Minocycline Induced Lupus: Case Series in the West of Scotland

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ABSTRACT. ***Objective.*** To describe the clinical symptoms and serology of drug-induced lupus in patients treated with the semisynthetic tetracycline derivative, minocycline.

Methods. For a 5-year period, all consultant rheumatologists and dermatologists in the West of Scotland were asked to report any suspected cases of a lupus-like syndrome to one center. Twenty cases were identified on the basis of arthritis, positive antinuclear factor and at least one other extraarticular feature following treatment for acne with minocycline. Case histories were reviewed to determine any demographic, clinical, or serological correlations.

Results. Minocycline had been prescribed for a mean of 25 months for the 20 patients identified with drug-induced lupus; 15 were female, 5 were male with a mean age of 24 years. All patients had arthritis and most had at least one other extraarticular feature including lethargy, myalgia, fevers, Raynaud's phenomenon, abdominal pain, and butterfly rash. None had renal involvement. All symptoms resolved at a mean of 15.7 weeks after discontinuation of minocycline treatment.

Conclusions Minocycline is widely used in the treatment of acne and increasingly in the treatment of rheumatic diseases. Although the absolute risk of developing drug-induced lupus is relatively low, it has been estimated that current use of minocycline is associated with an 8.5 fold increased risk of developing a lupus-like syndrome. Prescribing physicians must be vigilant for any of the characteristic symptoms to avoid unnecessary morbidity, investigations, and therapy. (J Rheumatol 2001;28:1004–6)

Key Indexing Terms:
MINOCYCLINE DRUG INDUCED LUPUS CLINICAL OUTCOME

Minocycline is a semisynthetic tetracycline derivative, widely used in the treatment of acne vulgaris and rosacea. In the UK alone, there are 900,000 prescriptions per year[1]. It is generally considered a safe drug and adverse effects are uncommon. Reported side effects include gastrointestinal toxicity, nephritis, vestibular symptoms, hepatitis, intracranial hypertension, pulmonary eosinophilia, and skin pigmentation. In addition, there have been over 60 case reports of a drug-induced lupus syndrome following treatment with minocycline since 1992[2], although the frequency of drug-induced autoimmune phenomena is likely to be underestimated. Following the first reported cases, 20 cases were identified in the West of Scotland over the last 5 years.

MATERIALS AND METHODS

All consultant rheumatologists and dermatologists in the West of Scotland were asked to report any suspected cases of a lupus-like syndrome to one center and case notes were then reviewed. Demographic, clinical and serological data were extracted and compiled.

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RESULTS.

After 5 years, 20 patients had been identified as having a lupus-like syndrome on the basis of arthritis, positive antinuclear factor, and at least 1 other extraarticular feature following treatment with minocycline. There were 15 females and 5 males, with a mean age of 24 years (range 16-49). All were Caucasian. Minocycline had been prescribed for acne for a mean of 25 months (range 3-60) prior to symptoms developing. The total number of patients from which the 20 cases were identified is not known. Since in the UK there are 900,000 prescriptions per year for minocycline, and since the West of Scotland serves a population of 1.5 million people, it could be estimated as a percentage that there would be about 50,000 prescriptions per year for minocycline in this area.

All 20 patients had arthritis and the majority also had extraarticular features: 6 had lethargy, 5 had myalgia, 7 had fevers, 4 had Raynaud's phenomenon, 2 had abdominal pain, and 2 had a characteristic butterfly rash. No patients had renal involvement. Twelve patients also had biochemical evidence of hepatitis. Two patients had marginal leukopenia and one patient had thrombocytopenia. All patients had a positive antinuclear factor (ANF) and were seronegative for rheumatoid factor at presentation. Extractable nuclear antigens were not detected. Two patients had anticardiolipin antibodies (one each of IgA and IgG) and one further patient had a perinuclear antineutrophil

cytoplasmic antibodies (p-ANCA) detected. Contrary to previous reports, 8/20 (40%) of our patients also had antibodies to double stranded DNA. Only 2 of these patients were crithidia positive. Antihistone antibodies were not measured. All but one patient showed an elevated erythrocyte sedimentation rate (ESR) at the time of their initial illness. Eleven patients had immunoglobulins measured and 9 had a significantly elevated IgG.

Symptoms resolved in all patients after discontinuing minocycline treatment at a mean of 15.7 weeks (range 2-56). Patients were followed for a mean of 19.4 months (range 7-60) and remained asymptomatic. All antibodies to dsDNA disappeared, and only 6 patients still had detectable antinuclear antibodies during followup, although at significantly lower titers. Despite being questioned about their usual medication, 6 patients initially denied taking any therapy, including minocycline. It was only when these patients restarted minocycline that the association was made. All 6 had recurrence of their symptoms within a mean of 4.5 days (range 2-7), with 2 patients requiring treatment with prednisolone and 5 requiring treatment with hydroxychloroquine (Table 1).

