Doxycycline-induced staining of permanent adult dentition

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Abstract
Background: Doxycycline is the most effective antibiotic for managing brucellosis. Although it is relatively free from side effects, complications involving the skin, nails and teeth may rarely be encountered.

Methods: Four patients with brucellosis developed yellow-brown discoloration of teeth following a 30-45 day course of doxycycline therapy during summer at a dose of 200mg/day.

Results: All four patients were diagnosed as having doxycycline-induced staining of the permanent dentition. In all cases, the staining completely resolved and the teeth recovered their original colour following abrasive dental cleaning.

Conclusions: These observations indicate that the incidence of staining of the permanent dentition, as a complication of doxycycline, may be much higher than the literature indicates, especially if treatment is administered during summer months. Fortunately, this complication is reversible and does not require termination of doxycycline therapy. Complete resolution following abrasive cleaning may suggest that an extrinsic mechanism within the dental milieu may be involved in its pathogenesis. Strict avoidance of sunlight exposure during high-dose, long-term doxycycline therapy might prevent the development of this complication.

Key words: Tetracycline, doxycycline, teeth staining, teeth discolouration, side effects.

INTRODUCTION
Since their introduction in 1947, tetracyclines have been used in the treatment of various infections. They are the most effective antibiotics in Brucella infections and constitute the basic component of any therapeutic scheme. Doxycycline is a semi-synthetic, lipophilic and potent tetracycline congener. Owing to its superior pharmacokinetics, long half-life, better safety profile, low resistance potential and lower cost, it is the drug of choice in brucellosis.

Although tetracyclines are relatively free from side effects, mucocutaneous complications may be encountered, especially if given in high doses and/or during summer-time. Despite their well-known reputation in causing enamel hypoplasia and irreversible staining of deciduous teeth, staining of the permanent adult dentition is not well-known by physicians. Herein, we present four cases of doxycycline-induced staining of permanent teeth.

Case 1
A 14 year old boy was referred to the Department of Infectious Diseases and Clinical Microbiology in June 2003 with fever, malaise, sweating and severe back pain. He used to work on his father’s farm and had a history of contact with animals. A blood culture yielded B. melitensis and standard tube agglutination (STA) for Brucella was positive with a titer of 1/1280. A combination treatment consisting of doxycycline 2x100mg/day and rifampicin 600mg/day was initiated. Despite advice to avoid sunlight exposure, the patient continued working on the farm. At one-month follow-up, the boy complained of yellow discolouration of his teeth. Oral examination revealed prominent yellow-brown staining, intensified at the gingival two-thirds of anterior incisors (Fig 1). Treatment for brucellosis was not interrupted and doxycycline was continued for two months along with warnings against sun exposure. Abrasive cleaning resulted in complete resolution of teeth discolouration.

Case 2
A 25 year old male presented in April 2003 with a three-month history of fever, chills, sweating and severe back pain. He used to work on his father’s farm and had a history of contact with animals. A blood culture yielded Brucella spp. The same combination protocol consisting of doxycycline
and rifampicin was initiated. A prominent band-like yellow-brown discolouration of maxillary teeth was noted at one-month follow-up (Fig 2). Dental hygiene measures and regular brushing were effective in clearing the discolouration.

Case 3
A 28 year old woman was admitted in July 2003 with a week-history of fever, profound sweating and right shoulder pain. STA test was positive (titer: 1/640). Brucella spp. were isolated from blood culture. The same combination protocol of doxycycline and rifampicin was initiated. At 45-day follow-up, she was completely symptom-free but had mild brown staining of anterior incisors. Abrasive cleaning resulted in complete resolution of teeth discolouration.

Case 4
A 12 year old boy presented in July 2003 with a five-month history of fever, chills, night-sweats and orchitis. STA was positive with a titer of 1/640. A combination protocol consisting of doxycycline 2x100mg/day and streptomycin 1gr/day was initiated. At one-month follow-up, oral examination revealed a slight brown discolouration of the right anterior incisor tooth. Abrasive cleaning was effective in clearing tooth staining.

