

1.1. Minocycline and erythema nodosum

Introduction

Minocycline (Minocin®) is a broad-spectrum tetracycline antibiotic. It is the most lipid-soluble of the tetracycline-class antibiotics and indicated for the treatment of *respiratory tract infections, gastro-intestinal tract infections, infections of nose, throat and ear and infections of skin, genital, and urinary systems*. Minocycline has been approved for the Dutch market since 1972 [1].

Erythema nodosum is characterized by red or violet subcutaneous nodules that usually develop on the anterior surfaces of both legs. Polyarthralgia, fever, and malaise frequently accompany erythema nodosum (sometimes in advance of skin findings). Erythema nodosum is presumed to represent a delayed hypersensitivity reaction to antigens associated with the various infectious agents, drugs and other diseases with which it is associated, although the pathogenesis is largely unclear. Erythema nodosum occurs in a variety of disorders for which the etiology remains unknown; for example, sarcoidosis, inflammatory bowel disease and Behçet's disease.

The annual incidence of erythema nodosum is approximately 1 to 5/100,000 persons, most often women aged 15 to 40 years. The female /male ratio is 5 to 1 [2].

Reports

In December 2006 and August 2015 Lareb received two reports of erythema nodosum associated with the use of minocycline.

Case A (62352)

This report from an medical specialist in internal medicine concerns a female aged 21-30 years, with erythema nodosum, generalized polyarthritits and vasculitis one month after the start of minocycline for acne. This was confirmed by a pathologist. Laboratory finding: ANCA anti-elastase positive. The patient is recovering after withdrawal and treatment with corticosteroids. Concomitant medications were ibuprofen and cyproteron/estrogen. Medical history: TBC in childhood; anorexia nervosa.

Case B (203361)

This report from a dermatologist concerns a female aged 51-60 years, with dyspnoea, arthralgia and erythema nodosum following administration of minocycline for rosacea with a latency of three years after start. The erythema nodosum was confirmed by a biopsy. She used 100 mg minocycline on an "as-needed" basis. The drug minocycline was withdrawn. The patient was treated with antibiotics (penicillin) for the dyspnoea and a suspicion of tonsillitis. However she did not recover from these complaints and was sent to a pulmonologist who diagnosed pulmonary infiltrates. The reporter indicated that the patient also had an increase of liver function tests (ALAT 109 and ASAT 140). One month after withdrawal of minocycline these were normalised. After rechallenge (about five months later) the erythema nodosum and arthralgia reappeared within a few hours. She also experienced fever. Two days after withdrawal of minocycline the patient had almost recovered. Concomitant medication was not reported.

The patient has no known medical history. The patient has no known past drug therapy.

Other sources of information

SmPC

The Dutch SmPC of minocycline does not mention erythema nodosum [1]. The US SmPC [3] mentions erythema nodosum and the UK SmPC [4] mentions erythema nodosum as a rare event.

Literature

Several case reports in the literature describe the occurrence of erythema nodosum while using minocycline.

Bridges et al [5] describe a case report of a 32-year-old woman who was in good health except for mild acne. Topical therapies were used without acceptable benefits and minocycline 100 mg twice daily was prescribed. Approximately four months later hyperpigmentation, pulmonary infiltration and erythema nodosum occurred. Bronchoalveolar lavage revealed both a neutrophilic and an eosinophilic alveolitis. The pulmonary and systemic symptoms promptly resolved after discontinuation of minocycline. The skin lesions resolved during an eight-week period.

Another case report [6] describes a 35-year-old woman who had been treated with minocycline for nodulocystic acne vulgaris with doses varying from 50 to 100 mg twice daily during the previous two years. She presented with erythema nodosum on the left leg. Skin and cervical biopsies revealed acute inflammation involving through-and-through necrosis of vessel walls. This fully resolved within three months after discontinuation of minocycline.

Geddes et al [7] describe a 23-year-old woman who developed erythema nodosum and progressive limb weakness after six months of treatment with minocycline 100 mg per day for acne vulgaris. Minocycline was discontinued upon hospital admission. Two weeks after discharge she was treated with prednisone and methotrexate for erythema nodosum. The erythema nodosum resolved nine months after cessation of minocycline.

Bassett et al [8] describe a 34-year-old woman who presented with an erythematous nodule on the left ankle, among other symptoms. She had been treated with minocycline for acne vulgaris over the preceding four years, with doses ranging from 100 to 200 mg daily. Skin biopsy of her ankle was consistent with erythema nodosum. Her symptoms resolved within days of stopping the minocycline.

Databases

Table 1. Reports of erythema nodosum associated with the use of minocycline in the Lareb, WHO and Eudravigilance database [9,10].

Database	Drug	Number of reports	ROR (95% CI)
Lareb	minocycline	2	-
WHO	minocycline	50	12.7 [9.6-16.8]
Eudravigilance	minocycline	13	11.5 [6.7-19.9]

Prescription data [11]

Drug	2010	2011	2012	2013	2014
minocycline	56,071	55,593	54,103	53,347	49,152

Mechanism

It is hypothesized that the dimethylaminogroup at the 7-position of minocycline might be metabolized into reactive intermediates by the cytochrome P450 enzymes in the liver. These potential reactive metabolites generated by minocycline may bind to tissue macromolecules thereby causing cell damage directly or they may act as haptens eliciting an immune response secondarily. Doxycycline and tetracycline lack this chemical structure and are therefore less susceptible for the forming of reactive metabolites [12]. A factor that put patients at increased risk for drug reactions induced by reactive metabolites is the presence of infections since they increase the degree of oxidative stress and cell injury [13,14]. The dyspnoea for which the patient in case B was treated with antibiotics might have served as an eliciting factor.

Discussion and conclusion

The Netherlands Pharmacovigilance Centre Lareb received two reports of erythema nodosum (EN) associated with the use of minocycline, which were confirmed by biopsy according to the reporter. The erythema nodosum occurred one month and three years after start respectively. One patient had a positive rechallenge. After rechallenge (about five months later) the erythema nodosum reappeared within a few hours. Minocycline-related autoimmune disorders develop an average of two years (range three days to six years) after starting drug therapy [8], which is in accordance with the reported latency in our patients. The patient in Case A also used an oral contraceptive pill, sporadically reported as the cause of EN [15]. Unfortunately, in both cases details regarding distribution of the skin lesions are not reported as well as lacking data on antinuclear antibody (ANA). In case A ANCA+ is mentioned but not specified c- or p-ANCA.

The association of minocycline and erythema nodosum is supported by a statistically significant disproportionality in the database of WHO and Eudravigilance and in the literature several case reports are described.

EN-like lesions may possibly be associated with SLE and drug-induced LE. Minocycline is known to provoke some autoimmune phenomena including drug-induced SLE, ANCA + vasculitis and serum

sickness. The SmPC mentions lupus-like syndrome as a rare ADR and the development or aggravation of Lupus erythematosus disseminates as a very rare ADR [1]. In both cases the EN could possibly be seen as a symptom in the context of autoimmune phenomena such as SLE. The cases described in the literature [5-7] also describe EN-like phenomena in the context of a complex of symptoms.

The Dutch SmPC does not mention erythema nodosum (either as a separate ADR or in the context of a broader auto-immune disorder), however the US and UK SmPC does [3,4].

- Erythema nodosum should be mentioned in the SmPC of minocycline

References

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This signal has been raised on March 2015. It is possible that in the meantime other information became available. For the latest information, including the official SmPC's, please refer to website of the MEB <http://www.cbq-meb.nl/>