

Sensitive gram-negative organisms include most strains of *Escherichia coli*, the meningococcus, gonococcus, *Hemophilus influenzae*, and *Pasteurella*, *Brucella*, and *Shigella* strains, *Aerobacter* and *Proteus* species vary considerably in their sensitivity to the tetracyclines. Some strains of *Pseudomonas aeruginosa* and *Bacteroides* have been found to be sensitive to the tetracyclines.

The tetracyclines are generally considered to be bacteriostatic agents; they suppress the multiplication of organisms and depend on the host defense mechanisms to eradicate the remaining organisms. When the host defenses are good, excellent therapeutic results will be obtained in certain infections, such as uncomplicated pneumococcal pneumonia, tularemia,²¹ and certain gram-negative bacillary urinary tract infections. On the other hand, superior results are obtained when a bactericidal agent such as penicillin is used in eradicating group A beta hemolytic streptococci from the pharynx; penicillin is also more effective in pneumococcal meningitis in which phagocytosis may be less efficient than in the lung and in which the cerebrospinal fluid concentrations are obtained more consistently with penicillin than with the tetracyclines.

Certain organisms develop resistance to tetracyclines more readily than others. Some gram-negative bacilli, such as *E. coli* and *Aerobacter* and *Proteus* organisms, readily become resistant. Staphylococci also develop resistance to this group of drugs.²² Pneumococci have not been observed to develop resistance. In one study, in which 218 strains of group A beta hemolytic staphylococci were tested, 42 strains (or 20%) were found to be resistant to tetracycline and demethylchlor-tetracycline.²³ It is difficult to tell whether resistance develops by means of mutation and selection in those organisms that were previously sensitive, or whether superimposed infections with organisms of established resistance occur after the strains have been eradicated. Probably both mechanisms occur under certain circumstances.

Adverse effects and toxicity

The tetracyclines are relatively safe antibiotics when given in moderate dosage and when the course of therapy is not prolonged. Even when therapy has been given over a long period of time, such as in chronic bronchitis, the adverse effects have been few if the patient was otherwise in good general health.

The most frequent untoward effects have been nausea, vomiting, and diarrhea. These effects can be minimized if the lowest effective dose is given after meals. The symptoms usually subside when the drug is discontinued.

Superimposed infection with other resistant organisms, particularly with *Staph aureus* and strains of *Pseudomonas*, *Proteus*, and other gram-negative organisms, has been the most serious hazard to patients receiving prolonged or large doses of the tetracyclines. This is particularly true in patients who are hospitalized with chronic debilitating illnesses, such as chronic pulmonary disease and neoplastic disease, in patients who are being treated with corticosteroids, or in those who are receiving radiation or antitumor therapy. This complication, however, is not limited to tetracycline therapy. These patients may develop superimposed infections regardless of therapy, and it is difficult to assess the role of tetracycline drugs in producing such effects.

Drug fever and rashes have been observed infrequently. Local application is more likely to be associated with dermatitis, but this form of therapy is rarely indicated. Photosensitivity, manifested by marked sunburn after exposure to direct sunlight, has developed during therapy with demethylchlorotetracycline. This reaction apparently occurs more frequently and is more severe in southern areas where the sunlight is more intense.

Blood dyscrasias have been observed in patients who have received tetracycline therapy, but causal relationship has not yet been definitely established. Patients who develop agranulocytosis and pancytopenia while receiving tetracyclines have recovered without discontinuation of the therapy.

Other less well-known adverse effects have been described and are of interest, although they are rarely of clinical importance. Each of the earlier homologues has produced morphologic and functional changes in the liver during prolonged intravenous therapy, a negative nitrogen balance, and increased riboflavin excretion into the urine.¹²

THERAPEUTIC INDICATIONS AND CLINICAL USE

The effectiveness of the tetracyclines in the treatment of a large group of infections has been well established. The tetracyclines have been in use longer than