Phosphodiesterase-5 inhibitors: Emerging nephroprotective drugs

Radiocontrast agents are the third most common cause of acute kidney injury (AKI) among hospitalized patients, accounting for approximately 12% of cases (1). Contrast induced nephropathy (CIN) is associated with prolonged hospital stay and increased risk of cardiovascular events; it represents an independent predictor of short and long term mortality (2). The mechanisms underlying CIN are not fully known; however, it involves: direct cellular toxic effect; increased perivascular hydrostatic pressure, high viscosity, changes in the balance of vasoactive substances such as nitric oxide (NO) and endothelin-1 (ET-1), which contribute to reduction of renal blood flow (RBF), particularly to the outer medulla, thus inducing ischemic damage and exaggerated production of reactive oxygen species (3). Despite intense research, there is still no effective therapeutic intervention to prevent CIN, except through oral and intravenous hydration prior, during and post exposure to radiocontrast agents (4, 5).

Based on the postulated pathogenesis of CIN, any promising therapeutic target should include reversal of the impaired RBF characterizing this clinical setting, via promotion of vasodilation. One of the potent vasodilators is NO, which acts via the soluble guanylate cyclase/cGMP system to induce vascular smooth muscle cell relaxation. Phosphodiesterase-5 (PDE5) inhibitors have a similar effect due to their ability to inhibit the breakdown of cGMP, the second messenger of NO and natriuretic peptides (NPs) (6). Although originally developed for the treatment of angina pectoris and subsequently for erectile dysfunction and pulmonary hypertension (7), there is increasing evidence that these agents possess nephroprotective effects in a setting of renal injury too. Specifically, few studies have demonstrated that PDE5 inhibitors exert renal beneficial effects in an ischemia reperfusion (I/R) rat model (8, 9), and post-cardiopulmonary bypass AKI in swine (10). In addition, we have demonstrated that tadalafil, a PDE5 inhibitor, reduces the sensitive biomarkers of AKI, namely NGAL and KIM-1, in I/R setting, which can be attributed to the anti-oxidant activity of these drugs. Özbek et al. (11) demonstrated support for this motion in an article of the *Anatolian Journal of Cardiology* entitled "The protective effect of single dose tadalafil in contrast-induced nephropathy: An experimental study," in this issue published. Where the authors examined the efficacy of tadalafil in reducing the severity of experimental CIN. For this purpose, the authors compared the renal toxic and oxidative impact of single inject of contrast media (meglumine diatrozoate, 6 mL/kg) to 48-h dehydrated rats in the presence or absence of tadalafil (10 mg/kg). Dehydrated rats that did not receive contrast media or tadalafil served as the control group. The animals were sacrificed after 48 h from the time of radiocontrast media administration, and their blood and kidneys were sampled biochemical and histological analysis, respectively. As expected, injection of contrast media resulted in AKI, as was evident by elevated levels of serum creatinine (SCr), blood urea nitrogen (BUN), serum cystatin C (Scys), and serum and renal malondialdehyde (MDA), as compared with the control group. Interestingly, treatment with tadalafil largely prevented adverse renal effects of radiocontrast as expressed by significantly lower levels of SCr, BUN, Scys, and circulatory and tissue MDA content as compared with the group that was given only contrast. Despite the beneficial effects of tadalafil, none of these parameters returned to baseline values. These results demonstrate the protective effect of tadalafil in the prevention of CIN in rats. Although this is an interesting and timely study, it has a few limitations. The blood and tissue samples were collected after 48 h from the time of radiocontrast media administration; this is a critical issue because levels of SCr are known to reach peak values 48-72 h after contrast-induced kidney injury and do not reach normal levels for up to 10 days. Likewise, changes in kidney function and renal hemodynamic parameters, such as GFR and RBF, are more accurate than levels if SCr, BUN, and Scys, which are influenced by hydration status. In addition, histopathological changes in the tissue might have been observed if the study was longer or immunocytochemistry for inflammatory markers or staining for markers of apoptosis were performed. The second limitation of this study was the absence of 24-h urine analysis. Metabolic cages are generally used for 24-h urine collection from rats and allow the calculation of creatinine clearance test. Finally, determination of the effect of tadalafil on urinary and plasma neutrophil gelatinase-associated lipocalin (NGAL) and kidney injury molecule-1 (KIM-1) levels would be more sensitive to detect kidney injury than levels of SCr, BUN, and Scys, which are all functional biomarkers. Despite these limitations, it seems that the nephroprotective effects of tadalafil are reliable and open a new window for the treatment of CIN. Indeed, an additional study that was published most recently supports this concept. Briefly, Lauver et al. (12) demonstrated that sildenafil (6 mg/kg) abolished the nephrotoxic effects of ioxilan (5 mg/kg IV) in New Zealand white rabbits, a species susceptible to developing CIN. Treatment with sildenafil was associated with lesser degree of histological injury, attenuation

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in SCr, and reduction in electrolyte derangement. Interestingly, the renal beneficial effects of sildenafil were observed only when the drug was given every 8h, for 48h (the duration of follow-up period). A single administration of sildenafil failed to exert such beneficial effect on kidney function and tissue integrity. These findings emphasize the importance of establishing the effective dosage of PDE5 inhibitor that should be administered. Moreover, carefully controlled large clinical studies are required before extrapolating the encouraging experimental findings to clinical indications. Additional issue that should the addressed is the mechanisms underlying the nephroprotective effects of PDE5 inhibitors. It is widely accepted that these agents exert their beneficial renal and cardiac effects via systemic and regional hemodynamics; however, since sildenafil significantly reduced necrosis and apoptosis of cultured myocytes exposed to ischemia and of renal cells, a direct effect independent of their vascular action may contribute to the nephroprotective effects of PDE5 inhibitors (12). Therefore, it seems that PDE5 inhibitors exert their beneficial effects via multiple mechanisms that involve both hemodynamic and molecular signaling pathways, including NO and cGMP and their downstream cascade. An important issue is whether PDE-5 inhibitors exert nephroprotective effects even when administered as post treatment in well-established CIN. In conclusion, although PDE5 inhibitors have an excellent safety record, they may provoke minor side effects such as dyspepsia, headache, and myalgia.

In conclusion, the encouraging results from animal studies suggest a possible role for PDE5 inhibitors in the treatment of clinical CIN.

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