

# Prescriber Update

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## Clozapine – Close Monitoring Required

### Key Messages

- ⌘ Clozapine is effective in treatment-resistant schizophrenia, but is associated with significant adverse reactions.
- ⌘ Close monitoring, particularly in the first few months of treatment, is essential to reduce the occurrence of serious, sometimes fatal adverse reactions.
- ⌘ Permanent discontinuation of clozapine treatment is recommended for patients showing evidence of agranulocytosis, myocarditis, cardiomyopathy, or QT prolongation greater than 500 ms if no alternative causes can be found.
- ⌘ Treatment interruption and review is recommended for patients showing evidence of neutropenia, severe constipation/ileus, venous thromboembolism, severe diabetes/metabolic abnormalities, seizures or severe orthostatic hypertension.

Clozapine is an atypical antipsychotic used for treatment-resistant schizophrenia. A number of serious adverse reactions are associated with its use including: agranulocytosis, myocarditis, cardiomyopathy, and severe constipation (ileus).

### Agranulocytosis and neutropenia<sup>1,2</sup>

Agranulocytosis, defined as an absolute neutrophil count (ANC) less than 500/ $\mu$ L, is the most widely recognised serious adverse reaction of clozapine and warrants regular blood monitoring (weekly for 18 weeks, then monthly for the duration of treatment). Monitoring reduces the risk of agranulocytosis approximately 20-fold (from 0.7% to 0.03%). This is why pharmacists will not dispense clozapine without an up-to-date white cell count<sup>1</sup>.

Neither dose nor plasma concentration of clozapine have been found to be associated with the risk of agranulocytosis<sup>2</sup>. Elderly patients appear to be at higher risk and are more likely to die when agranulocytosis occurs<sup>2</sup>.

Agranulocytosis tends to develop during the first six months of treatment, whereas neutropenia (ANC between 500 and 1500/ $\mu$ L) may occur at any time<sup>1</sup>. Agranulocytosis is a medical emergency and clozapine should be stopped immediately and patients referred for

acute medical assessment<sup>2</sup>. Patients showing evidence of a drop in white cell counts should be investigated and monitored closely and (usually) have their treatment interrupted if neutropenia occurs<sup>1</sup>.

Between 1 January 2000 and 31 December 2014, the New Zealand Centre for Adverse Reactions Monitoring (CARM) received 166 reports of agranulocytosis and neutropenia in patients prescribed clozapine (13% of the total reports for clozapine). Where reported, the onset time to agranulocytosis/neutropenia ranged from one day to more than 20 years of clozapine treatment. The reported age range of the patients was between 15 and 92 years.

### Myocarditis

Myocarditis generally occurs within the first few weeks after clozapine initiation. The absolute risk has been estimated at 0.015% to 0.188% of patients<sup>1</sup>. Mortality rates as high as 50% have been reported<sup>3</sup>. Cases occurring later in treatment are more often fatal<sup>3</sup>. Unsurprisingly, a delayed diagnosis results in worse outcomes<sup>4</sup>. There are also case reports of later onset myocarditis, apparently associated with the re-introduction of clozapine<sup>5</sup>.

The pathophysiology of clozapine-associated myocarditis is poorly understood but may be a hypersensitivity reaction and as such is not dose-dependent<sup>4</sup>.

Myocarditis has a variety of non-specific presenting symptoms. Those most commonly reported include fever, tachycardia and chest pain<sup>3</sup>. Other symptoms include: shortness of breath, dry cough, elevated white cell count, peripheral eosinophilia, diarrhoea, vomiting, dysuria and rash<sup>3</sup>.

Diagnosis is not straightforward, and suspected cases should be referred urgently for a cardiology opinion. C-reactive protein (CRP) elevation occurs as one of the earliest signs of myocarditis, around five days prior to troponin elevation. Where available, echocardiography is recommended as an initial diagnostic step.

A comparison has been made of differences between fatal and non-fatal myocarditis in patients taking clozapine<sup>6</sup>. Obesity, longer duration of clozapine use and creatine kinase >1000 U/L were all significantly associated with death<sup>6</sup>.

CARM received 63 reports of myocarditis associated with clozapine between 1 January 2000 and 31 December 2014. Time to onset of myocarditis, where provided, ranged from four days to over a year. The most frequently reported onset time was 12 to 16 days. In 48 of 56 cases where the onset time was reported, symptoms developed within one month of starting clozapine.

In 34 cases, the patient was reported to have recovered or be improving. At least three cases were fatal. The age of patients with clozapine-associated myocarditis ranged from 16 to 81 years.

### **Cardiomyopathy**

Cardiomyopathy usually occurs later in clozapine treatment than myocarditis<sup>2</sup>. Symptoms include signs of heart failure, flu-like symptoms, cough, fever, sinus tachycardia/palpitations, fatigue, hypotension and chest discomfort<sup>7</sup>. Prescribers should maintain a high index of suspicion for cardiomyopathy throughout treatment<sup>2</sup>.

