“Fenoldopam Prophylaxis” Works in Impending Acute Renal Failure: Recruiting the non-hemodynamic properties of fenoldopam?
A Salahudeen

Citation

Abstract
Recent analysis suggests that the incidence of acute renal failure is on the rise(1). This is perhaps not surprising given the aging population and the complicated illness we treat. Moreover, recent data also suggests that acute renal failure may heighten the mortality of critical ill patients (2). The latter finding is strengthened by the experimental evidence showing that acute renal injury may even contribute to distant organ injury(3). Acute renal injury, particularly in the critical care setting, is also accompanied by prominent acute inflammatory reactions, supporting the argument that injury associated with acute renal injury may contribute to systemic inflammation and patient mortality(4).

Currently, there are few effective treatments to prevent or mitigate acute renal failure. In this regard, the new finding that fenoldopam may mitigate mild form of acute renal failure of great interest (5). Fenoldopam, unlike other dopaminergic agents, is a selective D1 receptor agonist that continues to have vasodilatory properties even at higher doses. Thus, unlike dopamine, fenoldopam does not cause vasoconstriction, and this renal vasodilatory pharmacology of fenoldopam makes it an attractive candidate for its use in the early stages of acute renal injury and oliguria (6). The resulting renal vasodilatation, and increase in renal blood flow and urine output may abort or mitigate the incipient renal failure. Consistent with this consideration is the experimental studies indicating the salutary role of fenoldopam in models of acute renal injury(7). Unlike animal studies however, an earlier randomized control study in patients with moderately severe acute renal failure did not demonstrate any significant lessening of renal failure or patient mortality(8). In contrast, however, a recent randomized controlled trial that employed fenoldopam in a prophylactic manner demonstrated a significant reduction in the rate of occurrence of acute renal failure(5). In this study, administration of a low dose fenoldopam to septic patients with serum creatinine of less than 1.70 mg/dL was associated with a significant reduction in the rate of rise of serum creatinine compared to saline infused control patients (29 patients in fenoldopam group vs. 51 patients in saline group; p = 0.006). But the frequency of severe acute renal failure or patient mortality did not differ between the groups (5). While the latter finding may be disappointing, it should not be surprising as any underlying injury mechanisms, if severe enough and sustained, will likely cause severe injury and functional failure. Likewise, if the disease process is severe enough and again sustained, it will continue to contribute the patient mortality.

The finding that fenoldopam if administered early enough may mitigate renal injury has clinical implications. The benefits may arise from salutary renal homodynamic effect and possibly from the less clinically recognized (and yet to be proven) beneficial effect of hemoxygenase-1 (HO-1) induction, i.e., the “HO-1 preconditioning effect”. Several experimental studies have indicated that dopaminergic compounds, including fenoldopam, have the capacity to induce HO-1(9,10). HO-1 is a well characterized 32 kD microsomal protein whose primary function is to catabolize heme. Breakdown of heme leads to generation of iron, carbon monoxide, and bilirubin. Iron release through ferritin induction and carbon monoxide through nitric oxide generation via cyclic GMP may protect against issue injury(11). Thus, the renal protection noted in the Italian study (5) could have been due to the fenoldopam-mediated homodynamic as well as HO-1 induction effects.
In this issue of the journal Aravindan et al. demonstrate that fenoldopam suppresses the activation of nuclear factor B and downregulates the expression of a series of proinflammatory cytokines([12]). This finding if confirmed raises the possibility that fenoldopam's protection in acute renal failure may even involve an anti-inflammatory mechanism. Thus, there are multiple theoretical reasons why “fenoldopam prophylaxis” may prove to be effective therapy in impending renal failure. Further studies of “fenoldopam prophylaxis” may be warranted in patients with high risk for acute renal failure.

References
Author Information

Abdulla K. Salahudeen, M.D.
Department of General Internal Medicine, Ambulatory Treatment and Emergency Care, The University of Texas M. D. Anderson Cancer Center