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Dental Discoloration and Enamel dysplasia after Tetracycline Exposure in Children: A Nationwide Population-Based Study in Korea

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Background

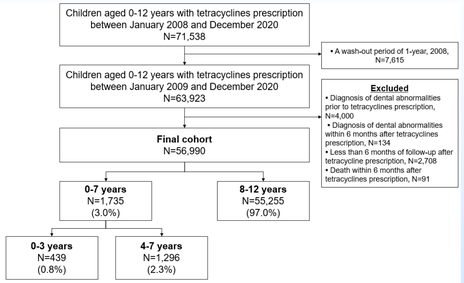
- ✓ **Tetracyclines, despite clinical usefulness, are prohibited in use under children under 12 years in South Korea and UK, and 8 in USA due to risk of dental discoloration and enamel dysplasia (dental abnormalities).**
- ✓ **There is insufficient evidence to assess whether the risk of dental abnormalities is increased in children aged 8–12 years.**

Objectives

- ✓ **To assess the incidence of dental discoloration and enamel dysplasia in Korean children prescribed tetracyclines (TC).**
- ✓ **To investigate whether the risk of dental abnormalities was greater in TC-exposed children compared to the general population.**

Methods

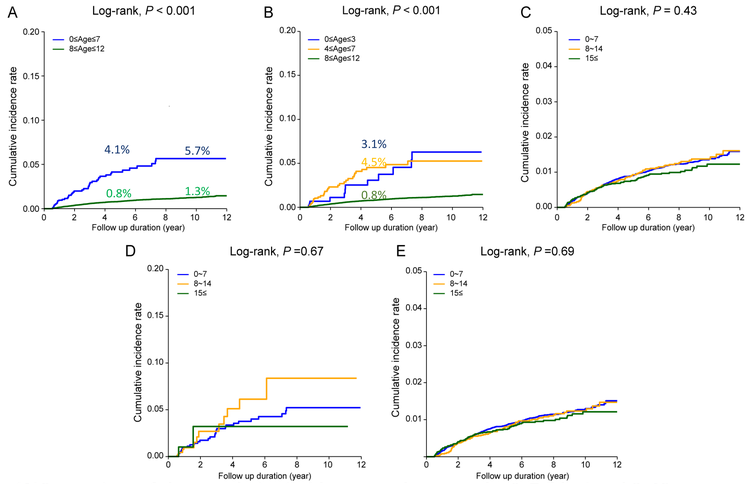
- ✓ **Study design: Nationwide, population-based retrospective study**
- ✓ **Data source: National Health Insurance Service (NHIS)**
- ✓ **Subjects: Children aged 0–12 years with a claim for TC prescription between, who were prescribed at least one day between January 2008 and December 2020**



- ✓ **Primary outcome: Incidence of dental abnormalities 6 months after TC exposure**
- ✓ **Secondary outcome: Standardized incidence rates (SIR) of dental abnormalities compared to general population**

Results

Cumulative incidence rate of dental abnormalities after TC exposure



(A)Comparison of the cumulative incidence rate between the 0–7 (blue) and 8–12 years age groups (green)

(B)Subgroup analysis of the cumulative incidence rate by age group: 0–3 (blue), 4–7 (orange), and 8–12 years (green).

(C) Comparison of the cumulative incidence rate according to duration of TC exposure (0–7 days, blue; 8–14 days, orange; and ≥15 days, green)

(D) The cumulative incidence rate in the 0–7 years age group according to the duration of TC exposure.

(E)The cumulative incidence rate in 8–12 years age group according to the duration of TC exposure.

Trend of TC prescription in Korea

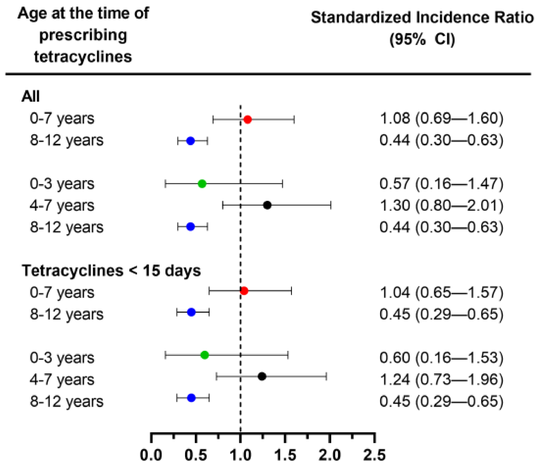
- ✓ **Since the implementation of Drug Utilization Review (DUR) in 2007, which monitors and inspects the prescription of contraindicated drugs, the number of children aged ≤ 12 years with TC prescription sharply decreased from 5,215 in 2008 to 3,216 in 2020.**
- ✓ **Among the prescribed TC, doxycycline and minocycline, were most commonly prescribed (61% and 35%, respectively)**

Incidence rate of dental abnormalities in children with TC exposure

Age * (years)	0–3	4–7	8–12	13–17	18–23	Total	Person-years	Incidence rate Per 100,000 person-years (95% Confidence Interval)
Age#								
0–7	5	24	17	N/A	N/A	46	6268.2	733.9 (537.3–978.9)
0–3	5	6	1	N/A	N/A	12	1768.3	678.6 (350.7–1185.4)
4–7	N/A	18	16	N/A	N/A	34	4500.0	755.6 (523.3–1055.8)
8–12	N/A	N/A	26	376	97	499	349886.8	142.6 (130.4–155.7)
Total	5	24	43	376	97	545	356155.0	153.0 (140.44-166.43)

- *Age at the time of dental abnormality diagnosis
- # Age at the time of tetracycline prescription
- N/A: not applicable

Standardized incidence ratio (SIR) of dental abnormalities



Summary of Results

- ✓ **The incidence rate of dental abnormalities after TC exposure was 153 per 100,000 person-years in Korean children aged 0–12 years during 12 year-period.**
- ✓ **The incidence of dental abnormalities in the 8–12 years age group was approximately 80% lower than that in the 0–7 years group.**
- ✓ **The 5- and 10-year cumulative incidence rates of dental abnormalities after TC exposure was 4.1% and 5.7% respectively in 0-7 years age group and 0.8% and 1.3%, respectively in 8-12 years age group.**
- ✓ **When the duration of TC exposure was limited to less than 15 days, there was no significantly increased risk compared to the general population.**

Conclusion

- ✓ **This is the largest investigation to determine the incidence of dental abnormalities in tetracycline-exposed children.**
- ✓ **TC is especially important therapeutic option for macrolide resistant-*Mycoplasma pneumoniae* (MRMP), which is emerging in the Asia-Pacific region.**
- ✓ **Our findings suggest that some countries, including Korea, need to reconsider the 8–12 years age restriction for tetracyclines such as doxycycline by lowering it from 12 to 8 years.**
- ✓ **Further studies using match-controlled methods should be conducted to substantiate our finding that the potential risk of tetracyclines in children is lower than expected to remove the age restriction.**