Pharmacologic Prophylaxis for Contrast-Induced Acute Kidney Injury

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KEYWORDS

• Contrast-induced nephropathy • Statins • N-acetylcysteine • Ascorbic acid

KEY POINTS

- Contrast-induced acute kidney injury (CI-AKI) is a known complication of angiographic procedures and exerts a negative prognostic impact in the short and long term.
- There is no single specific drug to treat the disease once it has developed.
- Several pharmacologic preventive strategies have been evaluated.
- Various clinical studies show a possible efficacy of certain pharmacologic agents on CI-AKI prevention in addition to the routine recommended preventive measures (ie, hydration and controlled volume of injected contrast medium).
- The evidence that CI-AKI prevention (using specific drugs) results in improved clinical outcome is limited.

INTRODUCTION

Contrast-induced acute kidney injury (CI-AKI) represents a known complication of angiographic procedures and is currently one of the most widely debated topics in cardiovascular medicine. It is associated with a significant increase in morbidity, mortality, prolonged hospital stay, and increased costs.[1] The prognostic impact of CI-AKI depends on the degree of kidney injury and the persistence of renal function deterioration over time.[2,3]

The pathophysiological mechanisms that contribute to the development of CI-AKI are multiple and not yet completely understood. However, alterations in renal hemodynamics, which lead to hypoxia of the renal medulla, and direct toxic effects of contrast media on renal tubular cells are recognized as the primary mechanisms in the pathogenesis of CI-AKI. These effects are amplified by preexisting chronic kidney disease and/or contrast-related inflammatory processes and oxidative stress causing further damage.[1]

Drugs Studied for CI-AKI Prevention

In the effort to prevent CI-AKI, several pharmacologic protocols have been tested that take advantage of their single or combined antioxidant, antiinflammatory, antiapoptotic, and renal vasoactive effects.[4] **Box 1** is a list of the principal pharmacologic agents tested for such prevention.[4–16]

To date, the results of most clinical studies and meta-analyses on the various drugs present inconclusive evidence regarding efficacy. There are issues of study bias and poor methodology in several analyses.[15] In addition, comparison of the various studies is often difficult because of the heterogeneity of designs and methods (**Box 2**). Therefore, no pharmacologic agent has been specifically recommended for prevention of CI-AKI in current guidelines.[4,16–18] The principal

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Box 1
Principal drugs tested for CI-AKI prevention

Fenoldopam
Dopamine
Calcium channel blockers
Atrial natriuretic peptide
L-Arginine
Prostaglandin E_1
Furosemide
Mannitol
Endothelin receptor antagonist
Prostacyclin I_2 analog (Iloprost)
Prednisone
Bicarbonate or citrate
Theophylline or aminophylline
NAC
Ascorbic acid
Statins

Data from Refs.[4–16]

prerequisites for use of any specific pharmacologic agent in the prophylaxis of CI-AKI are listed in **Box 3**.

This article focuses on the three most studied agents: statins, N-acetylcysteine (NAC), and ascorbic acid. Particular attention is paid to evidence regarding the impact of these drugs on (1) the prevention of CI-AKI and (2) adverse clinical events (cardiovascular and renal).

The possible pathophysiological mechanisms involved in the nephroprotective effect of these specific agents are shown in **Table 1**.

This article does not include sodium bicarbonate because the method of administration comports infusion of a solution with independent preventive effect due to intravascular volume expansion. See the article by Solomon and colleagues elsewhere in this issue for further discussion.

Box 2
Elements of heterogeneity among studies

Size of population
Diverse clinical settings
Different dose regimens
Time and duration of drug administration
Concomitant preventive measures
Type and dose of contrast medium
Different criteria used for CI-AKI definition
Scarcity of data relative to clinically relevant endpoints

Box 3
Characteristics of the ideal drug for CI-AKI prevention

Efficacy
  Especially in high-risk patients
  In addition to recommended preventive measures
Safety
Rapidity of action
Acute nephroprotection must result in improved clinical outcome
No negative pharmacologic interaction
Low cost

STATINS

Do Statins Reduce CI-AKI Occurrence?

In recent years, interest has grown in the possible beneficial effects of treatment with statins in the prevention of CI-AKI given their known multiple lipid-mediated and non–lipid-mediated (pleiotropic) effects with potential nephroprotective actions (see **Table 1**).[19]

Chronic statin treatment and CI-AKI occurrence

In 2005, Khanal and colleagues[20] first reported a retrospective study on a large cohort (28,871 subjects) showing evidence that chronic statin treatment before percutaneous coronary intervention (PCI) resulted in significantly lower incidence of CI-AKI (8.8% vs 11.9%, $P = .03$). Subsequent observational studies suggested a possible renoprotective effect of statin pretreatment (**Table 2**).[20–26] The largest meta-analysis of seven nonrandomized studies (31,959 subjects) by Pappy and colleagues[27] showed a nearly significant benefit associated with chronic statin treatment (odds ratio [OR] = 0.60, 95% CI 0.36–1.00, $P = .05$), albeit with significant heterogeneity among the studies (I^2 *index* 88%, $P<.0001$).

High-dose statin pretreatment and CI-AKI prevention

The first randomized controlled trials (RCTs) evaluating the possible beneficial effect of lipophilic statins (simvastatin and atorvastatin) as a preventive strategy for CI-AKI in coronary subjects produced conflicting results (**Table 3**).[28–34] Several factors might explain the discrepancies between