In a systematic review of published cases, the mean age of patients with clozapine-associated cardiomyopathy was 33.5 years with a mean clozapine dose of 360 mg/day<sup>7</sup>. The average onset latency was 14.4 months, with a range of three weeks to four years<sup>7</sup>. The mortality rate was around 15% in this review<sup>7</sup>.

Diagnosis of clozapine-associated cardiomyopathy is generally made on the basis of echocardiographic evidence of reduced ejection fraction. Electrocardiograms (ECGs) and blood tests, including raised B-type natriuretic peptide (BNP), provide supportive evidence. In general, patients with an ejection fraction of <25% at the time of diagnosis have a poor prognosis<sup>7</sup>.

Treatment includes cessation of clozapine and usual treatment for heart failure<sup>7</sup>.

Between 1 January 2000 and 31 December 2014, CARM received 30 reports of cardiomyopathy associated with clozapine. In four cases, the reported onset time was less than a month. This may have been due to underlying cardiac problems or that the patient had recently restarted clozapine. In 22 of the 28 cases with reported onset time, diagnosis of cardiomyopathy occurred after at least a year of treatment.

The youngest patient experiencing cardiomyopathy was 20 and the oldest 73. In two cases, the patient was reported to have died.

### **Constipation**

Constipation can develop at any stage of treatment and has been estimated to occur in 14% to 60% of patients. The risk is likely to be dose-related. Severe constipation can cause bowel obstruction, sepsis and death. More deaths are caused by clozapine-induced ileus/megacolon than by agranulocytosis<sup>1</sup>.

The most commonly reported signs and symptoms associated with severe constipation include moderate to severe abdominal pain, abdominal distension, vomiting, paradoxical 'overflow' diarrhoea, reduced appetite and nausea. However, many patients with schizophrenia have abnormally high pain tolerance, and may not report symptoms associated with constipation.

Many patients require routine use of a laxative, and this is often commenced during clozapine initiation. There is no clear evidence indicating which laxative is best. However, bulk forming and stimulant laxatives should be avoided in patients with suspected intestinal obstruction<sup>2</sup>.

Patients' bowel habits should be routinely monitored and those with suspected severe constipation should be referred urgently to gastroenterology or general medicine. Further information is available in an earlier edition of *Prescriber Update*, 'Clozapine: impacts on the colon'<sup>8</sup>.

Between 1 January 2000 and 31 December 2014 CARM received reports of 74 cases of constipation and more serious bowel conditions such as ileus, megacolon and intestinal ischaemia, necrosis, obstruction and perforation. The onset time (when reported) ranged from five days to over 10 years. The affected patients were 18 to 71 years of age.

### **Monitoring clozapine patients**

#### **Prior to initiation**

Before starting clozapine, patients should have a thorough medical evaluation, including baseline ECG, chest X-ray and possibly an echocardiogram. However, there is no evidence that routine repetition of ECG or echocardiograms will reliably detect clozapine induced cardiac toxicity<sup>3,7</sup>.

Baseline blood tests should check white cell count, troponins, CRP and possibly BNP<sup>3</sup>.

Patients with a history of cardiac disease or abnormal cardiac findings on examination

(such as QT prolongation) should be referred to a cardiologist<sup>7</sup>.

Any pre-existing constipation should be effectively treated before starting clozapine. Co-prescription of other constipating medicines should be avoided whenever possible. Patients should be warned about the risks of constipation and given information on diet, exercise and fluid intake<sup>2</sup>.

#### **First few months**

For the first 18 weeks after initiation, patients require routine weekly blood tests to detect emergent agranulocytosis or neutropenia. Troponins and CRP should be included in weekly blood work for the first four weeks of treatment (ie, on days 7, 14, 21 and 28)<sup>3</sup>.

Patients should be monitored at least weekly for the first four months, and/or co-prescribed a laxative, to avoid constipation.

#### **Longer term**

Patients should be assessed at least four times a year for symptoms of heart failure and constipation. Any patients with new symptoms consistent with heart failure/cardiomyopathy or constipation should be investigated further.

Monitoring for constipation should be continued regularly throughout treatment as the risk of constipation usually persists<sup>2</sup>.

#### **When to discontinue clozapine treatment permanently**

Clozapine should be permanently discontinued if no alternative causes for the following events are identified.

Agranulocytosis, (ANC less than 500/ $\mu$ L) should always lead to prompt permanent discontinuation of clozapine<sup>1</sup>.

If myocarditis is suspected, and troponin is more than twice the upper limit of normal or CRP is over 100 mg/L, clozapine should be discontinued permanently. Left ventricular function recovers rapidly on withdrawal of clozapine and significant improvement is usually seen within five days<sup>3</sup>.

