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The Effect of Streptomycin and Penicillin on Trace Metal Ions Level in Biological System

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Abstract: The potentiometric data of streptomycin and penicillin with trace metal ions show that Fe(III) and Cu(II) ions form very stable complexes with these antibiotics at physiological pH therefore prolonged therapy causes anemia. Cain) and Mg(II) ions do not form stable complexes. Cr(III) ions competes with Fe(III) binding sites. Co(II) and Ni(II) ions form complexes at neutral pH. The results indicate that these antibiotics lower the minerals level in the biological system. So it should be taken with minerals.

Key word: Trace Metals, ChelatiCn, Streptomycin and Penicillin

Introduction

Streptomycin was isolated from a strain of streptomyces by Waksmen in 1943. It is produced in organic or synthetic media. In low concentrations, it is bicteriostatic to a large number of Gram-negative and to some Gram-positive bacteria. It does not effect fungi protozoa or viruses. It had been extremely useful in the treatment of tuberculosis (Hussain and Naved, 1993). The antimicrobial activity of streptomycin, mechanisms of action and that of bacterial resistance is typical of other amino glycosides. They inhibit the protein synthesis by interfering with the binding of bacterial aminoacyl transfer ribonucleic acids to 30 S ribosomal subunit (Clark *et al*., 1992). It has a broad spectrum of action but due to resistance and severe side effects its usefulness is limited. It can cause deafness, harm the kidneys and cause muscle weakness in addition to severe allergic reactions (Wilson, 1990). Pencillin is highly effective antibiotic with an extremely wide margin of safety. It is an organic acid obtained from the culture of mold *Pencifflum chrysogenum.* Pencillin has common central core called B lactam ring fused to a thiazolidine ring. Certain bacteria can produce B lactamase or penicillinase which break the lectern ring. Thus pencillin is hydrolyzed to harmless form.

These bacteria are resistance to pencillin (Hussain and Naved, 1993). The main site of pencillin action is at the cell wall of bacterium, The cross links of peptidoglycan are the main target of drug action. Toxicity of pencillin is extremely low but very high dose can cause serum sickness, skin rash, fever, gastrointestinal disturbance, platelet days functioning and haemolytic anaemia (Clark *et al*., 1992), Metal ions play a vital role in a vast number of biological processes (Kaplan and Szabo, 1983). Fe(III) is essential for all forms of life. It is involved in transport of oxygen and electron transport (Raymond and Carrano, 1979). Cr(III) ions form essential parts of the glucose tolerance factor. It also controls the cholesterol levels in blood (Mertz, 1969). Cu(II) are involved in the structural stabilization of fibrous proteins of connective tissues (Hughes, 1981). Most of the Ni(II) requiring microbial enzymes are involved in some aspect of gas metabolism such as hydrogenase (Wolfe, 1991). Ca(II) and Mg(II) are important in many enzymatic processes (Spiro, 1983). Co(II) is involved in vitamin 812 synthesis which is cofactor in many biochemical reactions (Hutner, 1972). About 200 enzymes of biological system are Zn(II) containing enzymes and it stabilizes insulin molecule (Failla and Weinberg, 1977). Antibiotics are known to have chelating properties. These properties may be used in metal transport across the membranes or to attach the antibiotics to a specific site from which it can interfere with the growth of bacteria (Das, 1990). In the present work we have studied the formation of complexes of streptomycin with Fe(III), Cr(III), Cu(II), Co(II), Mn(II), Ca(II) Mg(II) and Zn(II), their relative stabilities and their metal ligand ratio.

Materials and Methods

All reagents were of AR grade. Solutions were made in deionized water and were also free from CO_2. For all pH measurement Orion pH meter model SA 720 was used. A0.05 M solution of potassium hydrogen pthalate. 0.05 M pH 4.01 at 25°C was used to calibrate the pH meter along with the standard buffer solutions made from BDH standard chemicals. For potentiometric titration a double walled glass cell was used. The temperature of cell was maintained throughout the experiment by circulating water. All the titration were done at 25°C. A 20 ml of 0.01 M salt solution in each case was mixed with 20 ml of 0.01 M streptomycin or pencillin solution and titrated with 0.1 M NaOH solution. The change in pH was noted after small increment (0.05 ml) of base at a time. The solution was stirred constantly with magnetic stirrer constantly. For each metal antibiotic solution, titration were performed twice to minimize the probable error. Far spectrophotometric measurements absorbance were recorded on Spectronic-21.

