Prescriber Update

Vol. 35 No. 4 December 2014

www.medsafe.govt.nz

ISSN 1172-5648 (print)
ISSN 1179-075X (online)

Contents

MEDSAFE
NEW ZEALAND MEDICINES AND MEDICAL DEVICES SAFETY AUTHORITY
A BUSINESS UNIT OF THE MINISTRY OF HEALTH
www.medsafe.govt.nz

MINISTRY OF HEALTH
MANATŪ HAUORA

New Zealand Government

Use of Sodium Valproate in Pregnancy

Key messages

- Sodium valproate (Epilim) is contraindicated in pregnancy.
- Sodium valproate should not be used in women of child-bearing potential unless other treatments are ineffective or not tolerated.
- The risk of congenital malformations in infants exposed to sodium valproate *in utero* has been estimated between 6 and 12%.
- The risk of autism spectrum disorder in children exposed to valproate *in utero* has been estimated at around 4%.
- Children exposed to valproate *in utero* have a reduced IQ compared with children exposed to other anti-epileptic medicines.
- Reducing the dose of valproate below 1000mg/day and using high-dose folate periconceptually reduces the risk of some malformations and cognitive impairment.
- Seizures during pregnancy and other anti-epileptic drugs have also been associated with risks of adverse developmental outcomes and malformations.

Sodium valproate (Epilim) was first introduced as an anti-epileptic in 1964[1]. It is currently indicated for treatment of primary generalised epilepsy, partial (focal) epilepsy, and bipolar disease.

Epilim is contraindicated in pregnancy due to the risk of congenital malformations and developmental effects. The data sheet also recommends that Epilim should not be used in women of child-bearing potential unless other treatments are ineffective or not tolerated. Women who could become pregnant should be given medical advice on the benefits and risks of treatment before Epilim is prescribed.

Congenital malformations

The first report of teratogenic effects of valproate was published in 1980. The term fetal valproate syndrome (FVS) was suggested in 1984[1]. A number of different anomalies have been associated with valproate exposure (see table), the clinical presentation varies between affected infants. The variability in clinical presentation may be influenced by a number of factors such as maternal seizures during pregnancy, folic acid intake, dose and timing of exposure of valproate, genetic susceptibility and parental factors such as IQ and socioeconomic status[1].

The risk of congenital malformations following *in utero* exposure to valproate is higher than the background rate of 2–3%[1].

Table 1: Anomalies most commonly associated with valproate exposure

Neural tube defects	Spina bifida	Anencephaly
Congenital heart defects	Ventricular septal defect Patent ductus arteriosus	Atrial septal defect Aortic stenosis
Limb defects	Radial ray defect Split hand Camptodactyly	Polydactyly Overlapping toes
Genitourinary defects	Hypospadias	
Skin abnormalities	Capillary haemangioma	
Dysmorphic features	Trigonocephaly Thin arched eyebrows Broad nasal bridge Thin upper lip Infraorbital grooves	Prominent metopic ridge Epicanthic folds Short anteverted nose Long philtrum

Data from pregnancy registries have found the following regarding the risk of congenital malformations in infants exposed to anti-epileptic drugs *in utero*:

- UK and Ireland Epilepsy and Pregnancy Registers (includes 1/3 of relevant pregnancies) estimate a rate of 6.7%[2].
- North American Anti-Epileptic Drug Pregnancy Registry rate estimate is 9.3%[2].
- International Registry of antiepileptic drugs and pregnancy rate estimate is 9.7%[2].
- Australian Pregnancy Registry (includes 1/12 of all relevant pregnancies) rate estimate is 12.4%[3].

In contrast the risk of malformations associated with carbamazepine was 2.6% (1.9–3.5%) and 2.3% (1.8–3.1%) with lamotrigine in the UK and Ireland Registries[2].

Valproate exposure has also been associated with a risk of spina bifida estimated at 1–2%; the background rate is 0.2–0.5%. The risk associated with carbamazepine exposure has been estimated at 0.5–1%[1].

Some registries show a dose-dependent effect with valproate exposure *in utero*[2,3]. In general, a dose of greater than 1000mg/day has been associated with a higher risk for the abnormalities described above[1]. Data from the Australian, UK and Ireland Registries show that mean maternal valproate doses of greater than 1000mg/day were associated with fetal malformations. The data also showed that in pregnancies that were unaffected, the mean maternal dose of valproate was between 850 and 900mg/day. The dose of maternal valproate has been decreasing in Australia over the last 5 years, which has been paralleled by a significant decrease in the rate of spina bifida and hypospadias[3].

The risk of a congenital malformation is increased when women require polytherapy[1].

Other anti-epileptics have also been associated with malformations, for example microcephaly has been associated with carbamazepine exposure *in utero*[1].

CARM reports

The Centre for Adverse Reactions Monitoring (CARM) has received 13 reports of fetal valproate syndrome; the first report was received in 1997 and the most recent report in 2014. The mother's dose of valproate was only available in two reports and was greater than 1000mg/day. The majority of the reports were made at least one year after the birth of the affected child and none of the reports mentioned whether folate was taken at conception.

