ORIGINAL INVESTIGATION

Minocycline and Lupuslike Syndrome in Acne Patients

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Background: Recently several case reports described the association between minocycline and lupuslike syndrome. Minocycline, one of the tetracyclines, is widely used to treat acne. We aimed to examine the association of exposure to minocycline and other tetracyclines with the development of lupuslike syndrome.

Methods: We conducted a nested case-control study in a cohort of 27 688 acne patients aged 15 to 29 years, using data automatically recorded on general practitioners' office computers in the United Kingdom. Controls were matched to cases on age, sex, and practice. The main outcome was lupuslike syndrome defined as the occurrence of polyarthritis or polyarthralgia of unknown origin, with negative rheumatoid factor or latex agglutination test, positive or unmeasured antinuclear factor, elevated or unmeasured erythrocyte sedimentation rate, and absence of or unmeasured antinative DNA antibody levels.

Results: We identified 29 cases and selected 152 controls. Current single use of minocycline was associated with an 8.5-fold (95% confidence interval [CI], 2.1-35) increased risk of developing lupuslike syndrome compared with nonusers and past users of tetracyclines combined. The risk of past exposure to any of the tetracyclines was closely similar to nonuse (relative risk, 1.3; 95% CI, 0.5-3.3). Current use of doxycycline, oxytetracycline, or tetracycline combined was associated with a 1.7-fold (95% CI, 0.4-8.1) increase of risk. The risk increased with longer use.

Conclusion: Current use of minocycline increased the risk of developing lupuslike syndrome 8.5-fold in the cohort of young acne patients. The effect was stronger in longer-term users. However, the absolute risk of developing lupuslike syndrome seems to be relatively low.

Arch Intern Med. 1999;159:493-497

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MINOCYCLINE IS a semisynthetic tetracycline antibiotic that is used to treat infections caused by several types of gram-positive and gram-negative bacterias, *Rickettsia*, *Chlamydia*, and *Mycoplasma* species. It became available in 1972 and has been widely used since then. Its long half-life, allowing for once- or twice-daily dosing, and the suggestion that minocyline rarely causes resistance makes it popular with both patients and physicians.[1-4] Tetracyclines are used orally in the treatment of moderate to severe inflammatory acne vulgaris and other infections sensitive to the actions of tetracylines. Because of its favorable dosing characteristics and the low rate of resistance, minocycline is now the most widely prescribed antibiotic for acne.[1] An estimated 800 000 prescriptions were written in 1993 in the United Kingdom,[1] and 65% of oral minocycline use in the United States was for treatment of acne.[5]

In 1959, 3 patients were described who developed a systemic lupus erythematosus–like clinical syndrome while being treated with tetracycline.[6] However, this association was likely based on a misperception, and no other cases of tetracycline-induced lupus have been published since then.[7] Minocycline, however, was related to lupus in numerous case reports, the first of which appeared in 1992.[8] Through the beginning of 1998, 64 minocycline users who developed lupuslike syndrome have been described in the literature.[7-19] The mean age of patients was 21 years and 85% were female. In most patients, the onset of arthralgia or arthritis accompanied by myalgia or malaise developed after prolonged periods of exposure to minocycline (mean duration, 24 months; range, 1.5-72 months). All were asymptomatic before treatment. Typical were the presence of antinuclear antibodies and elevated erythrocyte sedimentation rate but negative levels of antihistone antibodies and antinative DNA antibodies.