Results and Discussion

The potentiometric titration curves (pH Vs vol. of base added) for streptomycin, pencillin and their metal complexes i.e Fe(III), COW,

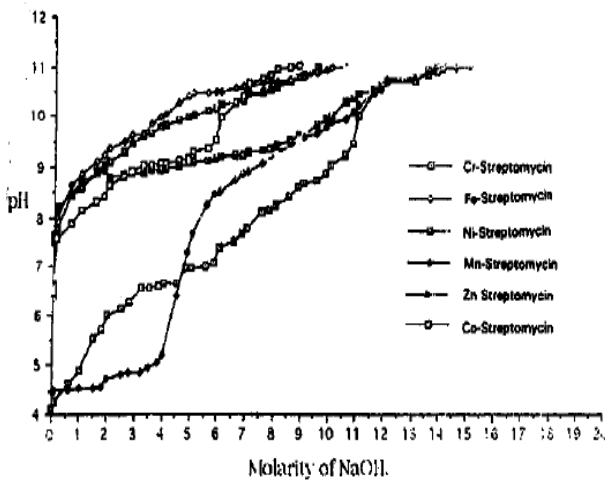

Fig. 1: Representation of streptomycin complexation at 25°C

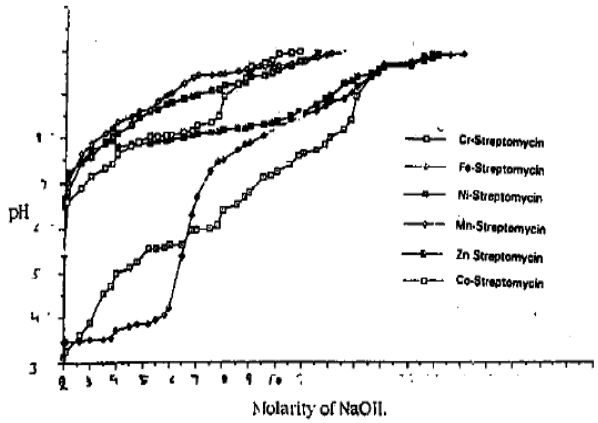

Fig. 2: Representatibn of Pencillin complexation at 25°C

Cu(II), Co(II), Ni(II), Zn(II), Ca(II) and Mg(II) are shown in Fig. 1 and 2. Table 1 and 2 show the pH values of metal ions complex and their absorbance. From these data following points are concluded:- There is no observable complexation between Mg(II) and Ca(II) with streptomycin and pencillin under the conditions of experiments detailed in this paper and it therefore seems very likely that these antibiotics does not have any affinity toward these ions.

On the other hand the results indicate that Ni(II) and Co(II) have fair complexation at neutral pH. Thus it can be concluded that these metals can form complexes with streptomycin and pencillin at neutral pH. In case of Zn(II) it was observed that complexation may start at slitghtly higher pH i.e. pH 8. 4. Among dispositive ions, Cu(II) forms most stable complexes. The interesting results were found when tri-positive ions Fe(III) and Cr(III) were studied. Fe(III) forms most stable complexes at pH 6 while Cr(III) forms complexes at pH 6.5.

Above observations indicate that antibiotics have high affinity for spherically symmetric +3 ions. Our results clearly demonstrate that the stability among these complexes can readily be explained on the basis of charge to radius ratio of metal ions. Therefore these antibiotics should have affinity for Fe(III) in the biological system among other biologically available metal ions that is the reason prolong therapy of these antibiotics may result in anemia of iron deficiency (Pancoast, 1988). This type of chelation studies of antibiotic are very important in drug metabolism. If this property is abolished by changing the structure their activity against the microorganisms is also abolished. Antibiotics also became unaffected, when they are used in metal free system. They can kill the bacteria very effectively when only traces of metal ions are present (Jasper and Silver, 1977). Therefor it is suggested that to show biological action, these antibiotics should be used with trace metal ions. As the data of mole ratio method shows in equimolar concentration of streptomycin and pencillin, they forms 1:1 complex with trace metal ions. This complex is active species but at higher concentration of the drug 1:2 complexes are formed such complexes are inactive.

Table 1: Absorbance of streptomycin complex at the ph of complexes formation

Metal ions	pH	*M:L	λmax	Absorbance
Fe(III)	6.75	1:1	500	0.339
Cr(III)	7.25	1:1	500	0.029
Cu(II)	8.00	1:1	480	0.017
Ni(II)	9.50	1:1	400	0.040
Co(II)	9.25	1:1	500	0.032
Mn(II)	10.00	1:1	510	0.015
Ca(II)	-	-	-	-
Mg(II)	-	-	-	-
Zn(II)	7.7	1:1	-	-

Table 2: Absorbance of pencillin complexes at the pH of complex formation

Metal ions	pH	*M:L	**λ max	***Absorbance
Fe(III)	7.5	1:1	500	0.296
Cr(III)	7.0	1:1	450	0.082
Cu(II)	5.5	1:1	480	0.02
Ni(II)	8.0	1:1	400	0.050
Co(II)	9.0	1:1	500	0.036
Mn(II)	8.0	1:1	510	0.1
Zn(II)	8.2	1:1	-	-

*Metal ligand ratio

**Wavelength of maximum absorbance

***Optical density

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