Other birth outcomes

The occurrence of generalised tonic-clonic seizures in pregnancy is associated with shorter gestational age and reduced birthweight. However, the majority of babies exposed to valproate *in utero* are of normal weight[1].

A recent study found no association between the use of anti-epileptic medicines in pregnancy and the risk of spontaneous abortion or stillbirth[4].

Babies exposed to valproate *in utero* may exhibit withdrawal symptoms at birth, such as feeding difficulties, hypoglycaemia, jitteriness, irritability and hypothermia[1].

Cognitive impairment and behavioural issues

Children with FVS have also been noted to have cognitive impairment. Global developmental delay has been noted in children with severe FVS. The most frequently affected developmental aspects are speech and language[1]. The average full-scale IQ of a child with FVS is in the 80–90 range. However, the verbal IQ is significantly lower[1].

Autism, Asperger's syndrome and autistic spectrum disorder have been diagnosed and reported more frequently in FVS but are also seen in valproate exposed children without FVS[1].

A population-based study in Denmark investigated the risk of autism spectrum disorder and autism[5]. Children exposed to valproate *in utero* were compared with the whole population and a cohort of children born to women with epilepsy.

The study showed the following for autism spectrum disorder:

- For the whole population, the absolute risk of autism spectrum disorder in children exposed to valproate was 4.4%. The absolute risk in the total population was 1.2%.
- For children who were born to women with epilepsy, the absolute risk of autism spectrum disorder in children exposed to valproate was 4.2%. The risk for children who were not exposed to valproate was 2.4%.

The study showed the following for autism:

- For the whole population, the absolute risk of autism in children exposed to valproate was 2.5%. The absolute risk in the total population was 0.5%.
- For children who were born to women with epilepsy, the absolute risk of autism in children exposed to valproate was 3%. The risk for children who were not exposed to valproate was 1%.

The Neurodevelopmental Effects of Antiepileptic Drugs (NEAD) study found a significant dose-related performance decline in parental ratings of adaptive functioning in children exposed *in utero* to valproate or phenytoin. Children of mothers who took valproate during pregnancy were at a greater risk for a diagnosis of Attention Deficit Hyperactivity Disorder (ADHD)[6].

Measurement of IQ in the NEAD study showed that the mean IQ of children (at age 6 years) exposed to valproate was in the normal range but lower than in children exposed to other anti-epileptics: 97 (95% CI 94–101) compared with 108 (105–110) for lamotrigine[7].

Management

Under the Health and Disability Code of Rights, women requiring valproate treatment during pregnancy must be informed about the benefits and risks of treatment and this information must be provided in writing if requested (Consumer Medicine Information is available: **www.medsafe.govt.nz/consumers/CMI/e/Epilim.pdf**).

It is important to note that none of the anti-epileptic medicines available are completely safe during pregnancy[1]. Seizures during pregnancy are also associated with poorer developmental outcomes.

For women requiring valproate treatment, the risk of malformations is reduced when the daily dose is below 1000mg. However, any dose adjustments should be made well in advance of pregnancy to ensure that seizures are still controlled[1].

High-dose folic acid is recommended, starting at least six weeks pre-conception[1]. Periconceptional use of folic acid has generally been associated with a reduced risk of autism[5]. The NEAD study results provide some support for use of preconception folate. Parents reporting maternal folate use noted fewer physical complaints and atypical behaviours in their children, and teachers endorsed lower levels of anxiety in these children[6]. IQ was also higher in children whose mothers had taken folate[7].

The UK and Ireland Pregnancy Registries showed that neural tube defects were slightly less frequent in infants whose mothers had folic acid supplementation periconceptually and during pregnancy[2].

Women should also be encouraged to address any other risk factors for adverse pregnancy outcomes.

References

1. Kini U. 2006. Fetal valproate syndrome: a review. *Paediatric and Perinatal Drug Therapy* 7: 123–130.
2. Campbell E, Kennedy F, Russell A, et al. 2014. Malformation risks of antiepileptic drug monotherapies in pregnancy: updated results from the UK and Ireland Epilepsy and Pregnancy Registers. *J Neurol Neuosurg Psychiatry* 85: 1029–1034.
3. Vajda FJ, O'Brien TJ, Graham JE. 2013. Dose dependence of fetal malformations associated with valproate. *Neurology* 81: 999–1003.
4. Bech BH, Kjaersgaard MIS, Pedersen HS, et al. 2014. Use of antiepileptic drugs during pregnancy and risk of spontaneous abortion and stillbirth: population based cohort study. *BMJ* 349: g5159.
5. Christensen J, Grønborg TK, Sørensen MJ et al. 2013. Prenatal valproate exposure and risk of autism spectrum disorders and childhood autism *JAMA* 309: 1696–1703.
6. Cohen MJ, Meador KJ, Browning N et al. 2013. 'Fetal antiepileptic drug exposure: adaptive and emotional/behavioural functioning at age 6 years. *Epilepsy & behaviour* 29: 308–315.
7. Meador KJ, Baker GA, Browning N, et al. 2013. Fetal antiepileptic drug exposure and cognitive outcomes at age 6 years (NEAD study): a prospective observational study. *Lancet Neurol* 12: 244–52

Keeping Patients Informed about Colchicine Use

Key messages

- Prescribers should educate and regularly remind their patients of the harms associated with colchicine and the dangers of taking more than instructed.
- Patients should be aware of the symptoms of colchicine toxicity and seek immediate medical advice if they experience these symptoms.

