

Still leaving stains on teeth—the legacy of minocycline?

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CASE STUDY

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ABSTRACT

Minocycline is widely used as a first-line agent for papulopustular acne, and has previously been reported as causing stains on teeth that are still forming. This article reports a case of staining to only the crowns of unerupted third molars in a girl prescribed minocycline at age 16 for papulopustular acne. We review the literature in the area of minocycline teeth staining, consider the role of minocycline as a first-line agent for papulopustular acne, and outline strategies on the prevention of minocycline teeth staining. The case highlights current deficiencies in the disclosure information for minocycline, and provides information that is relevant to practitioners who may prescribe this drug.

Key Words

minocycline, staining, unerupted, crowns, third molars

Implications for Practice:

1. What is known about this subject?

Minocycline is known to cause intrinsic staining of teeth that are still forming.

2. What new information is offered in this case study?

This case demonstrates that minocycline has the potential to stain unerupted third molar crowns in patients 16 years

or older, where formation should be complete, via the intrinsic staining process.

3. What are the implications for research, policy, or practice?

Minocycline should be considered a second-line agent for the treatment of papulopustular acne and greater product disclosure should be given on its ability to stain teeth at any age.

Background

Minocycline is a broad-spectrum, semi-synthetic antibiotic that may be used in the treatment of many common infections in children and adults. The incidence of prescribing for minocycline is perhaps at its greatest in the adolescent years by general practitioners and dermatologists for the management of papulopustular acne. It has been shown to cause pigmentation of a variety of tissues, including skin, thyroid, nails, sclera, teeth, conjunctiva, and bone.¹ Further, adult onset tooth discolouration after long-term treatment with minocycline has also been reported.²

We report an interesting case which highlights the adverse effects of minocycline on unerupted teeth of an adolescent aged 16 years. This paper aims to highlight the potential for minocycline to stain the crowns of unerupted third molars in adolescents, where teeth formation is generally considered complete. Ancillary aims are to question the role of minocycline as a first-line agent for papulopustular acne, provide strategies on how to prevent minocycline teeth staining, and call for greater product disclosure of the potential detrimental effects of drug ingestion that may not be well known amongst prescribing practitioners.

Case details

A 16-year-old female was referred to a dermatologist for management of papulopustular acne. The dermatologist commenced the patient on minocycline 50mg bd for six months with good effect. At age 21 the patient's third molars erupted; they were visibly discoloured while the rest

of the patient's existing dentition was completely unaffected. The third molars were partially impacted and the treating oral surgeon recommended extraction. Upon removal all the third molars had a marked grey-black stain to the crown, a distinct black band at the cemental enamel junction, and sparing of the roots (Figures 1 and 2).

Figure 1: Extracted third molar–crown apex



Figure 2: Extracted third molars–side view



Discussion

The causes of tooth discolouration are varied and complex, but are usually classified as being either intrinsic, extrinsic, or internalised in nature.³ With intrinsic staining the structural composition or thickness of the dental hard tissue is changed.⁴ Chromogenic material becomes incorporated into the enamel or dentin either during odontogenesis or after eruption⁵ and this is due to either a systemic or local cause. Systemic causes are drugs or genetic defects. Local causes are from pulpal haemorrhagic products, root resorption or ageing.⁴

Extrinsic discolouration results from dietary chromogens and other external elements depositing on the tooth surface or within the pellicle layer either directly or indirectly.³ Internalised stains arise from extrinsic stains entering the dentine via tooth defects such as cracks on the tooth surface.³

For minocycline there are three potential mechanisms by which staining can occur. First, the intrinsic theory, which occurs upon absorption with the minocycline molecule becoming highly protein bound and then preferentially binding to higher collagen containing tissue (i.e., teeth and bone) resulting in discolouration.^{2,6} Second, the extrinsic theory is based on the high concentration of minocycline excreted in the gingival fluid and that stains by etching into the enamel where the minocycline gets oxidised (i.e., turns black in colour) either by exposure to oxygen or bacterial activity.^{2,7–10} Third, the chelation of haemosiderin (a breakdown product of minocycline) with iron ions forms an insoluble complex within the teeth.^{2,11}

Minocycline stains teeth differently to tetracycline and doxycycline. Tetracyclines stain teeth through their ability to form a complex with calcium ions,² via chelation, and this complex is preferential deposited in dentine and to lesser extent enamel.¹² Given the mechanisms by which minocycline stains teeth it can stain teeth at any age, unlike tetracycline and doxycycline.