A diagnosis of cardiomyopathy should result in prompt, permanent discontinuation of clozapine<sup>1,7</sup>.

In addition, permanent termination of clozapine treatment is recommended when the QT

prolongation is greater than 500 ms using the correct (usually Fridericia) correction formula<sup>1</sup>.

#### **When to interrupt treatment<sup>1</sup>**

If neutropenia (ANC between 500 and 1500/ $\mu$ L) develops, clozapine therapy should be interrupted until the ANC normalises.

Clozapine withdrawal is indicated for severe constipation and ileus. Clozapine may be reintroduced after addressing inadequate dietary and bowel habits if present. A stimulant laxative may also be needed in the short term. Patients with no bowel movement in five days despite the use of laxatives should be admitted to hospital for treatment.

Other situations in which clozapine treatment should be interrupted, but may potentially be restarted with appropriate surveillance and management, include: venous thromboembolism, severe diabetes and metabolic abnormalities, seizures and orthostatic hypotension.

#### **Benefits of clozapine**

Clozapine has unique efficacy in patients with treatment-resistant schizophrenia, including anti-suicidal and anti-aggressive properties. Many clozapine-treated patients and their relatives report a substantial positive effect on their lives and wellbeing<sup>1</sup>.

Despite the serious adverse reactions of clozapine, a study of patients in Finland found that all-cause mortality with clozapine treatment was significantly lower than for any other antipsychotic<sup>9</sup>. New Zealand data confirm the benefits of clozapine in treatment resistant psychosis<sup>10</sup>.

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## Risk of Inhibitor Development with Factor VIII Replacement Products

### Key Messages

- ⌘ The risk of inhibitor (autoantibody) development is comparable for plasma-derived and recombinant factor VIII products.
- ⌘ The current data is insufficient to determine if the risk of inhibitor development varies between different recombinant products.

Recently published clinical studies have raised the possibility that different factor VIII replacement products are associated with different risks of inhibitor development.

Factor VIII replacement products are used to prevent and treat bleeding in patients with haemophilia. Factor VIII concentrates are either plasma-derived or recombinant products.

The major adverse reaction of concern is the development of autoantibodies known as inhibitors. Inhibitors prevent the clotting action of factor VIII risking fatal and disabling bleeds in the patient.

The risk factors for development of factor VIII inhibitors are numerous and not yet fully understood, they include patient related factors as well as therapy related factors.

In 2013, the results of the RODIN study were published<sup>1</sup>. In this study, there was no difference in terms of inhibitor development between plasma-derived and recombinant products<sup>1</sup>. However, comparison of different recombinant products found a higher incidence of inhibitor

development in patients treated with Kogenate FS compared to Advate<sup>1</sup>.

The Medicines Adverse Reactions Committee (MARC) has reviewed data from the RODIN study. In addition, information from cohorts and registries of haemophilia patients in France, Canada, the UK and Europe were considered<sup>2-5</sup>.

The MARC concluded these data were inconclusive and no definite difference between products was demonstrated. The MARC considered that prescribers and patients should continue to use the product that best suits the needs of the patient. The minutes from the meeting are published on the Medsafe website ([www.medsafe.govt.nz/profs/adverse/Minutes161.htm#3.2.1](http://www.medsafe.govt.nz/profs/adverse/Minutes161.htm#3.2.1)).

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## Macrolides – Don't Upset the Rhythm

### Key Messages

- ⌘ Macrolide antibiotics (azithromycin, clarithromycin, erythromycin and roxithromycin) are associated with a small increased risk of abnormal heart rhythms such as QT interval prolongation, which may rarely result in sudden cardiac death.
- ⌘ The risk is increased in patients with other cardiovascular risk factors and in patients taking other QT prolonging medicines.

Medsafe and the Medicines Adverse Reactions Committee (MARC) have recently completed a review of the risk of cardiac arrhythmias and sudden cardiac death associated with the use of macrolide antibiotics.

In New Zealand, azithromycin, clarithromycin, erythromycin and roxithromycin are macrolide antibiotics approved for use. The MARC concluded that the macrolide class of antibiotics are associated with a small increased risk of abnormal electrical changes in the heart such as QT interval prolongation. These changes may rarely lead to sudden cardiac death.

Healthcare professionals should consider the risk of QT prolongation when weighing the risks and benefits of macrolide antibiotics, particularly in at-risk groups. At-risk groups include:

- patients predisposed to QT interval prolongation such as those with a history of Torsades de Pointes or congenital long QT syndrome
- patients taking other medications known to prolong the QT interval such as antiarrhythmics

of classes IA and III (eg, amiodarone), antipsychotic agents (eg, risperidone, haloperidol), antidepressants (eg, citalopram), and fluoroquinolones (eg, ciprofloxacin)

- patients with electrolyte disturbance, particularly in cases of hypokalaemia and hypomagnesaemia
- patients with clinically relevant bradycardia, cardiac arrhythmia or cardiac insufficiency.

