SPECIAL REPORT

Effects of Tetracyclines on Skeletal Growth and Dentition:

A Report by the Nutrition Committee of the Canadian Paediatric Society

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THE tetracycline group of antibiotics includes chlortetracycline (Aureomycin), oxytetracycline (Terramycin), tetracycline (Achromycin, Tetracyn, Polycyclin) and demethylchlortetracycline (Declomycin).[1] The range of antibacterial activity of these drugs is so wide that they have come to be known as "broad-spectrum" antibiotics. For practical purposes, their therapeutic and toxic properties are quite similar. This memorandum reviews briefly certain pharmacological properties of the tetracycline group of drugs, in particular their effects on growing bones and teeth, and on this basis presents recommendations for the restriction of their use in pregnant women, infants and young children.

ABSORPTION, DISTRIBUTION AND EXCRETION OF TETRACYCLINES

Tetracyclines are absorbed primarily from the stomach and duodenum and to a lesser degree from the small intestine. Maximum plasma levels are attained after two to four hours and begin to decline after approximately six hours, although traces can be detected after 24 to 30 hours. According to Hirsch and Finland,[2] demethylchlortetracycline given orally produces a higher blood concentration and more prolonged antimicrobial activity (24 to 48 hours' duration) than chlortetracycline or oxytetracycline.

A variable proportion of absorbed tetracyclines is bound to plasma proteins and later deposited in unbound form in the tissues.[3, 4] These compounds are concentrated in the liver, and excreted by the biliary tract into the intestine from which they are partially reabsorbed. Administered tetracyclines may also be detected in the brain, cerebrospinal fluid, saliva, pleural, spermatic and prostatic fluid and in maternal milk, in about half the concentration achieved in plasma. These drugs are also deposited in the reticuloendothelial cells of the liver and spleen, in the bone marrow, and in the dentine and enamel of growing teeth.[5-8] They also cross the placenta and appear in the fetal blood. The concentration of chlortetracycline in cord blood is approximately 1/14 that of the maternal blood, whereas that of oxytetracyclines is ¼ that of the maternal blood.

Excretion occurs via both urine and feces, renal clearance varying both with renal function and with different tetracycline compounds. Some intestinal excretion follows both oral and parenteral administration.

MECHANISM OF ACTION

Three possible mechanisms have been suggested to explain the mode of action of tetracyclines:[9, 10] chelation, inhibition of protein synthesis and enzyme inhibition.

Chelation.—Tetracyclines can bind magnesium, manganese and calcium *in vitro.* They can also inhibit oxidative phosphorylation in mitochondria, but this is overcome by the addition of magnesium.

Inhibition of protein synthesis.—Tetracyclines inhibit protein synthesis in many bacteria, including *Staphylococcus aureus,* but they do not prevent the synthesis of nucleic acids by these organisms. Suppression of the protein synthesis might also result from the chelation of certain metals such as magnesium. However, the addition of magnesium has no effect on the inhibition of protein synthesis by chlortetracycline. Certain authors have suggested that the chelating action of tetracyclines could have a harmful effect on the ribosomes since the latter require magnesium in order to maintain normal activity.[11, 12]

Inhibition of Essential Enzymes.—Chlortetracycline can inhibit enzymes such as nitroreductase in extracts from animal cells; this effect is inhibited by manganese. This action of chlortetracycline (and possibly of other tetracyclines) is probably due to its capacity to chelate essential metals (e.g. manganese).

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TETRACYCLINE DEPOSITION IN BONE

In 1957, Milch, Rall and Tobie[13, 14] demonstrated the presence of tetracyclines in bones. Under ultraviolet light, they discovered a particular fluorescence in the skeletons of animals that had received oxytetracycline, tetracycline or chlortetracycline. This fluorescence could be observed for weeks or months after cessation of drug administration.

Bevelander and his collaborators[15-18] injected 0.1 mg. of tetracycline into the vitelline membrane of chick embryos between the fourth and eighth days of embryonic life and detected the antibiotic by its fluorescence in the calcified bones. Increasing the dose to 2.5-5.0 mg. on the sixth and eighth days resulted in a marked inhibition of bone growth. The skeleton was underdeveloped, under-mineralized and malformed. However, if the antibiotic was administered after the eighth day, the phenomenon was less pronounced.

