The “Triple Whammy”

Background

The term “triple whammy” refers to the risk of acute kidney injury when an ACEI or ARB is combined with a diuretic and NSAID. This combination might be seen in a patient with hypertension, congestive heart failure, or renal disease who has arthritis or other mild to moderate pain. Although the actual number of patients who are receiving the combination in the United States and Canada is not known, a survey of patients attending general practice clinics in Australia found that the combination was prescribed in 4.7% to 7.9% of patients.1 This article reviews the mechanism and studies of the triple whammy, and provides information to help clinicians prevent renal injury due to the triple whammy in their patients.

Mechanism

To understand how the triple whammy works, it is necessary to understand how each medication in the triple combo affects the kidney when given alone:

ACEIs or ARBs: reduce glomerular filtration pressure via vasodilation of the efferent arteriole;

Diuretics: reduce blood flow to the glomerulus via intravascular volume depletion;

NSAIDs: reduce blood flow to the glomerulus by inhibiting production of vasodilating prostaglandins.2

When renal perfusion is impaired by a diuretic/dehydration, renin secretion and angiotensin II production is triggered. Angiotensin II then works to improve renal blood flow by vasoconstricting the efferent arteriole to help maintain intraglomerular pressure. Prostaglandin synthesis is another compensatory mechanism; prostaglandins dilate the afferent arteriole to increase blood flow to the glomerulus. But when the patient is also on an ACEI or ARB and/or an NSAID, these compensatory mechanisms are impaired.2

Evidence suggests that patients on a diuretic and NSAID can usually maintain glomerular perfusion with the help of angiotensin II, but get into trouble when an ACEI or ARB is added. In patients not taking a diuretic, the effect of NSAIDs plus an ACEI or ARB on the kidney may be compensated by normal volume status.3

Studies of the Triple Whammy

Two observational studies have looked specifically at the association between use of a diuretic, an ACEI or ARB, and an NSAID on renal function. The first was a cross-sectional study of patients admitted to the general medicine ward of a teaching hospital in Australia over a three-month period.1 Prior consumption of ACEIs or ARBs, NSAIDs (including aspirin), and diuretics was assessed and correlated with creatinine clearance (if available) or serum creatinine upon hospital admission. Patients with a prior history of serious kidney disease (e.g., cancer of the kidney) were excluded, but patients with known renal failure were included but analyzed separately.1

Three hundred and one patients were identified. Of these patients, 135 (44.9%) were not receiving any of the agents, 87 (28.9%) were receiving one of the targeted medications, 60 (19.9%) were receiving two of the medications, and 19 (6.3%) were receiving all three medications. Women on two or three of the target medications, and men on three of the target medications, had significantly higher serum creatinine compared to patients taking none of the target medications. Higher diuretic doses were associated with higher serum creatinine and lower creatinine clearance. Increasing duration of diuretic use or NSAID use was associated with higher serum creatinine.1

Of note, patients taking aspirin, including “low-dose” prophylactic doses of aspirin, were included in the NSAID group. In fact, almost one-third of patients taking all three of the...
medications were taking low daily doses of aspirin. The authors note that in the elderly, it is especially important to limit the number of medications and to include low-dose aspirin on the medication list.\textsuperscript{1}

A drawback of this study is that they did not look at the association between triple therapy and a hard clinical endpoint such as acute renal failure. A subsequent case-control study utilized a large UK database of primary care records.\textsuperscript{3} A cohort of patients who received an antihypertensive between January 1, 1997, and December 31, 2008, with follow-up data available until December 31, 2010, was selected. Cohort entry date was the date of the first antihypertensive prescription. For patients who did not have at least a year of medical history before that date, the cohort entry date was moved forward so that there was at least a year of medical history before the cohort entry date. Patients were excluded if they had a history of cancer; kidney, liver, or connective tissue disease; rheumatoid arthritis; crush injury; HIV; or drug abuse. Included patients (n= 487,372) were followed until hospital admission for acute kidney injury, occurrence of an excluding diagnosis, death, or December 31, 2010.\textsuperscript{3}

Patients were followed for a mean of 5.9 years. There were 2215 cases of acute renal injury, or an incidence of 7/10,000 person-years. Use of double therapy with a diuretic, ACEI, or ARB plus an NSAID was not associated with acute renal injury. But the triple combination did increase risk (rate ratio 1.31, 95% CI 1.12 to 1.53). The risk peaked within the first 30 days of use (rate ratio 1.82, 95% CI 1.35 to 2.46). NSAIDs with half-lives of 12 hours or longer as part of triple therapy tended to be a risk factor as well.\textsuperscript{3}