The Centre for Adverse Reactions Monitoring (CARM) has received 28 case reports of heart rate and rhythm disorders associated with the use of macrolides. Four of these cases were reported with clarithromycin, 10 with erythromycin, four with erythromycin ethylsuccinate and 10 with roxithromycin.

The reactions most commonly reported include palpitations, tachycardia and QT interval prolongation. In the majority of cases reported to CARM, adverse heart reactions occurred within 24 hours of initiating the macrolide antibiotic.

Medsafe is working with the relevant sponsors to ensure all macrolide antibiotic data sheets contain consistent information about these risks.

Further information about drug-induced QT interval prolongation, arrhythmias and Torsades de Pointes is available at:

- [www.qtdrugs.org](http://www.qtdrugs.org)
- [www.medsafe.govt.nz/profs/PUArticles/DrugInducedQTProlongation.htm](http://www.medsafe.govt.nz/profs/PUArticles/DrugInducedQTProlongation.htm)

## Medicine Use in Lactation

### Key Messages

- ⌘ Most medicines may be safely used during breastfeeding. However, where possible, the lowest effective dose for the shortest possible duration should be used.
- ⌘ Physicochemical characteristics of the medicine and breast milk composition determine the concentration of medicines in breast milk.
- ⌘ Adverse reactions more commonly observed in nursing infants include sedation, gastrointestinal upset and irritability.
- ⌘ The benefits and risks of harm of treatment in both the mother and infant should be considered as well as the benefits and risks of harm of not treating.

Medicines are often needed by women who are breastfeeding. However, there is often a lack of, or ambiguous, information about the safety of medicines transferred to the infant in breast milk. This has meant that in the past breastfeeding has been stopped unnecessarily or a different, potentially less appropriate treatment prescribed<sup>1</sup>.

Although most medicines are excreted in breast milk to some degree, the amount is usually less than 10% of the maternal dose. Medicines excreted at less than 10% are considered compatible with breastfeeding. Therefore, with a few exceptions the majority of medicines may be used<sup>2</sup>.

Almost all medicines pass into breast milk via passive diffusion. The amount available is dependent on a number of factors such as:<sup>3,4,5</sup>

- oral bioavailability
- plasma half-life
- lipid solubility
- molecular weight or size
- ionisation
- percentage of maternal protein binding
- composition of the milk.

For example, breast milk is slightly more acidic than plasma (pH 7.1 compared with pH 7.4)<sup>5</sup>. Therefore, medicines with a higher pH (basic) such as  $\beta$ -blockers will diffuse into the milk more readily. The relatively acidic milk then changes the physicochemical structure of the medicine, shifting the equilibrium between the ionised and non-ionised forms to the ionised form. The ionised form is less able to diffuse back from the milk to the plasma, thereby becoming 'trapped' in the milk<sup>5</sup>.

In addition to being more acidic, breast milk contains more lipids and less protein than plasma. Because of breast milk lipophilicity, medicines with high lipid solubility are more likely to concentrate in the breast milk<sup>4</sup>.

Medicines with a high molecular weight (eg, insulin and heparin) do not readily transfer into breast milk as they are too large to cross mammary epithelium cell walls<sup>3</sup>. Active transport or dissolution in lipid membranes of cells is required, reducing the likelihood of these medicines passing into breast milk.

Highly maternally protein bound medicines are also less likely to pass into breast milk as the more

bound a medicine is, the less efficiently it can cross cell membranes<sup>3</sup>.

As all medicines have a combination of these factors and milk composition changes with time, there is variability in medicine transfer into breast milk.

The safety of breastfeeding whilst taking medicines also depends on the age of the infant as drug metabolism and clearance is reduced in the neonate<sup>6</sup>.

An up-to-date database of medicine levels in breast milk and infant blood and possible adverse reactions in the nursing infant is available at LactMed ([www.toxnet.nlm.nih.gov/newtoxnet/lactmed.htm](http://www.toxnet.nlm.nih.gov/newtoxnet/lactmed.htm)). The World Health Organization (WHO) has also produced a classification guide for medicines use in breastfeeding based on the WHO list of essential drugs ([www.who.int/maternal\\_child\\_adolescent/documents/55732/en/](http://www.who.int/maternal_child_adolescent/documents/55732/en/)).

Medicines with inherent toxicity or those with high infant exposure and therefore potential for significant toxicity are contraindicated during breastfeeding, and include:<sup>4</sup>

- cytotoxic agents
- immunosuppressive agents
- amiodarone
- lithium
- ergotamine
- gold salts
- isotretinoin.

Radiopharmaceutical administration also requires temporary cessation of breastfeeding<sup>7</sup>.

