Minocycline-Induced Hyperpigmentation

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A 70-year-old man developed hyperpigmentation of his forearms, hands, fingernails, sclerae, ears, and teeth after 9 years of therapy with minocycline for acne rosacea. Minocycline is widely used in the treatment of acne vulgaris and uncommonly produces the side effect of hyperpigmentation. This effect does not appear to be dose-dependent and usually resolves within months to years after discontinuation of therapy. Discoloration of adult teeth, however, is generally permanent.

Key words. Minocycline; hyperpigmentation; pigmentation; adverse effects; side effects. (*J Fam Pract 1995; 40:183-185*)

Adverse effects from minocycline hydrochloride are uncommon, and there are few reported cases of hyperpigmentation as a side effect of its use. The cutaneous hyperpigmentation usually resolves after cessation of the drug; however, tooth discoloration generally remains. Patients should be cautioned about this possible side effect, and the minocycline discontinued if hyperpigmentation develops.

Case Report

A 70-year-old white man presented with a 5-year history of progressive blue-gray pigmentation of his forearms, hands, fingernails, sclerae, ears, and teeth (Figure 1). He had been treated over the previous 9 years at another institution with minocycline 100 mg by mouth twice a day for a 20-year history of acne rosacea. The total dose he received was approximately 657 g.

His medical history included chronic obstructive lung disease, coronary artery disease, benign prostatic hypertrophy, glaucoma, and macular degeneration. His medications included theophylline, prednisone, inhaled beclomethasone dipropionate and metaproterenol sulfate, verapamil hydrochloride, oxybutynin chloride, ophthalmic dipivefrin hydrochloride, and topical metronidazole.

A biopsy of the dorsum of his hand revealed a normal epidermis with hyperpigmentation of the basal layer. Dark-brown pigment granules were seen both within macrophages and free in the dermis (Figures 2 and 3).

Since discontinuation of the minocycline in October 1992, there has been gradual resolution of the cutaneous pigment but no significant change in the discoloration of his teeth.

Discussion

Tetracyclines have a broad spectrum of activity against gram-positive and gram-negative organisms and are widely used to treat chlamydial, mycoplasmal, and rickettsial infections.[1]

Tetracyclines are known to chelate divalent and trivalent cations. Minocycline, a second-generation tetracycline, differs from the other tetracyclines in that it is completely absorbed from the gastrointestinal tract even when administered with dairy products. Maximum concentrations are reached within 2 to 3 hours, and its half-life is approximately 16 hours. Penetration of minocycline into tissues is excellent because it is the most lipophilic of the tetracyclines. This accounts for its high concentration in the brain, saliva, thyroid, lung, liver, reproductive organs, skin, and bones, and for its ability to cross the placenta and be excreted in breast milk.[2]

Submitted, revised, March 20, 1995.

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ISSN 0094-3509

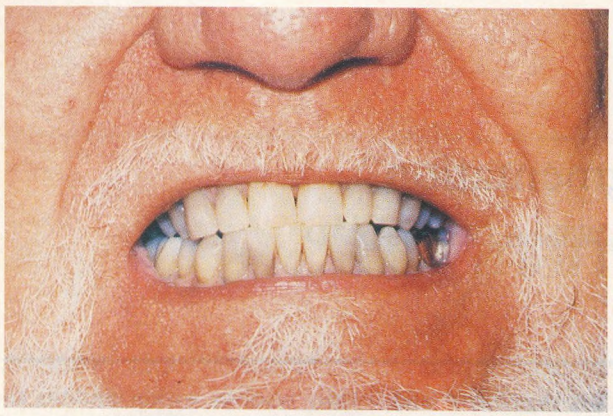

Figure 1. Tooth discoloration after 9 years of minocycline therapy.

Since it was first introduced in 1967, minocycline has been generally well tolerated, and is widely used in the long-term treatment of acne vulgaris, particularly in cases unresponsive to other tetracyclines. Its most common side effect, which appears to be related to both dose and frequency of administration, is gastrointestinal, manifested as abdominal discomfort, nausea, vomiting, or diarrhea. Minocycline rarely causes photosensitivity or an exaggerated sunburn reaction on exposure to sunlight. Elevated liver enzyme levels or, rarely, hepatitis may develop, especially in patients receiving large doses, and uremia may be aggravated in patients with renal disease. Vestibular toxicity, with symptoms of vertigo or dizziness, generally resolves after discontinuation. Long-term therapy may produce changes in the peripheral blood, including neutropenia, hemolytic anemia, and thrombocytopenia. Periodic laboratory evaluations of hematopoietic, renal, and hepatic functions should be performed to monitor for any changes. The only known interaction between minocycline and this patient's other medications is with theophylline. Theophylline's serum concentration, and therefore its toxic effects, may be increased by tetracyclines. Among this patient's medications, there are no interactions known to cause hyperpigmentation.

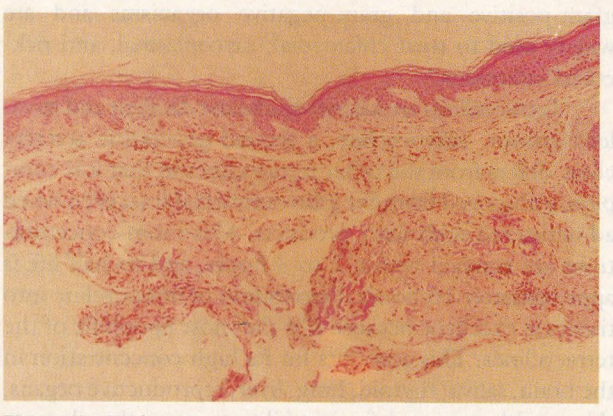

Figure 2. Light microscopy shows brown pigment granules within the dermis.

