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Antibacterial study of mixed ligand chelate and its application to tuberculosis

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ABSTRACT

Rifampicin, anti-tubercular drugs have been screened for their activity towards mycobacteria, Ecoli and Streptocoli.On Mycobacerium bacteriological activity have been conducted With metal chelates (complexes) of Pyrazinamide, Isoniazid and Rifampicin the results obtained were compared with that of the Parent drug. It is being shown that in many cases metal complexes were more potent than as compared with pure drug. The study revels that few metal chelates (complexes) show a remarkable resistance as compared with the Parent drug.

Key words: Bacteriological activity, Chelates (complexes), Pyrazinamide (Pyz), Isoniazid (Inz), Rifampicin (Rfn).

INTRODUCTION

It is evident that metal complexes play an important role in biological activity of drugs. Present[1-4] study was carried out to see the effect of metal complexes of Pyrazinamide. Isoniazid and Rifampicin on MTDR-Tb. It is being shown that in many cases metal complexes were more potent than as compared with pure drug[5-6]. The increase in potency is due to binding of a drug with metal ions dressed it up with some special physico-chemical properties helpful in its biological activity such as low redox potential and low dissociation constant, lipid solubility's and electron distribution[7]. Taking in consideration the above in present study metal complexes of Pyrazinamide, Isoniazid and Rifampicin, anti-tubercular drugs (synthesized in the study) have been screened for their activity towards mycobacteria, Ecoli and Streptocoli. The metal ions used for the present study and for the preparation of chelates include the essential elements required by the body, they are involved in wide variety of biochemical function in the body but most act primarily in enzyme system viz. La(III), V(II), Zr(IV), Tl(I), Cd(II).

MATERIALS AND METHODS

Isolation of Pyrazinamide Complexes

All the chemicals were used of high purity. A.R. grade Pure sample of Pyz, Inz, & Rfn were obtained from HOD Laboratories Ratlam India. Pyz, Inz & Rfn metal complexes were prepared by mixing of Pyz, Inz & Rfn metal salt in 1:1 molar ratio and refluxing the mixture for $4_{1/2}$ hour over water bath. The solution on concentration gave insoluble complex, which was filtered washed and dried (after recrystallisation) in vaccume. The complexes were stored in air tight bottles.

Characterization of Complexes

The composition of metal complexes was ascertained by conducting conductometric methods, potentiometric methods and I.R., N.M.R., E.S.R. spectrum of isolated complexes were recorded. Melting point electronic spectra was obtained.

Technique for detection and measurement of chemotherapeutic activity

The anti microbial agents are used for therapy of disease depend upon for effectiveness upon their capacity to inhibit the multiplication of or to kill the invading micro-organism under the condition which exist in vivo. This anti-tuberculosis activity was carried out in Microbiology Research Center, Lupin Laboratories, Mandideep, BHOPAL using the standard methods according to approved Laboratory Techniques. The anti-tuberculosis drug and its complexes were screened in vivo for the sensitivity test. The method use was the disc-colonies test due to Bauer et al[8] Material used for this study are as follows-Plastic Petri plates 90mm, Synthesized metal complexes of Pyrazinamide, Middle brook 7H11 Agar Base, Autoclave, Incubator.

Mechodology

Serial dilution were prepared so to obtain the desired concentration of 0.1 ug/ml, 0.01 ug/ml, 0.001 ug/ml in autoclaved distilled water. 10.5 grams 7H11 media was dissolved in 200ml of distilled water and stir properly and 2.5ml glycerol was added. The volume was make up to 450ml and media was autoclaved for 15 minutes at 121°C. After autoclaving the media was kept at 65°C for two hours and 20ml was poured into each plate under sterile conditions. Bacteria H37RV was added to serially diluted compounds so that the final concentration becomes 0.1ug, 0.01ug and 0.001ug and then plates were spread with the help of a spreader.

The observation was obtained after twenty one days. Which is tabulize in table – 1.

Observation

Table-1 Physical Properties and Antituberculosis Activity of Pyrazinamide Complexes

Temp	=	27°C
Time	=	21 days
Concentration	=	0.0.1 µg.
MIC of PZA, InZ, Rfn	=	0.1 µg.

S.No	Complex	Colour	M.P.	C.F.U. obtained
1.	Pure Pyz	White	180°C	03 Colonies
2.	Pure Inz	White	170°C	02 Colonies
3.	Pure Rfn	Dark Brown	190°C	02 Colonies
4.	Pure La^{+++}	White	200°C	04 Colonies
5.	Pure Cd^{++}	White	210°C	05 Colonies
6.	Pure Tl^{+}	White	230°C	04 Colonies
7.	Pure Zr^{++++}	White	250°C	05Colonies
8.	Pure V^{++}	Light Green	170°C	03 Colonies
9.	La^{+++}+Pyz+Inz	White	190°C	04 Colonies
10.	La^{+++}+Pyz+Rfn	Light Brown	180°C	03 Colonies
11.	La^{+++}+Inz+Rfn	Light Brown	210°C	05 Colonies
12.	Cd^{++}+Pyz+Inz	White	190°C	05 Colonies
13	Cd^{++}+Pyz+Rfn	Dark Brown	180°C	04 Colonies
14.	Cd^{++}+Inz+Rfn	Light Brown	160°C	06 Colonies
15.	Tl^{+}+Pyz+Inz	White	130°C	04 Colonies
16.	Tl^{+}+Pyz+Rfn	Yellow Brown	150°C	05 Colonies
17.	Tl^{+}+Inz+Rfn	Light Brown	160°C	07 Colonies
18.	Zr^{++++}+Pyz+InZ	White	180°C	08 Colonies
19.	Zr^{++++}+Pyz+Rfn	Light Brown	200°C	09Colonies
20.	Zr^{++++}+Inz+Rfn	Light Brown	230°C	09 Colonies
21.	V^{++}+Pyz+Inz	White	250°C	02 Colonies
22.	V^{++}+pyz+Rfn	Light Yellow	260°C	03 Colonies
23.	V^{++}+Inz+Rfn	Dark Brown	280°C	05 Colonies