In 1960, Frost and Villanueva[19] found that radioactive tetracyclines, whether administered orally, intramuscularly or intravenously, were deposited in mineralizing bones, teeth and hyaline cartilage. This characteristic appeared to be peculiar to this group of antibiotics.

In 1961, Cohlan, Bevelander and Bross[20] studied a non-viable premature infant who had weighed 900 g. at birth. The mother, a 24-year-old primipara, had been given 1 g. of tetracycline orally each day for three weeks before delivery. Examination of the fetal rib, femur, mandible and tooth fragments by the method of Day and Silverman[21] revealed the fluorescence characteristic of tetracycline. Subsequently, Bevelander and Cohlan[22] showed that a dose of 40 mg. per kg. per day of tetracycline administered to rats between the tenth and fifteenth days of pregnancy resulted in an approximate 28% diminution in the size of the fetus. When the same dose was given after the fifteenth day of gestation they noticed no ill effects. Cohlan, Bevelander and Tiamsic[23] studied 19 premature babies of whom seven had received tetracycline in a dose of 25 mg. per kg. six-hourly during a period of 9 to 12 days; six had received this dose during three periods of 9 to 12 days and the other six were untreated controls. Measurements of fibular growth revealed that the babies who had received no tetracycline showed a growth rate of 0.19 to 0.20 mm. daily whereas those who had received tetracycline showed a bone growth of only 0.11 to 0.12 mm. daily, indicating a growth inhibition of approximately 40%. Fibular growth rates returned to normal after tetracycline was discontinued. The same phenomenon was observed following daily administration of tetracycline to a mother during the last two weeks of pregnancy. Jolliffe[39] actually found an increase in weight gain of children given chlortetracycline while receiving diets low in animal protein. However, the nature of this study renders interpretation in the present context very difficult.

The mechanism by which tetracycline is fixed in bone remains controversial. Milch, Rall and Tobie[25] hypothesized that a chelation phenomenon occurred between tetracycline, calcium and the protein framework of developing bones. The presence of fluorescence in the endosteum and periosteum suggested a direct relationship between the blood transport and the localization of fluorophore in the bones.

Several theories have been advanced to explain the inhibition of bone growth by tetracyclines.[27-32, 34-36, 42] In essence, they include the three possibilities mentioned earlier, namely, formation of a tetracycline-calcium complex, inhibition of protein synthesis, or inhibition of enzymes essential to growth.

In summary, all tetracyclines produce a yellowish fluorescence in bones. These effects may be observed in newborn infants whose mothers have been treated with tetracyclines during pregnancy or in prematures treated with tetracyclines during the first four or five weeks of life.[23] In large doses, e.g. 25 mg. per kg. six-hourly for 9 to 12 days, they cause a transient inhibition of bone growth of approximately 40%. In smaller therapeutic doses, e.g. 7 mg. per kg. six-hourly, they inhibit bone growth to a lesser degree (25%).[38]

Since tetracyclines are capable of inhibiting bone growth, the question arises whether these drugs can cause congenital bone malformations. Skeletal anomalies have been reported both in rats[40, 41] and chick embryos[18, 43] following exposure to tetracycline. However, Hurley and Tuchmann-Duplessis[47] reported that tetracycline, given to the rat throughout gestation in 60 to 100 times the average therapeutic dose, did not result in fetal malformations. Rare suspected single instances of tetracycline-induced malformations in man have been reported.[44] Several authors[45, 46, 48] have reviewed the literature carefully and have been unable to detect any instances of human fetal malformation in which there was convincing evidence that these resulted from administration of tetracycline drugs during pregnancy.

TETRACYCLINES AND TEETH

There are several reports in medical literature concerning the effects of tetracyclines on teeth. These may be considered from three viewpoints:

(1) the effects of tetracyline administration to the pregnant woman on the teeth of her offspring; (2) the effects of tetracycline administration during infancy and childhood, and (3) the mechanisms of tetracycline effects on dental growth and development.

