Clinical Pharmacology & Toxicology Pearl of the Week

~ Doxycycline use in Pediatrics ~

Background:

- ✓ Tetracyclines are a group of broad-spectrum antibiotics which include tetracycline, minocycline, and doxycycline.
- ✓ Tetracyclines have historically been contraindicated in children less than 8 years of age due to the risk of teeth staining known since the 1960s.
- ✓ However, they can be first line treatment for specific illnesses such as rickettsia or Lyme disease, where there may not be a preferable or equally efficacious alternative.

Teeth Staining:

- ✓ Tetracyclines can cause permanent discoloration and possibly enamel hypoplasia of both the primary and permanent dentitions when given during tooth development. The calcification of permanent teeth is completed by 8 years of age.
- ✓ They can chelate calcium orthophosphate to form a complex that is irreversibly incorporated into teeth, cartilage, and bone. This causes a discoloration which varies from yellow or grey to brown. Initially with tooth eruption, the teeth can be yellow and gradually change over months to years to brown due to oxidation which is light induced. They will fluoresce under ultraviolet light.
    - When tetracycline is given to this population incidence of tooth discoloration ranges from 23% to 92%.
- ✓ Major risk factors for tooth staining are daily dosage and duration of therapy.

Tetracycline-stained teeth from: Sánchez et al. 2004.

Doxycycline:

- ✓ Doxycycline was developed after tetracyclines had been labeled potentially harmful.
- ✓ It has reduced ability to chelate calcium. The calcium binding capacity is 19% for doxycycline, vs 40 to 75% for other tetracyclines.
- ✓ In animal studies no increased incidence of skeletal or tooth anomalies occurs at doses equivalent to 17x the maximum human dose.
- ✓ To date there have been 7 studies of varying methodology examining tooth staining in the context of doxycycline use in children less than 8 years old.

STUDY	PATIENTS	DOSE, DURATION	RESULTS	COMMENTS
Forti et al, 1969	25 premature infants	1-2 mg/kg/day, 6-17d	1 dental staining	Patient may have had other tetracycline exposures, no control
Poloczek, 1975	282 children	2-4 mg/kg/day, 8 d	5 dental staining	Evaluation done at 1 year, assessed by dentist, no control
Lochary et al, 1998	10 children	30-200 mg/day, 8-10d	No dental staining	4 patients had higher color scores than median scores for controls
Volovitz et al, 2015	31 children	4-8 mg/kg/day, 10d	No dental staining	From an asthma clinic that had been using doxycycline for refractory pneumonia for 30 years
Todd et al, 2015	58 children	Mean 5.6 mg/kg/day, 1-10d	No dental staining	Treated for RMSF, Had control population
Poyhonen et al, 2017	38 children	5-10 mg/kg/day, 2-28d	No dental staining	No control
Brown et al, 2023	20 children	Mean 12.5 mg/kg/day	2 dental staining	Only via telephone survey

- ✓ Other side effects of doxycycline include nausea, vomiting, diarrhea, esophagitis, and photosensitivity.

Guidelines:

- ✓ The American Academy of Pediatrics suggests that doxycycline is permitted up to 21 days without regard for age.
- ✓ The Infectious Disease Society of America 2020 Lyme disease guidelines states that the use of doxycycline in children should be individualized and made with careful deliberation but is first line for chemoprophylaxis and neurologic disease.
- ✓ The Canadian Pediatric society does not commit to a specific recommendation but states due to its proven efficacy for treating LD, including meningitis it has prompted more permissive use.

Conclusions:

- ✓ There is a small amount of data suggesting minimal risk (~1%) of dental staining with doxycycline use, however this is based primarily on retrospective studies with short follow up and further large-scale data is needed to ensure its safety.
- ✓ Can be used with more reassurance in <8-year-olds where there is not a suitable alternative, such as for Lyme disease chemoprophylaxis, neurological Lyme disease, rocky mountain spotted fever (RMSF), and Q-fever. Additionally, may be a consideration in Lyme disease if severe beta-lactam allergy exists.
- ✓ Other tetracyclines continue to be contraindicated in children < 8 years of age.

References

1) Sánchez AR, Rogers RS, Sheridan PJ. Tetracycline and other tetracycline-derivative staining of the teeth and oral cavity. International Journal of Dermatology. 2004 Oct 1;43(10):709–15.
2) Cross R, Ling C, Day NPJ, McGready R, Paris D. Revisiting doxycycline in pregnancy and early childhood – time to rebuild its reputation? Expert Opinion on Drug Safety. 2016 Jan 25;15(3):367–82.
3) Stultz JS, Eiland LS. Doxycycline and tooth discoloration in children: Changing of recommendations based on evidence of safety. Annals of Pharmacotherapy. 2019 Jul 7;53(11):1162–6.
4) Wormser GP, Wormser RP, Strle F, Myers R, Cunha BA. How safe is doxycycline for young children or for pregnant or breastfeeding women? Diagnostic Microbiology and Infectious Disease. 2019 Mar 1;93(3):238–42.
5) Forti G, Benincori C. Doxycycline and the teeth. Lancet. 1969;1:782.
6) Poloczek SV. The possibility of tooth discoloration after doxycycline therapy in infants and toddlers. Z Allgemeinmed. 1975;51:549-550.

7) Lochary M, Lockhart PB, Williams WT Jr. Doxycycline and staining of permanent teeth. Pediatr Infect Dis J. 1998;17:429-431.10.
8) Volovitz B, Shkap R, Amir J, Calderon S, Varsano I, Nussinovitch M. Absence of tooth staining with doxycycline treatment in young children. Clin Pediatr (Phila). 2007;46:121-126.
9) Todd SR, Dahlgren FS, Traeger MS, et al. No visible dental staining in children treated with doxycycline for suspected Rocky Mountain spotted fever. J Pediatr. 2015;166:1246-1251.
10) Poyhonen H, Nurmi M, Peltola V, Alaluusua S, Ruuskanen O, Lähdesmäki T. Dental staining after doxycycline use in children. J Antimicrob Chemother. 2017;72:2887-2890.
11) Brown K, Corin S, Handel AS. Doxycycline for the Treatment of Lyme Disease in Young Children. Pediatr Infect Dis J. 2023 Oct 5

The Calgary Clinical Pharmacology physician consultation service is available Mon-Fri, 8am-5pm. The on-call physician is listed in ROCA. Clinical Pharmacology consultations are also available through Netcare e-referral process and through Calgary Zone Specialist Link. Click HERE for more details.

The Poison and Drug Information Service (PADIS) is available 24/7 for questions related to poisonings. Please call 1-800-332-1414 (AB and NWT) or 1-866-1212 (SK).