There are a range of health issues that affect women who are breastfeeding. These most commonly include infection, depressive disorders, pain, contraception, low milk supply and atopic conditions<sup>1</sup>. Table 1 provides information on the compatibility of medicines used in the treatment of these conditions with breastfeeding.

Consideration should be given to the benefits and risks of harm of treatment in both the mother and child prior to initiating therapy, as well as the risks of harm of not initiating or continuing therapy. The breastfed infant should be monitored for potential adverse reactions, most commonly sedation, gastrointestinal effects (eg, diarrhoea) and irritability<sup>5</sup>.

In addition to possible effects in the breastfed infant, some medicines may affect milk production, often through hormonal regulation of lactation. For example, oestrogen-containing contraception is not recommended if the mother is breastfeeding as it reduces milk production. Domperidone and metoclopramide increase prolactin, which promotes lactation<sup>2</sup>.

Breastfeeding mothers should use the lowest effective dose of a medicine for the shortest possible duration. For medicines with a short half-life, feeding the infant immediately prior to mother taking the next dose reduces the drug exposure in the infant.

If possible, medicines with short half-lives, high maternal protein binding, low oral availability and high molecular weight should be used.

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**Table 1: Compatibility of commonly used medicines with breastfeeding<sup>2,7,8</sup>**

Condition	Treatment	Breastfeeding Recommendation	Additional Information
Infection	<b>Antibiotics</b>		
	β-lactams (eg, amoxicillin)	Compatible	Gastrointestinal flora changes possible; monitor infant for diarrhoea, vomiting, thrush
	Macrolides (eg, erythromycin)	Compatible	Single dose of azithromycin considered safe
	Cephalosporins (eg, cephalexin)	Compatible	May also affect infant gut flora (third generation more likely)
	Fluoroquinolones (eg, ciprofloxacin)	Avoid if possible	Potential risk of arthropathies
	Trimethoprim	Compatible	
	Nitrofurantoin	Compatible	Avoid nitrofurantoin if infant less than one month old or premature
	Metronidazole	Avoid if possible	If single 2 g metronidazole dose given, discontinue breastfeeding for 12 hours
	<b>Antifungals</b>		
	Azoles (eg, fluconazole)	Compatible	If applying miconazole oral gel to nipples, apply after breastfeeding
	Nystatin	Compatible	
	<b>Antivirals</b>		
	Aciclovir	Compatible	

Condition	Treatment	Breastfeeding Recommendation	Additional Information
<b>Depressive disorders</b>	<b>Antidepressants</b>		
	SSRIs (eg, paroxetine)	Compatible	Paroxetine and sertraline preferred due to shorter half-lives
	TCA's (eg, amitriptyline)	Less preferred due to potential toxicity	Amitriptyline compatible in doses up to 150 mg/day
	<b>Anxiolytics</b>		
	Benzodiazepines (eg, temazepam)	Compatible in a single dose; avoid repeated doses	Short-acting benzodiazepines preferred as accumulation may occur Monitor infant for drowsiness
<b>Pain</b>	<b>Analgesics</b>		
	Paracetamol	Compatible	Paracetamol analgesic of choice
	NSAIDs (eg, ibuprofen)	Compatible	Avoid breastfeeding with long-term acetylsalicylic acid treatment
	Opiates (eg, codeine)	Compatible in occasional doses	Monitor infant for drowsiness, apnoea, bradycardia and cyanosis Use codeine with caution in rapid metabolisers
	Tramadol	Compatible	
<b>Contraception</b>	<b>Hormonal methods</b>		
	Progesterone	Compatible	Do not initiate before six weeks postpartum
	Oestrogen	Avoid if possible	May inhibit lactation
<b>Allergies and hay fever</b>	<b>Antihistamines</b>		
	Sedating (eg, promethazine)	Probably compatible	Occasional use probably safe Monitor for sedation in mother and infant
	Non-sedating (eg, loratadine)	Compatible	
	<b>Topical</b>		
	Corticosteroids (eg, hydrocortisone)	Compatible	If applying to breasts apply after feeding
<b>Asthma</b>	B2- adrenergics (eg, salbutamol)	Compatible	
	Corticosteroids (eg, budesonide)	Compatible	
<b>Other</b>	Warfarin	Compatible	
	Metformin	Compatible	

## MARC's Remarks: March 2015 Meeting

The Medicines Adverse Reactions Committee (MARC) met on 12 March 2015 to consider:

- development of inhibitors to **factor VIII replacement** products (further information can be found in this edition of *Prescriber Update*<sup>1</sup>)
- risk of cardiac arrhythmias with **macrolide antibiotics** (further information can be found in this edition of *Prescriber Update*<sup>2</sup>)
- cardiovascular risks associated with **ibuprofen**.

The MARC agreed that the ibuprofen data sheets should be harmonised so that information about cardiovascular risks is clear and consistent

across all data sheets. In addition, the MARC recommended that Medsafe communicates information about cardiovascular risks to consumers and healthcare professionals.

