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Occasional Surveys

Doxycycline: Are Its 'Side-effects' a Contra-indication to Its Use?

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Abstract

Objectives: To briefly outline the development and reasons for the decline in the clinical use of tetracyclines, and to consider if the side-effects of doxycycline a contra-indication to its use. ***Data Sources:*** Literature search of MEDLINE from 1950 to 2005. ***Study Selection:*** Literature and data related to doxycycline, tetracycline and tooth discolouration. ***Data Extraction:*** Relevant information and data were reviewed by the authors. ***Data Synthesis:*** The established side-effect of tooth discolouration has led to the formation of guidelines to restrict the use of the tetracyclines in susceptible groups of patients, such as pregnant women and throughout childhood. The severity of the discolouration is likely to be related to the different homologues of the tetracyclines, dose, frequency, the stage of odontogenesis, and the duration of the therapy. The majority of published clinical data indicates that doxycycline can be prescribed for children because it causes the least severe type of tooth discolouration. However, there has not been a prospective, randomised, double blind study that compared doxycycline with other tetracyclines to make a definitive statement about the decreased incidence of dental discolouration by doxycycline. The propriety of carrying out a clinical trial using doxycycline involving children when the side-effects of tetracyclines are already well known is also disputable. ***Conclusions:*** Caution should be exercised when prescribing doxycycline to children who should be kept under long term review because of the insufficient data concerning the discolouration of the developing teeth.

Key words Doxycycline; Tetracycline; Tooth discolouration

Introduction

There has been a resurgence of interest in the tetracycline group of drugs since they have been recommended for use in combination therapy for bone metastasis,[1] and in the treatment and prophylaxis of anthrax[2] and malaria.[3-7] For example, when chloroquine resistant malaria is encountered consideration should, according to the recommendations, be given to the use of combination chemotherapy using atovaquone/proguanil (Malarone, GlaxoSmithKline) plus doxycycline.[8] This approach of combination therapy is based upon the success of previous combination chemotherapies in the treatment of tuberculosis.

The addition of tetracycline to existing regimens can raise the cure rates and in turn may help to curtail the evolution of drug resistant strains of bacteria associated with secondary infections. Doxycycline is the favoured drug because it has a lower incidence of gastrointestinal symptoms than the other types of tetracyclines. The need for only a single daily dose further supports the use of doxycycline because this is likely to enhance patient compliance.

When a manufacturers' literature about a drug mentions 'side-effects', by implication, it suggests that the reactions are either temporary, or acceptable in nature.[9] However,

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this is not the case with tetracyclines because the varying degrees of discolouration of the teeth is permanent and can be disfiguring.[10-13] Thus, before combination chemotherapy can be considered to be wholly beneficial, the phenomenon of dental discolouration caused by tetracyclines and more specifically doxycycline needs to be taken into consideration. Therefore, it is proposed to briefly outline the development of and reasons for the subsequent decline in the clinical use of tetracyclines, and to consider the status of the more recent semi-synthetic derivative doxycycline.

Methods

A literature search was conducted using the MEDLINE database from 1950 to 2005 in English. The articles were successively search by the following keywords: doxycycline, tetracycline, tooth discolouration, and intrinsic tooth staining. Articles concerned with the subject of review were included if they were directly related to the administration of tetracycline and derivatives plus the occurrence of tooth staining.

Historical Background

Chlortetracycline was isolated by Duggar in 1948 and in the early 1950's, four chemically different homologues became available for clinical use; subsequently others have followed.[14] The low toxicity and broad antimicrobial spectrum resulted in the tetracyclines becoming popular for the treatment of infections, especially in children. Within a decade of their introduction tetracyclines were first implicated as being the cause of the permanent discolouration of children's teeth.[15] Subsequently, numerous reports of this phenomenon appeared in the literature.[16-18] The prevalence of tetracycline staining in published studies has ranged from 0.4% to 6%;[19-21] However, it was reported to be 16.6% in Hong Kong.[22]

