CARM REPORTS

# ACUTE RENAL FAILURE

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***In the five years from 2002 to 2006 CARM (Centre for Adverse Reactions Monitoring) received 72 reports of acute renal failure (ARF). Seventeen (24%) patients had pre-existing renal disease. The medicines most frequently implicated were non-steroidal anti-inflammatory drugs (NSAIDs), proton pump inhibitors (PPIs) and antibiotics.***

***The majority of patients with ARF attributed to NSAIDs were taking the maximum recommended or supra-therapeutic doses. ARF with colchicine is also dose-related and such reports have led to changes in prescribing advice for this medicine. ARF attributable to PPIs was usually a consequence of proven or suspected interstitial nephritis. ARF reported with lipid lowering agents was secondary to rhabdomyolysis and more than half of these patients had pre-existing renal disease.***

## HIGH PROPORTION OF PATIENTS WITH ARF RELATED TO DRUG USE HAD PRE-EXISTING RENAL DISEASE

Over the five-year period from January 2002 to December 2006 CARM received 72 reports of ARF. In 17 (24%) reports, patients had pre-existing renal disease and 11 (15%) of the remainder were aged > 80 years and were, therefore, likely to have a degree of renal impairment. The medicine classes most frequently implicated were NSAIDs, PPIs and antibiotics. Dose-related ARF and hypersensitivity reactions were also reported.

## HIGH DOSES OF NSAIDS FEATURED IN ARF REPORTS

ARF was attributed to NSAIDs in 12 reports. The most notable feature of these reports was the dose prescribed. Of the nine patients for whom dose was stated, eight were taking the maximum or greater than the maximum recommended daily dose. Four patients were aged over 80 years but three in their 20's were also affected. ARF attributable to NSAIDs is most often due to prostaglandin inhibition leading to reduced glomerular perfusion in those patients who are dependent on renal prostaglandins for maintenance of renal blood flow. Patients with dehydration or disorders such as congestive heart failure, hepatic dysfunction, sepsis, and renal dysfunction and the elderly are at greatest risk.

One patient in the CARM reports was taking NSAIDs together with a diuretic and an ACE inhibitor, a combination which can further impair glomerular perfusion in predisposed patients.[1] In two reports the underlying causes of renal failure were interstitial nephritis, one with acute tubular necrosis. COX-2 inhibitors have a similar renal adverse effect profile to conventional NSAIDs.

## PROTON PUMP INHIBITORS AND INTERSTITIAL NEPHRITIS

CARM received 14 reports of ARF attributed to PPIs over the five-year period. In most cases the renal failure was considered due to interstitial nephritis with biopsy confirmation in six patients. When considering individual patients this reaction is rare but it is occurring frequently in New Zealand because of the extent of PPI prescribing. Interstitial nephritis is not predictable and awareness of early symptoms is important so that the PPI can be withdrawn promptly. Signs may include rash and eosinophilia but symptoms are often non-specific.[2]

## FLUCLOXACILLIN AND CO-TRIMOXAZOLE ARE THE MOST FREQUENTLY IMPLICATED ANTIBIOTICS IN GENERAL PRACTICE

Penicillins, especially flucloxacillin, and aminoglycosides were the most frequently implicated antibiotics in CARM reports of ARF. Most were due to large parenteral doses. In reports for antibiotics given in oral doses, normally used in general practice, co-trimoxazole and flucloxacillin were most often implicated. Renal failure is a rare reaction to these medicines and can be due to interstitial nephritis.

## RENAL FAILURE WITH COLCHICINE HAS LED TO CHANGES IN DOSE RECOMMENDATIONS

Over the five years two reports of acute renal failure with colchicine have been reported. An elderly patient developed renal failure when she became dehydrated following diarrhoea and vomiting. Because of such reports, in New Zealand and overseas, the dose recommendations for colchicine were recently changed because of the risk of serious dose-related adverse effects, especially in susceptible patients.[3] The dosing interval for colchicine has been increased from two to three hourly to six hourly. For otherwise healthy adults the maximum dose of colchicine in the first 24 hours is 2.5 mg and the total dose given in an acute attack should not exceed 6 mg over four days. Furthermore, it is no longer considered safe to continue dosing until gastrointestinal adverse effects occur.[3]

## HYPERKALAEMIA

Two patients who had ARF precipitated by medications were also taking potassium supplements and/or a potassium-sparing diuretic and developed hyperkalaemia. Both were aged over 80 years. One of these patients was also taking digoxin and developed a fatal arrhythmia. These cases serve as a reminder to closely monitor such combinations.

## PRE-EXISTING RENAL DISEASE PROMINENT IN RHABDOMYOLYSIS REPORTS

Lipid-lowering agents were the fourth most common medicine group implicated in ARF reports. ARF in these reports was due to rhabdomyolysis attributed in five patients to simvastatin and in one patient to bezafibrate. Of note is that four of these patients had pre-existing renal disease, a known risk factor for statin-induced rhabdomyolysis.[4] Concurrent use of medicines that interact with simvastatin was also considered contributory in some of these reports.

## AVOIDING RENAL DAMAGE IS A CHALLENGE

Avoiding renal damage in predisposed patients who need multiple medicines is difficult and challenging. The reports suggest that attention to dose and close monitoring where there is pre-existing renal disease or where potentially interacting medicines are indicated may help reduce ARF. Recognition of early symptoms where ARF is unpredictable is also important.

### *References*


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3. Medsafe Pharmacovigilance Team. Colchicine – safe use is critical. Prescriber Update 2006;27(1):2.
4. Australian Adverse Drug Reactions Advisory Committee (ADRAC). Risk factors for myopathy and rhabdomyolysis with the statins. Aust Adverse Drug React Bull 2004;23(1):2.