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METHODS

We conducted a case-control study with data from the General Practice Research Database (GPRD). More than 4 million people in the United Kingdom are enrolled with selected general practitioners who use office computers provided by Value Added Medical Products (currently owned by Reuters Information Services, Toronto, Ontario) and who have agreed to provide data for research purposes to the GPRD, which is currently owned by the United Kingdom Department of Health. General practitioners have been trained to record medical information in a standard manner and to supply it anonymously. The information recorded includes demographics, medical diagnoses, and all drug prescriptions, since the physicians generate prescriptions directly with the computer. It contains the name of the preparation, route of administration, dose, and number of tablets for each prescription. Hospital discharge and referral letters are available for review to validate the diagnoses recorded in the computer record. A modification of the Oxford Medical Information System (OXMIS) is used to enter medical diagnoses. For the purpose of this study, OXMIS codes have been mapped onto *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD*) codes. The recorded information on drug exposure and on diagnoses in the GPRD is of high quality and is satisfactory for drug safety studies.[21,22]

For this study, 319 practices contributed information recorded on computer from January 1, 1991, through February 1996. From this population we identified all persons with acne (*ICD* codes 706.0 and 706.1), aged 15 to 29 years, without a history of lupus, arthralgia, rheumatoid arthritis, or chronic active hepatitis. Persons were excluded if they had any preexisting cancer of the blood or immune system (leukemia, lymphoma) or acquired immunodeficiency syndrome prior to the index date, if they used anticonvulsants (associated with lupuslike syndrome), or if the first diagnosis of acne occurred after the diagnosis of lupuslike syndrome (subsequently, the date of first-time diagnosis of the lupuslike syndrome will be referred to as the index date).

CASES AND CONTROLS

From the cohort of acne patients, we identified (blinded to any tetracycline exposure) all patients who had a first-time diagnosis of systemic lupus erythematosus or polyarthralgia/polyarthritis. We then asked general practitioners to send us patient records of these potential cases and assessed all available information. These hospital records and referral letters as well as laboratory reports were reviewed independently by 2 of us (C.R.M. and M.C.J.M.S.), again while blinded to exposure. Cases were included if they had negative rheumatoid factor or latex agglutination test, positive or unmeasured antinuclear antibody levels, elevated or unmeasured erythrocyte sedimentation rate, and absence of or unmeasured anti-DNA antibody levels.

To each case, we matched 8 controls from among all noncases in the base population of patients with acne on practice, age (same year), and sex. The same exclusion criteria and index date were applied to controls as to cases.

Exposure to minocycline, tetracycline, oxytetracycline, and doxycycline, as well as to other drugs that have been implicated as causing drug-induced lupus, was assessed from the computer record.[20] Drug use was classified as either "current use" (legend duration of prescription includes the index date or stops at a maximum of 14 days before) and "past use" (theoretical stop date >2 weeks prior to index date). The total cumulative exposure was assessed using defined daily doses and categorized "≤100 defined daily doses" and ">100 defined daily doses."[23] If study subjects used more than 1 tetracycline within the study period, we classified them as "multiple users," but their defined daily doses were summed.

ANALYSIS

Based on the number of cases occurring during current use of one of the tetracyclines and the number of prescriptions for the different tetracyclines, we assessed crude incidence rates and 95% confidence intervals (CIs) for exposure to the various study drugs, stratified by sex. For the case-control analysis, we obtained relative risk (RR) estimates (odds ratios) through conditional logistic regression analysis with the software program SAS (SAS Institute Inc, Cary, NC).

All patients recovered rapidly after drug removal, and antibody levels became normal. In several cases, rechallenge was positive, indicating a causal relationship.[7-19]

There is no consensus on the diagnostic criteria for drug-induced lupus, but it should be expected in patients who do not have a history of idiopathic lupus, who develop antinuclear antibodies, and who have at least 1 clinical feature of lupus after an appropriate duration of drug treatment.[20] We aimed to compare the risk of developing lupuslike syndrome in acne patients following exposure to minocycline or other tetracyclines with nonexposed subjects.

RESULTS

The study population consisted of 27 688 acne patients aged 15 to 29 years. The distribution of use of the tetracyclines by age and sex is given in **Table 1**. The distribution of use was comparable for the 4 tetracyclines; approximately 60% of the use occurred in males and about 70% of the prescriptions of the various tetracyclines were written for persons in the age range of 15 to 19 years.

