Prescriber Update

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Contents

MEDSAFE
NEW ZEALAND MEDICINES AND MEDICAL DEVICES SAFETY AUTHORITY
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NSAIDs and Acute Kidney Injury

Key messages

- ⌘ All NSAIDs (including COX-2 inhibitors) have been associated with the development of acute kidney injury.
- ⌘ Acute kidney injury is more likely to occur in patients with other risk factors — particularly hypovolaemic states.
- ⌘ Renal function should be monitored in at risk patients.
- ⌘ If acute kidney injury occurs, the NSAID should be stopped.
- ⌘ NSAIDs should be avoided in patients who develop or have a history of interstitial nephritis.

All non-steroidal anti-inflammatory drugs (NSAIDs) have been associated with the development of acute kidney injury.

NSAIDs and Acute Kidney Injury

NSAIDs can cause two different forms of acute kidney injury[1].

1. Haemodynamically mediated (eg, pre-renal injury and/or acute tubular necrosis).
2. Immune mediated (eg, acute interstitial nephritis).

Acute kidney injury represents a continuum of renal injury ranging from clinically asymptomatic changes in renal function to renal failure and death. Acute kidney injury is characterised by a rapid fall in glomerular filtration rate (GFR) over hours to days.

Presentation and Diagnosis

There are no specific signs or symptoms for NSAID induced acute kidney injury. Symptoms of acute kidney injury can be non-specific and may include shortness of breath, fatigue, confusion, nausea, decreased urine output and ankle/leg swelling[2].

Patients with pre-renal injury may have signs of volume depletion (eg, tachycardia, absolute or postural hypotension, low jugular venous pressure, dry mucous membranes). Patients with interstitial nephritis may have features of a systemic hypersensitivity including fever, arthralgia and a pruritic erythematous rash. Eosinophilia may also be present.

Pathogenesis and Risk Factors

NSAIDs reversibly inhibit the production of renal prostaglandins via their inhibition of COX-1 and COX-2. Maximal inhibition occurs at steady state plasma concentrations (usually 3–7 days).

Renal prostaglandins cause dilatation of the renal afferent arteriole. This mechanism is important for maintaining GFR when renal blood flow is reduced (ie, not in young, healthy people)[1]. Therefore, NSAID use is likely to have a greater effect on renal function in patients with other risk factors (Table 1).

It is unclear how NSAIDs induce acute interstitial nephritis. However, it has been suggested that cyclooxygenase inhibition causes preferential conversion of arachidonic acid to leukotrienes, which may then activate helper T cells[1].

Pre-existing chronic kidney disease and increasing age are the most common risk factors for developing acute kidney injury[3].

The 'Triple Whammy'

A recent nested case-control study found that current use of triple therapy (ACE inhibitor/ARB, diuretic and an NSAID) was associated with an increased rate of acute kidney injury (Rate Ratio 1.31, 95% CI 1.12–1.53) compared to double therapy (diuretic plus ACE inhibitor/ARB).

The greatest risk was observed in the first 30 days of use (Rate Ratio 1.82, 95% CI 1.35-2.46)[4]. This 'triple whammy' effect was first identified from case reports in early 2000 and was highlighted in *Prescriber Update* in 2002[5].

Treatment

Renal function will recover in most patients after withdrawal of NSAID therapy. Steroids may aid recovery in patients with interstitial nephritis who do not improve after stopping NSAID therapy. NSAID use should be avoided in the future in such patients[1].

New Zealand Information

NSAIDs are indicated to relieve moderate pain and inflammation associated with conditions such as rheumatic disorders, surgery and/or dysmenorrhoea.

Table 1: Risk factors for NSAID induced acute kidney injury[1,2]

Risk factor	Effect
Increasing age (particularly age >65), chronic hypertension and atherosclerosis	Narrowing of renal arterioles which may reduce their capacity for renal afferent dilatation
Pre-existing glomerular disease or renal	Renal afferent dilatation is likely to be required to maintain GFR
Volume depletion • True volume depletion (ie, GI or renal salt and water losses, blood loss, diuretic use) • Effective volume depletion (ie, cirrhosis or heart failure)	Lowers afferent glomerular arteriolar pressure and stimulates secretion of angiotensin II
Use of ACE inhibitors or ARBs	ACE inhibitors and ARBs prevent efferent arteriole vasoconstriction which is also important in maintenance of GFR
Use of the 'triple whammy' (ACE inhibitor or ARB plus diuretic plus NSAID)	Diuretic may cause volume depletion. See above for ACE inhibitor/ARB effects

ACE=Angiotensin Converting Enzyme; ARB=Angiotensin II Receptor Blocker

PHARMAC data indicates that ibuprofen is the most commonly prescribed NSAID in New Zealand. This is followed by diclofenac and naproxen.