Further information on this meeting can be found on the Medsafe website ([www.medsafe.govt.nz/profs/adverse/Minutes161.htm](http://www.medsafe.govt.nz/profs/adverse/Minutes161.htm)).

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1. Medsafe. 2015. Risk of inhibitor development with factor VIII replacement products. *Prescriber Update* 36(2): 21.
2. Medsafe. 2015. Macrolides — don't upset the rhythm. *Prescriber Update* 36(2): 22.

## Keeping it Renal: Drug-Induced Acute Interstitial Nephritis

### Key Messages

- ⌘ Acute interstitial nephritis is an important cause of acute kidney injury.
- ⌘ Over two-thirds of acute interstitial nephritis cases are drug-induced.
- ⌘ Antibiotics, non-steroidal anti-inflammatory drugs and proton pump inhibitors are most frequently associated with drug-induced acute interstitial nephritis.
- ⌘ Rapid identification and withdrawal of the suspect medicine is the mainstay of treatment.

### Background

Acute interstitial nephritis (AIN) is the third most common cause of acute kidney injury (AKI) after prerenal AKI and acute tubular necrosis<sup>1</sup>. Over two-thirds of AIN cases are drug-induced and infection-related AIN accounts for 5% to 10% of cases<sup>2</sup>.

### Medicines that can cause AIN

Antibiotics and non-steroidal anti-inflammatory drugs (NSAIDs) are most frequently associated with drug-induced AIN<sup>2</sup>. The role of proton pump inhibitors (PPIs) has also been highlighted more recently<sup>3</sup>. Medicines most commonly associated with AIN are shown in Table 1.

**Table 1: Medicines associated with acute interstitial nephritis<sup>1</sup>**

Medicine class	Examples
Antibiotics	β-lactam antibiotics*, fluoroquinolones*, rifampicin*, sulphur-based medicines*, vancomycin, minocycline, ethambutol, erythromycin, chloramphenicol
Analgesics	non-steroidal anti-inflammatory drugs* (eg, diclofenac), selective COX-2 inhibitors (eg, celecoxib)
Gastrointestinal medicines	proton pump inhibitors* (eg, omeprazole), h <sub>2</sub> -receptor antagonists (eg, ranitidine)
Antiviral medicines	aciclovir, abacavir, indinavir, atazanavir
Antiepileptic medicines	phenytoin*, phenobarbital, carbamazepine
Other medicines	allopurinol*, 5-aminosalicylates* (eg, mesalazine, sulfasalazine), captopril, interferon, ciclosporin, anti-angiogenesis medicines (tyrosine kinase inhibitors [eg, sunitinib]), diuretics (eg, furosemide)

\*most common causative medicines

The average time period between starting the medicine and the appearance of renal manifestations is 10 days<sup>4</sup>. However, this time period can be as short as one day after some antibiotics or as long as several months with NSAIDs<sup>4</sup>.

For PPIs, the interval is most commonly 10 to 11 weeks but this can vary between one week and nine months<sup>2</sup>.

### Clinical Features

Clinical suspicion of AIN in patients with AKI usually relies on:<sup>2</sup>

- the presence of general symptoms
  - malaise
  - anorexia
  - nausea
  - arthralgia
- hypersensitivity reactions
  - low grade fever
  - skin rash
  - eosinophilia
- urinalysis findings typical of AIN
  - microhaematuria
  - non-nephrotic proteinuria (some patients with NSAID-related AIN can present complete nephrotic syndrome)
  - leucocyturia.

Sterile pyuria and leucocyte casts are important clues for the diagnosis of AIN in patients with AKI<sup>2</sup>. An important number of cases have an oligosymptomatic presentation; the classical triad of rash, fever and eosinophilia are less commonly observed than was initially reported<sup>2</sup>.

The absence of hypersensitivity reactions and normal urinary sediment are important features to distinguish acute tubular necrosis from AIN<sup>2</sup>. AIN is difficult to diagnose. Ultimately, kidney biopsy is needed to confirm the diagnosis<sup>2</sup>.

### Treatment

Rapid identification and withdrawal of the suspect medicine is the mainstay of treatment<sup>2</sup>.

Early treatment with corticosteroids (within the first five days) can reduce the amount of tubulointerstitial fibrosis that develops and avoid incomplete recovery of renal function<sup>1,2</sup>. However, the use of corticosteroids is still controversial and further studies are required to confirm their place in the treatment of drug-induced AIN<sup>2</sup>.

### New Zealand Cases

The Centre for Adverse Reactions Monitoring (CARM) has received 189 case reports of AIN. However, some cases involve more than one suspect medicine.

The most common medicines reported were omeprazole, diclofenac, flucloxacillin and amoxicillin-containing medicines.

Average onset time of AIN following medicine initiation varied from within a few days to more than one year. This is consistent with onset times reported in the literature.

