Requiem for Tetracyclines

*Item:* In the year ending June 1973, more than 13,000 kg (approximately 15 tons) of tetracyclines in liquid pediatric dosage forms were certified by the Food and Drug Administration. This 1973 figure represents a 5% increase over the previous year. Assuming that these dosage forms were administered primarily to children, the quantity of tetracycline used in 1973 would treat more than 2.6 million children with 1 gm/day for five days.

*Item:* The *British Medical Journal* reported in 1973 that tetracycline deposits were identified in 70% of the deciduous molars extracted from 505 children aged 3 to 5 years old. These children had each received an average of two to four courses of therapy with the antibiotic during their first years of life. These results represent an increase in tetracycline administration in Britain when compared to the results of a survey conducted five years previously.

Who are the children receiving tetracycline syrup and drops and for what infections are these drugs being prescribed?

It is difficult to identify common pediatric infections for which an oral tetracycline would be a drug of choice. Penicillin G is preferable for streptococcal and pneumococcal infections; and, if allergy precludes the use of penicillin, erythromycin can be used. Amoxicillin is the first choice for *Hemophilus influenzae* respiratory infections. Gram-negative urinary tract infections in children can be treated with sulfonamides, nitrofurantoin, ampicillin, or cephalosporins. Mycoplasmal pneumonia is unusual before age 10 and is, in any case, responsive to erythromycin. It stretches the imagination to believe that 15 tons of tetracyclines were used in one year to treat relatively rare rickettsial infections in children. Is it possible that this amount was used as "shotgun" therapy for nondiagnosed febrile illnesses?

A recent survey in a major teaching institution (Johns Hopkins) showed that the tetracycline drugs are avoided by the pediatric staff. The expressed reasons for not using tetracyclines were the propensity of these drugs to cause dental staining and delayed bone growth.

For many years, these and other adverse reactions to tetracyclines have been described in the labeling for all the drugs in the tetracycline family (tetracycline, chlortetracycline, demeclocycline, doxycycline, methacycline, minocycline, oxytetracycline, and rolitetracycline). Since 1970, in fact, the labeling for all tetracyclines marketed in the United States has included the following warning:

The use of drugs of the tetracycline class during tooth development (last half of pregnancy, infancy, and childhood to the age of 8 years) may cause permanent discoloration of the teeth (yellow-gray-brown). This adverse reaction is more common during long-term use of the drugs but has been observed following repeated short-term courses. Enamel hypoplasia has also been reported. TETRACYCLINE, THEREFORE, SHOULD NOT BE USED IN THIS AGE GROUP UNLESS OTHER DRUGS ARE NOT LIKELY TO BE EFFECTIVE OR ARE CONTRAINDICATED.

Although dental staining is the most obvious adverse side effect of the use of tetracyclines in children, it is by no means the only one. The list includes enamel hypoplasia in both deciduous and permanent teeth; temporary inhibition of bone growth; "bulging fontanel syndrome"; *Candida albicans* overgrowth resulting in vaginitis, proctitis, and oral thrush; gastroenteritis; potential for precipitating or worsening renal failure, photo-
toxicity, rashes, allergic or hypersensitivity reactions, and so forth. Several excellent reviews of these adverse reactions are available.4-6 Also, fetal hepatotoxicity has been reported in children given intravenous tetracycline.7

Is there a better way than label warnings and journal education to discourage the use of this antibiotic for children? One study has shown that the use of tetracyclines in a community hospital is about three times greater than the use at a teaching hospital. In the latter, antibiotics under clinical study may be given only with the approval of the infectious disease group." This leads to the speculation that tetracyclines would be used less if their uses had to be defended on the basis of microbial susceptibility or risk to benefit ratio.

In Canada, members of the Department of Pediatrics of McGill University and of the Montreal Children's Hospital recently voiced their concern in a letter to the Canadian Medical Association Journal." They urged that the marketing of oral pediatric preparations of tetracycline be prohibited. In many ways this course of action would be more consistent than the present situation in this country. We have drug labeling stating that a drug "should not be used" for children up to the age of 8 years, but this warning accompanies a bottle of "pediatric drops" and gives schedules for small children.

CONCLUSION

There are few if any reasons for using tetracycline drugs in children less than 8 years old. This class of antibiotics is capable of producing many adverse effects, two of which are specific for younger children and one of which is irreversible. Accordingly, it is difficult to justify the continued availability of drop or syrup formulations of tetracyclines. As long as they continue to be marketed, physicians who care for children should make every effort to discourage their use and curtail prescribing tetracycline for pediatric patients.

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