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Dental staining after doxycycline use in children

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Background: The use of doxycycline has been avoided before 8 years of age due to known dental staining caused by tetracyclines, although doxycycline differs from classical tetracyclines in many ways. Doxycycline is still an important antimicrobial agent, but its dental safety is not well studied.

Objectives: To examine the state of permanent teeth after doxycycline exposure in children <8 years of age.

Methods: Details of doxycycline treatment were collected from medical records. After the eruption of permanent teeth the dental status was examined by an experienced paediatric dentist for detection of dental staining and enamel hypoplasia. The resulting dental photographs were evaluated by a second independent experienced paediatric dentist.

Results: The mean age of 38 study subjects at the time of doxycycline treatment was 4.7 years (range 0.6–7.9 years, SD 2.3). The doxycycline dose was 10 mg/kg/day (varying from 8 to 10 mg/kg/day) for the first 2–3 days and 5 mg/kg/day (varying from 2.5 to 10 mg/kg/day) thereafter. The mean length of the treatment was 12.5 days (SD 6.0) and ranged from 2 to 28 days. Tetracycline-like staining or enamel hypoplasia of developing teeth was detected in none of the subjects.

Conclusions: Doxycycline treatment of small children does not seem to induce permanent tooth staining.

Introduction

Tetracycline treatment in young children during the rapid calcification phase of teeth results in staining of permanent teeth, first described in 1959.¹ The rate of discolouration varies from 23% to 92%, depending on the duration of the exposure.² This is why the use of tetracyclines is contraindicated in young children.³ Doxycycline is a second-generation semi-synthetic tetracycline and it differs from classical tetracyclines in several aspects, e.g. in lower calcium-binding capacity.⁴ Doxycycline's long half-life permits once-daily dosing, penetrates the blood–brain barrier effectively, is fully absorbed enterally and is well tolerated.^{5,6} There are no reported cases of permanent dental staining possibly induced by doxycycline in young children. However, it has been recommended that the use of doxycycline be avoided in children aged <8 years.

In our hospital, doxycycline has been used in the empirical treatment of acute infection-related CNS symptoms mainly to cover *Borrelia burgdorferi*⁷ and *Mycoplasma pneumoniae*.⁸ The aim

of this study was to evaluate the state of permanent teeth of children treated with doxycycline before the age of 8 years.

Methods

The inclusion criteria were doxycycline exposure at the age of 0–7.9 years and a minimum age of 8 years at the time of dental examination. These age limits were selected based on the known dental mineralization timeline of tooth development.⁹ We reviewed the medical records of 1132 children hospitalized due to suspicion of CNS infection during 1994–2015 at the Department of Paediatrics and Adolescent Medicine, Turku University Hospital. The inclusion criteria were met by 56 children, of whom 39 agreed to participate in the study.

Details of treatment were collected from medical records. Dental examinations were performed by an experienced paediatric dentist (M. N.). Dental developmental stage was noted. The focus of the clinical examination was to detect tetracycline-like staining in the forms of diffuse discoloured bands of tooth crowns and enamel hypoplasia. Teeth were photographed using a mouth mirror from five perspectives with a Canon 7D camera (Canon, Tokyo, Japan). Photographs were evaluated by

Table 1. Patient characteristics and dental examination findings (N = 38)

Sex, n (%)	
male	24 (63)
female	14 (37)
Age at doxycycline exposure (years) ^a , mean (SD)	4.7 (2.3)
Diagnosis, n (%)	
encephalitis	18 (47)
neuroborreliosis	7 (18)
meningitis	3 (8)
borreliosis (other than neuroborreliosis)	3 (8)
status epilepticus and epileptic seizure	2 (5)
intracranial haemorrhage	1 (3)
other	4 (11)
Length of doxycycline treatment (days) ^a , mean (SD)	12.5 (6.0)
Age at dental examination (years), mean (SD)	14.2 (3.7)
Time between doxycycline exposure and dental examination (years), mean (SD)	9.6 (3.1)
Tetracycline-related dental findings, n (%)	
tetracycline-like discolouration	0 (0)
enamel hypoplasia	0 (0)
Dental findings not related to tetracyclines, n (%)	
molar incisor hypomineralization	7 (18)
unspecified developmental dental defects	5 (13)
fluorosis-like hypomineralization	3 (8)
Permanent teeth erupted, n (%)	22 (58)

^aFor a patient with two doxycycline courses, age at first exposure and combined length of both treatments.

a second experienced paediatric dentist (S. A.), blind to the results of the first examiner.

Ethics

The study subjects and/or their parents gave informed consent. This study was approved by the Ethics Committee of the Hospital District of Southwest Finland (T7/2015).