We identified by computer 78 potential cases with a diagnosis of systemic lupus erythematosus or multiple joint pain. After manual review of the computerized patient profiles, we retained 44 patients for whom we sent for additional information. Reasons for exclusion were mostly the lack of referral or further workup of the diagnosis. After review of the medical notes of the 44 patients, 15 were excluded from the subsequent analysis. Reasons for exclusion were a viral or bacterial infection just before the first diagnosis of polyarthralgia or polyarthritis (n = 4), a negative antinuclear antibody level (n = 9), or the presence of the condition prior to the first diagnosis of acne (n = 2). The remaining 29 patients presented with multiple joint pain; in only 3, the antinuclear antibody level was measured and elevated (all,

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Table 1. Study Cohort and Sex and Age Distribution of Tetracycline Users*

Drug Type	No. of Patients		No. of Prescriptions	% of Prescriptions				
						Age, y		
	Male	Female		Male	Female	15-19	20-24	25-29
Minocycline	3748	3388	28 032	59	41	68	24	8
Tetracycline	699	512	3063	64	36	69	22	9
Doxycycline	1175	1464	7470	55	45	67	24	9
Oxytetracycline	5587	4241	31 740	63	37	70	22	8

*Categories are not mutually exclusive since study subjects may have used more than 1 of the tetracyclines.

1:640) in combination with an elevated erythrocyte sedimentation rate. Eight patients were in the age range of 15 to 19 years at presentation, 11 between 20 to 24 years, and 10 between 25 and 29 years. Two cases occurred in males and 27 in females. Ten cases occurred in nonusers, 6 during current use of minocycline, 3 during current use of oxytetracycline, 1 during current multiple use, 1 in past minocycline exposure, 1 in past tetracycline exposure, 5 in past oxytetracycline exposure, and 2 in past multiple users. After applying the exclusion criteria to the matched controls, we retained a variable number of controls for each case; the average was 5 controls per case.

INCIDENCE RATES

The crude incidence rate and 95% CIs for lupuslike syndrome associated with current use of tetracyclines as a group was 14.2 cases per 100 000 (95% CI, 6.8-26.1) prescriptions. The rates for males and females differed significantly: 2.3 cases per 100 000 (95% CI, 0.07-13.0) prescriptions for males and 32.7 cases per 100 000 (95% CI, 14.9-62.1) prescriptions for females (RR, 14; 95% CI, 1.8-111). The incidence rates for the different tetracyclines could be assessed for minocycline and oxytetracycline only, since no cases occurred in current users of doxycycline or tetracycline, which may be explained by the low number of prescriptions for these latter drugs. The rate of lupuslike syndrome in females was 17.2 cases per 100 000 (95% CI, 2.1-62.1) prescriptions for oxytetracycline and 52.8 cases per 100 000 (95% CI, 19.4-115) prescriptions for minocycline (RR, 3.1; 95% CI, 0.6-15.2).

CASE-CONTROL ANALYSIS

Table 2 shows the association between the use of tetracyclines with the occurrence of lupuslike syndrome. Among the 29 cases and their 152 controls, current use of tetracyclines as a group resulted in an elevated risk of 3.5 (95% CI, 1.3-10) as compared with nonusers. The risk of past exposure to any of the tetracyclines was closely similar to nonuse (RR, 1.3; 95% CI, 0.5-3.3); we therefore combined never and past users into a single reference group for further analyses. Current single use of minocycline was associated with an 8.5-fold (95% CI, 2.1-35) increased risk of developing lupuslike syndrome compared with nonusers and past users of all tetracyclines combined. Current use of doxycycline, oxytetracycline, or tetracycline combined was associated with a 1.7-fold (95% CI, 0.4-8.1) increase of risk compared with nonuse and past use.

Table 2. Use of Tetracyclines and the Matched Association With Lupus on the Total Set*

	Cases, No. (%)	Controls, No. (%)	OR† (95% CI)
Exposure to Any Tetracyclines			
None	10 (34)	73 (48)	1.0 (Reference)
Past	9 (31)	59 (39)	1.3 (0.5-3.3)
Current	10 (34)	20 (13)	3.5 (1.3-10)
Exposure to Individual Tetracyclines			
None/past	19 (66)	132 (87)	1.0 (Reference)
Minocycline	6 (21)	6 (4)	8.5 (2.1-35)
Other tetracyclines	3 (10)	9 (6)	1.7 (0.4-8.1)
Multiple use	1 (3)	5 (3)	1.4 (0.3-5.8)

*Due to rounding, percentages may not add up to 100%. OR indicates odds ratio; CI, confidence interval.
†Matched for sex, age, and practice.