Tetracyclines and the Teeth

On entering the bloodstream, tetracyclines are taken up, as a fluorescent pigment, by calcifying tissues because their affinity for polyvalent cations which bind into heterocyclic rings by chelation.[23] Unlike tetracyclines incorporated into bone, which can be released during the course of normal bone resorption, tetracyclines remain within enamel and dentin, in locations consistent with the stage of development of the tooth when the drug was administered. Hence, a fully formed tooth is unaffected. The calcification of the crowns of primary (deciduous) teeth occurs from the 14th week *in utero* to one year of age while for the permanent teeth it takes place between 7 to 8 months *in utero* and 16 years. Even teeth that are undergoing odontogenesis during foetal life are not immune because tetracyclines can cross the placenta.[14,16,24,25] However, the transfer of the drug may not occur throughout pregnancy, but only during a certain period such as after the 29th week of gestation.[26] Tetracyclines can also be excreted in human milk.[27]

The different homologues of the tetracycline group of drugs produce different coloured pigmentations of the teeth.[17,28-30] The colours can be divided into four groups: (i) a grey-brown colour, this can be caused by chlortetracycline (Aureomycin), (ii) a yellow colour, is often caused by oxytetracycline (Terramycin), dimethylchlortetracycline (Ledermycin) and tetracycline (Achromycin), (iii) a blue-gray colour, is usually caused by minocycline (Minocin), and (iv) a brownish colour, which is like the 'ageing' (fading) of the yellow discolouration.[31,32] Affected teeth display a bright yellow fluorescence when exposed to ultraviolet light of 360 nm. On exposure to sunlight the pigmentation of discoloured teeth becomes more brown owing to the formation of a tetracycline oxidation product, and the fluorescent properties progressively decline.[23] The pigment derived from tetracycline hydrochloride contains a quinine-like structure, which is the main contributor to its colour. This quinine ring is dependent upon an oxidation reaction for its formation.[33] With further research and testing, it may be found ultimately that high doses of vitamin C or other antioxidants could protect patients from the risk of tetracycline-induced tooth discolouration.[34]

The severity of the discolouration is considered to be related to the dose, frequency,[35,36] the stage of odontogenesis,[37] and the duration of therapy.[29,35] As different serum levels have been reported for the different tetracyclines after similar post-administration periods,[38] and because they have different half-lives and rates of excretion,[39] the route of administration may be a significant factor.

The problem of discolouration of the teeth by tetracyclines cannot be considered to be an insignificant side-effect because it has medico-legal implications. In 1982, tetracycline was alleged to have caused discolouration of the teeth of two children. The legal action that was subsequently brought against the general medical practitioner was successful.[40] This established side-effect of

tooth discolouration then led to the formation of guidelines to restrict the use of the tetracyclines in susceptible groups of patients, such as pregnant women especially after the fourth month of gestation, and throughout childhood.[41-43] Appeals were even made to the Minister of Health of the United Kingdom to withdraw the licence for paediatric tetracycline products, and the recommended dosage of tetracycline products for children under 12 years of age.[9]

According to a report from the American Academy of Pediatrics, tetracyclines remain contraindicated for the treatment of common infections in children younger than 8 years of age. However, doxycycline is recommended as the drug of choice for the treatment of Rocky Mountain spotted fever in children of any age.[44]

Doxycycline has been said to cause the least severe type of tooth discolouration.[36,45] Is there any scientific evidence to explain this phenomenon?

Doxycycline Phamacology

Doxycycline (α-6-deoxy-5-oxytetracycline) which first became available in the 1960's, is produced as a polyphosphate, hydrochloride or hyclate. Doxycycline has been recommended for patients with renal impairment because unlike the other tetracyclines which are cleared by the kidneys, it is excreted by the liver.[46] It is also dissimilar to the other tetracyclines because its absorption is unaffected by food and milk.[46]

Results from infection studies in mice, involving a range of micro-organisms indicated that doxycycline, when administrated orally could produce levels of protection which were similar to those of the other tetracyclines, even when a much lower dose was administrated.[47] However, this difference did not occur when the doxycycline was given subcutaneously, possibly due to its superior absorption through the gastro-intestinal tract.[48] The attainable blood levels of doxycycline given orally were higher than those of the other tetracyclines, even when a lower dose was administrated.[49] In healthy volunteers who had taken oral doxycycline, the maximum doxycycline plasma concentrations (C_{max}) of 1.5 to 7.0 μg/ml were usually reached within 3 h, and the drug had a half-life of 14 to 24 h.[7,50] Furthermore, because of the extremely low faecal elimination rate, which was 4.9% of the dose absorbed after three days, and the urinary excrete rate, which over the same time period was 39.6% of the absorbed dose,[51] the drug could be administrated in relatively lower doses than the other tetracyclines and less frequently.[52]

