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EFFECTS OF NITRIC OXIDE (NO)-TIMOLOL ON THE BLOOD PRESSURE AND HEART RATE OF L-NAME-INDUCED HYPERTENSION IN THE RATS

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The study has evaluated the effects of timolol (Tim), β-blocker used in glaucoma therapy (1), and its parent compound NO-releasing derivative NO-timolol (NO-Tim), on the blood pressure and heart rate. These effects were evaluated in the rats to which hypertension was induced by three weeks treatment with L-NAME (400mg/L, in drinking water). To these 0.05 ml of 0.25, 0.5 and 5% Tim, or equivalent concentration of NO-Tim and saline were administered by injection into the conjunctival sac. All the administrations were performed twice daily, for three weeks (2).
Tim, at any dose considered, did not produce change of the pressor levels expressed by rats following treatment with L-NAME (ie, L-NAME, 198±7 mmHg). In contrast, 0.25% NO-Tim showed a significant antihypertensive effect which remained for the dose of 0.5% and disappeared for the dose of 5%. For example 0.25% NO-Tim, 147±5 mmHg, $p<0.01$. Equimolar concentrations of Tim and NO-Tim reduced the tachicardia induced by L-NAME. However, Tim had significant effect at high doses (5%), whereas NO-Tim is effective at low concentrations (0.25%), with an action which resulted markedly higher than that of 5% timolol. The tachicardic effect of L-NAME was almost restored by higher concentration of NO-Tim.
Therefore this study evidenced that NO-Tim possesses stronger effects on systemic blood pressure and heart rate, with respect to equimolar concentrations of Tim when administered into the conjunctival sac of L-NAME-induced hypertensive rats. Particularly active is the dose of 0.25% NO-timolol.

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References
1. Lewis et al., Am Fam Physician 59:1871-1879, 1999
2. D'Amico et al., Pharm Pharmacol Commun 5:361-364, 1999