Characterization of anti-hypertensive effect of a new class of metal-NONOates

M.Monti[1,3],V.Bargelli[1,3], R.Solito[1], L. Pasotti[2,3],E.Monzani[2,3],L.Casella[2,3], L.Morbidelli[1,3]

[1]Dept. of Life Sciences, University of Siena, Siena, Italy, [2]Dept. of Molecular Medicine, Biochemistry Unit, University of Pavia, Pavia, Italy, [3]Noxamet Lto, Milan, Italy

Nitric oxide (NO) is a gaseous transmitter with several physio-pathological functions in cardiovascular diseases, inflammation and cancer. NO controls smooth muscle functions, maintain vascular integrity and exerts anti-hypertensive effect. Metal-NONOates are a new class of NO donors, with potential therapeutic activity in various human diseases, but primarily related to the cardiovascular system. The metal-NONOates, in which the properties of NO release by specific prodrugs are modulated and enhanced as a result of their complexation with metal ions, represent a significant innovation with respect to the drugs traditionally used (Ziche et al., 2008).
In this study we characterized the vascular protective effect and the anti-hypertensive activity of the most effective compound of the new class of metal-NONOates, Ni(PipNONO)Cl, compared to the commercial DETA/NO.
When tested on culture microvascular endothelial cells, Ni(PipNONO)Cl exerts a protective effect on the endothelium, promoting cell proliferation and survival in the range of pM. Functional tests on pre-contracted isolated aortic ring from rat, demonstrated that Ni(PipNONO)Cl induced a relaxation of 40% higher than the reference compound (DETA/NO) at the same concentration, indicating a promising vasorelaxant effect useful in pathological condition. In view of these results, we measured blood pressure, through the tail cuff methods, in an animal model of hypertension, using spontaneously hypertensive rats (SHR). Dose response experiments of the compounds (3, 5 and 10 mg/kg/day) were performed in WT and SHR animals treated daily for 14 or 30 days. While the NO donors had no effects in WT rats, in SHR rats Ni(PipNONO)Cl reduced the mean blood pressure. The effect was particularly evident at the dose of 10 mg/kg/day given i.p. and reduction of blood pressure persisted for at least after 2 hours from the treatment. Similar results were obtained with DETA/NO but at a less significant manner.
Overall these data indicate that Ni(PipNONO)Cl exerts a vascular protective effects, an anti-hypertensive activity more relevant than the commercial compound DETA/NO and an overall safe profile.

Ziche M (2008).*ChemMedChem.*3(7):1039-47.