Doxycycline and the Teeth

A group of investigators who studied rats which were dosed daily by intraperitoneal, or intragastric injections of 50 mg/kg and 100 mg/kg body weight of different tetracyclines, concluded that doxycycline caused the least discolouration when compared with the other derivates: the appearance was of a patchy white opaque nature.[46] In a clinical study, 25 premature infants who were aged between 4 and 55 days received on day one 2 mg/kg body weight, followed by 1 mg/kg of doxycycline for a further one to 17 days. The total dose per individual varied from 9 mg to 37 mg. When the teeth of these children were examined under ultra-violet light after one year, only one of the subject's teeth exhibited fluorescence and white discoloured regions.[53] Forti and Benincori speculated that this was due to the lower calcium binding rate (19% compared to 74.5% of demethylchlortetracycline *in vitro*) and the lower therapeutic dose of doxycycline which was 1/10th of that of tetracycline hydrochloride).[53]

A retrospective, recall study was conducted to determine whether doxycycline, given in therapeutic doses for the treatment of Rocky Mountain spotted fever, caused discolouration of permanent teeth when administered during tooth development. The age range of the ten subjects, in the study, was from 11 to 19 years (mean 13.7 years), and the average age at the time of exposure was 5.1 years. The results, made by comparing the study and control, suggested that short courses of doxycycline, such as 50 mg bid for eight days, did not cause clinically significant discolouration of teeth.[54]

A non-selected group of 282 children in a medical practice in Germany received either drops or a syrup preparation of doxycycline. The children were aged between one month and 12 years (mean 29 months) and they received an average dose of 159 mg of doxycycline over a 5 to 8 day period. The drug regimen was 4 mg/kg on day 1, followed by 2 mg/kg body weight for the remaining 8 days of the course. If the condition, for which the drug had been prescribed, continued then the course was repeated; this occurred in 41 children (4 patients had 3 repeats and 2 had 4 repeats). The children's teeth were examined after 2 weeks, 4 weeks and 1 year. A total of 5 (2%) of the children had discoloured teeth, 3 had enamel hypoplasia and fluorescence, only in those 3 children did the author consider that there was a direct correlation between the drug and the defects exhibit by the teeth. Of the 83 children in the under 12 months age group, 2 had discolouration and enamel hypoplasia; while only one of

the 93 children aged between 12 and 24 months was similarly affected.[55] It was concluded by Poloczek that doxycycline was safe for use in children of all age groups; also that the discolouration of the teeth by the drug was related to the age of the recipient and the mode of administration.[55]

Goody and Bowers (1975) used four antibiotics which were randomly used to treat children, aged between 4 and 8 years, who suffered from secretory otitis media; one of the drugs was doxycycline syrup. The total dose of doxycycline (50 mg/5 ml) received per child was 400 mg; given as an initial dose of 100 mg followed by 50 mg daily for one week. The drug was taken with food or a drink of milk. The authors failed to provide any data on side-effects that may have been caused by this therapy.[56] The propriety of carrying out a clinical trial in which drugs are randomly assigned to children, especially when one of the drugs is tetracycline, is ethically wrong and was questioned in the literature.[57]

Discussion

Many researchers and drug committees have campaigned to make medical and dental practitioners aware of the side-effect of tooth discolouration caused by tetracyclines. Some have even attempted to have syrups and drops containing tetracycline totally banned. This would have an unfortunate effect on geriatric patients who cannot swallow tablets.[58] A simple logical solution is that preparations should be clearly labeled with warnings and that the paediatric dosage should not appear on the label, or even the accompany literature. If a drug of the tetracycline group is to be advocated for use in children as part of a combination therapy then this drug regimen has to be introduced and published in such a manner so as not to destroy all of the previous efforts to restrict the use of tetracyclines.

If combination drug therapies are to be recommended then the proprietary names of the drugs need to be listed in addition to the generic names. This is because many of the trade names do not necessarily indicate clearly what type, or even if a tetracycline is an active ingredient. This would help to avoid the accidental prescription of a tetracycline to a patient as part of a combination therapy and hence cause the undesirable side effect of discolouration of the teeth.

The use of doxycycline for adults, in whom odontogenesis is restricted to the third permanent molars, can, based upon the chronology of tooth development, be recommended as it will not cause dental discolouration that will be aesthetically displeasing. However, during pregnancy the situation is unclear. Based upon data for the other tetracyclines, doxycycline can be expected to cross the placenta, and subsequently be incorporated into the bones and teeth of a foetus. Thus, at this time it may be unwise to prescribe doxycycline during pregnancy and lactation because of the lack of clinical data.

