

EDITORIALS

Safety of coprescribing NSAIDs with multiple antihypertensive agents

Triple drug combinations are associated with increased hospital admission for acute kidney injury, but questions remain

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Current guidelines by the National Institute for Health and Clinical Excellence (NICE) recommend treatment with angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) for conditions such as hypertension,¹ chronic heart failure,² and proteinuric chronic kidney disease.³ In England, the prescription of these drugs has increased by 15.8% over the past four years.⁴ Because ACE inhibitors and ARBs are often coprescribed with non-steroidal anti-inflammatory drugs (NSAIDs) and diuretics, particularly in older people,⁵ we need to know more about the safety of such combinations.

In a linked paper (doi:10.1136/bmj.e8525), Lapi and colleagues used a large database that was representative of UK primary care to examine data on 487 372 patients taking antihypertensive drugs.⁶ They used a nested case-control design to examine whether adding an NSAID to an ACE inhibitor, ARB, or diuretic in double or triple therapy combinations increased the risk of subsequent hospital admission with acute kidney injury. Acute kidney injury is seen in more than 20% of hospital inpatients and is associated with around half of all potentially preventable deaths in hospital.^{7 8} Although recent observational evidence suggests a link between this condition and use of diuretics, NSAIDs, ACE inhibitors, and ARBs,⁹ such studies are confounded by indication. Patients who are prescribed a combination of these agents are usually at high risk of acute kidney injury, which makes it difficult to establish a causal association.

The authors of the current study used a strict case definition of acute kidney injury: cases were defined using the first diagnostic code and those in which acute kidney injury was just a secondary problem were excluded. They excluded people with chronic kidney disease and adjusted for other comorbidities in the analysis. Chronic kidney disease is associated with an increased risk of acute kidney injury and well informed patients may avoid taking NSAIDs, which could introduce confounding by contraindication.¹⁰

Adjusted analyses found a 31% higher risk of acute kidney injury (relative risk 1.31, 95% confidence interval 1.12 to 1.53) for a triple drug combination (adding an NSAID to an ACE inhibitor or ARB plus diuretic) but no clear evidence of an increased risk of acute kidney injury for double drug combinations (NSAID added to either a diuretic, ACE inhibitor, or ARB). These results remained consistent after several sensitivity analyses.

So can clinicians be confident that NSAIDs in double combination with an ACE inhibitor, ARB, or diuretic are not associated with acute kidney injury? Defining safety as the absence of adverse events provides us with the difficult statistical challenge of excluding the presence of associations. To make sure that a particular drug combination is safe, an extremely large dataset of a representative patient population must be randomised to a given drug combination versus a single drug class, with frequent follow-up to detect adverse events.

In the current study, confidence intervals for estimates of risk for double drug combinations were wide, so the evidence of safety is not strong. Indeed, there was a suggestion of an early increase in risk for a diuretic-NSAID combination. Secondly, this analysis could not adjust for over-the-counter NSAID use or tell us about instances when primary care doctors detected increases in serum creatinine and stopped drugs before patients needed hospital admission. Thirdly, drug associated acute kidney injury is often a complication of other illnesses.¹¹ Lastly, defining acute kidney injury in patients with chronic kidney disease is complex, but it is important to understand how acute kidney injury can be prevented in this high risk group.¹⁰ Therefore, Lapi and colleagues' study probably underestimates the true burden of drug associated acute kidney injury. The jury is still out on whether double drug combinations are indeed safe.

The implications of the current analysis are nevertheless important: clinicians must advise patients who are prescribed diuretics, ACE inhibitors, or ARBs of the risks associated with NSAID use and they must also be vigilant for signs of drug associated acute kidney injury in all patients. Importantly,

current NICE quality standards for people with chronic kidney disease advise a drug review and renal function check during acute illness.¹²

Lapi and colleagues' paper highlights how observational data can improve our understanding of the risk to benefit ratio of drugs in routine use in the general population (as opposed to the defined populations where initial clinical trials were undertaken). Work still needs to be done to understand whether drug associated acute kidney injury is preventable, and what role intercurrent illness plays. The role of prescribed drugs in increasing the severity or duration of hospital admission may be as important as single organ complications in the elderly population with multiple comorbidities to whom these drugs are mainly prescribed. The current study is an important step in the right direction, but a longer road of discovery is ahead.

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