



## Commentary

## High Dose Meclizine Prevents Renal Ischemia–Reperfusion Injury in Healthy Male Mice

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In this issue of *EBioMedicine*, Kishi et al. report on their intriguing finding that pre-treatment with meclizine prevents renal ischemia–reperfusion injury in male mice (Kishi et al. 2015). Furthermore, they provide a potential mode of action of this reno-protective intervention: intracellular accumulation of phosphoethanolamine, which in turn activates glycolysis and attenuates mitochondrial oxidative phosphorylation. These metabolic changes are associated with reduced ROS formation and reperfusion injury with secondary effects on IR-related inflammation and subsequent collateral damage. The authors must be congratulated for this timely contribution in this field, which stands in a long tradition from this group in their quest for new therapeutic options to prevent renal injury (Bonventre and Weinberg 1992). Ischemia–reperfusion injury is an important determinant of the clinical success of renal transplantation—it is likely involved in the pathogenesis of contrast nephropathy and plays an important role in renal injury due to shock as occurs in sepsis, or major (cardiovascular) surgery. Therefore, prevention of renal ischemia–reperfusion injury with a clinically safe and effective intervention is expected to have a significant impact on health care and survival (CHERTOW et al., 2005). In that regard, the translation of the reported therapeutic action of meclizine from mice to men seems (at least theoretically) rather straightforward since this drug is available as an over the counter drug both in Europe and the US as tablets of 12.5 mg to prevent motion sickness. A typical dose in humans is 25 mg in adults and in children this dose is reduced (12.5 mg in children > 6 years and 6.25 mg in children 3–6 years).

However, this is not the first intervention in animals that claims to prevent ischemia–reperfusion injury in the kidney or other vital organs such as brain and heart. Other successful interventions in animal models include ischemic conditioning (protective effect of short bouts of non-injurious ischemia and reperfusion of target or remote organ (WEVER et al. 2012a)), diannexin, metformin, dipyridamole, erythropoietin, adenosine, statins, cyclosporine and many others. This list includes drugs that are easily available by prescription or are not difficult to apply (remote ischemic conditioning). Nevertheless, evidence-based clinical management to prevent renal injury is still limited to optimization of organ perfusion and prevention of exposure to drugs that are toxic to the hypo-perfused kidney (i.e. aminoglycosides, NSAIDs and inhibitors of the renin-angiotensin-aldosterone system) because clinical

trials exploring other strategies to prevent ischemia–reperfusion injury are not conclusive or negative (Zuk and Bonventre 2015, EL MESSAOUDI et al. 2015b, EL MESSAOUDI et al. 2015a, ROSS et al. 2005). Thus, the conclusion is justified that, at least up to now, strategies that prevent ischemia–reperfusion injury in pre-clinical models are stuck in translation to the clinic (RONGEN and WEVER 2015).

What is the reason for these disappointments in the clinical development of promising pre-clinical interventions to prevent ischemia–reperfusion injury? First, as reviewed recently, pre-clinical studies in the field of ischemia–reperfusion often have serious methodological flaws, resulting in potential serious bias of results (RONGEN and WEVER 2015). In that regard, we should however compliment Kishi et al. for their accurate report of their methodology and findings: some important basic methodological essentials were addressed such as drop-outs, randomization and blinding. However, there is still some doubt: although most essential experimental conditions were well monitored, blood pressure and/or renal perfusion was not measured throughout the experiments. Differences in blood pressure (and therefore renal perfusion) between meclizine treated and control animals could theoretically have confounded the results, in particular when these differences occurred during reperfusion.

Assuming that the claimed effect of meclizine in male mice on renal ischemia–reperfusion injury is real, there are still a couple of uncertainties that hinder translation to humans. The observation might be species and/or gender specific (WEVER et al. 2012b). Replication in larger mammals including both sexes is therefore warranted before doing an (expensive) clinical trial. More importantly, Kishi et al. applied a very high intraperitoneal dose of 100 mg/kg. Unfortunately, we are not informed about the achieved plasma levels of meclizine in these animals. Although the mice may have tolerated this high dose surprisingly well, we are not sure whether this exposure to meclizine can be replicated in humans without inducing serious and unacceptable adverse events such as coma, epileptic insults and hypotension, known adverse events of meclizine overdose in humans. To overcome this problem, we may need more specific inhibitors of phosphoethanolamine metabolism which should be fully evaluated both pre-clinically and in phases 1–3 clinical studies before they can be applied in practice. Another issue is the age and health status of the animals. The healthy and relatively young animals as used by Kishi et al. differ from the aged population of patients with co-morbidity and co-medication who are at particular risk for renal ischemia–reperfusion injury. Replication of findings in more representative animal models are essential for appropriate

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translation to the clinic. Finally, meclizine was tested in an optimized and highly standardized experimental design with respect to timing of the intervention and duration of ischemia and reperfusion. This differs from the clinical reality in which patients experience a variable duration and severity of renal hypoperfusion and often present after the ischemic event has already taken place.

In conclusion, Kishi et al. report an intriguing finding that accumulation of phosphoethanolamine prevents renal ischemia–reperfusion injury. Furthermore, they show that this form of metabolic renal protection may be involved in the renal benefits of a high dose of meclizine given prior to a standardized period of renal ischemia and reperfusion in healthy male mice. Although meclizine is an over the counter drug that should be easily available for trials in humans, many questions and uncertainties need to be solved to allow appropriate translation to humans.

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