The majority of published clinical data indicates that a single, or even repeated short courses of doxycycline can be prescribed for children without a fear of causing in the prolonged use of doxycycline, the prescribed dose of the drug at the time of administration may be added to the dose which re-enters the circulation as a result of remodeling of bones that contain the drug, which was incorporated from previous administrations. Nevertheless, these type of data for children are unavailable.

As previously stated, Goodey and Bowers (1975)[56] were criticised by Faoagali (1975),[57] for using doxycycline in a clinical trial involving children, when the side-effects of tetracyclines were already well known. This was in spite of some data being presented that indicated that theoretically doxycycline could be expected to cause less discolouration of the teeth than the other tetracyclines. Only limited data have become available since that time. Therefore, are we justified to ignore Faoagali's warning?[57]

Even though tetracyclines have been in clinical use for almost half a century and their side-effects are well document, it remains unclear as to why some children develop discoloured teeth yet others do not. Possibly the variation in the magnitude of this side-effect is due to the influence of an environmental factor, such as the diet, which in turn affects the urinary pH so in one individual there may be only glomerular filtration occurring while in another there may some reabsorption of doxycycline via the tubules.[59] It has been suggested that the existence of antioxidants[34] and the extent of the mineralizing front of the tooth[60] are important variables. The extent of systemic absorption and the mode of administration may also play a role. The exact dose of the drug and compliance of the patient/parent, are other factors that may have an influence. In addition, exposure to sunlight can lead to colour changes in teeth that contain some tetracyclines.[17,33] Therefore, when only limited clinical data are available on the adverse effects of doxycycline, namely that of discolouration of the teeth, can it be justifiably concluded, that given time and the wider usage of doxycycline a similar pattern of tooth discolouration will not emerge?

As with the other tetracyclines, it appears, from the work

of Forti and Benincori,[53] and of Poloczek,[55] that not all of the patients that receive doxycycline can be expected to exhibit tooth discolouration; further, it appears that doxycycline does cause less discolouration than its analogues. However, the investigators in both of these studies could not have examined the affected teeth, as they would not have erupted and been visible within the one year examination time period. To date, there has not been a prospective, randomised, double blind study that compared doxycycline with other tetracyclines from which it is possible to make a definitive statement about the decreased incidence discolouration of the teeth by doxycycline. Therefore, doxycycline may present a clinical dilemma because of inadequate data concerning the staining of developing teeth. If this is true, then caution should be exercised when prescribing doxycycline and children who receive the drug should be kept under long term review.

Laboratory analysis has demonstrated that doxycycline has a lower affinity to form calcium phosphate complex than the other tetracyclines.[58] This is possibly why the clinical data presently available appear to indicate that doxycycline can be administrated to children without the fear of causing discolouration of the teeth that are forming at the time of the administration, However, it must be remembered that the available data are limited to only a few simple clinical trials and case reports. The lesson learnt from the other tetracyclines which were introduced and then freely used, and in some regions still are, should not be forgotten. If doxycycline is to be used then careful monitoring of the subjects who are prescribed the drug should take place. Detailed documentation of the dose, frequency, chronological and dental age of the recipients should be maintained until after eruption of the teeth that were forming during the time the drug was administrated.

