Preventing the Harm of a Closer Look: Contrasted-induced Nephropathy in Adults

Martina C. Holder, PharmD; Daniel A. Lewis, PharmD, BCPS; P. Shane Winstead, PharmD

Abstract: Contrast media is administered to many patients in hospitals nationwide. Although the use of contrast and dyes is widespread and has a well accepted use among the medical profession, contrast-induced nephropathy can be a common and potentially harmful complication. Identifying patients at risk, attempting to minimize risk, and using preventative strategies should be priorities to decrease the harmful effects that are associated with the administration of contrast media. This article provides a general overview of contrast-induced nephropathy and a brief review of the risk factors and prophylactic treatment.

DEFINITION AND PATHOPHYSIOLOGY

A clear outcome exists of risk associated with contrast-induced nephropathy, yet strictly defining it is more difficult. Many studies have looked at the associations with iodinated radiocontrast, yet the markers of nephropathy are often variable; therefore, incidences reported in the literature differ based on the definition used. The most commonly accepted definition of contrast-induced nephropathy is an increase in serum creatinine concentration by \(0.5\) mg/dL (44 µmol/L), or a 25% increase above baseline in the resulting 48-72 hours postinfusion of intravenous or intra-arterial contrast media.\(^{1-7}\)

The mechanism of contrast-induced nephropathy is not completely understood, but a consensus exists that the phenomenon is multifactorial.\(^8\)

Original compounds were highly ionic and had a characteristic high osmolality. Newer agents have a lower osmolality and often are nonionic, which has resulted in a decreased risk of contrast-induced nephropathy over the original compounds used; however, they still carry the risk of contrast-induced nephropathy.

In general, high osmolar agents should be avoided given the added risk for contrast-induced nephropathy. The current literature describes elements of vasoconstriction, subsequent lack of vasodilation, and direct toxicity as reasonable explanations for observed renal injury in contrast-induced nephropathy.\(^9,10\) Multiple animal studies have shown a rapid, prolonged decline in renal blood flow after the administration of contrast secondary to vasoconstriction.\(^9,10\) It has been proposed that blood flow decreases by 40% and subsequent hypoxia occurs in the outer medulla.\(^9\)

Ribeiro et al\(^10\) investigated the association of osmolality and nitric oxide production and dem-
onstrated a proportionate decrease in nitric oxide production with an increase in osmolality in an in vitro model. This could account for a decline in autoregulation of vasodilatation in the kidney resulting in prolonged vasoconstriction. However, this theory has not been proven in a human model, and a study by Sancak et al\(^1\) was unable to demonstrate a significant decline in nitric oxide metabolites in a small group of patients receiving contrast media.

Others have sought explanation with an increase in reactive oxygen species due to hypoperfusion and resultant hypoxia. Many investigations have shown an increase in reactive oxygen species, making it a likely culprit; however, Elias et al\(^2\) reported that no significant changes existed in antioxidant compounds between a treatment group and a control with no contrast group.

Due to the osmotic nature of contrast agents, an expected diuresis occurs after administration. Insult with highly osmolar substances leads to osmotic nephrosis and subsequent vacuolization, and it has been suggested to cause an element of acute uric acid nephropathy.\(^3\) Highly osmolar media may increase viscosity and decrease the deformability of erythrocytes, decreasing blood flow through capillaries and the renal tubule.\(^3\)

Furthermore, it is likely that a direct toxicity exists to the tubular cells, which could be explained by hypoxia due to other mechanisms, but also has a direct effect. Contrast-induced nephropathy remains poorly understood, but many promising mechanisms have been proposed.\(^8\)

**RISK OF CONTRAST-INDUCED NEPHROPATHY**

Although approximately 60% of patients experiencing an acute decline in renal function will have a partial or full recovery to baseline function, it can be a poor prognostic indicator.\(^4\) Acute mortality due to renal insufficiency is rare; however, the development of chronic renal failure in light of other disease states has been linked to increased mortality.

In a study by Nash et al,\(^1:\) of the 7.2% of general hospital patients who developed an element of hospital-acquired renal insufficiency, 11% were due to contrast-induced nephropathy. This was similar to the rates of contrast-induced nephropathy described in a parallel study published in 1983, which reported that 12% of hospital-acquired renal insufficiency cases were attributable to contrast-induced nephropathy,\(^5\) making contrast-induced nephropathy the third highest cause of hospital-acquired renal insufficiency.\(^4\)

In 1996, Levy et al\(^6\) evaluated >16,000 hospital patients, and although the incidence of contrast-induced nephropathy was <2%, the risk of death was 34% in those who developed contrast-induced nephropathy compared with 7% in the control group. When these data were adjusted for comorbid diseases, contrast-induced nephropathy was associated with a 5.5-fold increase in risk of death.