**Commentary**

Be especially cautious using the triple combo in patients with risk factors for acute kidney injury, such as older age, diabetes, renal insufficiency, ascites, or heart failure.\textsuperscript{2} Even NSAIDs alone can be risky in these patients. The American Board of Internal Medicine’s Choosing Wisely site (www.choosingwisely.org) aims to promote care choices that are evidence-based, necessary, and free from harm.\textsuperscript{4} In partnership with the American Society of Nephrology, they advise avoiding NSAIDs in patients with hypertension, heart failure, or diabetic or other chronic kidney disease.\textsuperscript{5} NSAIDs can increase blood pressure, cause fluid retention, and worsen renal function in these patients.\textsuperscript{5} Consider NSAID alternatives such as acetaminophen, tramadol, or short-term use of an opioid.\textsuperscript{5} If an NSAID must be used, avoid those with half-lives over 12 hours, such as oxaprozin (Daypro), nabumetone, naproxen, meloxicam, or piroxicam.\textsuperscript{3,6} An occasional dose of OTC ibuprofen or naproxen, or daily low-dose aspirin, should be safe for most patients.\textsuperscript{5,8} Topical diclofenac may also be acceptable since little is absorbed systemically.\textsuperscript{9} If an NSAID must be used in a high-risk patient, including those taking an ACEI, ARB, or diuretic, consider checking serum creatinine and potassium weekly for several weeks.\textsuperscript{10,11} Prescription NSAID labeling generally recommends checking a chemistry profile periodically in all patients.

All patients receiving the triple combo should be monitored closely during the first 30 days of combination therapy [Evidence level B; case-control study].\textsuperscript{3} Based on recommendations for monitoring ACEIs and ARBs, it may be prudent to check potassium and serum creatinine within a week of starting triple therapy, then in three to four weeks if stable.\textsuperscript{12,13} If serum creatinine is increased, check again in two to three weeks, and again in three to four weeks.\textsuperscript{13} If GFR decreases or serum creatinine increases by more than 30%, reduce the ACEI or ARB dose in half and monitor every five to seven days.\textsuperscript{13,14} If renal function does not return to baseline, or if there is more than a 50% decrease in GFR or 50% or more increase in serum creatinine, the ACEI or ARB should be discontinued.\textsuperscript{14} If hyperkalemia occurs, cut the ACEI or ARB dose in half, then check potassium every five to seven days. If potassium does not return to baseline within two to four weeks, the ACEI or ARB should be discontinued.\textsuperscript{14}

Once the dose, serum creatinine, and potassium are stable, monitor at least once or twice yearly, and when patient condition changes (e.g., when dehydration is a possibility).\textsuperscript{13,14} If GFR is 30 to 59 mL/min/1.73 m² or potassium is 4.6 to 5 mEq/L, recheck every three to six months.\textsuperscript{13} In patients with a GFR of <30 mL/min/1.73 m² or potassium over 5 mEq/L, monitor every one to three months.\textsuperscript{14}

Consider substituting a dihydropyridine calcium channel blocker for a diuretic. An
anomalide/ACEI combination has been shown to be better than an ACEI/thiazide combination for preventing cardiovascular events in a high-risk hypertensive population. Furthermore, the antihypertensive effect of dihydropyridines is not offset by NSAIDs. Dihydropyridines dilate the afferent arteriole, which is the opposite of what NSAIDs do.

When patients are ill, avoid dehydration. If the patient becomes dehydrated or orthostatic, hold the diuretic while the intravascular volume is replenished. Also, hold the ACEI or ARB until volume has normalized and the patient is no longer hypotensive. Make sure patients know to seek immediate medical care if they develop symptoms of renal insufficiency (e.g., edema, low urine output, confusion, nausea, etc). Also help identify and educate patients at risk for NSAID-associated renal injury. Red flags include use of ACEIs, ARBs, diabetes meds, heart failure meds, and meds for liver disease. The National Kidney Disease Education Program is developing an NSAID avoidance continuing education program geared toward community pharmacists. The program is slated to be available on their website (http://nkdep.ni.gov) by Fall 2013.

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Project Leader in preparation of this PL Detail-Document: Melanie Cupp, Pharm.D., BCPS

References


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**Levels of Evidence**

In accordance with the trend towards Evidence-Based Medicine, we are citing the LEVEL OF EVIDENCE for the statements we publish.

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<thead>
<tr>
<th>Level</th>
<th>Definition</th>
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<tbody>
<tr>
<td>A</td>
<td>High-quality randomized controlled trial (RCT) High-quality meta-analysis (quantitative systematic review)</td>
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<tr>
<td>B</td>
<td>Nonrandomized clinical trial Nonquantitative systematic review Lower quality RCT Clinical cohort study Case-control study Historical control Epidemiologic study</td>
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<tr>
<td>C</td>
<td>Consensus Expert opinion</td>
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<tr>
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<td>Anecdotal evidence In vitro or animal study</td>
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