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Could Torasemide be a prophylactic agent of contrast induced acute kidney injury? A review about this field

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Abstract. – Contrast Induced Acute Kidney Injury (CI-AKI), due to the use of contrast media in radiographic procedures, is the leading cause of acute renal failure in hospitalized patients, and is associated with prolonged in-hospital stay and increased morbidity, mortality, and costs. However only peri-procedural hydration is now used universally as its preventive strategy. Some studies indicates that renin-angiotensin-aldosterone system (RAAS) is possibly responsible for the development of contrast-induced nephrotoxicity through mediating abnormalities of renal perfusion and other mechanisms. And torasemide, known as loop diuretics, could inhibit RAAS through its anti-aldosteronergic function. Therefore, speculation about torasemide's prevention of CI-AKI could be firmly made. Intravenously administrated torasemide would be promising as a future prophylactic agent, possibly in combination with other strategies such as adequate peri-procedural hydration and other renal protective agents, in the prevention of CI-AKI.

In this context, we review the background and the role of RAAS on the development of CI-AKI, and discuss the pharmacologic individuality of torasemide on RAAS and torasemide's preventive effect on CI-AKI.

Key Words:
Contrast medium, Contrast-induced nephropathy, Acute kidney injury (AKI), Torasemide, Renin-angiotensin-aldosterone system, Aldosterone antagonists.

Introduction

Contrast Induced Acute Kidney Injury (CI-AKI), also termed as Contrast Induced Nephropathy, is the leading cause of Acute Renal Failure (ARF) in hospitalized patients, accounting for > 10% of all causes of hospital-acquired renal failure[1]. A considerable fraction of this in-hospital development of ARF has been due to the use of contrast media in radiographic procedures, of which the most notorious is percutaneous coronary intervention (PCI)[2]. CI-AKI after PCI has multiple definitions in the medical literature, among which the most popularly used is that a relative elevation ≥ 25% in serum creatinine (SCr) or an absolute increase of 0.5 mg/dL (44.2 μmol/L), or a combination of the two, at 48-72 hours after exposure to a contrast agent compared to baseline SCr values, without alternative explanations for renal impairment[3,4].

The prevalence of CI-AKI ranges widely (2.0% to 15% or 3.3% to 10.5%) depending on the definition used[4,5], and also depending on the patient-and contrast agent-specific factors. These factors include advanced age, female gender, underweight, preexisting renal impairment, diabetes mellitus, anaemia, congestive heart failure and other coherent complications influencing renal functions, volume and characteristics (osmolality, inoicity and viscosity) of contrast accepted[2,3-6].

CI-AKI is associated with prolonged in-hospital stay and increased morbidity, mortality, and costs[2,8-10], especially for those with renal impairment. A retrospective analysis of 16,248 patients exposed to contrast agent showed that even apparently small decreases in renal function can increase the risk of developing severe nonrenal complications that lead to excessive mortality rates independent of other risk factors[9]. ARF following PCI occurs almost exclusively in patients with chronic kidney disease or left ventricular dysfunction. These risk factors are also among the most powerful predictors of long-term mortality and are likely to explain most of the association between postprocedural ARF and long-term mortality. Therefore, postprocedural ARF maintains a clinically significant impact on mortality that must be taken into account for benefit vs. risk evaluation of PCI in individual patients[11].

Although various studies have been focused on the preventive strategies of CI-AKI, including

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adequate peri-procedural hydration with normal saline, use of N-acetylcysteine, keeping the volume of contrast media as low as feasible, and avoiding high-osmolal ionic contrast media[12], only peri-procedural hydration is accepted and used universally. Therefore, more efficient and cost-effective strategies should be explored as urgent demands.

Role of RAAS in the Development of CI-AKI

Although the pathogenesis of CI-AKI is not well understood, evidence times and again shows that it happens as a combination of direct nephrotoxicity, oxidative stress, ischemic injury, renal tubular obstruction and intra-renal vasoconstriction and probably later inflammation[12-14]. And in the development of CI-AKI are changes in renal hemodynamics due to the effects of contrast media on the action of many substances,such as an activated RAAS, increased endothelin, and reactive oxygen species (ROS)[15-17]. Renin, angiotensin, and endothelin-1 are some of the potential mediators leading to intra-renal vasoconstriction in experimental models of CI-AKI[16,17].

Larson et al[18] have successfully induced acute renal failure in animal models by administration of a contrast media bolus, and they found that sodium depletion accentuated both the magnitude and duration of the vasoconstrictive phase of the renal blood flow response to injection of contrast medium and blockade of the intrarenal renin-angiotensin system (RAS) shortened the duration of this response. And there is evidence that iodixanol, a nonionic, dimeric contrast media, causes increased oxidative stress and decreased NO production in outer medullary descending vasa recta (DVR), with consequent constriction of DVR and increased reactivity to angiotensin II[19]. Activation of RAS could also cause vasoconstriction of the efferent glomerular arteriole while at the same time increasing the ex novo synthesis of vasodilator prostaglandins resulting in almost stable or slightly increased intrarenal resistance. An angiotensin II-induced contraction of the magnitude, observed by Sendeski et al[20], might further aggravate, or halt most of the medullary perfusion, when superimposed on vessels that are already constricted by contrast media.