DISCUSSION

Systemic lupus erythematosus (SLE) is a multisystem disease of unknown etiology that may develop when a genetically susceptible host is exposed to an environmental trigger, such as drug therapy. Since the 1970s, at least 49 drugs have been reported to be associated with drug related lupus[3], of which hydralazine and procainamide are the most commonly implicated. There may be no clinical manifestations and only an ANF detected. For a drug to be implicated in drug-induced lupus, certain criteria must apply. First, there must be no suggestive history prior to using the implicated drug. Secondly, ANF must be positive on at least one occasion during the illness with at least one clinical feature of SLE[4]. Finally, there should be a rapid improvement in clinical symptoms and a fall in the titer of ANF when the drug is withdrawn. All our patients satisfied these criteria.

Although there is no diagnostic test for drug-induced lupus, there are certain differences between drug-induced and idiopathic disease. Drug-induced disease tends to have a delayed onset, usually between 1 month and 5 years of drug therapy. Fever, myalgias, arthralgias, and pleuropericardial features are commonly seen, whereas malar rash, alopecia and mouth ulcers, and the more life-threatening renal and neurological involvement are rarely seen[5]. Antibodies to native DNA are usually absent or detected in low titers, although 8 of our patients had significant levels of DNA antibodies. Other laboratory abnormalities such as leukopenia, thrombocytopenia, and hypocomplementemia are unusual in drug-induced disease.

Minocycline is among the most commonly prescribed drugs for acne. Until April 1994, there had been 11 reports to the Committee on Safety of Medicines suggesting drug-induced SLE and 16 reports of hepatitis associated with the use of minocycline, including 2 deaths and 1 patient requiring a liver transplant[6]. In the 24 year period from 1972-96, the FDA's MEDWATCH Reporting Program received only 1 report of a case of autoimmune hepatitis and 32 of a SLE-like syndrome[7]. Review of the information from the Medicines Control Agency from 1963-97 identified 292 musculoskeletal adverse effects, including 31 cases of SLE, and 105 patients with arthralgias. Female sex seems to be a risk factor for developing drug-induced disease, with 8 females to 1 male identified, although acne is more frequently treated in young women[8]. In addition, the use of minocycline may exacerbate pre-existing disease[9].

The majority of patients with minocycline-induced lupus are young, although this most likely represents the typical patient with acne. The time to developing symptoms is usually long, although recurrence after rechallenge is characteristically abrupt. Six of our patients had prompt recrudescence of their disease with rechallenge. Although the absolute risk of developing drug-induced lupus is relatively low, it has been estimated that current use of minocycline is associated with an 8.5 fold increased risk of developing a lupus-like syndrome[10].

Table 1. Characteristics of patients rechallenged with minocycline.

Patient	Age	Sex	Minocycline (months)	ANF (1/)	Resolution (weeks)	Comments
1	17	F	36	1000	14	Symptoms recurred 1 week after rechallenge. Treated with hydroxychloroquine.
2	18	F	4	2560	4	Symptoms recurred 2 days after rechallenge. Biochemical hepatitis.
3	23	F	27	640	4	Symptoms recurred 1 week after rechallenge. Biochemical hepatitis.
4	23	M	12	160	2	Symptoms recurred 1 week after rechallenge.
5	21	F	48	160	4	Symptoms recurred 2 days after rechallenge. Biochemical hepatitis. Required treatment with prednisolone.
6	17	M	7	2560	4	Symptoms recurred 2 days after rechallenge. Required treatment with prednisolone.

All our patients had a positive antinuclear antibody at time of diagnosis, with resolution or lowering in titer in all patients after discontinuing the drug. Contrary to previous reports[10], only one of our patients had a detectable p-ANCA; the reasons for this discrepancy are not clear, but may reflect methodology or sensitivity of the assay at the time the samples were analyzed.

Minocycline, with other tetracyclines, is recognized as having antiinflammatory, immunomodulatory, and inhibitory effects on matrix metalloproteinases[11]. Three large randomized controlled trials in a total of 345 patients[12-14] have raised interest in minocycline being used as a disease modifying agent in rheumatoid arthritis (RA). With increased use, side effects are undoubtedly going to be encountered more frequently. The challenge for physicians will be those patients who develop an increase in joint pain while receiving minocycline. To date, there have been no reports of minocycline-induced autoimmune phenomenon in patients with RA. ANF status and titer may prove beneficial in these circumstances, although there is questionable benefit in identifying patients who become ANF positive in the absence of any specific symptoms. Prescribing physicians should be aware of the risks of autoimmune diseases developing during therapy and be vigilant for any of the characteristic symptoms.

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