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**Role of Bio metals Cu (II) in antihistaminic behavior of
Chlorphenamine**

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Abstract

The co-ordination chemistry of Cu (II) in the environment of an anticancer drug, chlorphenamine has been explained to co-ordinate complex [Cu-chlorphenamine]. Metal-drug interaction in vitro in aqueous KCl phase was studied polarographically at physiological pH and temperature. On the basis of IR spectroscopic analysis it is concluded that in solid phase one chlorphenamine molecule with their C-N donor sites encompass the metal. Amperometric and polarographic studies also suggest the 1:1 metal ligand equilibria. The respective changes in the antihistaminic activity of the drug as a result of complexation has been determined and possible mechanism is suggested.

Keywords: Chlorphenamine, Cu (II) Complex, Antihistaminics

Introduction

Copper plays a very important role in our biological system (1, 2). Cu(II) forms stable complexes with N and O donor ligands, it is involved in redox reaction with thiol groups of proteins. It is a component of various enzymes and involved in energy production. It is an essential element for neurotransmission in the brain and is active in cell protection. The Cu complexes play an important role in facilitating the transport of Cu across cell membrane in various tissues.

The design of a new drug depends on the development of suitable chemical criteria for *in-vivo* reactions from *in-vitro* experiments.

Antihistaminic substances are used for the treatment of the diseases caused by histamine. Most of the work on histamine as a ligand has been concerned with its metal complexes (3, 4) and only a little attention has been focused on the Fe (III), Co(II) and Ni (II) interaction with antihistaminic compounds (5, 6). No attention has been made to evaluate biological properties of antihistaminics as a result of their interactions with biologically or metabolically important metal ions. The present paper leads to the bioinorganic study of the interaction of such biologically essential metal, copper (II) and an antihistaminic drug chlorphenamine. Changes in the biological properties of the pure drug have been evaluated

and underlying role of copper (II) in the antihistaminic activity of chlorphenamine (2[p-chloro- α [2-di methylamino) ethyl] benzyl] pyridine maleate (7) has been reported.

Experimental

Chemicals and Reagents

All chemicals used were of analytical grade. The drug sample was procured by Sigma Chemical company, USA. Double distilled water and absolute ethanol were used as solvents. Chlorphenamine was prepared by dissolving the requisite amount in distilled water. Stock solution of 1M potassium chloride was prepared by dissolving a requisite quantity of compound in distilled water. pH adjustment were made using dilute solutions of HCl, NaOH whenever necessary. The test solutions were deaerated by bubbling nitrogen gas for 10 min. before recording the polarogram / Voltammogram.

Apparatus

All the polarograms / voltammograms were recorded on an Elico DC polarograph model CL-657, coupled with an X-Y polarocard model LR-101. The polarographic cell consisted of an electrode assembly having a dropping mercury electrode, a saturated calomel electrode and a coiled platinum wire (auxillary electrode). A systronics digital pH meter-335 was used for the pH measurements. The amperometric titrations were performed on a manually operated set up, equipped with polyflex galvanometer (sensitivity 8.1×10^{-9} amp. per div) and an AJCO vernier potentiometer. The capillary characteristics of the DME had a $m^{2/3} t^{1/6}$ value of $2.5 \text{ mg}^{2/3} \text{ S}^{-1/2}$ at 60 cm effective height of mercury column. The IR spectrum of solid complex was recorded using KBr pellet on an shimadzer, Japan model 470 IR spectrophotometer.

Preparation of complex

For the study of metal: ligand (M:L) complexation equilibrium experimental sets were prepared by keeping overall Cu (II) and potassium

chloride (supporting electrolyte) concentration fixed at 1.0 mM and 0.1M, respectively. The concentration was varied, from 0.0 to 25mM. The volume was made up to 100ml with distilled water and the pH of each set was adjusted to 6.0 ± 0.1 using HCl/NaOH solution. The test solution was deaerated for 10min. before recording the polarogram/voltammogram.

Amperometric titration

Experimental sets, each having different but known amount of Cu(II) were prepared in appropriate quantity of supporting electrolyte and pH was adjusted to 6.0 and titrated separately against the standard solution of the titled chlorphenamine whose pH was also adjusted to that of the titrate (6.0 using HCl/NaOH) at -0.40 V vs SCE (the plateau potential of Cu (II)). The current after each addition of the titrant was read and a curve was plotted between current against volume of titrant added.

Synthesis procedure of solid complex

Copper sulphate solutions were prepared separately in water and were mixed in 1:1 molar ratio. The mixture was then refluxed in a round bottom flask for 2h. The residue (complex) was filtered and washed thoroughly to remove any unreacted material. The complex was dried at low temperature and stored over P_4O_{10} .

Antimicrobial screening

Reper's method (7) was followed for the microbial screening of the complex against various bacteria: *Staphylococcus aureus*, *Pseudomonas mangiferae*, *Salmonella typhi* and fungi. *A. fumigatus* and *Cryosporium* sp. The number of replicates in each case was calculated using the following formula.

$$\% \text{ inhibition} = \frac{a - b}{a} \times 100$$

Where "a" represents the diameter of the zone of inhibition for control and "b" represents Zone of inhibition for complex.

Antihistaminic screening

The influence of Cu (II) complex on the antihistaminic response of pure drug was assessed by two methods (8, 9).