The Centre for Adverse Reactions Monitoring (CARM) received 119 reports of renal adverse reactions associated with NSAID (including COX-2 inhibitor) use from 1 January 2000 (Figure 1).

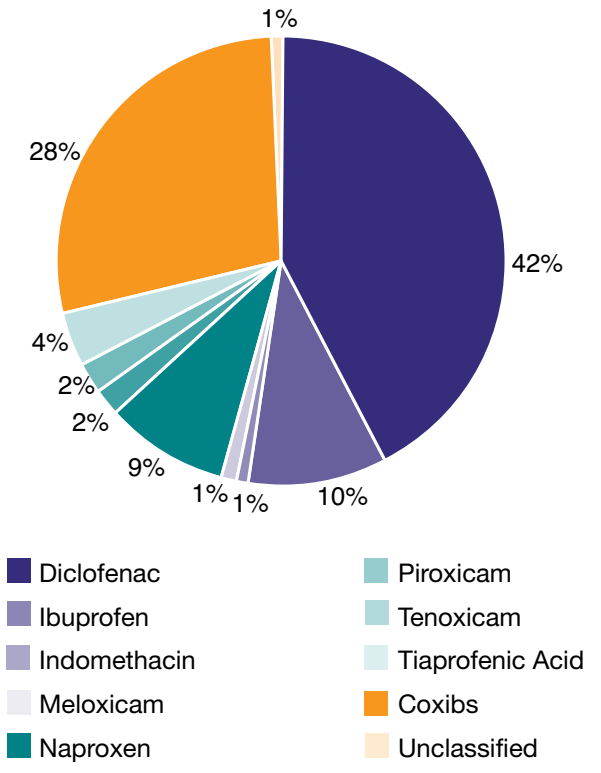

Figure 1: Renal adverse reaction reports from 1 January 2000 to 31 December 2012

Approximately 70% of reports were serious, including four deaths and 12 that were considered to be life-threatening. The majority of reports (74%) occurred in patients aged 50 years and over.

Diclofenac was the most commonly implicated NSAID (53 reports). In two thirds of the reports, other medicines were also considered suspect, including four reports that described the 'triple whammy'. Reports included acute renal failure (33 reports), renal tubular necrosis (5) and interstitial nephritis (12).

Healthcare professionals are encouraged to report suspected adverse reactions to NSAIDs to CARM.

References

1. Rose BD, Post TW. 2013. NSAIDs: Acute kidney injury (acute renal failure) and nephrotic syndrome. In *UpToDate*, Basow, DS. (ed). Waltham: UpToDate. URL: **www.uptodate.com** (accessed 10 May 2013).
2. Longo DL, Fauci AS, Kasper DL, et al. (eds). 2012. *Harrison's Principles of Internal Medicine*. New York: McGraw-Hill Education. URL: **www.accessmedicine.com** (accessed 10 May 2013).
3. Best Practice Advocacy Centre. 2012. Acute-on-chronic kidney disease: prevention, diagnosis, management and referral in primary care. *Best Practice Journal* 46: 10–5. URL: **www.bpac.org.nz/BPJ/BPJ.aspx** (accessed 10 May 2013).
4. Lapi F, Azoulay L, Yin H, et al. 2013. Concurrent use of diuretics, angiotensin converting enzyme inhibitors, and angiotensin receptor blockers with non-steroidal anti-inflammatory drugs and risk of acute kidney injury: nested case-control study. *BMJ* 346: e8525.
5. Savage R. 2002. A Dangerous Trio. *Prescriber Update* 23(2): 20. URL: **www.medsafe.govt.nz/profs/PUarticles/DangTrio.htm** (accessed 23 May 2013).