Results

Reliable information on doxycycline treatment was found for 38 of 39 study subjects. Thirty-seven subjects had received one course of doxycycline and 1 had received two courses. Twenty-four of the study subjects (63%) were male (Table 1). The mean age at the time of doxycycline treatment was 4.7 years (range 0.6–7.9 years, SD 2.3). The mean length of the treatment was 12.5 days (range 2–28 days, SD 6.0). The doxycycline dose was exactly reported in 30 of 39 courses. The loading dose for the first 2–3 days was 10 mg/kg/day (varied from 8 to 10 mg/kg/day). The average dose thereafter was 5 mg/kg/day (varied from 2.5 to 10 mg/kg/day). Doxycycline was administered once or twice daily. The administration route was first intravenous and later oral in 18 (46%), only oral in 12 (31%) and only intravenous in 9 (23%) courses. The indication of doxycycline treatment was suspicion of CNS infection in 38/39 courses. In 28 cases (74%) the final diagnosis was CNS infection. Of these, 18 (47%) met the criteria of encephalitis (persisting neurological symptoms with abnormal findings in CSF, electroencephalogram or brain MRI), 3 (8%) the criteria of meningitis (meningismus and pleocytosis) and 7 (18%) the criteria of neuroborreliosis

(facial palsy with diagnostic *Borrelia* serology). The aetiology of CNS symptoms in the remaining cases is shown in Table 1.

The mean follow-up time was 9.6 years (range 3.3–15.5 years, SD 3.1) and the mean age at the dental examination was 14.2 years (range 8.3–22.6 years) (Table 1). Fourteen subjects (37%) were at the phase of mixed dentition. Neither tetracycline-like dental staining nor enamel hypoplasia was seen in permanent teeth of the patients in the clinical examination or in the photographs (Tables 1 and 2).

Discussion

In this limited study population, doxycycline treatment of children under 8 years did not induce staining of permanent teeth. One-fifth of our subjects were aged <2 years during the exposure, i.e. in the calcification stage of the visible incisor teeth. Also, intravenous administration of doxycycline did not induce dental staining. Furthermore, in our series the doxycycline dose was high: a loading dose of up to 10 mg/kg/day for 2–3 days, followed by a dose of 5 mg/kg/day. A higher loading dose is routinely used to achieve optimal doxycycline concentration from the beginning of the treatment.⁸ In addition, the duration of treatment was long (average 12.5 days).

In agreement with our observations, two previous studies found no tetracycline-like tooth discolouration after doxycycline treatment in young children. In one study oral doxycycline was used for 10 days with a daily dose of 2–4 mg/kg in 2- to 7-year-old children with asthma,¹⁰ and in another study for 7 days with 2.3 mg/kg/day for Rocky Mountain spotted fever in 0.2- to 7.9-year-old children.¹¹ Including our study there are now 127 reported cases of children

Table 2. Dental examination findings according to age at doxycycline exposure

Patient characteristics and dental findings	Age at doxycycline exposure (years) ^a		
	0 to <2 (N = 7)	2 to <5 (N = 13)	5 to <8 (N = 18)
Length of doxycycline treatment (days) ^a , mean (SD)	11 (4.9)	12 (6.0)	14 (6.2)
Age at dental examination (years), mean (SD)	10.5 (2.3)	13.0 (3.5)	15.4 (3.6)
Tetracycline-related dental findings, n (%)			
tetracycline-like discolouration	0 (0)	0 (0)	0 (0)
enamel hypoplasia	0 (0)	0 (0)	0 (0)
Dental findings not related to tetracyclines, n (%)			
molar incisor hypomineralization	0 (0)	4 (31)	3 (17)
unspecified developmental dental defects	1 (14)	2 (15)	2 (11)
fluorosis-like hypomineralization	2 (29)	0 (0)	1 (6)
Permanent teeth erupted, n (%)	2 (29)	4 (31)	16 (89)

^aFor a patient with two doxycycline courses, age and length of treatment at first exposure.

treated with doxycycline before the age of 8 years. The combined prevalence of permanent tooth staining is 0/127. There is one reported case of slight spotted discolouration of one deciduous tooth after doxycycline use in a prematurely born infant <2 months of age.⁴ Considering that permanent teeth show less tetracycline effect than primary teeth,¹² data on possible discolouration of permanent teeth are lacking.

The antibacterial spectrum of doxycycline includes Gram-positive and Gram-negative bacteria. Both *in vitro* and *in vivo* activity is noted against atypical respiratory pathogens, *Rickettsia* and many uncommon organisms. Doxycycline has a myriad of labelled clinical indications.¹³ Many of our patients suffered from borreliosis, which is common in South-West Finland. Doxycycline has been shown to be as effective as ceftriaxone in the treatment of borreliosis.⁷ Doxycycline's benefits are efficient oral administration and effective blood-brain barrier penetration.¹⁴ It is of interest that doxycycline may have neuroprotective properties in the treatment of CNS infections, but clinical data are lacking.¹⁵

Our study has limitations. The study population was limited and only two children were treated before the age of 1 year. In infants the probability of side effects is larger, limiting the generalization of the findings. Only visible effects (discolouration and enamel hypoplasia) of permanent teeth were evaluated as these findings were considered the most relevant. In addition, the dental examination was performed at the phase of mixed dentition in one-third of patients, so the absence of staining in posterior molars cannot be excluded. However, we see possible discolouration in posterior molar teeth cosmetically as irrelevant because these teeth are only visible at dental examination.

The strength of this study is the clinical relevance of the endpoint: visible staining of the permanent teeth. This was examined by two independent experienced paediatric dentists with similar results. This is the first study on the safety of intravenous, high-dose or long doxycycline treatment in children.

In conclusion, our observations and those of others suggest that the age limit of 8 years in the use of doxycycline should be reconsidered. Doxycycline would be a very useful antibiotic in young children. It is inexpensive and could have wide use in developing countries.

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Transparency declarations

None to declare.

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