In vivo antihistaminic screening of drug and its complex was performed with groups of two guinea pigs ileum set up as described by the Schnieden and western year % except that the tissue was bathed with physiological salt gassed with 100% oxygen and contraction of the ileum was recorded using an isotonic frontal writing lever attached to a 3cm long piece of ileum. Two minutes after the addition of each drug of its complex the ileum was subject to the action of 5 μ g histamine. Three replicates were obtained to calculate an average response.

Results and Discussion

Polarographic study of M:L complexation equilibrium -

Cu(II) and its complex with chlorphenamine ligand were found to be reversible reduced in 0.1M KCl at pH 6.0. The reduction was found to be diffusion controlled, as revealed by plot of i_d versus \sqrt{t} corr. On gradual increase of drug concentration, that half wave potential of Cu(II) metal ion shifted to more electro negative value and the diffusion current also decreased there by showing complex formation between Cu (II) with chloro phenamine (10).

The composition and formation constant of the complex was studied by the plots of $\Delta E_{1/2}$ (Shift in the $E_{1/2}$) = $(E_{1/2}) - (E_{1/2})_S$ against $\log C_x$ (Logarithm of the concentration of the ligand). The plots were linear showing the formation of single complex species in solution. Ligane (10) method was therefore applied, which showed 1:1 (M:L)

complex formation with formation constant $\beta_1 = 3.6$

The analyte was found be fairly stable, as indicated by the reproducibility of the polarogram. The presented data has been compared with that observed using spectrophotometric method was found in good agreement.

Amperometric determination of chlorphenamine with Cu (II) under the above mentioned experimental conditions, Cu (II) gives a well defined polarographic wave in 0.1 M KCl at pH 6.0. The diffusion current was found to be proportional to its concentration. Chlorophenamine does not produce any wave under the said experimental conditions. The platue potential for the polarographic wave of Cu (II) i.e. -0.4 V vs SCE, was applied on the potentiometer for carrying out amperometric titration. Cu(II) was taken as titrate and the drug was taken as titrant. The current volume plots resulted in L shaped curve. The end point as located by graphical method revealed metal to drug ratio of 1:1 which is in agreement with author's observation on the metal legand complexation equilibrium using polarographic method. The standardised method was found be accurate for the analysis of complexes.

IR spectrol analysis of Cu (II) chlorphenamine complex IR bonds of the complex have been assigned with the analogy of reported drug spectrum (11, 12) indicated co-ordination through tertiary nitrogen. The band for the C-N (90 cm^{-1}) stretching was found to be affected in the spectrum of the complex. A bond is shifted to 1320 cm^{-1} from 1410 cm^{-1} Thus chlorophenamine acts as mono dentate N donar and forms a Cu(III) chlorphenamine complex (Table-1)

Table-1 Principal IR Signals (cm⁻¹) and their assignments for chlorphenamine and its Cu(II) complex

Chlorphenamine	Assignments	Complex
2970 and 2875	CH-Stretching	2970 and 12875
1440	CH-deformation for CH ₃	1440
1320	C-C stretching	1320
720	CH ₂ rocking	720
3030	C-H stretching and for	3030
1600	C = c aromatic	1600
1495		
1470		
1420		
620	C-Br	620
1410	C-N Stretching	1320

Antimicrobial activity of Cu (II) chlorphenamine complex- Antimicrobial activity of the complex is presented in Table-2 of the various human and

plant pathogens studied. This complex was found to be most toxic against *Pseudomonas magniferae* bacteria.

Table-2 Anti-microbial activity of [Cu-chlorphenamine] complex

S.No.	Micro-organisms species	Zone of Inhibition (mm)		% inhibition
		Complex	Control	
1.	Bacterial			
(a)	<i>Salmonella typhi</i>	10	15	33.3
(b)	<i>Pseudomonas mangiferae</i>	11	17	35.3
(c)	<i>Vibrio cloacae</i>	26	13	-100
(d)	<i>Bacillus pumilus</i>	16	16	0.0
2.	Fungal			
(a)	<i>Trichothesium</i>	13	14	7.1
(b)	<i>A. fumigatus</i>	20	16	-25

Including diameter of filter paper disc 6mm.

Pharmacological activity of Cu(II) - Chlorphenamine complex-

(I) *In vitro* - the complex was found to be a stronger anti histaminic agent than pure drug. Animals treated with chlorphenamine were protected against histamine for 4.2 min. whereas, 6.3 min protection time was recorded when these animals were treated with the complex.

(II) *In-vivo* - Responses of guinea pig ileum 2μ g/ml complex blocked the effect of histamine 60% whereas only 40% response of histamine was depressed by pure drug. Thus the complex shows 20% increased protection as compared to

the parent drug. Its significant results was that the Cu(II) family slightly stimulates the activity of histamine.

Conclusion

Copper increase the anti-histaminic response of pure drug by 20% Increased antihistaminic response may be explained if a ternary complex between metal chlorphenamine and histamine is supposed to be formed *in vivo*. Since, *in vivo* a strong complex with Cu(III) and antagonist is formed it is reasonable to purpose that the released histamine in the body may combine with

the complex and after the ligand displacement chemically antagonise itself by the ternary complex between Cu (II)- chlorphenamine-histamine has been confirmed by the polarographic method (13). The complex could also be used for the treatment of the diseases caused by histamine to the anemic patients.

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