The mean number of cumulative defined daily doses used were 110 defined daily doses (SD, 64) (range, 1-500 defined daily doses) for minocycline (1 defined daily dose = 200 mg). This was equal to the mean cumulative dose of the other tetracyclines, although the variation was larger: 119 ± 137 defined daily doses. Average daily doses were 0.5 defined daily doses for both groups. The risk for current use with high cumulative doses of minocycline (>100 defined daily doses) was higher (odds ratio [OR], 16; 95% CI, 1.5-175) than for current use with a low cumulative dose (≤100 defined daily doses) (OR, 6.1; 95% CI, 1.1-33), as compared with nonuse and past use combined. The effect of stratifying for short and long duration of use was more or less similar to that of cumulative dose due to the homogeneity in daily dose. Current exposure for less than 100 and 100 or more days resulted in RRs of 5.3 (95% CI, 0.7-39) and 14 (95% CI, 1.5-127), respectively.

Adjustment for current exposure to oral contraceptives did not materially influence the reported risk estimates. Smoking was not associated with lupuslike syndrome in this population nor was the current exposure to other drugs used to treat acne. We intended to evaluate the risk for current exposure to isotretinoin, but there were only 2 exposed cases. We also explored current exposure to other drugs that have been associated with drug-induced lupus, such as ibuprofen, oral contraceptives, and penicillins, but including exposure to these drugs

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in the logistic regression model did not change the results. None of the study subjects had used drugs that interact with the absorption of the tetracyclines (ie, antacids, iron) concomitantly with the tetracyclines.

COMMENT

The results of this population-based matched case-control study suggest that the use of tetracyclines and minocycline in particular increases the risk of developing lupuslike syndrome in females aged 15 to 29 years who suffer from acne. The risk of current exposure to all tetracyclines combined was 3.5-fold increased compared with never and past users combined. There was no effect of past use.

Analysis of crude incidence rates on all tetracyclines combined shows that females with acne between 15 to 29 years of age have a 14-fold increase of risk of developing lupuslike syndrome compared with males of similar age and with acne. Due to the fact that only 2 cases occurred in males, we could not assess the rates for the different types of tetracyclines stratified by sex.

Our study suggests that the risk of lupuslike syndrome is 3- to 4-fold higher following treatment with minocycline than with other tetracyclines (mostly oxytetracycline), although the differences were not significant. These differences between tetracyclines cannot easily be explained by different dosing patterns since both the average cumulative dose and daily dose were closely similar for minocycline and the other tetracyclines. Other tetracyclines have been suggested to be associated with lupus erythematosus in 1 report[7] in 1959, but the 3 cases presented there may have been attributed to tetracyclines erroneously. No formal epidemiological study has been published before that compared the risk of drug-induced lupus among users of different tetracyclines. Recently a review appeared on the comparative safety of these different tetracyclines.[7] The data, which were based on case series, indicated that drug-induced lupus is only reported for minocycline.[7] This is consistent with the differences in RR between the different tetracyclines that we observed in our study.

We found a strong effect of cumulative minocycline dose on the risk of developing lupuslike syndrome. Current exposure with cumulative doses of 100 or fewer defined daily doses was associated with a 6-fold increased risk, whereas the risk for current exposure to minocycline with cumulative doses above 100 defined daily doses, compared with nonusers and past users was associated with a 16-fold increased risk. Cumulative dose captures the effect of duration and a varying rate of daily exposure over time, and the use of defined daily doses allows for comparisons between drugs in the same class.[23] In this study, the daily dose of minocycline did not vary greatly; hence, the effects of cumulative daily dose and duration of exposure to minocycline were almost similar: longer duration is associated with a higher risk of developing lupuslike syndrome. These findings are in agreement with the case reports that mostly describe patients with prolonged exposure to minocycline.[7-19] Due to the homogeneity in daily dose, we could not explore the effect of different daily doses on the risk of developing lupuslike syndrome.