Reminder: Cough and Cold Medicines in Children

Key Messages

- ⌘ All cough and cold medicines are contraindicated in children **less than two years** of age.
- ⌘ Cough and cold medicines, with the exception of those containing only bromhexine or topical nasal decongestants, are contraindicated in children **less than six years** of age.
- ⌘ Cough and cold medicines should only be used in children six years and over on the advice of a healthcare professional.

As the winter season gets under way, healthcare professionals are reminded that the majority of cough and cold medicines are contraindicated in children less than six years of age.

In August 2009, the Cough and Cold Review Group recommended that all oral medicines indicated for the treatment of the symptoms of the common cold containing the substances in Table 1 be contraindicated for use in children less than six years of age[1]. In Australia, similar recommendations were made last year[2].

Table 1: Medicines containing the following substances are contraindicated in children less than six years of age

Substances	
Guaifenesin	Ipecacuanha
Dextromethorphan	Pholcodine
Oral phenylephrine	Pseudoephedrine
Brompheniramine	Chlorphenamine
Diphenhydramine	Doxylamine
Promethazine	Triprolidine

The Cough and Cold Review Group considered that these medicines lacked efficacy in children, were associated with serious adverse reactions and there was a risk of accidental overdose[3]. Serious adverse reactions reported internationally and in New Zealand include convulsions, increased heart rate, decreased level of consciousness, allergic reactions, abnormal heart rhythms and hallucinations[3].

Healthcare professionals are also reminded that **all** cough and cold medicines are contraindicated in children less than two years of age.

Coughs and colds are self-limiting conditions that will usually resolve without pharmacological treatment[4]. Cough and cold medicines are designed to treat the symptoms of the common cold. They do not cure the infection. In addition, there is evidence that infection with the common cold affects children and adults differently.

As a result of the recommendations of the Cough and Cold Review Group, warning statements are now included on the packaging of these products. Label requirements for any medicine can be found on the Medsafe website (**www.medsafe.govt.nz/regulatory/labelling.asp**).

As for any medicine, should you find the packaging does not comply with the labelling statements required by Medsafe, please contact the Medsafe Compliance Management Team (**recalls@moh.govt.nz**).

References

1. Medsafe. 2009. *Use of cough and cold medicines in children — New Advice*. URL: **www.medsafe.govt.nz/hot/alerts/coughandcold/infooct2009.asp** (accessed 8 May 2013).
2. Therapeutic Goods Administration. 2012. Changes to over-the-counter cough and cold medicines for children. *Medicines Safety Update* 35(6). URL: **www.tga.gov.au/pdf/msu-2012-06.pdf** (accessed 8 May 2013).
3. Medsafe. 2009. *Questions and Answers on over-the-counter cough and cold medicines*. URL: **www.medsafe.govt.nz/hot/alerts/coughandcold/QandAOct2009.asp** (accessed 8 May 2013).
4. Best Practice Advocacy Centre. 2013. Cold season in primary care: Advice is the best medicine. *Best Practice Journal* 52: 26–33. URL: **www.bpac.org.nz/BPJ/BPJ.aspx** (accessed 10 May 2013).

Steroid Rebound — A Topical Issue

Medsafe has become aware of a patient who suffered a severe rebound effect to topical steroids. Rebound of treated dermatosis, although not common, can be a significant issue with topical steroid use.

A young man was prescribed hydrocortisone 0.5% cream for a facial rash, which developed after exposure to a very cold climate. The rash, described as a little redness around his lower

eyelids and some puffiness/minor swelling, worsened over the following few weeks leading him to seek treatment. The hydrocortisone successfully cleared the rash. However, the problem returned when use of the cream was stopped.

The strength of hydrocortisone was increased to 1%. This improved the condition during treatment but the rash reappeared, with increasing severity, when treatment stopped.

The condition deteriorated over the next month or so until both eyelids were completely covered with an angry red rash along with the area around the eyes. In addition, a rash developed around his mouth.

The rash worsened to such an extent that the patient visited a dermatologist. A five-day course of clobetasone butyrate (Eumovate) was prescribed. This was followed by a five-day course of hydrocortisone. Again the rash reappeared once treatment was stopped and the patient was advised to repeat the course of treatment. This treatment course was unsuccessful and the area around the eyes became more swollen and was continually red and inflamed.

