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FROM THE EDITOR

Prescribers – don't miss out!

If you or your colleagues are not receiving these hard-copy issues of *Prescriber Update* by mail, then forward your name and postal address to the Editor (contact details on page 36). There is no cost for joining the *Prescriber Update* mailing list and your details will be used only for this purpose.

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Remember to report herbal medicine adverse reactions too

Use of herbal medicines, and other alternative therapies, by consumers is increasing. As with conventional medicines, there is potential for adverse effects and interactions to occur. While many of these are not documented, there is growing awareness of the effects of herbal medicines. Prescribers and pharmacists can assist by reporting suspected adverse reactions or interactions involving herbal medicines to the Centre for Adverse Reactions Monitoring (CARM) in Dunedin – see back cover for details on how to report. Remember to ask consumers if they are taking any herbal or complementary health products, particularly when there appears to be no explanation for an adverse event.

Key to *Prescriber Update* articles

To assist readers in knowing the origin of articles published by Medsafe, the symbols below will appear next to the article title, where applicable. As part of our editorial policy, articles displaying either of these symbols have undergone independent peer review. During the development of an article, the pharmaceutical company supplying the medicine referred to in the article may be given the opportunity to comment on the draft.

ADR UPDATE

Adverse Drug Reaction Update articles are written in response to adverse reaction reports lodged with the Centre for Adverse Reactions Monitoring (CARM) and material in the international literature. These articles may also be written to alert prescribers and pharmacists to potential problems with medicines.

MARC Rx ADVICE

MARC Prescribing Advice articles are recommendations from the Medicines Adverse Reactions Committee (MARC) in response to medicine safety issues and overseas experiences.

DRUG HYPERSENSITIVITY SYNDROME

ADR UPDATE

Marius Rademaker, Hon. Associate Professor, Dermatology Department, Waikato Hospital, Hamilton; and Tim Maling, Associate Clinical Professor of Internal Medicine and Clinical Pharmacology, Wellington Hospital.

This article was published on the Medsafe web site and e-mailed to electronic *Prescriber Update* subscribers in October 2003.

Drug Hypersensitivity Syndrome is potentially life-threatening with significant morbidity. It is characterised by fever, rash and internal organ involvement. Prompt diagnosis is vital, along with identification and early withdrawal of suspect medicines. Avoidance of re-exposure to the responsible agent is essential. Cross-reactivity to structurally-related medicines is common. First-degree relatives may be predisposed to developing this syndrome.

Fever and skin reactions the first indicators

Drug Hypersensitivity Syndrome (DHS) is sometimes called Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS). This syndrome is a severe, idiosyncratic multi-system reaction defined by the clinical triad of fever, rash and internal organ involvement (e.g. hepatitis, myocarditis, nephritis or pneumonitis), which may occur 1 - 8 weeks after medicine exposure.[1] Fever is a common early feature, usually preceeding a widespread and long-lasting papulopustular or erythematous skin eruption, which often progresses to exfoliative dermatitis. The severity of the skin-related changes does not correlate with the extent of internal organ involvement, which may remain asymptomatic or be life-threatening.[1] DHS mortality is estimated at around 8%.[2] Consequently, in patients presenting with fever and rash, blood tests should be done as soon as possible. Eosinophilia and atypical lymphocytosis are common, occurring in up to 30% of cases.[2] Allopurinol, anticonvulsants (particularly carbamazepine, phenobarbitone and phenytoin) and sulphonamides are amongst the most frequent causative agents.[1,2] The incidence of DHS with anticonvulsants has been estimated at 1 in 10,000 exposures.[2]

Medicines more often reported to cause Drug Hypersensitivity Syndrome[1-3]

- Abacavir
- Allopurinol
- Atenolol
- Azathioprine
- Captopril
- Carbamazepine
- Clomipramine
- Dapsone
- Diltiazem
- Gold salts
- Isoniazid
- Lamotrogine
- Mexiletine
- Minocycline
- Nevirapine
- Oxicam NSAIAs
- Phenobarbitone
- Phenytoin
- Sulphasalazine
- Sulphonamides
- Trimethoprim

Pathophysiology is unknown

The underlying mechanisms causing DHS are poorly understood.[1] Defective detoxification of reactive oxidative metabolites[1] and a genetic predisposition[4] have been implicated in the pathophysiology of this syndrome, as has slow acetylator status.[1] A role of viral co-infection is also suspected – specifically, a reactivation of the human herpes virus 6 (HHV6).[5]

Prompt recognition and medicine withdrawal improves prognosis

The variable presentations of DHS lead to considerable diagnostic confusion and a high index of suspicion of a medicine-related cause is essential. Diagnosis is based on clinical presentation (i.e. the triad of fever, rash and organ involvement), supported by a finding of eosinophilia and abnormal liver function tests. Treatment consists of immediate withdrawal of all suspect medicines, followed by supportive care of symptoms.

