than therapeutically effective quantities and there are no known specific indications for fixed combinations of antibiotics. In addition, the incidence of side effects and the expense to the patient is sometimes increased when mixtures are used.

In general, all of the tetracyclines have the same antibacterial spectrum when each tetracycline is tested against individual strains of organisms. In most instances, when an organism is resistant to one tetracycline it will be resistant to the other homologues.[9]

Pharmacology

The tetracyclines are incompletely absorbed from the gastrointestinal tract[8] and large amounts can be recovered from the stools after oral administration.[10] This property may contribute to the changes in fecal flora and anal irritation. Absorption is probably increased and higher blood levels are attained if the antibiotic is taken during the fasting state. On the other hand, some patients have less gastric irritation if the drug is taken after a meal.

The tetracyclines are inactivated by the formation of chelates when they combine with metallic ions, chiefly calcium and magnesium, in the gastrointestinal tract. Because of this property, various preparations, including combinations with citric acid, a phosphate complex, sodium hexaphosphate, and glucosaminic hydrochloride, have been developed. However, no significant therapeutic superiority has been demonstrated by the use of these combinations. Aluminum hydroxide markedly reduces absorption.[8, 11-13]

The tetracyclines are absorbed by the stomach, duodenum, and ileum, but very little is absorbed by the colon. The distribution of the tetracyclines in body tissues and fluids varies slightly with each homologue.[11, 12] The drugs are present in the milk of lactating women and pass through the placenta into the fetus; they also appear in the salvia, cornea, sclera, iris, and vitreous humor. Levels are lower in spinal fluid than in blood. The highest spinal fluid levels are obtained with tetracycline, the lowest with chlortetracycline, and intermediate levels occur with oxytetracycline. The concentrations of chlortetracycline in the bile are 8 to 16 times higher than those in the blood. Demethylchlortetracycline is also concentrated in the liver and bile.[13] The drugs have an affinity for fast-growing tissues, liver, tumors, and areas of new bone formation. This property has recently been utilized in the development of a test for gastric carcinoma.[14] Prolonged administration of the tetracyclines may produce a yellowish discoloration of the teeth.[15] Tetracycline has been found to diffuse into ischemic tissues in measurable amounts.[4, 16, 17]

The tetracyclines are bound to plasma protein in varying amounts. However, the binding is reversible and may be one of the most important factors responsible for the differences in renal clearance rate among the various tetracyclines.

The principal mechanism of excretion is by the kidneys, probably by simple glomerular filtration. Kunin and associates[18] have studied the excretion rates of the various homologues under various conditions of pH, urine flow, and renal function. They have shown that the half-life of tetracycline plasma levels is prolonged and is increased in the presence of oliguria and renal failure. The half-life may increase from a normal value of 8 hours up to 108 hours in patients with renal failure. Chlortetracycline is an exception; since it is rapidly inactivated in alkaline solutions at body temperature, its half-life is not significantly increased in the presence of renal failure.[4]

Adequate blood levels are obtained when tetracycline, oxytetracycline, and chlortetracycline are administered in doses of 250 to 500 mg four times daily. Demethylchlortetracycline produces somewhat higher and more prolonged blood levels because of its slower renal excretion and greater stability. Therefore, adequate blood levels are obtained when 150 mg is given 4 times daily.[3]

ANTIMICROBIAL SPECTRUM

The tetracyclines inhibit a broad range of microbial agents, including both gram-positive and gram-negative bacteria. *Mycobacterium tuberculosis*, rickettsial the psittacosis-lymphogranuloma venereum group of large viruses, and the agent of primary atypical pneumonia (Eaton agent).[19] The latter is now known to be a pleuropneumonia-like organism. The most sensitive organisms in the gram-positive group include the pneumococcus, *Streptococcus viridans*, some strains of staphylococci, and most strains of group A beta hemolytic streptococci.[20]