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Antiinflammatory Activity of 5-(2'-Hydroxyphenyl)-3-phenyl Pyrazolinates of Co(II), Ni(II), Cu(II): A Comparative Study

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5-(2'-Hydroxyphenyl)-3-phenylpyrazolinates of Co(II), Ni(II), Cu(II) were synthesized, characterized and evaluated for their antiinflammatory activity by the carrageenan induced rat paw edema test. A comparison of 5-(2'-Hydroxyphenyl)-3-phenylpyrazolinates of Co(II), Ni(II), Cu(II) with Co(II), Ni(II), Cu(II) complexes of diclofenac and plain diclofenac drug reveled that the 5-(2'-hydroxyphenyl)-3-phenyl pyrazolinates of Cu(II) and Co(II) were more effective than the Co(II), Ni(II), Cu(II) complexes of diclofenac and plain diclofenac drug itself.

Key Words: Pyrazolinates, Antiinflammatory activity, Diclofenac.

INTRODUCTION

In recent years it is increasingly apparent that the proper balance of the biologically available metals such as Fe, Co, Ni, Cu, Zn, *etc*. are necessary for the efficient metabolism and growth of human and animal organisms. Copper is an essential mineral/nutrient in human and animal health[1-9]. Interruptions in Cu transport or excretion are the basis for many chronic and spontaneous human and animal diseases, such as Alzheimer's disease, Mad Cow disease and Sway back. The coordinated forms of copper are always more stable compared to ionized forms, it exists in the biological systems as a variety of complexes[10-16]. In continuation of the work on complexation behaviour of 5-(2'-hydroxyphenyl)-3-phenylpyrazoline with some metallic moieties[17,18], it was thought worthwhile to report antiinflammatory activity of 5-(2'-hydroxyphenyl)-3-phenylpyrazolinates of Co(II), Ni(II) and Cu(II).

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EXPERIMENTAL

Appropriate metal(II) chlorides and other reagents used were of AR grade. Diclofenac sodium was obtained by Avlon Pharma Pvt. Ltd., Mumbai, India. Double distilled water was used throughout.

Synthesis of 5-(2'-hydroxyphenyl)-3-phenylpyrazolinates of Co(II), Ni(II), Cu(II): The ligand 5-(2'-hydroxyphenyl)-3-phenylpyrazoline and its complexes with Co^{2+}, Ni^{2+}, Cu^{2+} were prepared by reported method[17,18]. The synthesized 5-(2'-hydroxyphenyl)-3-phenylpyrazolinates of Co(II), Ni(II), Cu(II) were characterized by elemental analysis, magnetic susceptibility measurements, electronic, IR, ^{1}H NMR and ^{13}C NMR spectra[17,18].

Synthesis of diclofenac complexes: Co(II), Ni(II), Cu(II) complexes of the diclofenac were synthesized according to the reported method[19,20]. 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 were precipited as microcrystalline powders after a few minutes of mixing. The synthesized complexes were analyzed by elemental analysis, magnetic susceptibility measurements, molar conductance, electronic and IR spectra[19,20].

Antiinflammatory studies were performed using a plethysmometer to measure carrageenan induced rat volume following the method of Winter *et al.*[21]. 64 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, Co(II), Ni(II), Cu(II) complexes of diclofenac and 5-(2'-hydroxyphenyl)-3-phenylpyrazolinates of Co(II), Ni(II), Cu(II) was administered at a dose of 100 mg/kg body weight 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 was measured immediately before giving carrageeran and again 3 h later by means of plethysmograph. Edema was measured in a pre-calibrated plethysmographas 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[22] using the following formula:

$$\% \text{ Inhibition (I)} = 100 \times \left(1 - \frac{(a - x)}{(b - y)}\right)$$

where, x = mean foot volume of rates before the administration of carrageenan injection in the test and standard group; a = mean foot volume of rates after the administration of carrageenan injection in the test and standard group; y = mean foot volume of rates before the administration of carrageenan injection in the control group; b = mean foot volume of rates after the administration of carrageenan injection in the control group.

RESULTS AND DISCUSSION

Co(II), Ni(II), Cu(II) complexes of diclofenac and 5-(2'-hydroxyphenyl)-3-phenylpyrazolinates of Co(II), Ni(II), Cu(II) were tested for antiinflammatory effects, differences were observed between Co(II), Ni(II), Cu(II) complexes of diclofenac and 5-(2'-hydroxyphenyl)-3-phenylpyrazolinates of Co(II), Ni(II), Cu(II) and free drug (Table-1) which suggested that at equal doses the 5-(2'-hydroxyphenyl)-3-phenylpyrazolinates of Cu(II) and Co(II) were more effective than the Cu(II), Co(II) complexes of diclofenac and free drug. These results provide evidence for a unique metabolite copper-dependent metabolic process required for tissue maintenance. A metal coordinated compound may be responsible for the desired antiinflammatory activity of those agents, which have clinical usefulness[23-27].