As DHS can occur up to eight weeks post-exposure, a great degree of care is required when determining the responsible medicine. A temporal relationship between medicine use and the onset of the syndrome is the most important indicator of causality. Patients who develop DHS must avoid re-exposure to the causative medicine/s.

Systemic steroids may have some beneficial effects

Systemic corticosteroids are generally used in the more severe DHS cases involving significant exfoliative dermatitis, pneumonitis and/or hepatitis.[3] Relapses may occur as corticosteroid doses are tapered, and treatment may need to be continued for many weeks. The effect of corticosteroids on prognosis is unknown as controlled clinical trials are lacking.[2]

Beware of cross-reactions and family predisposition

Cross-hypersensitivity reactions are common between the three main aromatic anticonvulsants (i.e. phenytoin, carbamazepine and phenobarbitone), and all three must be avoided by patients who have experienced DHS with any one of these medicines.[1,4] Cross-reactions may also occur with non-steroidal anti-inflammatory agents (NSAIAs) such as the oxicams, e.g. piroxicam, tenoxicam. The evidence for this is based on limited case reports. Because genetic factors are suspected in DHS, first-degree relatives should be alerted to their elevated risk of developing hypersensitivity reactions to the same medicine/s.[1] Prescribers are reminded to report cases of DHS to the Centre for Adverse Reactions Monitoring (CARM) in Dunedin – see back cover for contact details.

Competing interests (authors): none declared.

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HRT – NEW ADVICE FROM THE MEDICINES ADVERSE REACTIONS COMMITTEE

MARC Rx ADVICE

Following consideration of new data, the Medicines Adverse Reactions Committee has updated its advice on the safety of hormone replacement therapy as outlined below:

- **Before hormone replacement therapy (HRT) is initiated or continued, women should be advised that the use of HRT is associated with an increased risk of pulmonary embolism, stroke and breast cancer. These risks increase with age and duration of use. Additionally, in women aged 65 years and older, HRT use is associated with an increased risk of developing dementia.**
- **HRT remains an appropriate treatment only for women with moderate to severe vasomotor symptoms of the menopause. It has no role in the primary or secondary prevention of cardiovascular or cerebrovascular disease.**
- **HRT should be taken at the lowest dose for the shortest period of time necessary to control symptoms. The need for continuing treatment should be reviewed at 6-monthly intervals.**

New data confirms MARC advice

Since the Medicines Adverse Reactions Committee (MARC) issued its advice[1] about HRT in September 2002, several new studies[2-4] examining the safety of HRT have been reported. These studies confirm the findings of the WHI study[5] published in 2002, namely that use of combined oestrogen and progestogen HRT is associated with increased risk of developing breast cancer, stroke, pulmonary embolism and heart disease.

Two studies, the Women's Health Initiative Memory Study[6] and the Million Women Study[3] have provided important new information about the safety of both combined HRT and oestrogen-only HRT.

Use of combined HRT in older women may increase the risk of dementia

The Women's Health Initiative Memory Study[6] (WHIMS) is a double-blind, placebo-controlled randomised study conducted as an ancillary of the WHI study.[5] The primary aim of WHIMS was to determine whether treatment with combined HRT decreased the risk of developing dementia from all causes in women aged 65 years and above. The results of the study demonstrated that combined HRT doubled the risk of developing dementia (RR 2.05; 95% CI 1.21-3.48), predominantly of the Alzheimer's type. This increased risk would result in an additional 23 cases of dementia per 10,000 women per year. The risk becomes apparent after one year of treatment with combined HRT.

Increase in breast cancer risk not confined to combined HRT

The Million Women Study[3] is an observational study of over one million women aged 50-64 years presenting for routine breast screening in the United Kingdom. The main aim of the study was to investigate the relationship between various patterns of HRT use and breast cancer incidence and mortality.

The Million Women study provided significant new information demonstrating that:

- the risk of breast cancer first becomes apparent within one to two years of commencing HRT and increases with duration of use;
- use of combined HRT is associated with a higher risk of developing breast cancer (RR 2.00; 95% CI 1.91-2.09, compared to no use) than oestrogen-only regimens (RR 1.30; 95% CI 1.22-1.38, compared to no use);
- all forms of HRT (including continuous and sequential HRT regimens, oestrogen-only HRT, HRT patches and implants) are associated with an increased risk of developing breast cancer;
- use of tibolone (a steroid exhibiting oestrogenic, progestogenic and androgenic activity) is associated with an increased risk of developing breast cancer (RR 1.45; 95% CI 1.25-1.67, compared to no use); and
- the risk of breast cancer decreases after stopping HRT, and within five years the residual risk is not significantly different from that observed for never-users of HRT.

