Diphenhydramine and Acute Kidney Injury

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INTRODUCTION

Acute kidney injury (AKI) can be caused by a commonly used over-the-counter and prescription medication, diphenhydramine (Benadryl, McNeil). We do not usually think of this drug as a major source of renal impairment, but it can cause problems in some predisposed patients, including elderly populations.

Previously called acute renal failure, AKI is usually described as a rapid yet reversible decline in renal function. It is associated with elevated serum creatinine (SCr) levels. Medications account for 8% to 60% of AKI cases, but not all drugs cause AKI by the same mechanism. For example, calcineurin inhibitors and vasopressors cause renal disease by vasoconstriction, whereas angiotensin-converting enzyme (ACE) inhibitors, angiotensin-receptor blockers (ARBs), and nonsteroidal anti-inflammatory drugs (NSAIDs) alter intraglomerular hemodynamics.

Amphotericin B (e.g., AmBisome, Abelcet, Fungizone) is thought to lead to renal disease through tubular cell toxicity, and the use of acyclovir (Zovirax, GlaxoSmithKline) has been associated with crystal deposition in the kidneys.

In addition, agents with anticholinergic properties, such as diphenhydramine, may lead to urinary retention, which can result in postrenal injury (see page 460). One case of diphenhydramine-induced renal disease involved a patient who presented with nontraumatic rhabdomyolysis complicated by oliguric AKI following an intentional ethanol and diphenhydramine overdose.

Many patients with AKI have mild symptoms and may display only transient increases in SCr or BUN levels. However, AKI can also be characterized by serious complications such as volume overload, hyperkalemia, metabolic acidosis, hypocalcemia, and hyperphosphatemia. Mental status changes may also complicate treatment in patients with severe AKI.

The pathophysiology of AKI may be classified as prerenal, renal (intrinsic), or postrenal. Common causes of AKI, inciting drugs, and drug classes are listed in Table 1.

Prerenal Injury

Prerenal injury (i.e., decreased blood flow to the kidney) is defined as hypoperfusion with or without arterial hypotension. Depletion in intravascular volume caused by hemorrhage, excessive gastrointestinal (GI) losses, dehydration, or diuretic therapy can result in hypoperfusion via systemic arterial hypotension.

Patients taking ACE inhibitors, ARBs, or NSAIDs may also experience prerenal AKI resulting from changes in afferent and efferent arteriolar tone. Initially at this stage, the kidneys compensate by stimulating the renin–angiotensin–aldosterone–system (RAS) and antidiuretic hormone to maintain blood pressure. However, if a patient previously had hypoperfusion, this compensatory mechanism may fail and the patient experiences a decreased glomerular filtration rate (GFR).

<table>
<thead>
<tr>
<th>Table 1 Medications Associated with Acute Kidney Injury</th>
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<tbody>
<tr>
<td><strong>Prerenal Injury</strong></td>
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<tr>
<td>Cause decreased renal perfusion</td>
</tr>
<tr>
<td>- ACE inhibitors</td>
</tr>
<tr>
<td>- ARBs</td>
</tr>
<tr>
<td>- NSAIDs</td>
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<tr>
<td>- Tacrolimus</td>
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<td>- Cyclosporine</td>
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</table>

ACE = angiotensin-converting enzyme; ARBs = angiotensin-receptor blockers; NSAIDs = nonsteroidal anti-inflammatory drugs.


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### Renal (Intrinsic) Injury

Radiocontrast dyes and aminoglycosides are known to cause renal ischemic injury or acute tubular necrosis. Intrinsics injury involves direct damage to the kidney; it can also lead to a decreased GFR and trigger an inflammatory response as well. Drugs that cause interstitial damage by stimulating a hypersensitivity reaction or inflammation of the renal interstitium can cause AKI to progress to interstitial fibrosis or tubular atrophy.

### Postrenal Injury

Anticholinergic medications, such as diphenhydramine, can cause postrenal obstruction (blockage of the urinary tract). Obstruction can occur from the urinary tubule to the urethra, resulting in urine accumulation and ultimately increasing upstream pressure and decreasing GFR.2

### TREATMENT

Regardless of the underlying mechanism, the treatment approach for drug-induced renal disease is similar for most patients. The suspected nephrotoxin should be immediately discontinued. Patients should be given supportive care, primarily fluid replacement such as normal saline at a rate of 250 to 500 mL intravenously over 15 to 30 minutes to provide adequate kidney perfusion.5

Patients should also be monitored for the following parameters: intake and output (I/O), weight, protein intake,5 and electrolyte balance. If fluid overload or pulmonary edema is present, a loop diuretic such as furosemide (e.g., Lasix, Sanofi) or bumetanide (Bumex, Roche), is recommended.8

Metabolic acidosis may also occur as a result of bicarbonate loss. It can be treated with dextrose 5% in water with 0.45% normal saline and 50 mEq of sodium bicarbonate as a bolus. Continuous infusions of sodium bicarbonate may be administered until the patient is adequately rehydrated and acidosis is resolved. Dialysis may be an option. If anemia develops, red blood cell transfusions should be considered to reach a hematocrit exceeding 30%.8 Fluid and electrolytes should be managed to maintain adequate cardiac output and blood pressure.

Hyperkalemia is a major concern because it can cause metabolic acidosis and arrhythmias. Treatment of hyperkalemia includes shifting potassium back into the cell with insulin or glucose, beta, agonists, and sodium bicarbonate or removing potassium from the body with sodium polystyrene sulfonate (Kayexelate, Sanofi-Aventis) or diuretics.9

Patients may also experience hyperphosphatemia and hypermagnesemia. A vasopressor such as dopamine or noradrenaline may be needed to maintain adequate tissue perfusion.

