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No Findings of Dental Defects in Children Treated with Minocycline

Antonio Cascio,[1]* Chiara Di Liberto,[2] Matteo D'Angelo,[2] Chiara Iaria,[3] Francesco Scarlata,[1] Lucina Titone,[1] and Giuseppina Campisi[2]

Istituto di Patologia Infettiva e Virologia, G. Di Cristina Hospital,[1] and Section of Oral Medicine, Department of Oral Sciences G. Messina,[2] Università di Palermo, Palermo, and Associazione Italiana per la Lotta contro le Malattie Infettive, Scuola di Specializzazione in Malattie Infettive, Università di Messina, Messina,[3] Italy

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Forty-one children <8 years of age treated for brucellosis with oral minocycline (2.5 mg/kg) twice daily for 3 weeks were recalled and examined to check for dental staining and defects. Dental staining and defects were found in 14 of 41 exposed children (34.1%) and in 30 of 82 matched controls (36.6%), respectively ($P > 0.2$).

Thanks to their broad antimicrobial spectrum, tetracyclines were found to be valuable for the treatment of many infections (10). Unfortunately, they irreversibly bind to calcifying tissues and are deposited along the incremental lines of dentine and enamel, causing defects and staining, from bright yellow to dark brown (3, 5, 8).

According to the American Academy of Pediatrics, tetracyclines are not indicated for the treatment of common infections in children younger than 8 years of age. However, doxycycline (a tetracycline analogue) is recommended for treatment of Rocky Mountain spotted fever in children of any age (1).

Minocycline has several advantages over other tetracyclines: it is better absorbed and capable of greater antimicrobial activity (11, 12); it is more lipophilic, thus facilitating tissue penetration (7, 12); and it chelates calcium to a lesser extent (9) and consequently will potentially stain teeth more rarely. To the best of our knowledge, no one has ever studied its effects on developing teeth.

We found a 3-week course of oral minocycline (2.5 mg/kg) in combination with intravenous rifampin (10 mg/kg), both twice daily, to be very effective in treating brucellosis at any age (4).

We thought to recall all the children that were <8 years of age when treated with this drug (all of these subjects were hospitalized from January 1984 through December 2000 for 21 days, and administration of oral minocycline had been directly observed by nurses) and to compare them with a control group to assess any intrinsic dental staining and enamel defects.

A free oral examination was offered as an incentive. Interested parents were sent a detailed description of the study, a consent form, and an appointment time.

Informed consent was obtained from the patients or from their parents, and the guidelines of the G. Di Cristina Hospital were followed in performing the clinical research.

Overall, 75 exposed individuals were identified; of these, 34 subjects could not be enrolled because 20 had moved away from the geographical area, 9 could not be reached, 4 refused to participate, and 1 was nonqualified because the teeth potentially involved had not yet erupted. Finally, 41 children (20 males and 21 females) participated in the study. The main demographic variables considered (age, gender, and geographical origin) of these 41 participants were not statistically different from those of the 34 subjects that could not be enrolled ($P > 0.2$). All of these subjects denied having received any other treatment with tetracyclines at any time. At the time that they were recalled (from March through May 2001), their mean age was 11.6 years (standard deviation [SD], 4.6; range, 5 to 22; 95% confidence interval [IC95%], 10.1 to 13). The median age at exposure was 5 years (SD, 2.1; range, 0.5 to 7.9; IC 95%, 3.7 to 5). The median interval between exposure and evaluation was 7.2 years (SD, 4.6; range, 1 to 19; IC95%, 5.8 to 8.7).

A control group of nonexposed subjects was enrolled consecutively (in the same period as the recruitment of the cases) during annual dental screening among students born and living in the same district. Controls were not chosen from the same hospital population. Indeed, since ours is a pediatric hospital and our cases were recalled on average 7 years after the treatment for brucellosis, it would have been extremely difficult to find aged-matched controls (age range of the cases, 5 to 22 years). All controls were Caucasian, with no statistically significant differences ($P > 0.2$) in socioeconomic status, nutritional habits, or mineral quality of the drinking water (data from the Sanitary Office of Palermo).

To increase the stringency of the study, during recruitment of the controls, subjects who had "a priori" a high probability of having dental defects [histories of exposure to tetracyclines ($n = 1$) or to fluorides ($n = 2$), presence or history of orthodontic braces ($n = 3$), trauma or restorations ($n = 12$), or teeth under evaluation for dental fluorosis ($n = 3$)] were excluded. Each exposed subject was matched with two control subjects of the same age and sex. Overall, 123 subject (41 exposed and 82 controls) were examined.