Earlier this year, the Centre for Adverse Reactions Monitoring (CARM) received a report of a patient who had died due to colchicine toxicity. The patient, who had a history of gout, had incorrectly self-administered colchicine to relieve acute severe pain.

Colchicine is indicated for the treatment of acute gout when non-steroidal anti-inflammatory drugs are contraindicated or have previously been unsuccessful.

While in this reported case the patient had been previously warned of the risk of taking more medication than was prescribed, it is an important reminder that incorrect use of colchicine can be fatal. Patients need to be informed that colchicine has a narrow therapeutic index and must understand that they must not take any more medicine than instructed.

Colchicine toxicity may also occur as a result of interactions. In particular, interactions occur with medicines that inhibit CYP3A4 (such as protease inhibitors, imidazoles and clarithromycin) and P-gp (such as ciclosporin, ketoconazole, protease inhibitors and tacrolimus).

Early symptoms of colchicine toxicity include nausea, vomiting, diarrhoea and abdominal pain. Delayed signs and symptoms include seizures, cardiac dysrhythmias, hypotension and pancytopenia as well as respiratory, renal and hepatic failure. Patients prescribed colchicine should be advised that if they experience these early symptoms they should stop the medicine and see a doctor immediately.

There is no specific antidote for colchicine toxicity; treatment is supportive.

Tramadol – the Highs and Lows

Key messages

- Tramadol is a centrally-acting synthetic analgesic with a dual mechanism of action – binding at μ-opioid receptors and inhibiting noradrenaline and serotonin re-uptake.
- The most notable side effects of tramadol include serotonin syndrome/toxicity, seizures (including lowered seizure threshold), respiratory depression, increased intracranial pressure and anaphylactoid reactions.
- Common adverse reactions include nausea, vomiting, constipation, dizziness, autonomic nervous effects (mainly dry mouth, perspiration), headache, sedation, asthenia (weakness) and fatigue.
- Tramadol is metabolised primarily by CYP2D6. CYP2D6 polymorphisms may affect the metabolism of tramadol alone as well as form the basis for interactions (eg, warfarin).

Tramadol is a centrally-acting synthetic analgesic used for the relief of moderate to severe pain. Tramadol and its principle metabolite *O*-desmethyltramadol (M1) have opioid-like effects since they bind to μ-opioid receptors distributed throughout the central nervous system (CNS). The binding affinity of tramadol for μ-opioid receptors is approximately 6,000-fold less than morphine and approximately 20-fold less for M1[1]. In addition to its opioid actions, tramadol also inhibits the neuronal re-uptake of noradrenaline (NA) and serotonin (5-HT). The data sheet provides more information on tramadol (**www.medsafe.govt.nz/profs/Datasheet/DSForm.asp**).

Key characteristics of tramadol

Dependence and opioid effects

The dual mechanism of action may reduce the risk of opioid-associated adverse reactions and the potential for tolerance, dependence or abuse. However, a risk still remains and caution is recommended when prescribing. Tramadol must not be used for opioid withdrawal treatment as it cannot suppress opioid withdrawal symptoms. In addition, tramadol is contraindicated in patients with acute intoxication due to alcohol, hypnotics, analgesics, opioids or psychotropic drugs[2].

Tramadol should be administered with caution in patients at risk of respiratory depression and in patients with increased intracranial pressure, head injury, shock or a reduced level of consciousness of uncertain origin[2].

The μ-opioid receptors are found throughout the CNS and are also found in the intestinal tract. Although less pronounced than with true opiate analgesics, tramadol may also cause constipation due to reduced gut motility[3]. Other commonly reported adverse reactions associated with tramadol use include nausea and vomiting, dizziness, autonomic nervous effects (dry mouth, perspiration/sweating), headache, sedation, asthenia (weakness) and fatigue[2].

Seizures

Tramadol, both alone or in combination with other medicines, may lower the threshold for seizures and is contraindicated in patients with uncontrolled epilepsy[4]. The Centre for Adverse Reactions Monitoring (CARM) has received a total of 19 reports of convulsions, grand mal convulsions or convulsions aggravated associated with the use of tramadol since 2000. The convulsions were life-threatening in two cases, and 14 patients required hospitalisation. The patients recovered in all cases except one where the outcome was unknown. In the majority of cases, symptom onset was within 12 hours of the start of tramadol administration.

