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Effect of Metal Ions on the Antimicrobial Activity of Tetracycline Hydrochloride

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The bioability of drugs at their sites of action can be enhanced or reduced by interactions with other drugs. Several studies concerned with the biochemical and pharmacological effects of antimicrobial agents when given with other drugs were carried out. The type of interactions involved competition for renal excretion, displacement from carrier sites increased metabolism, decreased protein synthesis and induced tissue toxicity [1]. The metal ions have also considerable effect on the antimicrobial activity of antibiotics, especially in the case of tetracycline. Tetracycline forms stable complexes with a number of metal ions such as calcium, magnesium, iron and aluminium [2, 3]. Newman and Frank [4] have shown that the mode of action of Tetracycline antibiotics is dependent upon the presence of certain metal ions.

A survey of literature shows that a great amount of work has been done by various workers covering the various aspects of stability [5–11]. But the possible role of biologically occurring metals on the activity of Tetracycline–HCl has not been extensively exposed. With this objective in view we have studied the effect of various metal ions on the antimicrobial activity of Tetracycline hydrochloride.

The solution of Tetracycline–HCl was treated with metal salts dissolved in sterile double distilled water. The quantity of metal salts and tetracycline–HCl in the final solution was kept the same (*viz.* 1 mg/1 ml each). The antibiotic activity was studied by the paper disc diffusion method. *Staphylococcus aureus* and *Escheria coli*, tetracycline sensitive strains were employed as test organisms. The zones of inhibition diameter were measured [12] in each case and results were tabulated (Table I).

The results showed marked variation in the activity of Tetracycline–HCl as influenced by metal salts. In case of manganese sulphate, ferric chloride, magnesium sulphate and calcium chloride increase in activity was observed in comparison to pure Tetracycline–HCl. However, copper acetate, cobalt acetate, uranyl acetate, ammonium acetate, cobalt chloride, zinc oxalate, zinc chloride and nickel chloride showed reduced activity. It is further observed that there is complete loss in activity of tetracycline–HCl solution due to copper ions in the presence of acetate ions. Whereas, complete inhibition of activity due to copper ions in the presence of sulphate ions could not be observed. It is also apparent from our table that zinc oxalate has reduced activity in comparison to zinc chloride. It appears therefore that anions also indirectly play some role in the antimicrobial activity of tetracycline.

TABLE I. Effect of Metal Ions on Antimicrobial Activity of Tetracycline–HCl in Solutions.

S. No.	Metal Salts	Diameter of Zone Inhibition	
		S. aureus (mm)	*E. coli* (mm)
1.	Tetracycline hydrochloride	16.0	12.0
2.	Magnesium sulphate	19.0	14.0
3.	Manganese sulphate	17.0	13.0
4.	Ferric chloride	17.0	13.0
5.	Calcium chloride	17.0	13.0
6.	Cobalt acetate	14.0	11.0
7.	Copper sulphate	13.0	10.0
8.	Manganese Nitrate	13.0	10.0
9.	Cobalt nitrate	12.0	9.0
10.	Cobalt chloride	11.0	8.5
11.	Nickel chloride	11.0	8.5
12.	Zinc chloride	10.0	7.5
13.	Uranyl acetate	10.0	7.5
14.	Ammonium acetate	9.5	7.0
15.	Zinc oxalate	9.0	7.0
16.	Copper acetate	–	–

Increased activity due to magnesium sulphate and manganese chloride support the idea of Newman and Frank who proposed that the mode of action of tetracycline antibiotics is dependent upon the presence of certain metal ions. The complex chemistry of tetracycline and the large number of potential binding sites for cations may be responsible for activity in the presence of metal ions. Further the kinetics and the properties of metal complexes of calcium and magnesium with tetracycline were also studied by the above authors. They suggested that from an antimicrobial standpoint, the tetracycline complexes of Mg^{++} and Ca^{++} are probably the most important because the concentrations of these cations and the large formation constants of their complexes with tetracycline indicates that *in vivo* tetracycline would exist as one of these two complexes. Our studies on the effect of Ca^{++} and Mg^{++} ions on antimicrobial activity of tetracycline against *Staphylococcus aureus* and *Escheria coli* support the above viewpoint. However, the loss in activity due to other metal ions present cannot be explained on the basis of Newman's observation. It is a well established fact that apart from Ca^{++} and Mg^{++} ions, various other metal ions form complexes with tetracycline. We are of the opinion that the decrease in activity with other metal ions may probably be due to either insoluble complex formation or shielding effect by formation of a weak interaction bond on the pharmacophoric group responsible for antimicrobial activity.

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