TABLE-1
A COMPARATIVE STUDY OF EFFECT OF 5-(2'-HYDROXYPHENYL)-3-PHENYLPYRAZOLINATES OF Co(II), Ni(II), Cu(II), DICLOFENAC DRUG AND Co(II), Ni(II), Cu(II) COMPLEXES OF DICLOFENAC ON CARRAGEENAN PAW EDEMA IN RATS

Compounds	No. of animals used	Dose (mg/kg) body wt.	Initial volume* 0.0 h	Final volume* after 3 h	Volume of edema*	Inhibition (%)
Control	8	100	0.575	1.105	0.530	–
Diclofenac sodium drug	8	100	0.540	0.905	0.365	31.13
Cu(II)-drug complex	8	100	0.725	0.925	0.200	62.26
Co(II)-drug complex	8	100	0.710	0.963	0.253	52.26
Ni(II)-drug complex	8	100	0.720	1.090	0.370	30.19
5-(2'-Hydroxyphenyl)-3-phenyl pyrazolinate of Cu(II)	8	100	0.819	0.931	0.112	78.87
5-(2'-Hydroxyphenyl)-3-phenyl pyrazolinate of Co(II)	8	100	0.821	0.950	0.129	75.56
5-(2'-Hydroxyphenyl)-3-phenyl pyrazolinate of Ni(II)	8	100	0.750	1.098	0.348	34.43

*Average of four readings.

Conclusion

The present study revealed that 5-(2'-hydroxyphenyl)-3-phenyl pyrazolinates of Cu(II), Co(II) were more effective than the Co(II), Ni(II), Cu(II) complexes of diclofenac and free drug. These results provide evidence for a unique metabolite Cu-dependent metabolic process required for tissue maintenance. 5-(2'-Hydroxyphenyl)-3-phenyl pyrazolinates of Co(II), Ni(II), Cu(II) compounds may be responsible for the desired antiinflammatory activity of those agents, which have clinical usefulness.

REFERENCES

1. A. Dancis, D.S. Yuan, D. Haile, C. Askwith, D. Eide, C. Moehle, J. Kaplan and R.D. Klausner, *Cell*, **76**, 393 (1994).
2. B. Zhou and J. Gitschier, *Proc. Natl. Acad. Sci. (USA)*, **94**, 7481 (1997).
3. J. Lee, J.R. Prohaska, S.L. Dagenais, T. Glover and D.J. Thiele, *Gene*, **254**, 87 (2000).
4. J. Lee, M.M.O. Pena, Y. Nose and D.J. Thiele, *J. Biol. Chem.*, **277**, 4380 (2002).
5. S. Puig , J. Lee, M. Lau and D.J. Thiele, *J. Biol. Chem.*, **277**, 26021 (2002).
6. J. Lee, J.R. Prohaska and D.J. Thiele, *Proc. Natl. Acad. Sci. (USA)*, **98**, 6842 (2001).
7. Y.M. Kuo, B. Zhou, D. Cosco and J. Gitschier, *Proc. Natl. Acad. Sci. (USA)*, **98**, 6836 (2001).
8. E.J. Underwood, Trace Elements in Human and Animal Nutrition, Academic Press, New York, edn. 4 (1977).
9. S. Puig and D.J. Thiele, *Curr. Opin. Chem. Biol.*, **6**, 171 (2002).
10. G.W. Evans, *Physiol. Rev.*, **53**, 535 (1973).
11. C.J.S. Gubler, M.E. Lahey, G.E. Cartwright and M.M. Wintrobe, *J. Clin. Invest.*, **32**, 405 (1953).
12. I.H. Scheinberg and I. Sternlieb, *Pharmacol. Rev.*, **12**, 355 (1960).
13. I. Sternlieb, A.G. Morell, W.D. Tucker, M.W. Greene and I.H. Scheinberg, *J. Clin. Invest.*, **40**, 1834 (1961).
14. A. Eden and H.H. Green, *Biochem. J.*, **34**, 1202 (1940).
15. P.Z. Neumann and A.S. Kortsak, *J. Clin. Invest.*, **46**, 646 (1967).
16. C.J. Earl, M.J. Moulton and B. Selverstone, *Am. J. Med.*, **17**, 205 (1954).
17. N.S. Chattree and T.C. Sharma, *Asian J. Chem.*, **6**, 405 (1994).
18. U.N. Tripathi, K.V. Sharma, A. Chaturvedi and T.C. Sharma, *Polish J. Chem.*, **77**, 109 (2003).
19. R. Kesherwani and P. Singh, *J. Indian Chem. Soc.*, **72**, 803 (1995).
20. R. Kesherwani and P. Singh, *Asian J. Chem.*, **8**, 618 (1996).
21. C.A. Winter, E.A. Risley and G.W. Nuss, *Proc. Soc. Exp. Biol. Med.*, **162**, 544 (1963).
22. B.B. Newbould, *Br. J. Pharmacol.*, **21**, 127 (1963).
23. R.J.S. John, *J. Med. Chem.*, **19**, 35 (1976).
24. R.J.S. John, *J. Inflamm.*, **1**, 31 (1976).
25. M.W. Whitehouse, *J. Inflamm. Res.*, **6**, 201 (1976).
26. M.W. Whitehouse and W.R. Walker, *J. Inflamm. Res.*, **8**, 85 (1978).
27. A.J. Lewis, *J. Inflamm. Res.*, **8**, 244 (1978).

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