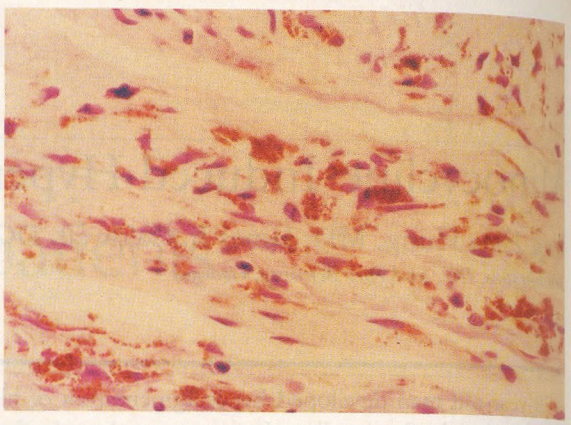

Figure 3. Higher magnification of the pigment granules within the dermis.

Minocycline-induced hyperpigmentation of the skin was first reported in 1978.[3] Since then, scattered reports have documented other cases of skin darkening[4–14] as well as pigmentation of conjunctival cysts,[15,16] sclerae,[8,10,14] gingiva secondary to underlying pigmented bone,[11] teeth,[8,17] nails,[8,10] skeleton,[8] and thyroid.[18–20] Black galactorrhea has also been reported.[21]

There are three basic types of skin pigmentation caused by minocycline. The first is a blue-black pigmentation localized to areas of scarring or previous sites of inflammation. This pigment, found within dermal macrophages, stains positive for iron, and is found by electron microscopy in nonmembrane-bound granules.[22] The second type, a muddy-looking brown color on sun-exposed areas, is thought to be caused by increased epidermal melanization.[22] The third is a localized blue-gray pigment in areas of previously normal skin, preferentially affecting the lower legs and areas exposed to sunlight. These pigments are found membrane-bound or free within dermal histiocytes. Iron, melanin, or a minocycline derivative chelated to iron or calcium may be the cause of this pigment, or this chelated compound may then be further oxidized by intralysosomal enzymes to produce a colored quinone.[9]

Although tetracycline, if given after 8 years of age, has not been reported to cause discoloration of the permanent teeth, minocycline can cause a gray discoloration that usually does not resolve. In a retrospective survey, minocycline-induced tooth discoloration was noted in 4 of 72 (5.6%) patients.[23] A later study that examined 100 patients found only 2 with discoloration of the teeth.[24]

This pigment is usually located on the incisal one half to three fourths of the crown, sparing the gingival aspect, with a characteristic darker band of discoloration in the middle of the tooth.[23,25] This differs from tetracycline, which generally produces staining of the gingival one third of the tooth.[25]

The mechanism of the discoloration is unclear. Adult teeth are minimally active metabolically. Dentinogenesis continues throughout life at a greatly reduced rate after eruption; however, minocycline deposition in the dentine is unlikely to affect the color of an adult tooth.[26] Tetracyclines have been known to demineralize enamel in vitro. Minocycline may etch the tooth surface through long-term contact by attaching to glycoproteins in the acquired pellicle. It then may become oxidized on exposure to oxygen or bacterial activity.[26] Minocycline is also found in gingival fluid at a concentration five times that of serum and may intrinsically stain the enamel by diffusing through the pulp.[24] Minocycline's strong affinity for iron and its ability to form insoluble salts also may play a role.[23,25]

In similiar cases, excessive pigmentation caused by minocycline has been attributed to ecchymoses, uneven tans, or poorly applied make-up. The etiology in this particular patient was discovered through a careful history. However, the differential diagnosis included hemochromatosis, ochronosis, and hyperpigmentation induced by a drug or heavy metal. Most patients in whom hemochromatosis is diagnosed are between the ages of 40 and 60. Ninety percent of these patients have excessive pigmentation, most often seen on the face, neck, extensor forearms, hands, genitalia, lower legs, and in scars. Ochronosis results from a deficiency of homogentisic acid oxidase and leads to deposition of homogentisic acid in tissues. Its earliest manifestations are pigmentation of the sclerae and ears that is usually seen in patients between the ages of 20 and 40. Phenothiazines,[10] antimalarials,[11] imipramine hydrochloride,[21] amiodarone hydrochloride, and heavy metals, such as silver, also should be considered in the differential diagnosis of acquired, widespread hyperpigmentation.

Pigmentation associated with minocycline most often appears in patients after long-term therapy, usually at doses greater than 100 mg per day. However, there has been a report of pigmentation after taking minocycline for only 3 weeks, indicating that this phenomenon is not always dose-related.[5] The extent of hyperpigmentation also does not appear to correlate with the amount of drug taken. In most cases, resolution of the cutaneous pigment occurs after cessation of the drug, with the time to resolution proportional to the severity of the pigmentation. Discoloration of the teeth, however, is generally permanent.

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