Renal replacement therapy can also be considered in cases of severe acid–base imbalances, electrolyte imbalances, intoxication with nephrotoxins or other toxic medications, or fluid overload in patients with uremia.3 Intermittent hemodialysis rapidly removes volume and solutes to correct electrolyte abnormalities, but it is associated with a risk of hypotension.

Continuous renal replacement therapy (CRRT)—which includes continuous venovenous hemofiltration (CVVH), continuous venovenous hemodialysis (CVVHD), and continuous hemodiafiltration (CVVHDF)—is used to remove solutes and volume at a slower rate and provides improved outcomes in critically ill patients. CRRT can also be used to remove small water molecules, such as amino acids and micronutrients; therefore, patients should increase their daily protein intake.5

Patients should undergo routine laboratory blood tests at least once or twice daily. Monitoring parameters should include intake and output (I/O), weight, blood pressure, heart rate, mean arterial pressure, and serum levels of potassium, sodium, chloride, bicarbonate, calcium, magnesium, phosphate, BUN, SCR, and glucose.

Urinalysis should also be performed to determine the creatinine clearance (CrCl) and the fractional excretion of sodium. All doses of medications should be adjusted according to kidney function.10

The following patient was recently seen at our hospital.

### Case Study

A 61-year-old African-American man with a history of hypertension, chronic obstructive pulmonary disease (COPD), and pancreatic neuroendocrine tumor following resection was admitted to the emergency department (ED) for evaluation of suprapubic discomfort for the past 3 or 4 days. He described the pain as sharp and intense. His pain score was 10 out of 10 on a Visual Analogue Scale. The pain was not relieved by acetaminophen with codeine (e.g., Tylenol #3, McNeil). He also complained of urinary frequency, urgency, and hesitancy.

The patient stated that he had been using oral diphenhydramine (Benadryl) for 1 week to alleviate pruritus near the placement of his ileostomy. He denied that he was having fever, chills, malaise, nausea, vomiting, flank pain, or hematuria. Upon admission to the ED, his serum potassium level was elevated and equal to 6.9 mEq/L (normal, 3.6–5 mEq/L). T-wave electrocardiographic (ECG) changes were noted.

BUN, which was elevated, was equal to 87 mg/dL (normal, 7–20 mg/dL), and his SCR level, also elevated, was equal to 2.1 mg/dL (normal, 0.5–1.4 mg/dL). Two weeks before admission, his baseline SCR had been 0.9 mg/dL. Creatine kinase (CK) levels were unremarkable throughout the admission.

In the ED, the patient was immediately treated for hyperkalemia with calcium polystyrene sulfonate (Kayexalate, Sanofi-Aventis) or diuretics.9

### Table 2: Laboratory Values of the Case Patient

<table>
<thead>
<tr>
<th></th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
<th>Day 4</th>
<th>Day 5</th>
<th>Day 6</th>
<th>Day 7</th>
</tr>
</thead>
<tbody>
<tr>
<td>BUN (mg/dL)</td>
<td>87 H</td>
<td>58 H</td>
<td>36 H</td>
<td>30 H</td>
<td>21</td>
<td>14</td>
<td>13</td>
</tr>
<tr>
<td>Scr (mg/dL)</td>
<td>2.1 H</td>
<td>1.7 H</td>
<td>1.5 H</td>
<td>1.4 H</td>
<td>1.1</td>
<td>0.9</td>
<td>1</td>
</tr>
<tr>
<td>Na+ (mEq/L)</td>
<td>130 L</td>
<td>134 L</td>
<td>129 L</td>
<td>128 L</td>
<td>127 L</td>
<td>132 L</td>
<td>133 L</td>
</tr>
<tr>
<td>K+ (mEq/L)</td>
<td>6.9 H</td>
<td>5.1 H</td>
<td>4.6</td>
<td>4.8</td>
<td>4.7</td>
<td>4.5</td>
<td>4.4</td>
</tr>
</tbody>
</table>

BUN = blood urea nitrogen; H = high; K = potassium; L = low; Na = sodium; SCR = serum creatinine.
chloride, regular insulin plus dextrose 50% in water, furosemide, and sodium polystyrene sulfonate (Kayexelate). Potassium levels returned to a normal value of 4.9 mEq/L. To improve his kidney function, fluid hydration was initiated with normal saline. BUN and Scr levels began to decline over the following days. After 5 days of supportive therapy, BUN and SCR levels returned to normal baseline measures.

His symptoms, laboratory values (Table 2), and medical history were consistent with diphenhydramine-induced renal toxicity. A Foley catheter was placed to relieve the urine buildup caused by acute urinary retention, which was attributed to the anticholinergic effects of diphenhydramine.

Morphine sulfate injections were also ordered to relieve abdominal pain. The patient was started on tamsulosin (Flomax, Boehringer Ingelheim/Astellas) to relieve urinary retention.

Topical 1% hydrocortisone cream was substituted for oral diphenhydramine to control the initial problem of itching at the ileostomy site. This was an effective alternative, because the cream was not absorbed systemically and it resolved the pruritus.

ECG changes, urinary retention, and impaired renal function were noted, but rhabdomyolysis did not occur.

CONCLUSION

The case study presented illustrates an example of diphenhydramine-induced renal disease in a middle-aged veteran. Antihistamines with anticholinergic properties can cause postrenal obstruction, resulting in delayed bladder emptying. This can result in urine accumulation and lead to increased pressure and a decreased GFR. As a result, extra precautions should be implemented before diphenhydramine or other anticholinergic agents are prescribed for older individuals. Other symptoms may include dysuria, urinary frequency, and hesitancy.

If AKI develops, the offending agent should be discontinued immediately and supportive therapy should be initiated to prevent complications such as electrolyte imbalances and the progression of renal damage.

REFERENCES