Following some personal research, the patient decided to stop treatment with the topical steroids. After one month, the redness had subsided slightly but still flared regularly. The rash spread considerably to other parts of his body.

Three-and-a-half months after stopping the steroids, his eyelids and surrounding area have almost regained their normal colouration and the swelling has subsided.

With topical corticosteroids, a number of adverse reactions are recognised, including irritancy, change in barrier function, allergy, tolerance, dependency, rebound and lack of response (Dermatologist personal communication, 19 February 2013).

The risk of an adverse effect depends on the strength of the steroid, the length of the application, the site of application and the skin problem.

Steroids are absorbed at different rates from different parts of the body. The palms of the hands absorb 0.1%, while the face absorbs 7%, and the eyelids absorb 30%[1]. In atopic dermatitis, where there is a defective epidermal barrier, the penetration of topical steroids is 2–10 times greater than that through healthy skin[2].

Topical steroids vary in strength from mild, such as hydrocortisone, to very potent, such as clobetasol propionate (Table 1). Topical steroids are also available in combination with antibacterial and antifungal medicines.

If you suspect a rebound reaction to a topical steroid, specialist advice should be sought.

References

1. New Zealand Dermatological Society Incorporated. *DermNet NZ: the dermatology resource*. URL: **www.dermnetnz.org** (accessed 14 May 2013).
2. Hengge UR, Ruzicka T, Schwartz RA, et al. 2006. Adverse effects of topical glucocorticosteroids. *Journal of the American Academy of Dermatology* 54: 1–15.

Table 1: Topical Steroids Currently Funded in New Zealand*

Class	Substance	Brand name
Class 1 Very potent	Clobetasol propionate 0.05% Betamethasone dipropionate 0.05%	Dermol Diprosone OV
Class 2 Potent	Betamethasone valerate 0.1% Betamethasone dipropionate 0.05% Diflucortolone valerate 0.1% Hydrocortisone 17-butyrate 0.1% Mometasone furoate 0.1% Methylprenisolone aceponate 0.1%	Beta, Betnovate Diprosone Nerisone Locoid m-Mometasone, Elocon Advantan
Class 3 Moderate	Clobetasone butyrate 0.05% Triamcinolone acetonide 0.02%	Eumovate Aristocort
Class 4 Mild	Hydrocortisone 1%	Pharmacy Health, DP Lotion HC

* This table does not include any topical steroid combination products.

Medicines and Use in Pregnancy

Key Messages

- Medicines should be used with caution in pregnancy.
- Medicines should only be prescribed in pregnancy if the expected benefits to the mother are considered to be greater than the risk to the mother and foetus.
- First trimester exposure to medicines presents the greatest risk of foetal malformations.
- Third trimester exposure to medicines may be associated with withdrawal effects in the newborn.

There are increasing concerns about the safety of medicines in pregnancy. Careful consideration and discussion of the risk and benefits of all medicines are required in the management of pregnant women or women intending to become pregnant.

All available information about the medicine, as well as any circumstances unique to the patient, should be considered. It is also worth considering any medicines the male partner of a pregnant woman is taking as rarely these may also cause problems (eg, finasteride).

Medicines should only be prescribed in pregnancy when the expected benefits to the mother outweigh any potential risks to the mother and foetus. If possible, medicines should be used at the lowest effective dose for the shortest possible duration. First-trimester medicine exposure (particularly days 18 to 56 post-conception) is associated with the highest risk of malformation. Use of some medicines in the third trimester may be associated with withdrawal effects in the foetus (eg, SSRIs).

The Australian categorisation system for prescribing medicines in pregnancy is a useful source of information for healthcare professionals considering the risks and benefits of medicines in pregnancy (**www.tga.gov.au/hp/medicines-pregnancy.htm**).

The categorisation system takes into account the known harmful effects of medicines on the developing baby. This includes the potential to cause birth defects, unwanted pharmacological effects around the time of birth, and/or problems in later life. However, this categorisation system is a guide only and is not intended as a substitute for a prescriber's advice.

Definitions of the Australian Categories for Prescribing Medicines in Pregnancy

Medicines allocated Category A are considered to be relatively safe for use in pregnancy.