In the exposed group, identification of the teeth in development at the time of drug exposure (i.e., teeth to be tested) was carried out, taking into account the mineralization stage at the

* Corresponding author. Present address: Associazione Italiana per la Lotta contro le Malattie Infettive, c/o Scuola di Specializzazione in Malattie Infettive, Università di Messina, Via Consolare Valeria n. 1, 98125 Messina, Italy. Phone: 39 090 221 2033. Fax: 39 090 2939512. E-mail: acascio@unime.it.

TABLE 1. Classification and codes for enamel defects

Types of enamel defect[a]	Index	Definition
Opacity, white/cream	1	Qualitative defect, change in translucency of enamel, with white or discolored areas being detectable.
Opacity, yellow/brown	2	Same definition of defect but different color
Hypoplasia (pits)	3	Quantitative defect, break in continuity of the enamel, reducing its thickness and giving rise to a variety of pits or grooves
Hypoplasia (horizontal grooves)	4	Same definition of hypoplasia but different form
Hypoplasia (vertical grooves)	5	Same definition of hypoplasia but different form
Hypoplasia (missing enamel)	6	Same definition of hypoplasia but different form
Discolored enamel	7	Abnormal appearance of hard tissue in color or distribution, excluding colored opacities

[a] For each type of defect, the number and demarcation have been noted as follows: single, a defect well demarcated from the adjacent normal enamel, with only one lesion visible on the tooth surface; multiple, more than one defect, with margins well demarcated from the adjacent normal enamel; diffuse, fine white lines (distinct lines of opacity which follow the pattern of perikymata); and diffuse, patchy, irregular, cloudy areas of opacity lacking well-defined margins.

time of therapy for brucellosis. The same teeth were evaluated in the two matched controls. This procedure was performed by an examiner (C.D.L.) who prepared a schedule, without any indication of the group, for a blinded examiner (G.C.). A simplified variant of the Developmental Defects of Enamel index (Commission on Oral Health-Federation Dentaire Internationale, 1982) (6) was used to classify the dental findings (Table 1).

Apart from two cases and the related four matched controls examined during primary dentition, all subjects were investigated for permanent dentition.

Student's *t* test, Pearson's chi-square test, and Fisher's exact test were used as appropriate. A P value of ≤ 0.05 was considered statistically significant.

The enamel defects observed in the two groups are shown in Table 2; the prevalence was not statistically different ($P = 0.79$; chi-square = 0.07) between the exposed and the control group, 34.1% (14 of 41) and 36.6% (30 of 82), respectively (odds ratio, 0.90; IC95% for odds ratio relative risk, 0.56 to 1.56; difference between the two percentages, 2.5; IC95%, -15.8 ± 20.6).

In the primary dentition, opacity was not found in the exposed group, but one case among the controls with diffuse fine white lines was revealed.

Opacity was the most commonly detected type of enamel defect in both the exposed (11 of 14; 78.6%) and control (20 of 30; 66.6%) groups. On the contrary, discolorations were found in only two cases in each group, diffuse and single, in the study and control groups, respectively.

Some limitations of our study in addition to its retrospective nature should be noted. First, the relatively small number of cases did not permit us to perform a logistic analysis. Second, controls were not obtained from a secondary hospital base. Third, there was a lack of data about the prevalence of enamel defects and staining in the general population from the same region (β error not calculated). Nevertheless, these findings represent unique data on the likelihood that minocycline will stain developing teeth. Moreover, the frequencies of enamel defects found in both the groups were within the range of prevalence found in randomized children from a closed area of southern Italy (2).

TABLE 2. Distribution of enamel defects in developing teeth among the 41 exposed and 82 control individuals

Defect type[a]	No. and demarcation	No. of subjects (%)	
		Exposed	Controls
Opacity, white/cream (DDE 1)	Single	5 (12.2)	9 (10.9)
	Multiple	1 (2.4)	4 (4.9)
	Diffuse, fine white lines	3 (7.3)	5 (6.1)
	Diffuse, patchy	2 (4.9)	2 (2.4)
	Subtotal	11 (26.8)	20 (24.4)
Opacity, yellow/brown (DDE 2)	Single	0	0
	Multiple	0	2 (2.4)
	Diffuse, fine white lines	0	2 (2.4)
	Diffuse, patchy	0	0
	Subtotal	0	4 (4.9)
Hypoplasia (pits) (DDE 3)	Single	1 (2.4)	1 (1.2)
	Multiple	0	3 (3.7)
	Subtotal	1 (2.4)	4 (4.9)
Discolored enamel (DDE 7)	Single	0	2 (2.4)
	Multiple	0	0
	Diffuse, fine white lines	1 (2.4)	0
	Diffuse, patchy	1 (2.4)	0
	Subtotal	2 (4.9)	2 (2.4)
	Total	14 (34.1)	30 (36.6)

[a] DDE, defects of dental enamel.

In conclusion, the present study suggests that minocycline could be used (for a maximum of 3 weeks) to treat infections in pediatric patients when indicated.

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