Despite the high RR of developing lupuslike syndrome following use of minocycline, especially in females, the absolute risk is relatively low (52.8 cases per 100 000 prescriptions).

Several mechanisms have been suggested for drug-induced lupus and include the possibility that a reactive metabolite binds to the class II major histocompatibility antigen and, thus, induces an autoimmune reaction analogous to a graft-vs-host reaction.[7] A drug or its potentially reactive metabolites may bind directly to histones and act as haptens, producing an antigenic complex capable of stimulating autoantibody formation.[7] Factors that have been implicated in causing drug-induced lupus include use of the drug for long-term therapy, dose dependency, and the presence of a functional group that is easily oxidized to a reactive metabolite. Shapiro et al[7] hypothesized that the presence of an amino acid side chain in minocycline, which may yield a reactive metabolite, and the absence of such a functional group in the other tetracyclines might explain why drug-induced lupus is observed merely in minocycline users.

Potential confounders, such as smoking or use of other drugs that are associated with lupuslike syndrome, did not affect our risk estimates.

Acne itself could explain our findings, as it may cause polyarthralgia, but this is observed predominantly in male acne patients (80%).[24,25] In our study, 93% of the patients were female. Furthermore, the onset of acne-related arthralgia usually coincides with the onset of acne, while the onset on our study occurred after prolonged periods of acne.[24] These observations, the clinical and biochemical resolution after withdrawal of the drug, the fact that all patients suffered from acne, and the lack of effect observed in past users weigh against confounding by indication.

Selection bias might have occurred if minocycline-exposed subjects were more likely to undergo laboratory tests. However, cases were sampled between January 1991 and February 1996, which was during the period that a potential association between minocycline and lupuslike syndrome was hardly recognized. This is supported by the fact that almost all cases were identified in the database by a diagnosis of polyarthralgia and not systemic lupus erythematosus, or drug-induced lupus, and only few cases underwent laboratory tests specific for drug-induced lupus.

A potential bias in this study could be the rather unspecific case definition and lack of information on the majority of antinuclear antibody tests, which may lead to misclassification of disease. This bias will be undifferential due to the prospective data collection and blind review of case status, and, therefore, lead to a conservative risk estimate. Furthermore, this cannot explain the differences in risk we observed between the individual tetracyclines.

We have found an 8.5-fold increased risk of developing lupuslike syndrome for current minocycline users compared with nonusers and past users combined. This effect was strongest in females and for longer-term use of minocycline. Since lupuslike syndrome is uncommon, and since the syndrome seems to be reversible after stopping minocycline intake, this increase has only a

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moderate effect on the risk to benefit balance associated with the treatment of acne with this widely used drug.

Accepted for publication August 6, 1998.

The Boston Collaborative Drug Surveillance Program is supported in part by grants from Astra Hässle AB, Mölndal, Sweden; Berlex Laboratories, Montville, NJ; Bayer AG, Leverkusen, Germany; Glaxo Wellcome Inc, Research Triangle Park, NC; Hoffmann-La Roche, Basel, Switzerland; Novartis Pharmaceuticals, Barcelona, Spain; RW Johnson Pharmaceutical Research Institute, Raritan, NJ; and Pfizer Inc, New York, NY. Christoph R. Meier, PhD, MSc, is supported in part by a grant from the Swiss National Science Foundation, Berne, and the Holder-Bank Stiftung, Holderbank, Aargau, Switzerland. Miriam C. J. M. Sturkenboom, PhD, PharmD, MSc, is supported by a grant from the Dutch Inspectorate for Health Care, The Hague, the Netherlands.

We thank the participating general practitioners for their excellent cooperation and Alan Dean, MD, and his team for their generous help.

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