Tetracycline Administration During Pregnancy—The Effects on the Teeth of the Offspring

In 1964, Kline, Blattner and Lunin[60] published observations on 13 children whose mothers had received either tetracyclines (oxychlortetracycline, tetracycline or demethylchlortetracycline—nine cases) or erythromycin (four cases). Seven of the nine children treated with tetracyclines showed, in addition to deposits of the drug in bones, yellow discoloration, decay and enamel hypoplasia of the teeth. When tetracyclines had been administered after the fourth month of pregnancy dental changes were seen in all cases. When the drug had been given before the fourth month, no dental abnormalities were recognized.

Toaff and Ravid[64] examined 94 children aged 3 to 6 years whose mothers had been treated with tetracycline or oxytetracycline during pregnancy, with an average dose of 1 g. per day for about 15 days. They observed characteristic dental discoloration in 13 of the 94 children. Of the 47 children exposed to tetracycline *in utero* between the 15th and 24th weeks of embryonic life, none showed tooth discoloration. Among the 15 children exposed between the 25th and 28th weeks of pregnancy, only one was affected, whereas nearly half of the fetuses exposed between the 29th week of pregnancy and term showed yellow discoloration of the teeth.

Dental Effects of Tetracycline Administration in Infancy and Childhood

(a) Premature and term newborns:

Wallman and Hilton[57] studied 46 premature infants, of whom 13 had received tetracycline in the neonatal period (total doses of 120 to 750 mg.) and 21 had been treated with oxytetracycline (total dose of 620 mg.) Dental abnormalities were recognized in all infants treated with tetracycline and in two of the 21 treated with oxytetracycline.

Zegarelli *et al.*[62] described 28 premature infants who had received oxytetracycline in a dose of 5 mg. per kg. every 12 hours from birth to 120 hours of age. Nineteen who were subsequently examined between the ages of 6 and 8 years presented a yellow discoloration of the teeth. The intensity of the discoloration was more pronounced in the permanent teeth than in the primary dentition. This phenomenon can be explained by the fact that the crowns of the first teeth were almost completely calcified at the time when tetracycline was administered, while the second teeth were still developing. Wallman and Hilton[33] examined 50 babies treated with tetracycline. The majority had received the antibiotic during the first week of life, either prophylactically or for treatment of various infections. Among the 50 babies so treated, 46 subsequently showed teeth with yellow or brown discoloration. The authors concluded that the larger the total dose of tetracycline per kilo of body weight, the more pronounced were both the discoloration of the teeth and the hypoplasia of the enamel and dentine.

Kowalewska, Szotowa and Winiarska-Majczyno[63] examined 23 children aged 2 to 5 years who had been treated with tetracycline during the neonatal period. Eighteen had received tetracycline in a dose of 50 mg. per kg. daily for 3 to 5 days. The other five had received an identical dose of oxytetracycline during the same period. Fifteen of the 18 children treated with tetracycline showed a yellowish-brown discoloration of their teeth, whereas only one child treated with oxytetracycline showed similar changes. A few showed signs of hypoplasia of the enamel.

(b) Older infants and children:

In 1956, Shwachman and Schuster[49] reported on 300 infants and children who had been given doses of 10 to 20 mg. per kg. per day of oxytetracycline or chlortetracycline during periods of one year or more. They discovered that 5% of the children showed a yellow-brown discoloration of their first teeth. The following year, Milch, Rall and Tobie[13] confirmed these observations. Zegarelli *et al.*[53] reported on 52 children with cystic fibrosis of the pancreas whose ages ranged from 6 months to 16 years. They had received large doses of antibiotics, particularly tetracycline, for prolonged periods for the treatment of respiratory infections. Thirty-eight of the 52 children had teeth whose colour varied from grey to brown and even to black.

Similar observations have been made in children who received tetracycline in a wide range of dosage for a variety of illnesses.[20, 33, 54-59] These patients had one feature in common: all had been exposed to tetracycline either during the prenatal period or relatively early in life.

Mechanism of Dental Effects of Tetracyclines: Experimental Observations

Bevelander, Rolle and Cohlan[50] observed that administration of 5 mg. per kg. per day of tet-

racycline to 2-week-old rats caused fluorescent bands to appear in the enamel and dentine of molars and incisors; these bands were also hypomineralized. At about the same time, Owen[51] conducted experiments in which he injected a total of 750 mg. of tetracycline in divided doses into 8-week-old dogs, over a period of four weeks. When they erupted, the teeth were yellow in colour, and examination of tooth fragments under ultraviolet light revealed characteristic fluorescence in the dentine and enamel. Boyne and Miller[52] have reported similar results in comparable experiments using oxytetracycline and chlortetracycline.

