Introduction

The “triple whammy” is a term used to describe the deleterious nephrotoxic effect resulting from the concurrent use of an angiotensin converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB), a diuretic, and a non-steroidal anti-inflammatory drug (NSAID) - including low dose prophylactic aspirin and cyclooxygenase-2 (COX-2) selective antagonists. This combination of agents can lead to acute renal disease with an estimated fatality rate of 10%. [1,2,3] This combination of factors is significantly higher in patients with only minor deteriorations in renal function. [4]

Risk Factors

Greater risk is observed at the first 30 days of starting the regimen. [5] Older patients are predisposed to renal insufficiency and consequently acute renal disease because of diminished renal blood flow that occurs at a rate of about 1% each year after the age of 30. [6] These patients commonly present with other concomitant diseases (e.g. cardiovascular diseases, diabetes, heart failure, hypertension, pre-existing renal impairment, and arthritis) which warrant healthcare professionals to be more vigilant, since 70% of acute renal impairment cases occur at age 70 or older. [7]

Pathophysiological Mechanisms

In normal situations when renal perfusion pressure falls due to dehydration for instance, the kidneys compensate by two methods. The first method is the activation of the rennin-angiotensin system. Angiotensin II is a potent vasoconstrictor hormone which regulates the intraglomerular pressure by causing vasoconstriction of the efferent arterioles. It also promotes sodium retention and acts as a diuretic. The second compensatory method stimulates the production of prostaglandins which dilates the afferent arterioles, thus enhancing the glomerular blood flow. [8] The mechanism underlying acute renal injury is the synergistic effect related to the alterations in renal haemodynamics as following: [6]

1. ACEIs/ARBs: By inhibiting the action of angiotensin II, ACEIs and ARBs dilate the efferent arterioles. This causes a decrease in the renal blood flow, the glomerular perfusion pressure, and consequently the glomerular filtration rate (GFR).

2. Diuretics: Can cause volume depletion and reduced renal blood flow, thus leading to dehydration as well as electrolyte imbalance. [6,11]

3. NSAIDs: The primary mechanism by which NSAIDs may contribute to acute renal injury is the diminished renal blood flow caused by the inhibition of prostaglandin synthesis. Prostaglandins have anti-hypertensive properties as they induce the dilation of afferent arterioles which reduces the glomerular perfusion pressure and consequently maintaining GFR.
This protective mechanism is alleviated by NSAIDs.\cite{6,13}

**Clinical Outcomes**

Few clinical studies have investigated the relationship between receiving the triple therapy and elevated serum creatinine.\cite{3} A cross-sectional Australian study was conducted to examine the correlation between the risk of acute renal disease and the triple therapy over a three-month period. The investigators found a remarkable positive relationship between the number of administered drugs, creatinine (Cr), and creatinine clearance (CrCl), including subjects on reduced daily divided doses (DDD). This suggests that the concurrent intake of low doses of the problematic medications will not necessarily decrease the risk of adverse reactions.\cite{3}

Another case-control study was recently conducted in the UK. The research examined the impact of double or triple therapy on acute renal disease. The study population included (487,372) patients who were followed for a mean of 5.9 years. The authors have concluded that the risk of developing acute renal disease associated with taking double therapy was not generally increased, while the triple therapy was associated with 31% increase in risk of acute renal injury. They also found that the risk was greater within the first 30 days of concurrent therapy.\cite{6}

**Prevention Strategies**

Avoid combination of triple therapy if possible, especially the addition of NSAIDs. Attentive monitoring for acute renal impairment signs and symptoms is exceptionally important, since renal function can be returned to baseline levels with early intervention and aggressive treatment.\cite{11}

Lab assessment is an essential tool for the diagnosis of acute renal impairment that shows an increase in serum blood creatinine. Patients often are asymptomatic or the only symptom of note may be a reduction in urine output, although urine output occasionally remains normal. Worsening renal function results in the accumulation of blood urea nitrogen (BUN), increased electrolytes, and acid-abnormalities. This leads to symptoms such as oedema, itching, drowsiness, shortness of breath, fatigue, confusion, chest pain, seizures, or coma in severe cases.\cite{8}

The healthcare team should work to develop non-pharmacological strategies to reduce the risk of injury, either by increasing hydration to minimize the risk of dehydration or by intensified monitoring.\cite{12} Patients at high risk of acute renal impairment should be counseled on the risk of self-prescribing, sick days and the use of NSAIDs or other over-the-counter (OTC) medications without discussing their use with their physicians or pharmacists. When harm outweighs benefits, alternatives or discontinuation of the drug may be warranted.\cite{12} Alternatives such as paracetamol (acetaminophen) may be more appropriate for mild pain, with opioids considered for moderate to severe pain.\cite{12,13}

**Conclusion**

One of the major concerns about chronic polypharmacy is the adverse drug reactions, particularly on renal function. Triple whammy has been previously reported and reinforced by the observational studies. Whilst ACEIs/ARBs and diuretics are commonly used due to their significant efficacy in hypertension, heart failure, stroke prevention, and other cardiac and health conditions. Equally important is to achieve maximum and safer benefit to the patient but not at the price of adding renal insufficiency, particularly in older patients. It is better to avoid NSAIDs in conditions that may lead to renal impairment such as hypertension and diabetes. However, if there is a necessity for the triple combination, prescribers should be more alert about creatinine monitoring and dehydration, with special attention during the first 30 days of initiating NSAIDs therapy.
References:

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