The suspect medicine was withdrawn in 170 of the 189 cases. Of these 170 cases, there was definite improvement in 108 and the result not known in 50. It is not known if treatment with corticosteroids occurred in any of the reported cases.

Healthcare professionals are encouraged to report any adverse events to medicines, including drug-induced AIN, to CARM. Reports may be submitted on paper or electronically (<https://nzphvc.otago.ac.nz/>).

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## New Oral Anticoagulants – Interactions Still Important

With three new oral anticoagulants available in New Zealand, prescribers are reminded of the importance of interactions and the clinical significance of these risks.

The three new oral anticoagulant medicines available in New Zealand are: dabigatran etexilate (Pradaxa), rivaroxaban (Xarelto) and apixaban (Eliquis)<sup>1,2,3</sup>. Dabigatran is a coagulation factor IIa inhibitor. Rivaroxaban and apixaban are factor Xa inhibitors.

### Pharmacodynamic

The risk of bleeding with anticoagulants is increased with concomitant use of non-steroidal anti-inflammatory drugs (NSAIDs), selective serotonin reuptake inhibitors (SSRIs), and anti-platelet agents such as aspirin.

In addition, pharmacokinetic interactions can increase the risk of bleeding as well as reducing therapeutic effect.

### Cytochrome P450 3A4

Rivaroxaban and apixaban are metabolised by cytochrome P450 3A4 (CYP3A4). Inter-individual variability in CYP3A4 activity is high<sup>4</sup>. Therefore, the concomitant administration of factor Xa inhibitors with CYP3A4 inhibitors or inducers will have important effects in some patients.

Factor Xa inhibitors are contraindicated for patients receiving HIV protease inhibitors (such as ritonavir) which are strong inhibitors of CYP3A4 enzymes<sup>2,3</sup>.

Co-administration with inducers of CYP3A4 enzymes such as phenytoin may lead to a reduced rivaroxaban or apixaban plasma concentration and inadequate therapeutic effect<sup>2,3</sup>.

Further information about CYP3A4 and medicines that inhibit or induce CYP3A4 can be found in the *Prescriber Update* article 'Drug Metabolism – the importance of cytochrome P450 3A4'<sup>4</sup>.

### P-glycoprotein

Patients taking dabigatran, rivaroxaban or apixaban, have an increased risk of bleeding if they also take P-glycoprotein inhibitors. This is especially relevant because verapamil

or amiodarone may be prescribed for atrial fibrillation<sup>5</sup>.

More examples of medicines that inhibit P-glycoprotein can be found in the *Prescriber Update* article 'Medicines interactions: the role of P-glycoprotein'<sup>6</sup>.

Many drugs that have an effect on P-glycoprotein also have an effect on CYP3A4. For example, carbamazepine and St. John's Wort which reduce absorption of oral anticoagulants through inducing P-glycoprotein activity also induce CYP3A4 metabolism of rivaroxaban and apixaban.

P-glycoprotein functions as a biological barrier by extruding toxins and xenobiotics out of intestinal cells back into the intestine. The contribution of intestinal P-glycoprotein to overall drug absorption is usually not large unless the oral drug dose is small, or the dissolution and diffusion rates of the drug are very slow. P-glycoprotein based interactions usually do not change plasma concentrations as much as CYP450 interactions<sup>6</sup>.

As with all medicines, healthcare professionals are encouraged to report any suspected adverse reactions to the Centre for Adverse Reactions Monitoring (CARM).

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# Adverse Reactions Following Zoledronic Acid Infusion

## Key Messages

- ⌘ Patients who are treated with zoledronic acid can experience acute phase reactions.
- ⌘ Symptoms include fever, diffuse musculoskeletal pain, gastrointestinal effects, and eye inflammation.
- ⌘ The risk of renal reactions can be prevented by keeping patients adequately hydrated prior to and following infusions.

## Acute Phase Reactions

Zoledronic acid (marketed as Aclasta and Zometa in New Zealand) is a bisphosphonate administered to patients by intravenous infusion. Prescribers are reminded that patients may experience an acute phase response or adverse effects on renal function following administration.

Acute phase reactions may present with the following symptoms: chills, fever, influenza-like symptoms, night sweats, rigors and shivering, diffuse musculoskeletal pain, gastrointestinal effects, and eye inflammation<sup>1</sup>.

Acute phase responses can occur at any time up to approximately two weeks following an infusion<sup>1</sup>. The majority of patients will experience symptoms within the first three days after an infusion<sup>1</sup>. These reactions are usually self-limiting and resolve completely within 24 to 48 hours<sup>2</sup>. However, in some patients symptoms may persist for longer periods.

Supportive and symptomatic management with paracetamol and non-steroidal anti-inflammatory drugs is recommended, once other serious causes of fever such as infection have been excluded<sup>2</sup>. Pre-treatment with paracetamol or ibuprofen may also be helpful for some patients<sup>2</sup>.