References

1. Saikali Z, Singh G. Doxycycline and other tetracyclines in the treatment of bone metastasis. Anticancer Drugs 2003;14:773-8.
2. Benavides S, Nahata MC. Anthrax: safe treatment for children. Ann Pharmacother 2002;36:334-7.
3. Chin W, Intraprasert R. The evaluation of quinine alone or in combination with tetracycline and pyrimethamine against falciparum malaria in Thailand. Southeast Asian J Trop Med Public Health 1973;4:245-9.
4. Ponnampalam JT. Doxycycline in the treatment of falciparum malaria among aborigine children in West Malaysia. Trans R Soc Trop Med Hyg 1981;75:372-7.
5. Metzger W, Mordmuller B, Graninger W, Bienzle U, Kremsner PG. High efficacy of short-term quinine-antibiotic combinations for treating adult malaria patients in an area in which malaria is hyperendemic. Antimicrob Agents Chemother 1995;39:245-6.
6. Taylor WR, Widjaja H, Richie TL, et al. Chloroquine/doxycycline combination versus chloroquine alone, and doxycycline alone for the treatment of Plasmodium falciparum and Plasmodium vivax malaria in northeastern Irian Jaya, Indonesia. Am J Trop Med Hyg 2001;64(5-6):223-8.
7. Newton PN, Chaulet JF, Brockman A, et al. Pharmacokinetics of oral doxycycline during combination treatment of severe falciparum malaria. Antimicrob Agents Chemother 2005;49: 1622-5.
8. Petersen E. Malaria chemoprophylaxis: when should we use it and what are the options? Expert Rev Anti Infect Ther 2004;2: 119-32.
9. Tetracyclines: children's teeth played down in manufacturers' literature. Drug Ther Bull 1973;11:64.
10. King NM, Wei SH. Developmental defects of enamel: a study of 12-year-olds in Hong Kong. J Am Dent Assoc 1986;112:835-9.
11. Sean FL. Tetracycline and doxycycline applications. Prim Care Update 1996;3:224-7.
12. Cheek CC, Heymann HO. Dental and oral discolorations associated with minocycline and other tetracycline analogs. J Esthet Dent 1999;11:43-8.
13. Sanchez AR, Rogers RS 3rd, Sheridan PJ. Tetracycline and other tetracycline-derivative staining of the teeth and oral cavity. Int J Dermatol 2004;43:709-15.
14. Johnson RH, Mitchell DF. The effects of tetracyclines on teeth and bones. J Dent Res 1966;45:86-93.
15. Schuster A, Shwachman H. The tetracyclines; applied pharmacology. Pediatr Clin North Am 1956;27:295-303.
16. Harcourt JK, Johnson NW, Storey E. In vivo incorporation of tetracycline in the teeth of man. Arch Oral Biol 1962;7:431-7.
17. Wallman IS, Hilton HB. Teeth pigmented by tetracycline. Lancet 1962;1:827-9.
18. Zegarelli EV, Kutscher AH, Denning CR, Fahn BS, Hoffman PJ. Tooth Fluorescence and Tetracycline Therapy: Studies in Patients with Cystic Fibrosis of the Pancreas. J Dent Med 1965; 20:97-8.
19. Suckling GW, Pearce EI. Developmental defects of enamel in a group of New Zealand children: their prevalence and some associated etiological factors. Community Dent Oral Epidemiol 1984;12:177-84.
20. Berger RS, Mandel EB, Hayes TJ, Grimwood RR. Minocycline staining of the oral cavity. J Am Acad Dermatol 1989;21: 1300-1.
21. Crooks MC. Prevalence of developmental defects of enamel in children and young adults in the Cook Islands. N Z Dent J 1990; 86:39-41.
22. King NM. Developmental defects of enamel in Chinese girls and boys in Hong Kong. Adv Dent Res 1989;3:120-5.
23. Love RM, Chandler NP. A scanning electron and confocal laser microscope investigation of tetracycline-affected human dentine. Int Endod J 1996;29:376-81.
24. Charles D. Placental transmission of antibiotics. J Obstet Gynaecol Br Emp 1954;61:750-7.
25. Hochberg B, Kutscher AH. Tetracycline discolouration of deciduous teeth (induced by etracycline administered ante-partum). J Clin Stomatol Conf Clumbia 1964;5:7-8.
26. Toaff R, Ravid R. Tetracyclines and the teeth. Lancet 1966;2: 281-2.

