Medicines Evidence Commentary

commentary on important new evidence from Medicines Awareness Weekly

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Risk of acute kidney injury with concurrent use of antihypertensives and NSAIDs

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A UK observational study found that current use of triple therapy consisting of a diuretic plus an ACE inhibitor or an angiotensin receptor blocker (ARB) along with an NSAID was associated with an increased rate of acute kidney injury. This supports the advice from the MHRA about the need for caution when prescribing NSAIDS in people taking these cardiovascular medicines.

Overview and current advice

NSAID use accounts for approximately 15% of all cases of drug induced acute renal failure. The Medicines and Healthcare products Regulatory Agency (MHRA) has previously reminded prescribers about the risk of renal impairment and renal failure associated with NSAID therapy. Risks may be highest in vulnerable people, especially older people and those on concomitant medications which may precipitate reduced renal function (such as ACE inhibitors, ARBs, and diuretics).

Current guidelines from NICE recommend treatment with ACE inhibitors, ARBs and diuretics for conditions such as hypertension and chronic heart failure; and concurrent use of ACE inhibitors or ARBs with a diuretic for these conditions is common.

Many people with heart failure or hypertension may also have chronic inflammatory diseases or chronic pain, and so the use of NSAIDs may be indicated.

A NICE clinical guideline on acute kidney injury is in development. The scoping document refers to nephrotoxic drugs in the section on preventing deterioration in those at high risk of acute kidney injury or those with suspected or confirmed acute kidney injury.

New evidence

A UK observational study assessed whether double therapy consisting of a diuretic or an ACE inhibitor or an ARB with the addition of an NSAID, and triple therapy consisting of a diuretic plus an ACE inhibitor or an ARB in addition to an NSAID increased the risk of acute kidney injury.
A cohort of 487,372 people using antihypertensive drugs between 1 January 1997 and 31 December 2008 was identified from the UK Clinical Practice Research Datalink (CPRD), and followed up for a mean of 5.9 years. People with a history of renal disorders were excluded. Within the cohort, 2215 cases of acute kidney injury were identified (equating to an overall incidence rate of 7/10,000 person years) and matched to up to 10 controls.

For all cases and controls, drug history between the cohort entry date (date of first prescription for any antihypertensive drug) and the index date (earliest date of admission for acute kidney injury or dialysis procedure) was obtained. To be considered double or triple therapy, the drugs of interest had to be prescribed on the same day or their specified durations of use had to overlap for at least one day during follow up. Patients were classified as current users (treatment overlapping the 90 days immediately before the index date), past users (treatment after cohort entry but ending before the 90 days before the index date) or never users (absence of use between cohort entry date and index date) of double or triple therapy.

In the primary analysis, current users of double therapy were compared with patients currently using these antihypertensive drugs without NSAIDs. The same comparison was made for current users of triple therapy. Secondary analysis included assessing whether the risk of acute kidney injury varied dependant on half-life of the NSAID and length of exposure to double or triple therapy.

After adjusting for age, sex, BMI, lifestyle factors, hospital admissions, other medical conditions, blood pressure and other medications, current use of double therapy with diuretics plus NSAIDs was not associated with a statistically significant increase in the rate of acute kidney injury (rate ratio 1.02; 95% confidence interval [CI] 0.81 to 1.28). In addition, current use of double therapy with ACE inhibitors or ARBs plus NSAIDs was not associated with a statistically significant increase in the rate of acute kidney injury (rate ratio 0.89; 95% CI 0.69 to 1.15). However, current use of triple therapy (diuretics plus ACE inhibitors or ARBs plus NSAIDs) was associated with a statistically significant increase in rate of acute kidney injury (rate ratio 1.31; 95% CI 1.12 to 1.53). Risk was highest in the first 30 days of triple therapy use (rate ratio 1.82; 95% CI 1.35 to 2.46).

This study had several limitations. Firstly, identification of acute kidney injury may have been subject to some misclassification. Secondly, as this is an observational study, residual confounding by indication and disease severity may have been present, although the authors did attempt to adjust for this. Thirdly, the authors were unable to control for exposure to nephrotoxins (such as aminoglycoside antibiotics) that may have contributed to the risk of acute kidney injury. Finally, some misclassification of exposure could have occurred in relation to NSAID use because NSAIDs obtained over the counter could not be accounted for. The authors report that the risks observed in the study could therefore be an underestimate.

**Commentary**

This is an observational study which can only suggest an association, not prove causation, and may be prone to confounding. Nevertheless, the study highlights the renal risks associated with these commonly prescribed combinations of medicines.

In addition to concerns about the renal safety of NSAIDs, there are also concerns about cardiovascular and gastrointestinal toxicity. The MHRA has previously warned about these risks and advised that patients should use the lowest possible dose of an NSAID for the shortest possible time. Given that patients with hypertension and heart failure are at an increased cardiovascular risk, the additional possibility of an increased risk of acute kidney injury is another reason to avoid use of NSAIDs in these patient groups where possible.
NICE clinical guidelines for the treatment of osteoarthritis (OA) (currently being updated) and lower back pain recommend considering paracetamol ahead of oral NSAIDs, and the OA guidance also advises considering topical NSAIDs. The NICE clinical guideline for treatment of rheumatoid arthritis (RA) recommends considering analgesics such as paracetamol, codeine or compound analgesics for people with RA whose pain control is not adequate, to potentially reduce their need for long-term treatment with NSAIDs or COX-2 inhibitors.

Where NSAID therapy is unavoidable, this paper highlights the need for careful consideration around the choice of antihypertensive agent, particularly early on in the course of treatment, and in people at higher risk of acute kidney injury, such as older people.

NSAIDs and renin-angiotensin system drugs (ACE inhibitors and ARBs) are key therapeutic topics identified to support the QIPP medicines use and procurement work stream.

Study sponsorship

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References


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