Category A

Medicines which have been taken by a large number of pregnant women and women of childbearing age, without any proven increase in the frequency of malformations or other direct or indirect harmful effects on the foetus having been observed.

Medicines allocated Category B are subcategorised based on animal data, with human data lacking or inadequate.

Category B1

Medicines which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human foetus having been observed. Studies in animals have not shown evidence of an increased occurrence of foetal damage.

Category B2

Medicines which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human foetus having been observed. Studies in animals are inadequate or may be lacking, but available data show no evidence of an increased occurrence of foetal damage.

Category B3

Medicines which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human foetus having been observed. Studies in animals have shown evidence of an increased occurrence of foetal damage, the significance of which is considered uncertain in humans.

Medicines in Category B do not imply greater safety than medicines in Category C.

Category C

Medicines which, owing to their pharmacological effects (risk based on the mechanism of action of the medicine), have caused or may be suspected of causing harmful effects on the human foetus or neonate without causing malformations. These effects may be reversible.

Medicines in Category D are not absolutely contraindicated during pregnancy. However, there is a higher risk of malformations (eg, many anticonvulsants).

Category D

Medicines which have caused, are suspected to have caused, or may be expected to cause, an increased incidence of human foetal malformation or irreversible damage. These medicines may also have adverse pharmacological effects.

Medicines in Category X are absolutely contraindicated in pregnancy with a high risk of permanent damage (eg, medicines are teratogenic).

Category X

Medicines which have such a high risk of causing permanent damage to the foetus that they should not be used in pregnancy or when there is possibility of pregnancy.

It should be noted that this system only applies to the recommended therapeutic doses in women. It cannot be applied to situations such as overdose, occupational exposure or other situations where the recommended therapeutic dose has been exceeded.

Additionally, some classes of medicines are exempted from pregnancy categorisation including:

- herbal medicines
- traditional Chinese medicines
- mineral and nutritional supplements
- parenteral nutrition preparations.

This does not imply medicines that are exempt are safe during pregnancy. Rather, data are very limited and insufficient to determine their safety.

Full details of exempted classes of medicines may be found on the Therapeutic Goods Administration website (**www.tga.gov.au/hp/medicines-pregnancy-exempt.htm**).

The New Zealand Formulary (NZF) uses the Australian categorisation system. In many cases the NZF also provides additional notes. This includes identifying medicines, which are not known to be harmful in pregnancy and identifying medicines, which may have harmful effects in pregnancy with indication of trimester of risk. Further information is available at the NZF website (**www.nzformulary.co.nz/**).

The Centre for Adverse Reactions Monitoring (CARM) has received a total of 106 reports where a pregnant female has been administered a medicine resulting in a reaction involving the foetus or where a reaction has been noted in the child (Table 1). Many of these reports identified multiple suspect medicines and reactions.

Table 1: Medicines for which five or more reports involving a pregnant female or the child that were received by CARM in the period January 2000 until December 2012

Medicine	No of reports
Sodium Valproate	10
Paroxetine	9
Venlafaxine	8
Citalopram	6
Fluoxetine	6

The receipt of a report by CARM does not necessarily imply that these medicines are any less safe than other medicines. There are other important factors which may stimulate reports (eg, wide use). Vaccines and oral contraceptives were excluded from this search.

Healthcare professionals are encouraged to report these reactions to CARM and to include as much information as possible to help identify other medicines associated with an increased risk of malformations or withdrawal effects in the foetus.

Further information about how to submit an adverse reaction report can be found on the Medsafe website (**www.medsafe.govt.nz/profs/adverse.asp**) or on the CARM website (**https://nzphvc-01.otago.ac.nz/carm-adr/reporting.php**).

Monitoring Blood Glucose

Medsafe has been notified of observed variations between readings provided by the CareSens meter and other blood glucose meters.

Differences in readings can be a matter of concern for patients and clinicians, so it is important to differentiate between acceptable variation in meter readings and those that may have clinical consequences.

From March 2013, the CareSens range of blood glucose meters and testing strips became the only blood glucose testing devices funded by PHARMAC. These meters will be new to most patients and include:

1. CareSens II: manual coding (requires entry of a test strip code), 250 test memory, 14 day averaging
2. CareSens N: no coding, 250 test memory, 14 day averaging
3. CareSens N POP: no coding, 500 test memory, 1/7/14/30 90 day averaging.