DISCUSSION
Due to their deposition in actively calcifying teeth and bones, tetracyclines are contraindicated in pregnant females and in children less than eight years of age.4,5,6,14 Their use during development of dentine and enamel may cause permanent yellow-brown discolouration of teeth and hypoplasia of enamel.4-6,15-17 The discolouration varies with the specific tetracycline congener, the duration of therapy, the dosage of offending agent, the number of separate treatment courses, the concurrent activity of calcification and the proximity of the deposits to dentino-enamel junction.5,6,16,17

Tetracycline-induced discolouration in developing deciduous teeth results from the formation of insoluble tetracycline-calcium orthophosphate complexes which are deposited in dentine and enamel and darken upon exposure to light.13,17-20 Calcification of permanent teeth begins around 4-6 months of life and is largely complete by 5-6 years. The risk of dental staining is considered negligible after the age of five years, especially if treatment duration is less than a few weeks and multiple courses are avoided.14

The relative lack of free calcium protects the erupted permanent adult dentition against tetracycline hydrochloride-induced tooth discolouration. However, green-grey or blue-grey staining of previously normal-coloured and fully mineralized permanent adult teeth as a complication of long-term minocycline or doxycycline therapy has been documented.15,21 The discolouration may develop as early as one month after initiation of therapy and affects 3-6 per cent of patients receiving minocycline at doses greater than 100mg/day.15,18,19,21 However, this complication is not absolutely dose-dependent and requires an inherent predisposition.15 Clinically, the staining is pronounced at the incisal and middle third of crown and may fail to resolve after discontinuation of treatment.1,3,13,18,19,21 The mechanism of minocycline-induced discolouration in permanent teeth remains controversial. The intrinsic theory proposes that minocycline is directly deposited in teeth by binding to plasma proteins and diffusing into collagen-rich tissues like dental pulp and slowly being oxidized upon exposure to light.18 Dentinogenesis continues life-long, albeit at a greatly reduced rate after the eruption of permanent teeth. Although theoretically possible, intrinsic minocycline deposition is not likely to have a profound influence on the apparent colour of permanent dentition.15 Doxycycline binds less calcium than other tetracyclines and theoretically it is less likely to produce intrinsic discolouration of teeth.5,6,20 According to extrinsic theory, the attachment of minocycline to acquired pellicle's glycoproteins etches the enamel and oxidation upon air exposure or as a result of bacterial activity transforms the complex into insoluble black quinone.11,15,18 The concentration of...
minocycline in the gingival fluid is five times that of serum and the drug has the ability to form insoluble salts by chelating with divalent metal ions like iron in saliva or gingival fluid. An alternative theory depicts that haemosiderin, the breakdown product of minocycline, may chelate with iron and form an insoluble complex. Thus, extrinsic deposition of minocycline or doxycycline on the surface of teeth seems the most plausible mechanism for discolouration of permanent dentition.

CONCLUSION

Poor oral hygiene and intense sunlight exposure may be exacerbating factors in prominent staining of permanent dentition by doxycycline. All patients presented herein had poor oral hygiene and all were treated during summer and had more prominent staining of UV-exposed upper incisors. Advising oral hygiene measures and strict avoidance of sunlight, particularly in countries with a sunny climate, may prevent staining of permanent dentition in patients receiving high-dose, long-term doxycycline therapy. For minocycline, reduction of dose to less than 100mg/day and use of vitamin C have been reported as alternative prophylactic measures. Vital bleaching with H2O2 and composite/porcelain veneers/crowns remain as the best possible therapeutic approaches for staining of permanent dentition by tetracycline analogues. In our patients, the staining was reversible, responded to abrasive dental cleaning along with proper mouth hygiene measures and did not require cessation of doxycycline therapy. This may implicate extrinsic staining in the pathogenesis of doxycycline-induced discolouration of permanent dentition.

REFERENCES