Number of additional breast cancers from HRT use (compared to no HRT use) per 1000 women by age 65[3]

Type of HRT	Duration of HRT use (from age 50)	
	5 years	10 years
Oestrogen-only	1.5	5
Combined oestrogen-progestogen	6	19

MARC recommends 6-monthly review of patients on HRT

While the absolute risk of developing breast cancer associated with HRT use is small, the overall benefit-risk assessment for HRT indicates that other than for short-term use, the risks of treatment outweigh the benefits. The MARC therefore does not recommend the long-term use of HRT and advises that prescribers discuss the need for continued HRT every six months with patients using any HRT regimen.

When a decision is made to stop HRT, it should be withdrawn gradually. Information on how to reduce HRT can be found in the 2002 *HRT Guideline Update* on the New Zealand Guidelines Group website: www.nzgg.org.nz

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THROMBOSIS WITH TRANEXAMIC ACID FOR MENORRHAGIA

ADR UPDATE

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This article was published on the Medsafe web site and e-mailed to electronic *Prescriber Update* subscribers in October 2003.

Tranexamic acid is an effective treatment for heavy menstrual bleeding and can now be prescribed for this indication without specialist recommendation. Tranexamic acid has the potential to cause thrombotic disorders and is contraindicated in patients with active thrombotic or embolic disorders. It should not be prescribed for patients with risk factors for thromboembolic disease unless the potential benefits clearly outweigh the potential for harm. Patients should be made aware of symptoms suggestive of venous or arterial thrombosis or embolism.

New Zealand report of fatal pulmonary embolism

The Centre for Adverse Reactions Monitoring (CARM) has received nine reports of adverse reactions with tranexamic acid, including one report of a fatal pulmonary embolism, and one of parietal haemorrhage followed by a venous sinus thrombosis in a patient taking both mefenamic acid and tranexamic acid.

Tranexamic acid (Cyklokapron®) is an antifibrinolytic agent used to treat or prevent haemorrhage in a variety of bleeding disorders. It has been shown to reduce menstrual blood loss in menorrhagia. The New Zealand Guidelines Group's guideline on heavy menstrual bleeding[1] considered effectiveness, side effects and patient acceptability when assessing medical interventions for menorrhagia. Using these criteria tranexamic acid, as well as non-steroidal anti-inflammatory agents, ranked second to the levonorgestrel intrauterine device. Tranexamic acid for heavy menstrual bleeding can now be prescribed by general practitioners without specialist recommendation.

Link with thrombosis mainly supported by case reports

There are several published case reports of thrombotic or embolic disorders occurring with tranexamic acid use. These include three reports of deep vein thrombosis or pulmonary embolism.[2-4] Two of these patients had bleeding disorders,[2,4] and the other had a subarachnoid haemorrhage.[3]

Amongst the case reports of arterial thrombosis are two young women who developed cerebral artery thromboses while taking tranexamic acid for menorrhagia.[5] The World Health Organisation's international drug monitoring database holds 528 reports of suspected reactions to tranexamic acid. There are 56 reports of deep vein thrombosis, pulmonary embolism or both and these include reports of cerebral and retinal vein thrombosis. Additionally there are 22 reports of cerebral embolism and nine of arterial thrombosis.

In contrast to the above reports, a study of 256 pregnant women taking tranexamic acid, of whom 169 delivered by caesarean section, found no increased risk of thrombosis.[6] However, a Cochrane review[7] of antifibrinolytics for the treatment of menorrhagia noted the absence of randomised control trial data to assess the risk of thromboembolic events with tranexamic acid.

Avoid tranexamic acid if active thromboembolic disease is present

The New Zealand product data sheet[8] states that tranexamic acid is contraindicated in patients with active thromboembolic disease such as deep vein thrombosis, pulmonary embolism and cerebral thrombosis. While there are no formal epidemiological studies demonstrating a link between tranexamic acid and thrombotic disorders, with respect to its use for menorrhagia prescribers should be aware of the possible link suggested by the case reports. Information about a personal or family history of thromboembolic disease, or the

presence of other thrombosis risk factors should be elicited; where these are present, the risks of tranexamic acid compared with its potential benefit need to be carefully considered. Patients should be informed about the symptoms of thrombotic or embolic disorders, as well as short-term risk factors such as surgery and immobility.