The manufacturer states that the meters meet the international standard and have been tested for acceptability in New Zealand (Christchurch Diabetes Centre).

It is possible that two blood glucose meters meeting the same standard will give different results. This does not mean that either of the meters is wrong. The international standard for blood glucose meters requires that they are accurate to within plus or minus 20% of a laboratory test result, 95% of the time.

Medsafe acknowledges that even a small difference in readings may worry diabetics. Consumer information and support for diabetics changing to the CareSens blood glucose meters is available from the CareSens website (**www.caresens.co.nz/page/faq.aspx**).

Information on how to report a medical device issue can be found on the Medsafe website (**www.medsafe.govt.nz/regulatory/DevicesNew/9AdverseEvent.asp**). If you wish to report a potential issue with a meter to Medsafe, please include:

- details of the meters (models and serial number)
- the lot numbers of the testing strips
- examples of differences in readings between the two meters using blood samples drawn and tested at the same time
- examples of any unusual variability between serial readings taken on the meter
- any information on clinical issues with glucose meters.

Prescription Medicines — Up in Smoke

A recent case has highlighted that patients may unknowingly be exposed to prescription medicines. Importantly, this exposure may have come through an unusual route, such as smoking. Unscrupulous suppliers are dealing in prescription medicines and other hazardous substances, which may have serious consequences for consumers.

In March 2013, Medsafe successfully prosecuted a Blenheim retailer for importing, possessing, manufacturing and selling a herbal smoking material that contained the prescription medicine, zaleplon. The defendant had imported and added zaleplon to a herbal smoking material for sale under the name 'Wacky Backy Vivid Dreams'.

Zaleplon is a hypnotic medicine used in the short-term management of insomnia and has sedative properties. Zaleplon can also have paradoxical effects such as excitation leading to hostility, aggression and disinhibition. High doses can cause slow or shallow breathing and low blood pressure. These reactions can be serious especially when mixed with other medicines or illicit drugs. Zaleplon is currently not in any approved products in New Zealand.

Packages destined for the defendant were intercepted by Customs New Zealand in late 2011 and early 2012 and referred to Medsafe. The premises were subsequently searched by Medsafe investigators, Customs staff and Police. The retailer pleaded guilty to four charges under the Medicines Act 1981. The retailer was sentenced to 180 hours' community work, a fine of $1500 and was ordered to pay analysts' fees of $6950.

MARC's Remarks: March 2013 Meeting

The latest meeting of the Medicines Adverse Reactions Committee (MARC) took place on 14 March 2013.

The minutes of this meeting are available on the Medsafe website (**www.medsafe. govt.nz/profs/adverse/Minutes153.htm**).

The MARC reviewed the report following the completion of the Intensive Medicines Monitoring Programme (IMMP) for **varenicline** (Champix). The MARC noted that of the top 10 adverse events reported in the study, 'nightmare' was the only single event not included in the current New Zealand data sheet. The MARC recommended 'nightmare' be added to the Champix data sheet. The MARC also recommended that the precaution regarding psychiatric events in the data sheet be amended to make it more succinct and clearer. The MARC agreed that the benefit-risk profile of varenicline remains positive.

The MARC reviewed the benefits and risks of **calcitonin**-containing medicines due to a concern of increased risk of cancer with long-term use. The MARC agreed that the available evidence was insufficient to confirm a causal association between exposure to calcitonin-containing medicines and cancer.

The MARC agreed that the potential association between calcitonin-containing medicines and cancer had the potential to affect the balance of benefits and risks for some of the approved indications. The MARC recommended that data sheet changes be made to reflect this.

The MARC first reviewed the risk of **reversible cerebral vasoconstriction syndrome** (RCVS) associated with the use of **serotonergic agents** (Selective serotonin reuptake inhibitors [SSRIs] and/or triptans) in March 2012.

At that time, the MARC concluded that the available evidence was insufficient to confirm a causal association between the use of triptans or SSRIs and the development of RCVS. The MARC recommended that SSRIs/triptans and RCVS/thunderclap headache be placed on Medsafe's M² monitoring scheme. In addition, to raise awareness of RCVS, a *Prescriber Update* article was published in June 2012[1].