Serotonin Syndrome/Toxicity

As tramadol inhibits re-uptake of NA and 5-HT, use with other serotonergic agents increases the risk of serotonin syndrome/toxicity. Tramadol should be used with caution in patients requiring selective serotonin re-uptake inhibitors (SSRIs), serotonin-noradrenaline re-uptake inhibitors (SNRIs) and tricyclic antidepressants. Use of tramadol is contraindicated in patients also taking monoamine oxidase inhibitors (MAOIs) and those who have taken MAOIs within the last 14 days[2].

CARM has received six reports since 2000 where tramadol use may have contributed to serotonin syndrome/toxicity. In four of these reports, the patient required hospitalisation. Concomitant medicines included paroxetine, citalopram, fentanyl, methylene blue, fluoxetine, sibutramine and sertraline (some patients were taking more than one contributing medicine). If serotonin syndrome/toxicity is suspected, prompt withdrawal of the serotonergic medicines is recommended.

Serotonin syndrome/toxicity usually occurs after initiating or increasing the dose of a serotonergic medicine. A serotonin syndrome/toxicity reminder is available at: **www.medsafe.govt.nz/profs/PUArticles/SerotoninSyndromeToxicityReminder.htm**.

Interactions

Tramadol is metabolised to its principal active metabolite M1, through *O*-demethylation by cytochrome p450 (CYP) isoenzyme 2D6 (CYP2D6). Poor metabolisers of medicines via CYP2D6 may therefore get less benefit from tramadol use due to reduced formation of the active metabolite[3,5].

The isoenzymes CYP3A4 and CYP2B6 are involved in the metabolism of tramadol via *N*-demethylation to a secondary metabolite M2[1]. The addition of a CYP3A4 inhibitor may also inhibit the metabolism of tramadol and reduce the therapeutic response (eg, erythromycin, itraconazole).

Six reports of an interaction between oral tramadol and warfarin have been submitted to CARM since 2000. An elevated international normalised ratio (INR) was described in four reports, with onset occurring up to seven days after tramadol was commenced in patients stabilised on warfarin. In five cases, the patients developed haemorrhage-related symptoms, such as melaena, anaemia and purpura. The mechanism for this interaction has not been fully elucidated but may be due to CYP2D6 polymorphism, which subsequently increases competition for CYP3A4 metabolism (involved in metabolism of R-warfarin)[6]. Caution should be exercised if tramadol and warfarin are used concurrently[2].

CNS depressants such as alcohol, opioids, anaesthetic agents, phenothiazines and sedative hypnotics may potentiate the sedating effects of tramadol and should therefore be used with caution and in reduced doses[2].

Overdose

Although some evidence suggests there is less risk of respiratory depression with tramadol, the symptoms of tramadol overdose are similar to other centrally acting analgesics and include coma, convulsion, respiratory depression, respiratory arrest and cardiovascular collapse[2]. Seizures may also occur with overdose.

Tramadol Dosing Guidelines

Tramadol is currently available as drops, capsules and tablets for oral use and solution for intramuscular or intravenous injection. Sustained release tablets and immediate release capsules are fully funded in the community. The dose of tramadol should be titrated to the severity of the pain and the clinical response of the individual, taking into account patient-specific factors.

Maximum daily dose in adults and children over 12 years of age:

- **Injectable tramadol** 600mg per day (post-operative pain only); normally 400mg per day
- **Oral tramadol** 400mg per day
- **Paediatric (2 years and older)** recommended dose 1–2mg/kg up to a maximum daily dose to the lesser of 8mg/kg/day or 400mg per day)
- **Elderly (75 years and older)** 300mg per day.

As tramadol is metabolised by the liver and excreted by the kidneys, doses should be reduced in patients with hepatic or renal impairment.

Healthcare professionals are encouraged to report any adverse events, including events associated with tramadol, to CARM. Reports may be submitted on paper or electronically (**carm.otago.ac.nz/**).

References

1. Grond S and Sablotzki A. 2004. Clinical Pharmacology of Tramadol. *Clinical Pharmacokinetics* 43(13): 879–923.
2. bioCSL (NZ) Limited. 2013. *Tramal Data Sheet* April 2013. URL: **www.medsafe.govt.nz/profs/datasheet/t/TramalcapSRtabinjoraldrops.pdf** (accessed 6 October 2014).
3. Shipton EA. 2000. Tramadol – Present and Future. *Anaesthesia and Intensive Care* 28(4): 363–374.
4. Kaye K. 2004. Trouble with Tramadol. *Australian Prescriber* 27: 26–27.
5. Zahari Z, Ismail R. 2014. Influence of Cytochrome P450, Family 2, Subfamily D, Polypeptide 6 (CYP2D6) Polymorphisms on Pain Sensitivity and Clinical Response to Weak Opioid Analgesics. *Drug Metabolism and Pharmacokinetics* 29(1): 29–43.
6. Hedenmalm K, Lindh JD, Sawe J et al. 2004. Increased liability of tramadol-warfarin interaction in individuals with mutations in the cytochrome P_{450} 2D6 gene. *European Journal of Clinical Pharmacology* 60 (5): 369–372.

