

THE TRIPPLE WHAMMY - SAFE PRESCRIBING - A DANGEROUS TRIO

1

1. ACE inhibitor or angiotensin II receptor antagonist ('sartan')
2. Diuretic
3. Non-steroidal anti-inflammatory drug (NSAID) or COX-2 inhibitor ('coxib')

- ▶ AVOID THIS COMBINATION OF MEDICINES IF POSSIBLE
- ▶ BE AWARE OF THE RISK FACTORS FOR ACUTE KIDNEY INJURY
- ▶ TAKE SPECIAL CARE WITH OLDER ADULTS
- ▶ ADVISE PEOPLE PRESCRIBED ACE INHIBITORS AND DIURETICS NOT TO 'SELF MEDICATE' WITH NSAIDS

Triple Whammy – 'three simultaneous deleterious blows with compounded effect'.¹ The combination of medicines above can result in significant harm. Used individually or combined, these three types of medicines are involved in more than half of all reported iatrogenic acute renal failure cases.²

AVOID THIS COMBINATION OF MEDICINES IF POSSIBLE

The combination of these medicines should be avoided particularly if people have risk factors for renal failure.³ The simplest way to avoid the triple whammy is by avoiding NSAIDs. When an ACE inhibitor/ARB with a diuretic is prescribed, highlight in the patient's notes or medication allergy/alerts section to avoid NSAIDs in future and advise them not to purchase NSAIDs themselves.³ Although the focus of adverse effects from NSAIDs is usually on the gastrointestinal consequences, there are other risks such as the development of chronic heart failure and acute kidney injury. Older adults and people with co-morbidities such as heart failure or severe liver disease or dehydration from acute illness have an increased risk of acute kidney injury. (AKI)^{3,4,5}

ACE inhibitors and NSAIDs adversely affect renal blood flow and diuretics have the potential to cause dehydration. Each of these medicines affects renal function, either directly or indirectly; a 'double whammy' can be harmful if people already have risk factors for AKI. Further, NSAIDs antagonise beneficial antihypertensive effects of ACE inhibitors and diuretics in people with heart failure.¹ If NSAIDs are unavoidable, use at the **lowest dose** for the **shortest duration** possible⁶; check renal function at baseline and periodically during treatment.⁵

Monitoring Recommendations^{3,7}

Medicine type	Interaction with NSAIDs	Recommendation
ACE inhibitors	↓ Antihypertensive effect ↑ Risk of acute kidney injury Hyperkalaemia	Monitor blood pressure, weight and renal function Monitor serum potassium
Diuretics	↓ Diuretic effect ↑ Risk of acute kidney injury Heart failure may be exacerbated	Monitor blood pressure, weight and renal function
ACE inhibitors + diuretics	↑ Risk of acute kidney injury	AVOID combination with NSAIDs if possible

The Centre for Adverse Reaction Monitoring (CARM) in New Zealand received 119 reports of renal adverse reactions associated with NSAID use from January 2000 to December 2012. This included four deaths, and 12 cases that were considered life-threatening. Most of the reports were in adults over 50 years of age. The 'Triple Whammy' was described in four reports. CARM encourage all healthcare professionals to report suspected adverse reactions to NSAIDs.⁸

Cases of acute kidney injury attributed to NSAIDs often involve people taking the maximum or greater than the maximum recommended daily dose.⁹

BE AWARE OF THE RISK FACTORS FOR ACUTE KIDNEY INJURY

Dehydration from vomiting, diarrhoea and sepsis can be a trigger for acute kidney injury; minor illness can place susceptible people at risk if they are taking 'Whammy' combinations.² Advise people to avoid hypovolaemia (drink plenty of water) and to seek medical advice if they become acutely unwell.^{10,11}

▶ THE TRIPPLE WHAMMY

2

Vomiting → hypovolaemia → precipitation of renal failure

Prescribers may also wish to **consider stopping NSAIDs** in these circumstances and to monitor renal function and serum potassium levels.¹²

Māori and Pacific people are also at greater risk of AKI so are more likely to be affected by the *Triple Whammy*.³ In addition, Māori have an elevated cardiovascular risk, so take special care when considering NSAIDs for them.⁶

Although a risk of nephrotoxicity has been identified with these three medicines, internationally there is a lack of clear recommendations about the frequency of monitoring where this combination cannot be avoided.¹³

In general, most people aged over 75 years will require a renal function test at least once per year. This is either because of declining health, or they are taking medicines that require monitoring such as for dose adjustments, or to assess whether the medicine needs to be discontinued.³

TAKE SPECIAL CARE WITH OLDER ADULTS

Older adults are especially vulnerable to the *Triple Whammy* because they often have a degree of pre-existing renal impairment.^{2,12} Other reasons may include: sensitivity to the renal effects of NSAIDs, being prone to diuretic-induced dehydration and hypotension, and inadequate fluid intake.¹²

Due to the increased susceptibility of adverse effects from NSAIDs, the New Zealand Formulary recommends the following:

Osteoarthritis, soft-tissue lesions, or back pain

- Try weight reduction first (if obese), warmth, exercise, and use of a walking stick

Osteoarthritis, soft-tissue lesions, back pain or rheumatoid arthritis pain

- Try paracetamol first OR low-dose NSAID (eg ibuprofen up to 1.2g daily)
- If inadequate, try full-dose paracetamol plus a low-dose NSAID
- If necessary, increase NSAID dose **OR** use an opioid analgesic (note constipation risk) **with** paracetamol

Note: Anyone with renal impairment is at risk, especially if they are dehydrated.

Prescribing NSAIDs in older adults¹⁴

The Health Quality and Safety Commission Atlas of Healthcare Variation revealed that 20,000 people in New Zealand 65 and over were dispensed the triple whammy in 2017. Rates were significantly higher in younger Māori and Pacific people. **Note:** This does not include over the counter NSAIDs.¹⁵

ADVISE PEOPLE WHO ARE PRESCRIBED ACE INHIBITORS AND DIURETICS NOT TO 'SELF-MEDICATE' WITH NSAIDS

Combination ACE-inhibitor or angiotensin II receptor antagonists **with** diuretics (eg Accuretic®) are useful products, but always advise people to avoid self-medicating with 'over-the-counter' NSAIDs. This combination has been associated with a 31% increased rate of acute kidney injury; the risk of injury doubles in the first 30 days of NSAID use.¹⁶

There remains a high prevalence of NSAID use among people with relative contraindications, such as people with chronic conditions or who are at risk of drug-related adverse events. A study examining NSAID use in people with identified contraindications, found that 22% of them purchased their NSAIDs exclusively over-the-counter. Of those, 1 in 5 did not report the use of NSAIDs to clinical staff; this may reflect that they consider these medications to be insignificant.⁴ Although some people may be unaware of the risks of NSAIDs, others may choose these medicines because they offer relief of pain that is not achieved through other means.

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▶ THE TRIPPLE WHAMMY

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▶ For further information on other high-risk medicines visit our website at : www.saferx.co.nz

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DISCLAIMER: This information is provided to assist primary care health professionals with the use of prescribed medicines. Users of this information must always consider current best practice and use their clinical judgement with each patient. This information is not a substitute for individual clinical decision making. Issued by the Quality Use of Medicines Team at Waitemata District Health Board, email: feedback@saferx.co.nz