acne. It is organized as a flowchart with the provider beginning at the top of the chart and answering simple yes or no questions.
which lead to the appropriate treatment for that patient. It further assists the provider with a timeframe for treatment, as well as a method to recognize and avoid minocycline DIL in patients. Coming up with specifics for the flowchart was challenging, since the information currently available on minocycline DIL is vague regarding signs, symptoms, onset, and diagnosis. The time frames and monitoring suggested are based on the current available literature and suggest conservative estimates on laboratory values. To assist clinicians accurately and affordably, the flowchart should be included in a further study which would measure not only the feasibility of the tool but with enough use could help clinicians further understand required versus recommended lab work; appropriate or predictable time frames of use; and, reveal possible unknown patterns in the course of minocycline DIL. Further research is also needed in the analysis of risk factors, genetic predisposition, and different treatment methods of minocycline DIL.

Conclusion

There are appropriate times and uses for the medication minocycline in the adolescent with acne vulgaris. As primary care providers it is our duty to be able to recognize and also to understand the risk and correct monitoring of minocycline DIL. This article has provided an overview of current treatment recommendations of the different levels of severity of acne; the current research and understanding of minocycline DIL; and, provides a flowchart for use in practice to forward the understanding and correct monitoring of minocycline DIL reducing the morbidity and mortality of the disease course for future patients
Appendix A

Diagnosis of moderate acne?

Start treatment for mild acne with a combination of topical medications.

Failed trial of combination topical medication over at least 6 weeks?

Begin oral treatment with first line second generation tetracycline.

Failed trial with second generation oral tetracycline recommended for acne treatment besides minocycline?

Is the patient experiencing signs and symptoms of minocycline DIL?

Redraw baseline lab work every month of treatment, continue to monitor for signs and symptoms of minocycline DIL.

Begin treatment with oral minocycline 100mg/day plus topical medication.

At time of treatment required baseline lab work include:
- ESR, ANA, CRP, and liver panel

Discontinue immediately, draw lab work including:
- ESR, ANA, CRP, liver panel, hepatitis A,B,C, Epstein-Barr, ELISA, rheumatoid factor, ANCA, dsDNA. Refer to specialist.

CAUTION: treatment longer than 3 months increases risk of resistant p.acnes
CAUTION: cumulative dosage above 50000mg significantly increases risk of DIL
References


