Editorial

Can selective inhibitors of cyclic guanosine monophosphate (cGMP)-specific phosphadiesterase type 5 (PDE 5) offer protection against contrast induced nephropathy?

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Abstract: Parenchymal hypoxia within the renal outer medulla plays an important role in the pathogenesis of contrast induced nephropathy (CIN). Nitric oxide (NO) is crucial for medullary oxygenation by enhancing regional blood flow. Augmenting the effect of NO in the renal medulla by the use of selective inhibitors of cyclic guanosine monophosphate (cGMP)-specific phosphadiesterase type 5 (PDE 5) such as sildenafil (Viagra™), vardenafil (Levitra™) or tadalafil (Cialis™) could reduce the severity of the hypoxic insult induced by the contrast medium and reduce the risk of CIN. Prophylactic administration of one of these drugs particularly the long acting one tadalafil before and after the administration of CM could offer a simple and rational approach to reduce the risk of this complication. This hypothesis deserves serious investigation to determine its clinical efficacy.

Keywords: Selective inhibitors of cyclic guanosine monophosphate (cGMP)-specific phosphadiesterase type 5 (PDE 5); Viagra; contrast induced nephrotoxicity; prevention

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Contrast induced nephropathy (CIN) remains an important complication following interventional cardio-vascular procedures and can lead to an increase in patient's morbidity and even mortality (1-4). Several regimes were reported in the literature to reduce the risk of this complication (2,3). The current consensus advocates the provision of adequate hydration before and after contrast medium (CM) administration and using the lowest possible dose of the contrast agent that offers the essential diagnostic information (1). The use of drugs whether renal vasodilators, antioxidants or inhibitors of endogenous mediators such as endothelin or adenosine to prevent CIN has not offered consistent success (2,3). The failure of pharmacological manipulation to prevent CIN is partly due to incomplete understanding of the pathophysiology of this condition (4,5). However, it is widely acknowledged that the vulnerable region of the outer renal medulla is where most of the CM induced damage occurs as this region of the kidney normally exists in a state verging on hypoxia (5-8). The low medullary oxygenation is caused by intense tubular transport activity in the medullary thick ascending limb of loop's of Henle (mTALs) in a region with limited blood supply (5-7). The medullary blood and oxygen supply is delivered through peritubular capillaries which depends on limited blood flow through vasa recta that emerge from juxta-medullary nephrons (8). Nitric oxide (NO) is an important endogenous vasodilator that is involved in enhancing the blood flow in the renal medulla (9). The passage of CM through the kidney is associated with an increase in the metabolic activity of the outer renal medulla and medullary vasodilatory response mediated by the release of prostanoids and NO. The interference of the CM with the reabsorption of sodium and water in the proximal renal tubules leads to diuresis and natriuresis precipitating increases in the active uptake of sodium in the medullary thick ascending limb of loop's of Henle (mTALs) and increase in oxygen consumption (4-7). Decline in NO availability would intensify the hypoxic insult and contribute to the development of CIN (6,7). Clinical experiences with

drugs that induce global renal vasodilation demonstrated ineffective protection against CIN (2-4). These drugs cause an increase in renal perfusion predominantly in the cortex causing a shunting of the blood away from the vulnerable renal medulla exacerbating the hypoxic insult induced by CM in this region (2-4). Thus, it is important for the prevention of CIN is using a drug that induces predominantly medullary renal vasodilation. Drugs currently used for treatment of erectile dysfunction by enhancing the vasodilatory effect of released NO could offer protection against CIN by sustaining the vasodilatory effect of released NO in the renal medulla. These drugs act by selective inhibition of the enzyme cyclic guanosine monophosphate (cGMP)-specific phosphadiesterase type 5 (PDE 5), that metabolise cGMP the principal mediator of NO induced smooth-muscle relaxation and vasodilatation (9-13). These drugs include sildenafil citrate (Viagra™), vardenafil (Levitra™), and tadalafil (Cialis™) all work by inhibiting PDE5 (9-13). Tadalafil's has the advantage of longer half-life (17.50 hours) compared to sildenafil and vardenafil (both 4.0-5.0 hours) resulting in longer duration of action (13,14). Clinical experience with these drugs indicates that they are safe with only mild adverse reactions (12).

The author of this commentary proposes that a well structured clinical study to investigate the potential of PDE 5 inhibitors in prevention of CIN should be explored. The long acting tadalafil might be more appropriate and can be given orally (10 mg) couple of hours before CM administration and the dose to be repeated for two consecutive days after the procedure. Tadalafil is absorbed rapidly after oral administration with maximum concentration observed at 2 hours (12). Adequate hydration regime should also be provided before and after the CM administration.

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