There are convincing data that renin-angiotensin-aldosterone system (RAAS) is a major mediator of renal injury. RAS, especially angiotensin II, contributes to kidney injury through the angiotensin II type 1 receptor, transforming growth factor-beta (TGF-β) receptor, Smad and epidermal growth factor receptor (EGF) by affecting general angiostasis and vascular remodeling, indirectly modulating inflammation and cell reactions[21], and its proinflammatory action can lead to upregulation of chemokines, adhesion molecules, and other fibrogenic growth factors that culminate in a decline of renal function[22]. What's more, in acohort of critically ill white patients, the angiotensin converting enzyme (ACE) insertion genotype (ACE II) is identified as a valuable risk factor in the development and outcome of AKI[23], CI-AKI included. Apart from these, aldosterone, a steroid hormone, has been reported to be involved in renal injuries, including renal inflammation, oxidative stress, fibrosis, mesangial cell proliferation, and podocyte injury in various animal models, through the activation of mineralocorticoid receptor (MR)[24-29].

From above all, RAAS is possibly responsible for the development of contrast- induced nephrotoxicity through mediating abnormalities of renal perfusion[15,30]. Theoretically, RAAS as endocrine factors can be inhibited by ACE inhibitors (ACEIs), angiotensin II receptor blockers,and MR antagonists[15,31]. Evidences have shown that RAAS blockers have a potentially protective effect on renal function of patients undergoing PCI. Using a large prospectively collected database of 7, 230 patients undergoing a coronary intervention, ACEIs were found retrospectively to decrease the risk of CI-AKI by 39% in patients with GFR < 60 ml/min[32]. Caldicott et al[33] showed that renal vasoconstriction occurs after CM administration, and the renin-angiotensin system is responsible for this vasoconstriction. ACEIs preferentially dilate the efferent arteriole and, therefore, increase the renal medullary plasma flow by diminishing the filtration fraction. It is conceivable that ACEIs could mitigate a decrease in the reduction of medullary blood flow induced by the contrast agent. Inhibition of angiotensin II prevents vasoconstriction and generation of ROS and increases the synthesis and bioactivity of nitric oxide (NO)[34]. And treatment with MR antagonists (eplerenone) ameliorated interstitial fibrosis, tubular atrophy and inflammation, and reversed changes in peroxisome proliferator-activated receptor-gamma (PPAR-γ) expression and TGF-beta/Smad signaling[35]. Put all of the above together, it is convincing that RAAS blocking could mitigate acute renal injury after contrast agent administration.

Pharmacologic Individuality of Torasemide on RAAS

Torasemide belongs to the group of medicines known as loop diuretics. Loop diuretics can reduce oxygen demand in the medullary thick ascending loop of Henle by inhibiting the $Na^+/K^+/Cl^-$ pump on the luminal cell membrane surface. Thus, timely administration of loop diuretics might attenuate renal injury and reduce the severity of ARF. Similarly, loop diuretics may have additional benefit in patients with ARF by increasing urine output and thereby facilitating fluid, acid-base and potassium control[36].

However,torasemide (LUPRAC) shows not only an effective loop diuretic action but also a potassium sparing action due to its anti-aldosteronergic effect, and the diuretic profile of torasemide was equal to that of the concomitant use of furosemide and an anti-aldosteronergic drug, spironolactone[37]. A randomized, open-label, crossover study has shown that the plasma norepinephrine level was increased after azosemide treatment but remained unchanged after torasemide treatment, and that the plasma level of aldosterone was significantly decreased after torasemide treatment[38]. Animal experiments found that torasemide inhibited the binding of aldosterone to its receptor in the cytoplasmic fraction of rat kidney in a dose-dependent manner, while furosemide produced no effect. Moreover, torasemide also inhibited vasoconstriction induced by thromboxane A_2 in isolated canine coronary artery[39,40]. In sum, as pharmacologic individuality, torasemide could inhibit RAAS through its anti-aldosteronergic function.

Torasemide's Prevention on CI-AKI

Based on these observations and experiments that RAAS is possibly responsible for the development of CI-AKI through mediating abnormalities of renal perfusion and other mechanisms, and that torasemide could inhibit RAAS through its anti-aldosteronergic function, speculation about torasemide's prevention of CI-AKI could be firmly made.

What's more, *in vitro* both human endothelial and renal epithelial cells responded to torasemide with enhanced secretion of the vasodilator prostaglandin prostacyclin (PGI2)[41]. And torasemide could decrease the activity of prostaglandins degradative enzymes which are present in both the cortex and medulla, leading to increased plasma level of PGE2 and PGI2, as a result intra-renal vascular dilation might happen and renal blood flow might be improved, researches have showed prostaglandin-based renal protection against CI-AKI[42].

In the aging era, with the prevalence of coronary heart disease, more and more diagnostic and interventional procedures should be performed through contrast agent administration, so attentions should be paid to CI-AKI as one of the main drawbacks and limitations of PCI. And our speculation may provide an efficient, feasible, and cost-effective strategy for the prevention of CI-AKI. Intravenously administering torasemide would be promising as a future prophylactic agent, possibly in combination with other strategies such as adequate periprocedural hydration and other renal protective agents, in the prevention of CI-AKI.

Unfortunately some reports have implicated that ACEIs were nephrotoxic[43] and exacerbated renal failure with CI-AKI, especially for patients with pre-existing renal impairment[32] and the olderly[44]. Accordingly large, randomized, controlled trials of high quality, are urgently needed to deeply investigate torasemide's preventive effect on CI-AKI.

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Conflict of Interest

None.

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