**DIFFERENCES AMONG THE CONTRAST MEDIA**

Contrast media used for studies is generally divided into 3 main categories: high-, low-, and iso-osmolar. The osmolarity refers to the ratio of iodine atoms and dissolved particles, with a higher ratio leading to better attenuation of radiographs. Rates of contrast-induced nephropathy have lowered with new iso- and low-osmolar agents.\(^5\)

Although early studies did not show significant differences between high- and low-osmolar, much of this has been credited to the fact that these studies had small numbers of high-risk patients with preexisting renal dysfunction.\(^7,8\)

Rudnick et al\(^7\) reported a significant difference in the percentage of contrast-induced nephropathy in at-risk populations (existing renal insufficiency with or without diabetes mellitus) undergoing coronary angiography. This finding was subsequently validated in a 1993 meta-analysis.\(^9\)

Multiple studies have postulated that iso-osmolar has a lower risk of contrast-induced nephropathy than low-osmolar, including the NEPHRIC study by Aspelin et al,\(^9\) which showed a 3.1% incidence in the iso-osmolar arm vs 26.2% in the low-osmolar. Many investigators have reported this significance when evaluating high-risk patients.\(^10-22\)

However, in modern practice, iso- and low-osmolar are more often used.

**RISK FACTORS FOR DEVELOPMENT**

Multiple risk factors have been identified in the literature (Table 1). However, a few basic risk factors have been well de-

<table>
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<th>Table 1</th>
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| **Selected Risk Factors for Development of Contrast-induced Nephropathy**

- Renal insufficiency
- Diabetes mellitus
- Age >70 years
- Dehydration or volume depletion
- Use of nephrotoxic drugs (eg, NSAIDs, aminoglycosides, vancomycin)
- Preprocedural hemodynamic instability or sepsis
- Vascular disease
- Anemia
- Volume of contrast media
- Congestive heart failure
- Hypoalbuminemia
- Readministration of contrast media within 72 hours after initial exposure

Abbreviation: NSAIDs, nonsteroidal anti-inflammatory drugs.
Adequate intravenous hydration

- 6-12 hours before exposure
- 4-12 hours after exposure
- Use of low- or iso-osmolar contrast media
- Hold medications that could adversely affect renal function

<table>
<thead>
<tr>
<th>Estimated Glomerular Filtration Rate</th>
<th>Risk of Contrast-Induced Nephropathy</th>
<th>Prophylactic Measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥60 mL/min</td>
<td>Very low risk</td>
<td>Adequate intravenous hydration</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6-12 hours before exposure</td>
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<tr>
<td></td>
<td></td>
<td>4-12 hours after exposure</td>
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<tr>
<td></td>
<td></td>
<td>Use of low- or iso-osmolar contrast media</td>
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<tr>
<td></td>
<td></td>
<td>Hold medications that could adversely affect renal function</td>
</tr>
<tr>
<td>45-59 mL/min</td>
<td>Low risk</td>
<td>Adequate intravenous hydration</td>
</tr>
<tr>
<td>~&lt;45 mL/min</td>
<td>Moderate risk</td>
<td>Use of low- or iso-osmolar contrast media</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hold medications that could adversely affect renal function</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Consider acetylcysteine</td>
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<tr>
<td></td>
<td></td>
<td>600-1200 mg twice daily 12-24 hours before exposure</td>
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<tr>
<td></td>
<td></td>
<td>600-1200 mg twice daily 24 hours postexposure</td>
</tr>
<tr>
<td>Unstable renal function, acute illness, acute renal failure</td>
<td>High risk</td>
<td>Adequate intravenous hydration</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Use of low- or iso-osmolar contrast media</td>
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<tr>
<td></td>
<td></td>
<td>Consider acetylcysteine</td>
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<tr>
<td></td>
<td></td>
<td>Obtain a serum creatinine 24-72 hours postexposure</td>
</tr>
</tbody>
</table>

Although serum creatinine is a relative indicator of renal function, due to variations in muscle mass, age, and sex, it is a relatively variable factor, and estimations of creatinine clearance or glomerular filtration rate are more reliable. Myoglobinuria and hyperuricemia have also been mentioned in the literature as possible risk factors, but these characteristics are often associated with decreased renal function and have not been reported as independent factors.