27. van der Bijl P, Pitigoi-Aron G. Tetracyclines and calcified tissues. Ann Dent 1995;54(1-2):69-72.
28. Owen LN. The effects of administering tetracyclines to young dogs with particular reference to localization of the drugs in the teeth. Arch Oral Biol 1963;8:715-28.
29. Stewart DJ. Tetracyclines: their prevalence in children's teeth. Br Dent J 1968;124:318-20.
30. Korstanje MJ. Drug-induced mouth disorders. Clin Exp Dermatol 1995;20:10-8.
31. Weyman J. The clinical appearances of tetracycline staining of the teeth. Br Dent J 1965;118:289-91.
32. Cheek CC, Heymann HO. Dental and oral discolorations associated with minocycline and other tetracycline analogs. J Esthet Dent 1999;11:43-8.
33. Davies AK, Cundall RB, Dandiker Y, Slifkin MA. Photo-oxidation of tetracycline adsorbed on hydroxyapatite in relation to the light-induced staining of teeth. J Dent Res 1985;64:936-9.
34. Bowles WH, Bokmeyer TJ. Staining of adult teeth by minocycline: binding of minocycline by specific proteins. J Esthet Dent 1997;9:30-4.
35. Conchie JM, Munroe JD, Anderson DO. The incidence of staining of permanent teeth by the tetracyclines. Can Med Assoc J 1970; 103:351-6.
36. Grossman ER, Walchek A, Freedman H. Tetracyclines and permanent teeth: the relation between dose and tooth color. Pediatrics 1971;47:567-70.
37. Davies PA, Little K, Aherne W. Tetracyclines and yellow teeth. Lacet 1962;1:743.
38. Steigbigel NH, Reed CW, Finland M. Absorption and excretion of five tetracycline analogues in normal young men. Am J Med Sci 1968;255:296-312.
39. Kunin CM, Dornbush AC, Finland M. Distribution and excretion of four tetracycline analogues in normal young men. J Clin Invest 1959;38:1950-63.
40. Medical Protection Society. Annual report and accounts. Med Protection Soc 1982;90:30-1.
41. Ray WA, Federspiel CF, Schaffner W. Prescribing of tetracycline to children less than 8 years old. A two-year epidemiologic study among ambulatory Tennessee medicaid recipients. JAMA 1977; 237:2069-74.
42. Kumana CR, King NM, Li KY. Exposure of Hong Kong children to tetracyclines: a probable cause of wide-spread dental discolouration. Hong Kong Practitioner 1986;8:1938-40.
43. British National Formulary. British Medical Association and Royal Pharmaceutical Society of Great Britain. Br Natl Formulary 1998;35:447-515.
44. American Academy of Pediatrics. Rocky Mountain spotted fever. In: Peter G, ed. 1997 Red Book: Report of the Committee on Infectious Diseases. 24th ed. Elk Grove Village, IL: American Academy of Pediatrics, 1997:452-4.
45. McIntosh HA, Storey E. Tetracycline-induced tooth changes.4. Discoloration and hypoplasia induced by tetracycline analogues. Med J Aust 1970;1:114-9.
46. McFarland JJ Jr. The tetracyclines. Ear Nose Throat J 1981;60: 226-7.
47. English AR, Lynch JE. Alpha-6-deoxyoxytetracycline. II. Activity in chemotherapeutic studies in the mouse. Proc Soc Exp Biol Med 1967;124:586-91.
48. English AR. Alpha-6-deoxyoxytetracycline. I. Some biological properties. Proc Soc Exp Biol Med 1966;122:1107-12.
49. Schach von Wittenau M, Delahunt CS. The distribution of tetracyclines in tissues of dogs after repeated oral administration. J Pharmacol Exp Ther 1966;152:164-9.
50. Welling PG, Koch PA, Lau CC, Craig WA. Bioavailability of tetracycline and doxycycline in fasted and nonfasted subjects. Antimicrob Agents Chemother 1977;11:462-9.
51. Fabre J, Pitton JS, Kunz JP. Distribution and excretion of doxycycline in man. Chemotherapy 1966;11:73-85.
52. Forti G, Benincori C, Auriti R, Ravagnan L. Treatment of infection in premature infants with a new tetracycline: doxycycline. Antibiotica 1967;5:271-82.
53. Forti G, Benincori C. Doxycycline and the teeth. Lancet 1969; 1:782.
54. Lochary ME, Lockhart PB, Williams WT Jr. Doxycycline and staining of permanent teeth. Pediatr Infect Dis J 1998;17: 429-31.
55. Poloczek SV. Possibility of tooth discoloration after doxycycline therapy in infants and small children from the view point of the residential pediatrist. Z Allgemeinmed 1975;51:549-50.
56. Goodey RJ, Bowers M. Antibiotic treatment of secretory otitis media assessed by impedence audiometry. N Z Med J 1975;82: 187-8.
57. Faoagali JL. Letter: Tetracyclines in children. N Z Med J 1975; 82:316.
58. Brock PG, Roach M. Tetracycline preparations for children. Br Med J 1979;1:126-7.
59. Schach von Wittenau M. Some pharmacokinetic aspects of doxycycline metabolism in man. Chemotherapy 1968;13:Suppl: 41-50.
60. Bevelander G, Rolle GK, Cohlan SQ. The effect of the administration of tetracycline on the development of teeth. J Dent Res 1961;40:1020-4.