During the six month M² monitoring period, there were three reports of severe or thunderclap headache in patients receiving SSRI or triptan therapy. The MARC recommended that thunderclap headaches and/or RCVS be added to the adverse effects section of all SSRI and triptan data sheets.

The MARC reviewed an updated report investigating concerns about mortality and cardiovascular adverse events with **tiotropium** (Spiriva). This follows the publication of two recent editorials calling for the withdrawal of the Spiriva Respimat inhaler. The MARC noted that the Respimat inhaler is not available in New Zealand and that to date no concerns have been raised with the currently available tiotropium powder formulation.

The MARC agreed that cardiovascular issues with the Respimat mist inhaler may be a signal. However, the Committee agreed that the benefit/risk profile of Spiriva had not changed since the last MARC review in 2011. The MARC supported the manufacturer's decision to not market the Respimat product in New Zealand until the results of the TioSpir study are available.

References

1. Medsafe. 2012. Reversible Cerebral Vasoconstriction Syndrome – Medicine Induced? *Prescriber Update* 33(2): 14–5. URL: **www.medsafe.govt.nz/profs/PUArticles ReversibleCerebralVasoconstrictionSyndromeJune 2012.htm** (accessed 15 May 2013).
2. Beasley R, Singh S, Loke YK, et al. 2012. Call for worldwide withdrawal of tiotropium Respimat mist inhaler. *BMJ* 345: e7390.
3. Jenkins CR, Beasley R. 2013. Tiotropium Respimat increases the risk of mortality. *Thorax* 68: 5–7.

New Medsafe Website

Medsafe is pleased to announce the launch of our new website. The content is still the same but has been reorganised to make finding things easier. There is still a section specifically for healthcare professionals. We have also added a News and Events section to help you keep up to date with the latest information. The website address will remain the same (**www.medsafe.govt.nz**).

Chlorhexidine — Risk of Anaphylaxis

Severe allergic reactions including anaphylaxis have been reported following use of chlorhexidine.

The Centre for Adverse Reaction Monitoring (CARM) has received eight reports of anaphylactic reactions to chlorhexidine and lignocaine combination products in men undergoing urinary catheterisation. The patients' age ranged from 22 to 79 years.

Of the eight cases, five reported the results of a skin prick test of which four were positive for chlorhexidine sensitivity.

In addition to the above cases, CARM have received 61 reports of anaphylactic reactions to medicines containing chlorhexidine since 2000. Of the 61 reports, 55 occurred in males and six in females.

A number of medicines, including over-the-counter products, contain chlorhexidine including antiseptic creams/gels, dressings, mouthwashes, eye drops, throat sprays, contact lens solutions and nasal sprays. The ingredients of approved products can be checking using the product application search on the Medsafe website (**www.medsafe.govt.nz/regulatory/DbSearch.asp**).

In a recent case series on anaphylaxis attributed to chlorhexidine in lubricants used in urethral catheterisation, the variety and increasing use of chlorhexidine containing products was postulated to result in sensitisation to chlorhexidine[1]. This could lead to an increase in life-threatening allergic reactions to chlorhexidine.

If healthcare professionals suspect a patient has an allergy to chlorhexidine, an alternative product should be used. Chlorhexidine-free products are approved in New Zealand for patients with an allergy to chlorhexidine.

Healthcare professionals are encouraged to report all anaphylactic reactions to products containing chlorhexidine to CARM. Reporting of these reactions is important as CARM can then record a warning on the National Alert System for that patient.

References

1. Parkes AW, Harper N, Herwadkar A, et al. 2009. Anaphylaxis to the chlorhexidine component of Instillagel: a case series. *British Journal of Anaesthesia* 102: 65–8.

Pramipexole and Heart Failure

Key Messages

- Pramipexole use has been associated with a small increased risk of heart failure, which is possibly greater in the first three months of use and for those aged 80 years and over.
- Prescribers should take this into account when assessing the risks and benefits for an individual patient.
- Prescribers should continue to follow recommendations in the current pramipexole data sheet.
- Patients should be advised to seek medical attention if they experience symptoms of heart failure.