Importing Medicines for Personal Use

Key messages

- ⌘ Some patients may seek authority from authorised prescribers to release imported medicines for personal use.
- ⌘ Authority is granted when an authorised prescriber completes and signs the Medsafe form.
- ⌘ An authorised prescriber must be satisfied that the patient's health and safety have been protected in compliance with all health codes and Medical Council guidelines[1].
- ⌘ Imported medicines have not been approved for use in New Zealand and are of unknown quality.

Situation

A consumer can import a prescription medicine only if it is lawfully prescribed by a New Zealand authorised prescriber.

Medsafe, in conjunction with NZ Customs Service, operates a border program for imported medicines. If a prescription medicine for personal use is imported, Medsafe sends a letter to the importer that requires approval from an authorised prescriber.

In general, there are two categories of medicines imported for personal use.

Medicines purchased over the internet

Consumers frequently purchase medicines over the internet for reasons of cost or confidentiality. Medsafe strongly discourages this practice because the medicines may be of poor quality,

sub- or super-potent, contaminated, adulterated or counterfeit. Although these medicines may appear to be from a pharmacy in a well-regulated country, this is frequently not the case.

Medicines sent from family or medical clinics

People who have moved to New Zealand or are visiting here may prefer to source their medicines from their home country. These medicines may have been lawfully prescribed and dispensed in their originating country so prescribers need to consider this when deciding whether or not to authorise the imported medicine.

Authorisation requests

The details of the medicine(s) will be listed on the form. Prescribers should consider whether it is appropriate to prescribe the medicine for this patient. Prescribers should also consider such factors as possible issues with the quality of the product.

Medsafe recommends that if a medicine, or clinically acceptable alternative, is available in New Zealand, then that should be prescribed instead.

Providing authorisation

Authorised prescribers who choose to provide authorisation need to complete and sign the form and return it directly to Medsafe. Please note that Medsafe is not licensed to dispense medicines therefore cannot divide a pack and cannot provide pharmacy labels with dosage instructions.

If the amount of medicine exceeds three months' supply (or six months' supply of oral contraceptives) this cannot be supplied directly to the patient. However, prescribers may choose to have the medicine sent to them to be dispensed in compliance with medicines legislation.

For further information, please contact: **medclearance@moh.govt.nz**

Reference

1. Medsafe. Use of unapproved medicines and unapproved use of medicines. Revised 22 October 2014. URL: **www.medsafe.govt.nz/profs/RIss/unapp.asp** (accessed 10 October 2014).

Pump up Testosterone Levels Safely

Key messages

- Testosterone products are indicated for testosterone replacement in primary and secondary male hypogonadism.
- Current findings in the published literature do not provide significant statistical evidence to support an association between testosterone *replacement* and an increased risk of cardiovascular events.

Background information on testosterone

Testosterone products are indicated for testosterone replacement in primary and secondary male hypogonadism.

Hypogonadism is defined as a clinical syndrome that comprises both symptoms and biochemical evidence of testosterone deficiency[1].

Testosterone treatments for anti-ageing in males and for building muscle are examples of unapproved ('off-label') indications. The safety and efficacy of testosterone when used for unapproved indications are unknown.

In New Zealand, approved testosterone replacement products are available as intramuscular injections, oral capsules and transdermal patches.

Testosterone replacement and risk of cardiovascular events

Recent publications[2,3] have suggested an association between testosterone replacement and an increased risk of cardiovascular events, such as myocardial infarction, venous thromboembolism and stroke.

The Medicines Adverse Reactions Committee (MARC) recently considered the available data on this safety concern. Based on current evidence, the MARC concluded that there is no significant statistical evidence to support an association between testosterone *replacement* and myocardial infarction, venous thromboembolism or stroke.

Longer-term, adequately powered, placebo-controlled clinical trials are required to investigate testosterone replacement and the risk of cardiovascular events.

Adverse effects with testosterone replacement

Testosterone replacement used at recommended doses for approved indications has been associated with adverse effects, summarised in Table 1.

Further information is available in the product data sheets, which are available on the Medsafe website (**www.medsafe.govt.nz/profs/datasheet/dsform.asp**).

References

1. Muraleedharan V, Jones H. 2014. Testosterone and mortality. *Clinical Endocrinology* 81(4): 477–487.
2. Vigen R, O'Donnell C, Barón AE, et al. 2013. Association of testosterone therapy with mortality, myocardial infarction, and stroke in men with low testosterone levels. *JAMA* 310(17): 1829–1836.
3. Finkle WD, Greenland S, Ridgeway G, et al. 2014. Increased risk of non-fatal myocardial infarction following testosterone therapy prescription in men. *PLoS One* 9(1): e85805.
4. Bhasin S, Cunningham GR, Hayes FJ, et al. 2010. Testosterone therapy in men with androgen deficiency syndromes: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 95(6): 2536–2559.

