THE HYDROGEN SULFIDE-RELEASING DERIVATIVE OF DICLOFENAC DISPLAYS CARDIOPROTECTION IN ISCHEMIC REPERFUSED RABBIT HEART

Rossoni Giuseppe [a], Sparatore Anna [b], Moore Philip K. [c], Manfredi Barbara [a], Tazzari Valerio [d], Del Soldato Piero [d], Berti Ferruccio [a]

[a] Departement of Pharmacology, Chemotherapy and Medical Toxicology, University of Milan, Italy; [b] Institute of Medicinal Chemistry, University of Milan, Italy; [c] Department of Pharmacology, National University of Singapore, Singapore; [d] CTG Pharma, Milan, Italy

Evidence is accumulating that hydrogen sulfide (H_2S), like nitric oxide (NO) and carbon monoxide, is an endogenous gaseous mediator in the multilevel regulation of physiologic and pathologic functions in mammalian cardiovascular tissues. This study investigated the pharmacological activity of novel H_2S-releasing derivative of diclofenac (S-diclofenac; 2-[(2,6-dichlorophenyl)amino]benzeneacetic acid 4-(3H-1,2-dithiole-3-thione-5-yl)-phenyl ester) (1, 2) in the isolated rabbit heart submitted to low-flow ischemia-reperfusion damage.
S-diclofenac (from 3 to 30 µM), in spite of inhibiting prostacyclin generation by cardiac tissues (-80% at 30 µM; $P < 0.001$ *vs* controls), achieved dose-dependent normalisation of coronary perfusion pressure, whit a reduction of left ventricular contracture during ischemia and remarkable improvement of left ventricular developed pressure at reperfusion. These events were paralleled by a significant reduction of both creatine kinase and lactate dehydrogenase activities (-79%, $P < 0.001$ and -74%, $P < 0.001$ *vs* controls, at 30 µM) in heart perfusates during reperfusion. S-diclofenac's cardioprotective effects were accompanied by substantial release of reduced glutathione (GSH) in the heart perfusates, indicating that the H_2S moiety of S-diclofenac may have up-regulated cysteine transport. The anti-ischemic activity of S-diclofenac and the H_2S-donor sodium hydrosulfide (NaHS) were prevented by the K_{ATP} channel antagonist glibenclamide (100 µM), suggesting a mechanism similar to that involved in H_2S-induced cardioprotection in metabolic ischemic preconditioning. Perfusion of the heart with the NO synthase inhibitor N^G-monomethyl-L-arginine, 10 µM, worsened the myocardial ischemia-reperfusion damage, but this was dose-dependently prevented by both S-diclofenac and NaHS, suggesting an interaction between NO and H_2S.
This study indicates that S-diclofenac has marked anti-ischemic activity in reperfused ischemic rabbit hearts in spite of prostaglandin generation, and GSH-increased formation, i.e. meaning activation of K_{ATP} channels may have contributed to the effect. The favorable pharmacological profile of S-diclofenac, and its documented anti-inflammatory activity with less gastrointestinal side effects, open the way to therapeutic applications in a broad range of cardiovascular diseases.

1) Sparatore A. and Del Soldato P. Patent No. WO 2006111791
2) Li L., Rossoni G., Sparatore A., Lee L.C., Del Soldato P. and Moore P.K. (2007) Free Radic Biol Med 42: 706-719.