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Anti-inflammatory Effects of Co(II), Ni(II) and Cu(II) Complexes of Diclofenac Sodium

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Complexes of Co(II), Ni(II) and Cu(II) with anti-inflammatory drug diclofenac sodium have been synthesized and evaluated for their anti-inflammatory activity by the carrageenan induced ratpaw edema test. A comparison of the compounds with Diclofenac sodium revealed that the Cu(II) and Co(II) complexes were more effective than the drug itself.

INTRODUCTION

In recent years it has increasingly apparent that the proper balance of the biologically available metals such as Fe, Co, Ni, Cu and Zn etc. are necessary for the efficient metabolism and growth of human and animal organisms. A thorough study to search the literature in relation to the biological requirements and toxicity of Cu led to the following conclusions. Copper is an essential element and is required for normal metabolism in man[1–3]. Since co-ordinated forms of Cu are always more stable forms, compared to ionized form, it exists in the biological system as a variety of complexes.[3–7]

EXPERIMENTAL

Diclofenac sodium was obtained by courtesy of M/s Lupin Laboratory Pvt. Ltd., Aurangabad, India; appropriate metal chlorides and other reagents used were of AR grade. Doubly distilled water was used throughout.

Synthesis of the Complexes

Co(II), Ni(II) and Cu(II) complexes of the diclofenac were synthesized according to the following procedure. To a hot aqueous solution of the metal salt, solution of the ligand in the same solvent in stoichiometric ratio 1 : 2 were added. The solution was refluxed for 1 h on water bath. The complexes precipitated as microcrystalline powders after a few minutes of mixing. The synthesized complexes were analysed by elemental analysis, magnetic susceptibility measurements, molar conductance, electronic and IR spectra.[11]

Anti-inflammatory studies were performed using a plethysmometer to measure carrageenan induced paw volume following the method of Winter *et al.*[8] Forty adult male wister albino rats (90–125 g) were fasted for 18 h but with free access to water. Each treatment *i.e.*, plain drug and complexes was administered at a dose of 100 mg/kg body wt. orally in 0.2% CMC suspension. Half an hour following the treatment 0.1 mL of 1% solution of a carrageenan was injected in

the right hind paw planter aponeurosis, the paw volume was measured immediately before giving carrageenan and again 3 h later by means of plethysmograph. Edema was measured in a precalibrated plethysmograph as the difference between the volumes of the paw measured before and 3 h after giving carrageenan. The per cent inhibition of inflammation after 3 h was calculated by the method of Newbould[9] using the following formula:

$$\text{Per cent inhibition, } I = 100\left(1 - \frac{a-x}{b-y}\right)$$

where

x = mean foot volume of rates before the administration of carrageenan injection in the test and standard group,

a = mean foot volume of the rates after the administration of carrageenan injection in the test and the standard group,

y = mean foot volume of rats before the administration of carrageenan injection in the control group,

b = mean foot volume of rats after the administration of carrageenan in the control group.

RESULTS AND DISCUSSION

The Co(II), Ni(II) and Cu(II) complexes of the drug diclofenac sodium were tested for anti-inflammatory effects, differences were observed between complex and free ligand which suggested that at equal doses the copper and cobalt complexes were more effective anti-inflammatories than the ligand. These results provide evidence for a unique metabolite Cu-dependent metabolic process required for tissue maintenance. A metal co-ordination compound may be responsible for the desired anti-inflammatory activity of those agents which have clinical usefulness. That is to say, Cu-coordination compounds which have not been generally recognized as possible active metabolites may be responsible for the anti-inflammatory activity of the clinically used anti-inflammatory agents.[10]

TABLE-1
EFFECT OF VARIOUS COMPOUNDS ON CARRAGEENAN PAW EDEMA IN RATS

Compound	No. of animals used	Dose (mg/kg) body wt.	Initial v vol.* 0.0 h	Final vol.* after 3 h	Vol. of edema* (5) – (4)	Per cent inhibition
'A' Control	8	100	0.575	1.105	0.530	—
'B' Plain drug	8	100	0.545	0.900	0.350	33.01
'C' Cu-drug complex	8	100	0.730	0.930	0.200	62.26
'D' Co-drug complex	8	100	0.705	0.960	0.255	51.88
'E' Ni-drug complex	8	100	0.725	1.085	0.360	32.07

*Average of four readings

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Amperometric Trace Determination of Arsenic with 2-mercapto and 3-Mercapto Propanoic Acids

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Ref. Nos. 15–18 should be read as follows:

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