The onset of staining can vary from one month to many years after the start of therapy.¹³ Specific to minocycline is the singular occurrence of “black bones”, “black or green roots”, and blue-gray to gray hue darkening the crowns of permanent teeth. The prevalence of minocycline staining has been reported to be 3–6 per cent.²

Human tooth development has been well studied and the time frame for the development of maxillary and mandibular third molars are summarised in Tables 1 and 2, respectively.¹⁴ Based upon the recognised schedule of development of the crowns for third molars, our patient's crowns should have been formed. However, there is variation in the timing of individual tooth maturation and it may be large for most stages of tooth formation; the timing for tooth maturation also increases with age. Liversidge found that standard deviations for most stages of tooth development was from just less than a year to just over two years, and that when using dental maturity to estimate age for a 95 per cent confidence interval it is likely to yield a range of 3–4.5 years.¹⁵

Table 1: Development (time) of permanent maxillary (upper) teeth

Development stage	3 rd molar
Initial calcification	7-9 yrs
Crown completed	12-16 yrs
Root completed	18-25 yrs

Table 2: Development (time) of permanent mandibular (lower) teeth

Development stage	3 rd molar
Initial calcification	8-10 yrs
Crown completed	12-16 yrs
Root completed	18-25 yrs

The intrinsic staining process is the most likely cause for staining in our patient's teeth. The extrinsic theory can be excluded on the basis that the third molars were unerupted, hence there could be no exposure to gingival fluid. The chelation mechanism is less likely to have played a role because the roots of the third molars were still forming and they were unaffected. This is consistent with the findings of Antonini et al. where acne was treated with tetracycline between the ages of 15 and 22 years and only the roots of the third molars displayed annular discolourations.¹⁶ In this respect, the staining that occurred to the crowns of our patient's third molars is unique, but clearly demonstrates the potential for permanent staining of third molar crowns.

Logically, the next question is whether minocycline should be a first-line agent for the treatment of papulopustular acne. Simonart et al. systematically reviewed the results of clinical trials investigating oral tetracyclines for the treatment of inflammatory acne and to determine the relative effectiveness and optimal dosage of these antibiotics. Their research suggests that there is a lack of evidence in the literature over the relative effectiveness of tetracyclines.¹⁷ Second-generation tetracyclines (i.e., doxycycline and minocycline) are known to have a better pharmacokinetic profile than first-generation tetracyclines (i.e., tetracycline hydrochloride and oxytetracycline).^{18–19} Minocycline has also greater antimicrobial effects on papulopustular acne than first-generation tetracyclines and doxycycline, and higher lipid solubility in pilosebaceous units.²⁰ However, comparison of antibiotics on the basis of reduction in lesion number demonstrated all tetracyclines to be similarly effective. Therefore, the choice of tetracycline should be based on cost and safety as opposed to efficacy.¹⁷

Our report of minocycline staining of the crowns of unerupted third molars in a 16-year-old female should elicit

concern because it shows this drug has the potential to leave a permanent “scar” without any clear benefit when used as a first-line agent for papulopustular acne. In addition, the current product information merely states: “beyond the age of eight years tooth discolouration has been reported”—this case clearly highlights that detrimental effects can occur well into adolescent years. We suggest that a more reasonable statement is required that more realistically highlights the age-range within which adverse effects can occur.

Strategies that may be employed to avoid minocycline teeth staining are as follows:

1. Avoid minocycline until all crowns are complete (16 years + 2–3 years).
2. Avoid long-term use of minocycline.²¹
3. Decrease the dose of minocycline from 100mg/day to 50mg/day for long-term treatment provided the indication allows.
4. Decrease the dose of minocycline from 100mg/day to 50mg/day in patients being treated for acne.²²
5. Administer vitamin C with minocycline as it has been shown to decrease the formation of the degradation product (the quinine ring structure) that is a component of the actual stain.²³

Conclusion

It is well known that tetracyclines can lead to teeth staining before the age of eight years. Similarly, it is recognised that up to the age of 16 years staining of third molar crowns can occur. After the age of 16 years typically third molar roots are only affected. Our case demonstrates that staining of third molar crowns is possible beyond the age of 16 years. The ubiquitous prescribing of minocycline in the adolescent population of 16 years and above, as a first-line agent for papulopustular acne, generates significant concern as there is the potential to permanently stain unerupted teeth and cause an enduring cosmetic defect. This issue seems to be largely unreported and the product information for minocycline is currently inadequate in regard to providing adequate information about the risks of teeth staining across the different age groups.

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PEER REVIEW

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CONFLICTS OF INTEREST

The authors declare that they have no competing interests.

PATIENT CONSENT

The authors, Raymond J, Cook D, declare that:

1. They have obtained written, informed consent for the publication of the details relating to the patient(s) in this report.
2. All possible steps have been taken to safeguard the identity of the patient(s).
3. This submission is compliant with the requirements of local research ethics committees.