Table 1: Potential adverse effects of testosterone replacement [adapted from Bhasin et al]

Adverse effects for which there is evidence of an association	– erythrocytosis (leading to polycythaemia) – acne – detection of subclinical prostate cancer – reduced sperm production thereby impairing fertility
Uncommon adverse effects with weak evidence of an association	– gynaecomastia – male pattern balding (familial) – induction or worsening of obstructive sleep apnoea
Adverse effects specific to different dosage forms	**Intramuscular injections** – fluctuation in mood or libido – pain at injection site – excessive erythrocytosis (especially in older patients) **Transdermal patches** – frequent skin reactions at application site

MARC's Remarks: September 2014 Meeting

The Medicines Adverse Reactions Committee (MARC) met on 11 September 2014 to review a number of medicine-related safety issues.

The MARC reviewed information on the risk of cardiovascular events (myocardial infarction, venous thromboembolism and stroke) with **testosterone** replacement therapy. Further information can be found in this edition of *Prescriber Update*[1].

The MARC initiated a discussion on the possible mechanisms for migration and related complications with **Jadelle** subcutaneous implants, including insertion technique, implant location difficulties, the effect of subcutaneous fat and the quality of the device. The MARC requested further information and will discuss this topic again at the next meeting.

Data on efficacy and safety of **bromocriptine** when used to treat premenstrual symptoms and mastalgia were reviewed by the MARC. The MARC noted there was very little information available to support the use of bromocriptine in these indications. Therefore, the MARC recommended that the indications for treating premenstrual symptoms and mastalgia be removed from the bromocriptine data sheet.

The MARC reviewed the available information on the possible association between **macrolides** and Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS). The MARC considered that there was insufficient evidence to support this association.

The publication of a meta-analysis on the use of **oseltamivir** by Jefferson et al in the British Medical Journal was reviewed by the MARC. The MARC noted that there were significant limitations to this analysis. Therefore, the MARC concluded that no action or change to current advice was required regarding the safety and effectiveness of oseltamivir as a result of this meta-analysis.

Further information on these issues can be found on the Medsafe website (**www.medsafe.govt.nz/profs/adverse/Minutes159.htm**).

References

1. Medsafe. 2014. Pump up Testosterone Levels Safely. *Prescriber Update* 35(4): 52

Can I Have a Drink with That?

Key messages

- ⌘ Alcohol consumption should be avoided or minimised with many medicines.
- ⌘ Drugs that act on the central nervous system tend to increase the effect of alcohol, but other interactions are possible.

Alcohol is one of the most commonly used recreational drugs in New Zealand; however mixing alcohol and some medicines can be harmful. Probably the best known alcohol-drug interaction is an intentional one with disulfiram (Antabuse), prescribed to aid abstinence from alcohol. Disulfiram inhibits acetaldehyde dehydrogenase, which blocks the metabolism of alcohol and leads to an accumulation of acetaldehyde in the blood. This disulfiram-alcohol interaction provokes a number of unpleasant symptoms: facial flushing, dyspnoea, palpitations, pyrexia, sweating, dizziness, throbbing headache, nausea and vomiting. Ingestion of large amounts of alcohol with disulfiram may also cause a drop in blood pressure that results in fainting and syncope. Further information can be found in the data sheet (**www.medsafe.govt.nz/profs/datasheet/a/Antabusetab.pdf)**

Many medicines that act on the central nervous system may potentiate the depressant and other actions of alcohol. Benzodiazepines, zopiclone and sedating antihistamines are examples of medicines that act on the central nervous system. Other less expected interactions are also seen, for example with selective serotonin re-uptake inhibitors (SSRIs) and other antidepressants. Exaggerated or pathological alcohol intoxication has been repeatedly observed in individuals who consumed moderate, previously well-tolerated quantities of alcohol. Many patients experienced memory impairment or mood change, whilst

some exhibited aggressive and violent behaviour[1]. Medsafe has previously noted cases of alcohol potentiation in patients taking varenicline (Champix) **(www.medsafe.govt.nz/safety/EWS/monitoring-communication-archive.asp#17-June-2013)**.

The table below provides further examples of medicines with which alcohol consumption should be avoided (this is not an exhaustive list).

Please note this information is advisory only. Data sheets for individual medicines should be checked for information on possible alcohol interactions.

Prescribers are reminded that alcohol-drug interactions are common but have been little studied. Reports to CARM are particularly encouraged.

References

1. Menkes DB, Herxheimer A. 2014. Interaction between antidepressants and alcohol: signal amplification by multiple case reports. *Int J Risk & Safety in Medicine* 26: 163–170.