The use of pramipexole, a dopamine agonist used to treat Parkinson's disease, has been associated with a risk of heart failure in two separate studies[1,2]. Prescribers should be aware of possible signs and symptoms of heart failure in patients taking pramipexole and report any adverse events to the Centre for Adverse Reactions Monitoring (CARM).

The first study was a case-control study conducted within a cohort of almost 27,000 users of anti-parkinsonian drugs from the United Kingdom General Practice Research Database[1]. The 783 newly diagnosed heart failure cases were matched to 7454 controls.

The results demonstrated an increased rate of heart failure with the current use of any dopamine agonist compared to no use (Relative Risk [RR]: 1.58, 95% CI: 1.26–1.96). However, this was particularly so for pramipexole use (RR: 1.86, 95% CI: 1.21–2.85) and cabergoline use (RR: 2.07, 95% CI: 1.39–3.07) compared to no use.

The second study was another case-control study within a cohort of Parkinson's disease patients[2]. The 518 incident cases of heart failure were matched to a total of 38,641 controls. Results found that, compared to levodopa use, there was no increased risk of heart failure for any individual ergot dopamine agonist, or for non-ergot dopamine agonists as a class.

Among the individual non-ergot dopamine agonists, only pramipexole was associated with an increased risk of heart failure (Odds Ratio [OR]: 1.61, 95% CI: 1.09–2.38). This was especially so in the first three months of use (OR: 3.06, 95% CI: 1.74–5.39) and for patients aged 80 years and over (OR: 3.30, 95% CI: 1.62–7.13).

In contrast to the previous study, this study did not find a statistically significant increased risk of heart failure for cabergoline users.

In New Zealand, there have been only two reports of cardiovascular adverse events associated with pramipexole use. Causality was assessed as unlikely in both these reports.

Medsafe are currently working with the relevant pharmaceutical companies to update the datasheets and clarify the potential risk of heart failure. This includes the following wording:

> "In clinical studies and post-marketing experience cardiac failure has been reported in patients with pramipexole. In a pharmacoepidemiological study, pramipexole use was associated with an increased risk of cardiac failure compared with non-use of pramipexole".

As always, please report any adverse events to CARM. This can be done via either the Medsafe website (**www.medsafe.govt.nz/profs/adverse.asp**) or by reporting directly to CARM (**http://carm.otago.ac.nz/**).

References

1. Renoux C, Dell'Aniello S, Brophy JM, et al. 2012. Dopamine agonist use and the risk of heart failure. *Pharmacoepidemiology and Drug Safety* 21: 34–41.
2. Mokhles MM, Trifiro G, Dieleman JP, et al. 2012. The risk of new onset heart failure associated with dopamine agonist use in Parkinson's disease. *Pharmacological Research* 65: 358–64.

WE NEED YOUR HELP!

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

M² MEDICINES MONITORING

Medicine	Potential safety issue	Active monitoring ends
Ondansetron	Serotonin Syndrome (Toxicity)	30 June 2013
Varenicline	Interaction with alcohol	31 December 2013

- M² 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 M² scheme does not replace routine adverse reaction reporting. Find out how to report at: **www.otago.ac.nz/carm** or **www.medsafe.govt.nz**

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A BUSINESS UNIT OF THE MINISTRY OF HEALTH
www.medsafe.govt.nz

CARM
CENTRE FOR ADVERSE REACTIONS MONITORING

New Zealand Government

* The appearance of a possible safety issue in this scheme does not mean Medsafe and CARM have concluded that this medicine causes the reaction.

Withdrawal Symptoms After Use of Hyoscine Patches

Withdrawal symptoms can occur after removal of hyoscine patches.

The Centre for Adverse Reactions Monitoring (CARM) has received three reports of withdrawal symptoms in patients after using hyoscine patches for prevention of nausea.

In all three reports, the withdrawal symptoms occurred after the hyoscine patches were used for more than three days.

Reported symptoms included nausea and vomiting, headache, balance disorders (vertigo), dizziness and blurred vision. In one case, it was reported that these symptoms resolved after reapplication of the patch. Overall, these symptoms may take several days to settle after patch removal.

Healthcare professionals should advise patients of the risk of withdrawal symptoms and counsel patients not to drive or operate machinery if they experience such symptoms.

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