Biomedical & Pharmacology Journal Vol. **1**(1), 163-166 (2008)

Metalloantibiotics-I

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(Received: February 12, 2008; Accepted: April 04, 2008)

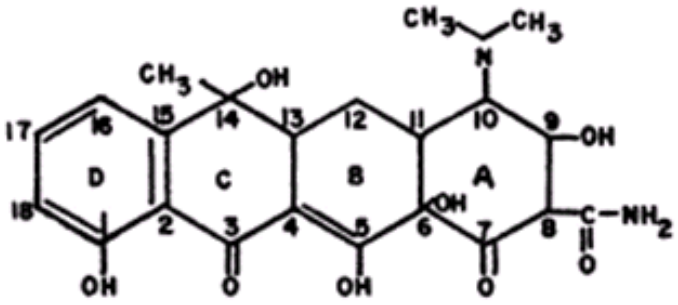
ABSTRACT

Metal ions after forming complexes with an antibiotics alters the antimicrorial activity of an antibiotics alone.

Key words: Metal ions,antibiotics.

INTRODUCTION

A strong affinity of tetracycline and oxy- and chlortetracycline for metallic ions was reported by Albert (3, 8) who observed the formation of drug-metal complexes of 1:1 and, as the pH is raised, of 2:1. The cations tested (in the order of decreasing stability of the drug-metal complexes) were: Fe++, Al+++, Cu2+ , Ni++, Fe++,Co2+, Zn2+, and Mn2+. The iron complexes of the tetracyclines are red, the Cu2+, and Ni2+ complexes are green, and the Al3+,Co2+,Zn2+, and Mn2+ complexes are yellow. In contrast,Oxford (77) was not able to obtain colored complexes of chlortetracycline with Zn2+or Mn2+but did observe stable yellow complexes with Cu2+, Ni2+, Co2+ Mg2+, Ca2+ and Sr4+.The tetracycline structure contains numerous sites at which chelation with metallic ions might occur. Perhaps the most important sites lie along the system marked by atoms 1 through 7which consists

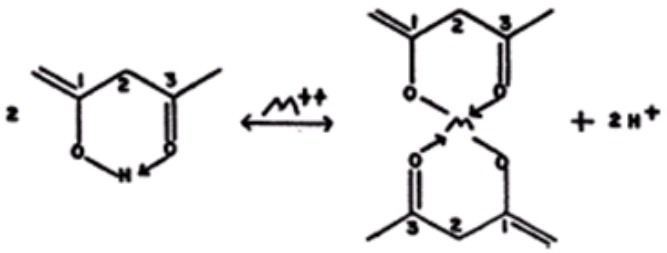


TETRACYCLINE

Scheme 1

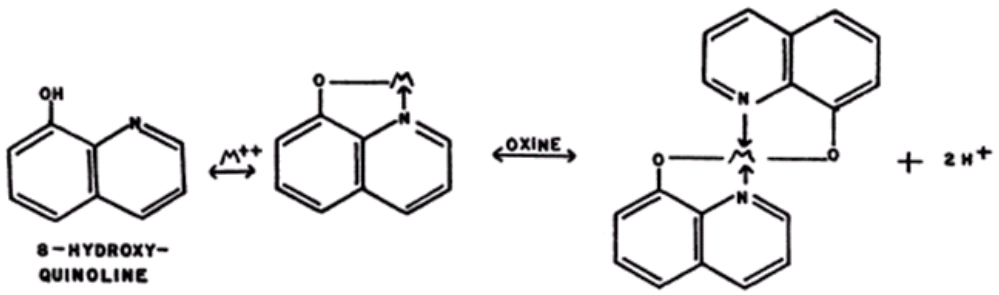
essentially of two 1,3 diketones with two of the keto groups in the enol form.Such monoenols in 1,3 diketones chelate with metallic ions very readily to form six-membered. In each ring, the two atoms that bind the metallic ion are oxygen atoms (23):

The tetracycline compounds have been described as uncouplers (21) and inhibitors (107)of oxidative phosphorylation and inhibitors of respiration (91, 99, 106), fatty acid oxidation , arginine catabolism (55), nitro reduction (92, 93, 94), and adaptive enzyme formation (15).



Effect on Enzyme Systems

Scheme 2



Scheme 3

The possibility that metallic ions might enhance the activity of the drugs was during the series of growth tests described above. Moderate enhancement was observed with low concentrations of Mn2+ or with high concentrations of Fe+ with P. aeruginosa (112,113). Previously, chlortetracycline had been found to be enhanced by similarly low concentrations of Mn+l in its antibiotic effect against C. cucullus (65).The resistant strains tested to date include a strain of M. pyogenes whose average minimum inhibitory concentration of tetracycline and oxy- and chlortetracycline is 120 pg per ml and a strain of Penicillium notatum which requires 750 pug per ml of the drugs for suppression of growth. Fe2+ and Mg2+ are active with the bacterium and Fe+H with the fungus.

8-hydroxyquinoline

Molecular Structure and Affinity for Metallic Cations of seven isomeric mono-hydroxyquinolines, only 8-hydroxyquinoline (oxine) can chelate metallic ions (9, 90): observed that the Cu2+, Ni2+ , Cd++,

and Ag+compounds of 8-hydroxyquinoline are as fungistatic as oxine itself; and Manten et al. (67)reported that neither Zn+, Cu++, Mn2+ nor

Mo2+-suppresses the toxicity of oxine toward Aspergillus. Other investigators reported that Cations Cu2+ and Fe2+ enhance antifungal activity (10)and that conalbumen suppresses the antibacterial action of 8-hydroxyquinoline (36). Gram positive bacteria are more susceptible to oxine than are gram negative species and trace amounts of Co2+ excess amounts of Fe++ suppress the activity of 8-hydroxyquinoline against the former organisms whereas Fe2+, Zn2+ or Cu2+ suppress the toxicity of oxine towards the latter bacteria. Furthermore, with Micrococcus pyogenes, an increase in the concentration of 8-hydroxyquinoline results in a paradoxical decrease in toxicity. Subsequent studies revealed that small concentrations of Fe2+ Cu2+, or Cd2+ are required for toxicity towards gram positive species and that a 2:1 oxine-Fe- molar ratio is maximally toxic.

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