The nephroprotective potential of trimetazidine in chronic inflammation and oxidative stress in renal disease

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Abstract

The available studies provide an apparent compilation of diverse and solid research evidence on the possible nephroprotective role of trimetazidine. However, large, randomized, placebo-controlled, preferably multicentre studies are necessary to confirm this hypothesis in non-dialyzed, chronic renal failure and haemodialyzed patients. The extent of the challenge would also be related to specific molecular parameters chosen to demonstrate nephroprotection in the case of trimetazidine.

Key words: trimetazidine (TMZ), oxidative stress, renal disease, nephroprotection.

Although the scope of current research evidence on nephroprotective properties of trimetazidine is quite limited, the accumulated data appear to support nephroprotective action of trimetazidine, mainly in particular settings of diverse experimental models of acute renal failure, ischaemia and reperfusion injury and angiography contrast-induced nephropathy.

The biochemical evidence indicates that trimetazidine (1-[2,3,4-trimethoxybenzyl] piperazine dihydrochloride) binds to two characterized subtypes of receptors on both the inner and outer mitochondrial membrane [1] and appears to preserve mitochondrial permeability elicited by Ca^{2+} overload due to the reaction initialized by reactive oxygen species (ROS) [2]. Under certain, unfavourable circumstances conventional coronarography may be associated with contrast-induced, ROS-mediated nephropathy. Recent findings have demonstrated the lack of effect of trimetazidine, an anti-ischaemic agent, on serum total antioxidant capacity; however some beneficial effects of trimetazidine on the reduction of contrast-induced nephropathy incidence were noted on a preliminary basis [3]. Also, trimetazidine was quite recently demonstrated to enhance the expression of hypoxia-inducible factor-1 and decrease ischaemia-reperfusion injury in an animal model of acute renal failure (ARF) [4]. Additionally, trimetazidine pretreatment at 5 mg/kg *i.v.* appeared to reduce tubulointerstitial fibrosis and accelerate tubular repair due to increased expression of stathmin [4].

The therapeutic potential of trimetazidine and trimetazidine related renoprotection in ischaemia-reperfusion injury is still being debated. Most of the evidence of an *in vivo* antioxidant effect of trimetazidine comes from ischaemia/reperfusion (I/R) injury models [5]. Some studies implied the effective protection of trimetazidine against dephosphorylative degradation of nucleotides in an animal model of ischaemia reperfusion injury [6]. Animal models of ischaemia/reperfusion injury showed restoration of depleted kidney

activities of glutathione reductase, catalase and superoxide dismutase in parallel with effects of preservation of renal function due to trimetazidine pretreatment [7]. The molecular and redox abnormalities underlying ischaemia-reperfusion injury were apparently linked with the probability of acute rejection and complications in attaining full functionality of grafted renal tissue. This was attributed to the injury originating at the mitochondrial level and protection of mitochondrial function was postulated as the crucial resource to limit I/R injury [8]. Trimetazidine supplementation in preservation fluids was related to decreased inflammatory cell infiltration and decreased vascular cell adhesion molecule-1 (VCAM-1) expression in autotransplanted pig kidneys [9]. Relatively large doses of trimetazidine (3 mg/kg, *i.p.*) reportedly markedly decreased acute proximal tubular necrosis due to ferric nitrilotriacetate induced oxidative damage in rodents. These properties of trimetazidine were attributed to its effect on activities of renal glutathione reductase, catalase, superoxide dismutase and end products of lipid peroxidation [10]. Furthermore, the functionality of transplanted kidneys in animal models was improved with trimetazidine supplemented solutions and some evidence seemed to correlate these actions with decreased interstitial fibrosis and lowered CD4 and CD8 positive immune cellularity [11]. Appropriate clinical trials with trimetazidine in large cohorts of patients in diverse stages of chronic renal failure and those treated with haemodialysis are still pending. A few existing human studies in haemodialyzed (HD) patients appear to provide some confidence in the safety of trimetazidine in HD patients and a decrease of the lipid peroxidation parameter, as in the case of malondialdehyde, over a several-month observation period [12].

The apparent rationale for trimetazidine application in chronic renal failure patients is not only related to its hypothetical renoprotective properties. Chronic renal failure is indeed associated with increased cardiovascular risk [13], and risk of sudden death in patients with chronic renal failure increases along with the extent of renal failure, reaching nearly 50% of all deaths in patients on maintenance HD [14, 15]. Increased cardiovascular risk was demonstrated as the glomerular filtration decreased below 75 ml/min and each decrease of 10 ml/min correlated with a 10% increase in the rate of sudden cardiovascular incidents [16]. Therefore, the anti-ischaemic properties of trimetazidine may be as desired as its anti-inflammatory and anti-oxidative potential in patients with chronic renal failure [17, 18].

The review of existing evidence provides an apparent compilation of diverse and solid research evidence on the possible nephroprotective role of trimetazidine; however, placebo-controlled, well-designed studies are required to verify this hypothesis in non-dialyzed, chronic renal failure and HD patients. The extent of the challenge would also be related to specific molecular parameters chosen to demonstrate nephroprotection in the case of trimetazidine [18].

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