Nitric Oxide Release by an Edavarone Derivative Containing NO-Donor Furoxan Moiety Contributes to the Resolution of Renal Injury After Ischemia/Reperfusion in the Rat

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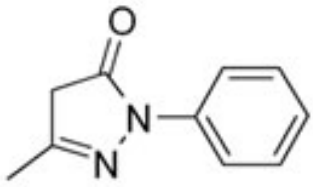
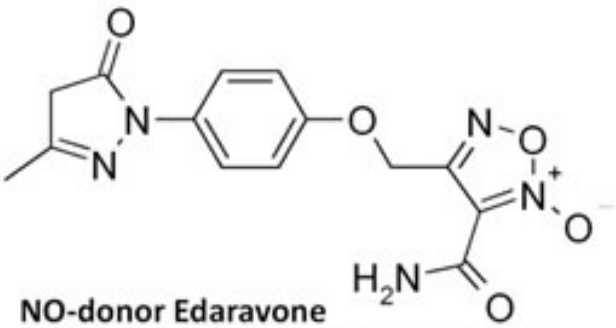
Edaravone (3-methyl-1-phenyl-2-pyrazolin-5-one, EDV) is a novel free radical scavenger that has been demonstrated to reduce ischemia-reperfusion (I/R)-associated tissue injury in the brain, heart, skeletal muscle and kidney and it is now clinically employed in patients with acute cerebral infarction (Feng S. et al., 2011). Experimental evidence clearly show that in conditions associated with I/R, the enhanced formation of NO is beneficial, as it can cause local vasodilation, inhibit platelets and leukocytes adhesion and promote angiogenesis (Luque Contreras D. et al., 2006). Here we investigated the hypothesis that the protective effects of EDV against renal I/R injury may be enhanced by using a EDV derivative bearing NO-donor furoxan moiety (NO-EDV), which has been recently synthesized and characterized by members of the research team, showing antioxidant and vasodilator properties (Chegaev K. et al., 2009). Male Wistar rats were subjected to 60 minutes of bilateral renal ischemia, followed by 6 hours of reperfusion, as previously described (Collino M. et al., 2011). EDV (0,2 – 5 mg/kg, i.v.) and the EDV derivative containing NO-donor furoxan moiety (NO-EDV, 0-1 – 2 mg/kg) were administered at the beginning of the reperfusion (Figure 1). Serum and urinary indicators of renal injury and dysfunction were measured, specifically serum creatinine, serum urea, creatinine clearance, urine flow, and urinary N-acetyl-β-D-glucosaminidase (NAG). Administration of either EDV or NO-EDV significantly attenuated all markers of renal injury and dysfunction caused by I/R in a dose-dependent manner. Most notably, NO-EDV exerted protective effects at lower doses than is required for EDV, being more active than the lead. The potential beneficial effect of NO release by NO-EDV was investigated by evaluating its ability to affect selective expression/activity of NO synthase (NOS) isoforms and to activate NO-dependent signalling pathway, including important signal for cell survival such as members of the phosphoinositide 3-kinase signal transduction enzyme family and MAPK. Overall, we document here for the first time that the NO-donor moiety significantly contributes to the protection against renal I/R injury afforded by EDV treatment in the rat. These results suggest that new NO-donor EDV co-drugs are worthy of additional study as innovative pharmacological tools in the treatment of complex vascular disorders, whose onset and progression involve oxidative stress and decreased NO availability.

Figure 1



Edaravone
(5-methyl-2-phenyl-2,4-dihydro-3H-pyrazol-3-one)



NO-donor Edaravone
(3-{[4-(3-methyl-5-oxo-4,5-dihydro-1H-pyrazol-1-yl)phenoxy]methyl}-furoxan-3-carboxamide)

Feng S. et al., (2011) *Cochrane Database Syst Rev*. (12):CD007230.
Luque Contreras D. et al., (2006) *Pharmacol Ther.* 112, 553-63.
Chegaev K. (2009) *J Med Chem.* 52, 574-8.
Collino M. (2011) *Free Radic Biol Med.* 50, 345-53.