(Pyz-Pyrazinamide, Inz-Isoniazid, Rfn-Rifampicin CFU=Colony Formation unit)

RESULTS AND DISCUSSION

Pyz, Inz and Rfn anti-tuberculosis agent possess chelating site and forms, Stable chelate with many biologically interesting metallic ions Anti-tuberculosis activity of Pyz, Inz and Rfn metal complex is caused by their metal binding properties [(9)]. The study revealed an effective increase in potency of Pyz, Inz and Rfn when chelated with some metal ions. At an effective concentration 0.01 µg/ml of all compounds as well as pure Pyz, Inz and Rfn states that there was a pronounced decreased in the number of colonies as compared to pure Pyz, Inz and Rfn La, Cd Complexes of Pyz, Inz and Rfn inhibited the M tuberculosis more effectively Whereas Tl, V Complex show moderate effect on mycobacterium tuberculosis. While Zr complex show less effect on mycobacterium tuberculosis.

Higher antituberculosis activity of certain metal complexes than the original drug may be Due to the fact that complexation with metal imparts some important characteristics to the Drug. Which are helpful in its biological activity e.g. low dissociation constant (strong metal ligand bond) Special redox potential, electron distribution and solubilitys. It also helps in The natural process of bond formation and bond cleavage and the group transfer reactions[(10)] As a result, the metal complex has increased duration of action and possess enhanced blood Concentration, which may probably be due to a comparatively faster diffusion of the metal chelate and through the organisms due to its more liposoluble (more covalent metal to ligand bond) on being co-ordicated with the metal ion forming stable chelates. The higher biocidal activity of the metal chelate may also due to the combined bioactive effect of the metal and the ligand and the higher concentration of the ligand in the chelate1:2(M.L.).

The anti growth (inhibition) of the bacteria species may be due to the exchange of trace metal of the metaloenzyme with the metal ions of the chelate under test and/or due to steric control of the encumbered and bulky chelate molecule. The results of present study clearly indicate formation of (M:L) 1:2 chelates with involvement of N-atom in metal to ligand – bond resulting in a sufficient high covalent – nature of chelate molecules and hence lipid – solubility. The activity of a drug depends on its bio-availability, which in turn depends, apart from other factors, upon its particle size. It has been shown that reduction in particle size increases activijty. [11,12] it increases the solubility of the drug and hence its bio-availability. In most of the case the complex having high activity have micro-particle size, which helps their higher solubility.

CONCLUSION

The mechanism of action suggest that Pyz, Inz and Rfn may be active as a prodrug. Suseptable Organism produce deaminidase, and La, Cd Complexes of Pyz, Inz and Rfn inhibited the M tuberculosis more effectively whereas Tl, V Complexes show moderate effect on mycobacterium tuberculosis. While Zr complex show less effect on mycobacterium tuberculosis.

REFERENCES

[1] Eicchorn, G.L. “Co-ordination Compound in Natural Products” in J.C. Bailor Reinhold New York.
[2] Eicchorn, G.L. and Baiolor J.C. *J.Am. Chem. Soc.* 75, 2905. (**1953**)
[3] Smith E.L., *Proc. Natr Acad. Sci. U.S*., 35, 80, (**1949**)
[4] Scott, D.A. and Fischers A.M. *Biochem. J.* (London), 29, 1048 (**1935**)
[5] Sigel, H. (**1982**-84) Metal Ions in Biological system, Vol. 10-40 marcel Dekker, New York.
[6] Mukherjee. S.L. Nahi, J., Rahymahasya, S., Lashker, Sl. And Gupta R.P. (**1955**) *J. Pharma. Pharmacol* 7:36.
[7] Weinberg, E.D. (**1957**). *Bacterial Revs*. 21:46.
[8] Becuer, A.W. Kirby, W.M.M. Sherris, J.C. and Truck. M. (**1966**) *Amer. J. Clin.Pathol* 45:493.
[9] Pramer, D. *Arch Biochem, and Bioghys*, 62, 265.(1**9**56)
[10] Florence, A.T. & Atthood (**1986**) Physico Chemical Principles of pharmacy Mc. Millan. London.
[11] Goodman and Gilman (**1985**) the pharmacological Basis of Therapeutics, Mc. Millan N.Y.
[12] Heifets, I.B. et al *Antimicrob. Agent chemother*, 33, 1252, (**1989**)