Table 1: Examples of medicines that should not be taken with alcohol

Medicine	Effects when taken with alcohol
Metronidazole	Disulfiram-like effects
Sedating antihistamines	Increased drowsiness and dizziness; impaired driving
Tricyclic antidepressants	Increased drowsiness and dizziness; impaired driving
Benzodiazepines and zopiclone	Severe sedation, respiratory and/or cardiovascular depression; disinhibition
Methylphenidate	Impaired concentration, dizziness, drowsiness
Warfarin	Acute ingestion of a large quantity of alcohol can increase the INR, which increases the risk of pathological bleeding. By contrast, chronic heavy alcohol intake may induce the metabolism of warfarin, reducing its effects
Monoamine oxidase inhibitors (MAOIs)	Hypertensive crisis; increased alcohol effects
Sulphonylureas	Exaggerated hypoglycaemic effects; sudden changes in blood pressure, other disulfiram-like reactions
Metoprolol	Dizziness, fainting, drowsiness, arrhythmia
Statins	Liver damage
Anti-epileptics	Increased CNS depressant activity, increased risk of seizures, unusual behaviour, suicidal ideation
SSRIs	Memory impairment, disinhibition, aggression

Simvastatin Interactions and Fatal Reports

Key messages

- ⌘ Simvastatin is contraindicated with the concomitant use of potent CYP3A4 inhibitors due to the increased risk of serious adverse reactions.
- ⌘ If a potent CYP3A4 inhibitor must be used, simvastatin must be stopped for the duration of therapy.
- ⌘ Predisposing risk factors for life-threatening myopathy and rhabdomyolysis with simvastatin include age of 65 years or older, female, uncontrolled hypothyroidism and renal impairment.

The Centre for Adverse Reactions Monitoring (CARM) continues to receive reports of life-threatening and fatal cases of rhabdomyolysis with the concomitant use of medicines

that interact with simvastatin. Health care professionals are reminded that the concomitant administration of simvastatin with a potent cytochrome P450 3A4 (CYP3A4) inhibitor is contraindicated.

CYP3A4 inhibitors dramatically increase the plasma concentration of simvastatin, which results in potentially life-threatening adverse reactions, such as myopathy and rhabdomyolysis (breakdown of skeletal muscle) with or without acute renal failure. Advanced age (≥ 65 years), female gender, uncontrolled hypothyroidism and renal impairment may also increase the risk of myopathy and rhabdomyolysis.

Examples of potent CYP3A4 inhibitors include:

- macrolide antibiotics (eg, erythromycin, clarithromycin)
- azole antifungals (eg, itraconazole, ketoconazole)
- protease inhibitors (eg, ritonavir, telaprevir)
- ciclosporin.

Since 2000, CARM has received a total of 14 reports associated with this interaction, all of which were fatal. In seven reports, the patient's death was due to the adverse reaction. In the other seven reports, simvastatin may have contributed to the fatal outcome. In the majority of cases, patients were aged ≥ 65 years. The most commonly reported interactions occurred following the initiation of a macrolide or azole antifungal (strong CYP3A4 inhibitors) for acute infection while taking long-term simvastatin therapy. In patients who took the moderate CYP3A4 inhibitor diltiazem, adverse reactions occurred after an increase in simvastatin dose.

Atorvastatin is metabolised by CYP3A4 to a lesser extent than simvastatin. Although CYP3A4 inhibitors are not contraindicated with atorvastatin, they should be avoided if possible. Fluvastatin, pravastatin and rosuvastatin are not significantly metabolised by CYP3A4 and should be considered in patients requiring long-term treatment with a statin and CYP3A4 inhibitor.

Further information about medicines that interact with simvastatin may be found in the medicine data sheet at **www.medsafe.govt.nz/profs/datasheet/DSForm.asp**.

Quarterly Summary of Medsafe's Early Warning System Communications

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

Date	Communication	Topic
20 October 2014	Monitoring communication	Zoledronic acid and possible risk of tendon injury/tendinitis added to the medicines monitoring scheme
13 October 2014	Monitoring communication	Reduced adhesion and efficacy noted by some patients using Mylan Fentanyl Transdermal patches

If you would like to receive Medsafe's early warning communications, you can subscribe at **www.medsafe.govt.nz/profs/subscribe.asp**

Reporting Suspected Adverse Reactions Electronically

In 2009, Medsafe launched the electronic adverse drug reaction (eADR) reporting tool to help healthcare professionals working in GP practices to report suspected adverse reactions more easily. This tool was one of the first in the world to significantly reduce data entry requirements and deliver direct electronic reports from GPs to the Centre for Adverse Reactions Monitoring (CARM). Electronic reporting minimises human error and streamlines assessment.

Currently GPs use this tool to submit around a quarter of their reports. The GP Practice Management System automatically includes the patient's medical history and medicine history in the report. The system also allows additional information such as laboratory results and a description of the events to be included.

More information on how to use eADR is available at: **www.bpac.org.nz/BPJ/2014/April/reaction.aspx**.

Alternatively, reporters can use an adverse drug reaction (ADR) reporting app developed by CARM for the iPhone (ADR Online) which can be accessed at: **nzphvc.otago.ac.nz/app**. The app is compatible with iPhone, iPad and iPod touch.

Reports of suspected adverse reactions can be completed online at **nzphvc.otago.ac.nz**. Those who register with CARM will have their contact details automatically populated into the report. This reporting method allows attachments to be added easily to the report and reduces the amount of data entry.