In 1961, Bevelander, Rolle and Cohlan[50] administered 5 mg. of tetracycline daily for five days to 2-week-old rats during the period of development of their incisors and molars. The tooth enamel and dentine subsequently showed five clearly defined bands and were also slightly hypocalcified. If larger doses were injected, partial or even total inhibition of mineralization occurred.

Other authors have confirmed the occurrence of significant fluorescence in the mineralizing teeth and a less obvious fluorescence in areas of incomplete mineralization.[37, 51, 65, 66]

Whether all the tetracyclines in clinical use are equally liable to cause these types of damage to the teeth remains an unsettled question. Many authors believe that oxytetracycline offers more security from these effects than the other tetracyclines;[33, 63, 64, 70, 71, 73] however, Zegarelli and associates[62] recommend caution when using oxytetracycline in children. Further information is required to establish more accurate margins of safety for each of the tetracyclines.

The effects of varying dosage and duration of treatment, in experimental as well as in clinical situations, are incompletely understood. However, Bevelander and Nakahara[72] recently studied the consequences of administering tetracyclines in single or divided doses to rats of different ages. They concluded that both fluorescence and discoloration of the dentine and enamel were more pronounced in the animals which had received larger doses (500 mg. per kg.) whether the tetracycline was given in one dose or in divided doses over many days. Furthermore, the intensity of fluorescence was more apparent in younger than in older rats, possibly because of the larger number of zones that were incompletely mineralized. These results resemble those of several other investigators.[33, 66, 74]

The preferential deposition of tetracyclines in teeth may be explained by their power of chelation with metals such as calcium, and possibly by the formation of an ortho-phosphate-calcium tetracycline complex.[13, 14, 24, 26, 57, 67] Bevelander and Nakahara[68] observed that the localization of ^{45}Ca and of tetracycline in the teeth were the same; the fluorophore in these tissues is thus confined to the areas which are in the process of mineralization.

The brown colouring of teeth could be due to an oxidation product of tetracycline, the synthesis of which would be accelerated by the action of light. The discoloration is permanent and its intensity increases with time.[33, 60] Thus, the first teeth may be less discoloured than the permanent teeth.[62]

The hypoplasia of the enamel and dentine can be explained by one of the three mechanisms suggested earlier.[10] Since the crowns of the teeth calcify progressively, beginning in the fourth or fifth month of intrauterine life and continuing until the age of 5 or 6 years[33, 69-71] and since tetracyclines can cross the placenta,[10] clinicians should be fully aware of these facts in selecting an antibiotic for any woman after her fourth month of pregnancy and for any child from birth to 6 years of age. Furthermore, since the fetal teeth develop more rapidly during the seventh month of gestation,[33, 72] they are more sensitive at that period to the toxic effects of tetracyclines. Hence the greater frequency of hypoplasia of the enamel and dentine in premature babies treated with tetracyclines.

Certain authors[75-77] have suggested that tetracyclines could diminish tooth decay because of their antimicrobial effect on the buccal flora. Others,[33, 78, 79] however, have asserted that a careful examination of children treated with tetracyclines showed a higher incidence of dental decay. In 1963, Weyman and Porteous[80] reported an equal incidence of dental decay in children treated with tetracycline and in untreated controls.

EFFECTS OF TETRACYCLINES ON NAILS AND SKIN

In addition to the changes in teeth, abnormalities in the nails of patients treated with chlortetracycline have been described. In 1950, Shaffer *et al.*[81] described changes in the nails of five patients suffering from chronic liver disease who had been treated with chlortetracycline, 2 g. daily. The changes noted in four of the five patients followed exposure to the sun. Discontinuation of the medication was followed by a gradual improvement in the lesions.

Later, Orentreich, Harber and Tromovitch[82] observed changes in nails and photosensitivity reactions in 7 out of 27 patients treated for acne with demethylchlortetracycline. The patients, whose ages ranged from 12 to 67 years, had re-

ceived a total dose averaging 21 g. (8 to 45 g.)