In addition, medications that orthopedic patients may be taking can contribute to renal dysfunction and increase risk; therefore, attention should be paid to nonsteroidal anti-inflammatory drugs (NSAIDs) and antibiotics, such as vancomycin and aminoglycosides. Due to comorbid conditions, patients may be on diuretics, immunosuppressants (eg, cyclosporine), and certain chemotherapy agents that have been associated with increased risk of contrast-induced nephropathy.

Adding the complication of anemia to already low partial pressure of oxygen combined with postcontrast vasoinception can, in theory, lead to hypoxic damage. According to the available literature, the most common procedures that result in contrast-induced nephropathy are coronary angiography and contrast-enhanced computed tomography, and the risk is higher in patients receiving intra-arterial contrast opposed to intravenous contrast. Rates of contrast-induced nephropathy are lower when volumes <140 mL are used, whereas volumes >5 mL/kg are stronger indicators of a need for dialysis. Repeat administration of contrast media within 48 hours should be avoided because this can lead to an increased risk of contrast-induced nephropathy.

Orthopedic patients may be at a lower risk for contrast-induced nephropathy because they are undergoing procedures that carry a lower risk, yet factors such as age >70 years, diabetes mellitus, and medication complications still ex-
**Strategies for Risk Assessment and Prevention**

Patients undergoing procedures in which contrast media is to be administered should be assessed for the risk of contrast-induced nephropathy. If possible, a serum creatinine and subsequent estimated glomerular filtration rate within 1 week before procedure for an inpatient or patient with more variable renal function. Patients with an estimated glomerular filtration rate <45 mL/min would be considered at a moderate risk for contrast-induced nephropathy, and consideration should be made to initiate preventative strategies, such as those listed in Table 2. Before administration of contrast media, alternate imaging studies not requiring contrast media should be evaluated.

If a study using contrast is necessary, care should be given to ensure adequate hydration of the patient before the procedure in combination with the use of low- or iso-osmolar media. In addition, minimizing the total volume of contrast media used can be beneficial. Nephrotoxic drugs and those that could cause dehydration or renal vasoconstriction should be discontinued 24 to 48 hours before administration, if appropriate. Common agents associated with contrast-induced nephropathy include aminoglycosides, vancomycin, diuretics, and NSAIDs. Generally, it is not practical to hold antibiotics for an imaging study; therefore, the added risk from these agents should be carefully considered.

Strategies for prevention range from controlling the volume of contrast media to administering additional fluids and medications. Fluid administration is a universally accepted preventative measure (Table 3). Bicarbonate and normal saline solutions have been investigated for use in the prevention of contrast-induced nephropathy.

Earlier studies showed that bicarbonate solutions may have had an advantage in prevention, but newer investigations seem to show that the 2 solutions are likely interchangeable. Oral hydration has not been adequately studied but is likely an option for those with low to moderate risk where intravenous hydration is impractical. A meta-analysis published in 2000, where 600 mg of acetylcysteine taken orally twice daily for 2 days prior to the procedure was used as a preventative strategy. However, the results of studies and meta-analyses have been conflicting. Of 11 meta-analyses studied in a 2006 review, 9 showed risk reduction with acetylcysteine; however, the heterogeneity within the analyses calls the results into question. Although multiple doses have been evaluated with conflicting results, acetylcysteine is not associated with major side effects at preventative doses, and therefore can be

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**Table 3**

<table>
<thead>
<tr>
<th>Fluid</th>
<th>Timing of Administration</th>
<th>Recommendation</th>
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<tbody>
<tr>
<td>Normal saline</td>
<td>12 hours before procedure</td>
<td>1 mL/kg per hour for 12 hours before and after contrast administration</td>
</tr>
<tr>
<td>Isotonic saline or sodium bicarbonate solution</td>
<td>1-3 hours before procedure</td>
<td>3 mL/kg per hour for 1-3 hours before and 6 hours after contrast administration</td>
</tr>
<tr>
<td>150 mEq sodium bicarbonate in dextrose</td>
<td>1 hour before procedure</td>
<td>3 mL/kg per hour for 1 hour before and 1 mL/kg per hour for 6 hours after administration</td>
</tr>
</tbody>
</table>

*At a minimum, 300-500 mL of intravenous fluids should be administered before contrast.*
considered for use but is not a substitution for hydration.

Although consensus statements and guidelines do not offer definitive outlines for the use of acetylcysteine, it is recommended as an option for patients at an increased risk. Furthermore, many dosing regimens have been evaluated, yet no specific dose has been proven to be safer or more effective. Most common dosing regimens are 600 to 1200 mg orally twice daily 24 to 48 hours before contrast administration to be continued for 24 hours after the procedure.34,36,39

REFERENCES