## Renal Reactions

Renal reactions can also occur shortly after infusion. Adequate hydration can help to reduce the risk of renal deterioration after a zoledronic acid infusion<sup>4-6</sup>. Renal deterioration, progression to renal failure and dialysis has been reported in patients following the initial dose of zoledronic acid<sup>5</sup>. If patients show signs of renal function decline after infusion, the benefits and risks of harm of continued treatment should be evaluated.

Factors which may increase the risk of renal deterioration following zoledronic acid infusions are:

- dehydration
- pre-existing renal impairment
- multiple cycles of zoledronic acid or other bisphosphonates
- concomitant use of nephrotoxic drugs
- a shorter infusion time than recommended.

Bisphosphonates are also associated with ocular inflammatory effects such as uveitis and scleritis<sup>3</sup>. Ocular complications are uncommon. However, patients should be advised to seek immediate medical attention if they experience any ocular symptoms while being treated with a bisphosphonate

The Centre for Adverse Reaction Monitoring (CARM) has received 153 reports of musculoskeletal adverse reactions starting within one month after a zoledronic acid infusion. CARM also received 26 reports of ocular adverse reactions and 33 reports of urinary adverse reactions within one month following an infusion.

Healthcare professionals are encouraged to report all suspicions of medicine adverse reactions to CARM.

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## Quarterly Summary of Medsafe's Early Warning System Communications

The early warning system provides current and historical information on safety concerns for medicines and medical devices. These warnings are intended to help consumers and healthcare professionals make informed decisions about their use of medicines and medical devices.

More information about the early warning system can be found on the Medsafe website ([www.medsafe.govt.nz/Projects/B2/EWS.asp](http://www.medsafe.govt.nz/Projects/B2/EWS.asp)).

Date	Communication	Topic
22 December 2014	Alert	Domperidone (Motilium, Prokinex) – conclusion of review of benefits and risks of harm
9 February 2015	Monitoring	M <sup>2</sup> UPDATE – Bisphosphonates and possible risk of optic neuritis
7 April 2015	Monitoring	M <sup>2</sup> Guaifenesin (Guaiphenesin) and possible risk of tinnitus added to the medicines monitoring (M <sup>2</sup> ) scheme
29 April 2015	Alert	Changes to the use of bromhexine or codeine-containing cough and cold medicines in children

If you would like to receive Medsafe's early warning communications you can subscribe at [www.medsafe.govt.nz/profs/subscribe.asp](http://www.medsafe.govt.nz/profs/subscribe.asp)

## WE NEED YOUR HELP!

Please send your reports for these potential safety issues\* listed in the table below.



Medicine	Potential safety issue	Active monitoring ends
Guaifenesin (Guaiphenesin)	Tinnitus	31 October 2015

- M<sup>2</sup> is a Medsafe scheme designed to collect more information on potential safety signals for specific medicines.
- Safety signals are identified from reports of adverse medicine reactions sent to the Centre for Adverse Reactions Monitoring (CARM). For further information see the Medsafe website.
- The M<sup>2</sup> scheme does not replace routine adverse reaction reporting. Find out how to report at: [www.otago.ac.nz/carm](http://www.otago.ac.nz/carm) or [www.medsafe.govt.nz](http://www.medsafe.govt.nz)



New Zealand Government

\* Although active monitoring will cease at this date please continue to submit reports for these medicines after this date as with all medicines.

**Patient Details**

Surname:	First name/s:	NHI No:	
Address:		Date of birth:	Sex:
		Ethnicity:	

**All medicines in use \*asterisk suspect medicine/s\*** Include over-the-counter (OTC) and alternative medicines

Medicine or Vaccine+batch no.	Daily Dose	Route	Date Started	Date Stopped	Reason for Use

**Description of Adverse Reaction or Event**

Date of onset: \_\_\_\_\_

Recovered  Not yet recovered but improved  Not yet recovered  Unknown  Fatal  - Date of Death: \_\_\_\_\_

Severe? - Yes  No  Rechallenged? - No  Yes  Result \_\_\_\_\_

**Other Factors** - Please tick or specify as appropriate

Renal disease  Allergy : \_\_\_\_\_ Other Medical Conditions : \_\_\_\_\_

Hepatic disease  Nutritional Suppl or OTC use : \_\_\_\_\_ Industrial Chemicals : \_\_\_\_\_

**Reporter** - Please tick as appropriate Doctor  Pharmacist  Dentist  Other \_\_\_\_\_

Name: \_\_\_\_\_

Address: \_\_\_\_\_ Signature: \_\_\_\_\_

Phone: \_\_\_\_\_ Date: \_\_\_\_\_

**Send completed form to CARM**

Freepost 112002, CARM, PO Box 913, Dunedin 9054 or Fax: (03) 479 7150

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