De Veber[59] reported the case of a 10-year-old girl who had been given a total dose of 30.6 g. of demethylchlortetracycline over a six-month period, and who showed photosensitivity, loss and discoloration of the nails and discoloration of the teeth. The nails had lost their normal consistence and had a diffuse, blackish coloration. Once again, these followed exposure to sunlight. Two weeks after stopping the medication, significant improvement in the lesions was noted.

In 1963, Segal[56] observed the same association of photosensitivity, change in nail colouring and onycholysis in a 60-year-old patient treated for urinary infection with tetracycline; the dose consisted of 500 mg. four times daily for 17 days.

No clear relation between the type of tetracycline used, the dose and the duration of treatment has emerged from these observations. Segal has suggested that all the aforementioned complications can be seen in infants and children because the teeth and the nails are then in the process of growth, whereas in the adult only the nails can be affected since they alone maintain an active state of growth.

Other signs of toxicity (gastrointestinal ailments, the de Toni-Debré-Franconi syndrome from catabolized tetracyclines, increased intracranial pressure, photosensitivity, negative nitrogen balance) have been noted after tetracycline administration. It is probable that all types of tetracycline are capable of producing these disturbances in some degree.

SUMMARY AND CONCLUSIONS

This review has attempted to indicate certain important skeletal and dental side effects caused by the use of tetracyclines in pregnancy, infancy and childhood. A review of the pertinent literature reveals the importance of certain effects of tetracyclines upon growing bones, teeth and nails, namely:

(1) A specific yellowish fluorescence in the bones and in the enamel and dentine of the teeth.

(2) Discoloration of the teeth varying from grey to yellowish-brown to black.

(3) A transient inhibition of bone growth.

(4) Hypoplasia of tooth enamel and dentine.

(5) Discoloration of the nails and onycholysis, particularly following exposure to the sun.

The severity of these complications is probably related to the size of the dose administered; however, most of the effects have been observed following ordinary therapeutic dosage.

Tetracyclines can cross the placental barrier, thereby affecting the bones and teeth of the fetus. The susceptibility to changes in the teeth is greatest between the fourth month of fetal life and the age of 6 years, i.e. until both the first and second teeth become fully calcified.

This committee concludes that tetracyclines should be prescribed with extreme caution for any pregnant woman, particularly after the fourth month of gestation.[83] The same caution should apply to the use of these drugs throughout infancy and up to approximately 6 years of age. In most types of pediatric infections, other less toxic antibiotics are equally or more effective.

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MEDICO-LEGAL

Allergies Ignored: Routine Versus Thought

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So multifarious and multitudinous are the dangers to which patients are exposed during much modern investigative and therapeutic work that it is scarcely possible for a doctor to feel confident that he has arranged all the important precautions necessary for his patient's protection. To ensure precautions against uncommon but known and dangerous mishaps, doctors, hospitals, clinical departments, operating rooms, almost everyone connected with the care of patients, tend to evolve routines, acts or procedures that will be done invariably and these, properly used, are tremendously effective.

The routine, however, must be used; its use must be thoughtful, not thoughtless. Routine substituted for thought is no more than an additional menace. It must be used as a guide to thought.

Allergies to naturally occurring substances are not common; most people are not sensitive to pollens, for example; a few are and a few are sensitive to shellfish, to animal dander and things of that kind. Allergies to synthetic substances—most important in this context, synthetic drugs—are becoming increasingly common and are of increasing importance both to patients and doctors. Most people are aware of their own sensitivities to natural substances; their exposure is frequent enough and their symptoms unpleasant enough that they tend to volunteer information about their sensitivities. They volunteer less often information about sensitivity to therapeutic agents; they are exposed to them less often and think less often of them. When they are sick and may need therapeutic agents, their illnesses are uppermost in their minds and they forget to mention their sensitivities. Information about the sensitivity to therapeutic agents often is gained only by enquiry. Like the patients, doctors can fail to think about these sensitivities; they can fail to enquire about them or having enquired forget about them. Routines applicable and suitable to their own practices have been set up by many doctors to avoid these lapses. Routines have been set up by clinical departments in hospitals to ensure that knowl-

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