CARM and Medsafe find it useful if reports include as much information as possible. This helps Medsafe and CARM to identify possible risk factors for the suspected reaction. Providing information on the outcome and successful treatments helps Medsafe and CARM offer helpful advice for other patients experiencing the same problem. The medical assessors at CARM also appreciate other documents such as discharge letters as these help to evaluate the report.

The World Health Organization (WHO) has recently analysed the quality of international adverse reaction reports. The WHO looked at both the number of reports per million inhabitants and completeness of these reports. New Zealand was one of the top five countries for adverse reaction reporting when both parameters are considered (**www.who-umc.org/graphics/28289.pdf**).

All methods of electronic reporting are secure.

Patient details held at CARM remain completely confidential and original reports are never released. Any data that is extracted from the database (for example for Medsafe or the Medicines Adverse Reactions Committee) is always anonymised for the patient and reporter.

More information is available on the CARM website **nzphvc.otago.ac.nz**.

If in doubt report it, you don't need to be certain just suspicious!

TEST YOUR KNOWLEDGE

Have you read your copy of *Prescriber Update* in 2014?

Have you kept up to date with emerging safety signals?

Test your knowledge with the end-of-year *Prescriber Update* quiz.

Answers to the quiz are available at:

www.medsafe.govt.nz/profs/PUarticles/QuizAnswersDec2014.htm

1. Which statement regarding priapism is false?

a. Priapism is a persistent penile erection not associated with sexual stimulation that lasts more than four hours.

b. Drug-induced priapism most commonly occurs with vasoactive erectile agents.

c. At least 95% of all cases of priapism occur by an ischaemic (low-flow or veno-occlusive) mechanism.

d. Priapism requires immediate medical attention to prevent long-term complications.

2. Which statement is correct?

a. Zopiclone can significantly impair driving performance for at least 6 hours after taking the medicine.

b. In adults, the usual dose of zopiclone is 7.5 mg shortly before bedtime for a maximum of 2–4 weeks.

c. The initial dose of zopiclone in older people (aged 65 years and older) is the same as that for adults.

d. Zopiclone impairs the driving performance of females more than the driving performance of males.

3. Which of the following is true?

a. Women have lower CYP3A4 activity than men.

b. St John's Wort is an inhibitor of CYP3A4 activity.

c. CYP3A4 activity is absent in new-borns.

d. The kidney is the organ with the highest CYP3A4 activity.

4. Select which medicine(s) should not be taken with alcohol.

a. Metronidazole b. Fluoxetine c. Tranylcypromine d. Diazepam

5. Someone who is starting terazosin for the first time should take their first dose:

a. At bedtime

b. Anytime, as long as it is **with** food

c. Anytime, as long as it is **without** food

d. Anytime

6. Which classes of antibiotics have been associated with superficial teeth discolouration in reports to CARM?

a. Macrolides and Beta-lactams

b. Beta-lactams and Tetracyclines

c. Macrolides and Tetracyclines

d. Tetracyclines and Cephalosporins

7. **Which of the following sets of medicines are all CYP3A4 inhibitors?**
   a. Fluconazole, Ciclosporin, Phenytoin
   b. Carbamazepine, Clarithromycin, Itraconazole
   c. Erythromycin, Carbamazepine, Fluconazole
   d. Clarithromycin, Fluconazole, Ciclosporin

8. **Name two medicines that are currently on Medsafe's Medicine's Monitoring M² scheme.**
   a.
   b.

9. **Which medicine class is most commonly reported to be associated with anaphylaxis to CARM?**
   a. Contrast Media b. Antibacterials c. Vaccines d. Anaesthetics

10. **To whom should you report problems with medical devices?**

WE NEED YOUR HELP!

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

M² MEDICINES MONITORING

Medicine	Safety concern	Active monitoring ends
Zoledronic acid	Tendon injury/Tendinitis	30 April 2015
Alendronate, Pamidronate, Zoledronate	Optic neuritis	31 December 2014

- 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**

MEDSAFE
NEW ZEALAND MEDICINES AND MEDICAL DEVICES SAFETY AUTHORITY
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.

Medsafe
New Zealand Medicines and Medical Devices Safety Authority
A business unit of the Ministry of Health

Editor
Andrea V Govender,
Medsafe, PO Box 5013,
Wellington 6145, New Zealand
Ph: (04) 819 6800, Fax: (04) 819 6806
Email: Andrea_Govender@moh.govt.nz

Prescriber Update is published and distributed by Medsafe in the interests of safer, more effective use of medicines and medical devices.

Medsafe also acknowledges the contribution of the New Zealand Pharmacovigilance Centre in providing data and advice for articles.

An electronic version of *Prescriber Update* is available at **www.medsafe.govt.nz/profs/PUarticles.asp**

To receive *Prescriber Update* electronically, please register at **www.medsafe.govt.nz/profs/profs.asp**

Data sheets, consumer medicine information, media releases, medicine classification issues and adverse reaction forms can be found at **www.medsafe.govt.nz**

Prescriber Update is a member of the

INTERNATIONAL SOCIETY OF DRUG BULLETINS

New Zealand Government