Prescribers should also be aware that other treatments used for heavy menstrual bleeding, such as progestogens in doses greater than those used for contraception, can also increase the risk of venous thromboembolism. If a patient is at risk of thrombosis, then an alternative agent should be used.

Competing interests (author): none declared.

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ITRACONAZOLE-INDUCED CONGESTIVE HEART FAILURE

ADR UPDATE

Medsafe Editorial Team

This article was published on the Medsafe web site and e-mailed to electronic *Prescriber Update* subscribers in October 2003.

Antifungal treatment with itraconazole has been associated with congestive heart failure. Prescribers are reminded of this rare but serious adverse reaction, and the need to consider the risks and benefits of itraconazole therapy in individual patients. Before starting itraconazole treatment, patients should be informed of the signs and symptoms of congestive heart failure.

Itraconazole indicated for treatment of local and systemic fungal infections

Itraconazole (Sporanox®) is a synthetic triazole derivative approved in New Zealand for the treatment of skin and nail fungal infections, vulvovaginal candidiasis, and systemic mycoses.[1] Itraconazole has a broad antifungal spectrum and acts by inhibiting the synthesis of ergosterol, an essential component of fungal cell membranes.[2,3]

New Zealand case report of CHF associated with itraconazole use

Itraconazole has been shown to have a negative inotropic effect, and has been associated with reports of congestive heart failure (CHF).[4] The Centre for Adverse Reactions Monitoring (CARM) has received the following case report of CHF associated with itraconazole therapy.

A fit, 41-year-old man was prescribed three-month pulse treatment (one week per month) with itraconazole (400mg/day) for a fungal toenail infection. During each week of pulse treatment, he experienced ankle swelling, weight fluctuations, shortness of breath on exertion, and puffiness around the face. Four months later, the fungal toenail infection returned, and the patient was prescribed further pulse treatment with itraconazole (400mg/day) for six months. Five months into the second treatment period, the patient presented to his GP with significant weight gain (6kg in one month), peripheral oedema and dull left-sided chest pain. He was found to be hypertensive. An echocardiogram was performed; the findings were within normal limits except for mild left ventricular hypertrophy, which may represent an athletic (fit) heart. The patient, who had no other medical conditions and was on no other medicines at the time of the itraconazole therapy pulses, was admitted to hospital where he was assessed as being in heart failure. Treatment with itraconazole was discontinued and the patient recovered without sequelae.

Consider itraconazole-induced CHF even in patients with no risk factors

The mechanism of itraconazole-induced CHF is presently undetermined, and neither is it known whether the heart damage is reversible. There are insufficient data to provide a comparative likely incidence of CHF developing in patients with risk factors for CHF and those without. Therefore, prescribers are reminded that itraconazole can cause CHF in any individual and that it should not be used in patients who have a history of CHF unless the benefit clearly outweighs the risk. The risk-benefit assessment should consider the severity of the indication, and individual risk factors for CHF such as pre-existing cardiac or respiratory disease. Patients with risk factors should be informed of the signs and symptoms of CHF before treatment begins. In patients on itraconazole who present with oedema or shortness of breath, consider CHF as part of the differential diagnosis. If CHF develops during itraconazole use, the risk-benefit profile of continued treatment should be reassessed against the availability of other systemic antifungal medicines.

Competing interests (authors): none declared.

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WAVING THE WAND OVER MEDICAL DEVICES TO FACILITATE SAFETY MONITORING

On 1 January 2004, it is expected that the *Medicines (Database of Medical Devices) Regulations 2003* will come into force. From that date, a sponsor[a] wishing to market a new medical device in New Zealand will be required to enter details into a medical device database within 30 days of placing the product on the market. This will progressively provide a record of medical devices on the New Zealand market, facilitating post-market surveillance activities such as overseeing recalls and responding to safety alerts.

The database is called WAND (Web-Assisted Notification of Devices) and will be accessible to sponsors from the Medsafe web site. WAND is a notification database only and an entry in the database does not indicate that the medical device has undergone any evaluation or been approved by Medsafe for distribution in New Zealand.

For existing medical devices (i.e. those already on the market prior to 1 January 2004 that are still being supplied), sponsors will have a period of one year to complete a notification on the database.

There will be some medical devices that are exempt from being notified on the database. These include:

- products made specifically in accordance with a request by a registered health professional and intended to be used only in relation to a particular individual
- imported devices held in bond for export
- in-house *in vitro* diagnostic devices (IVDs) for use on site only
- medical devices supplied as part of a clinical trial
- items imported for personal use.

A more comprehensive regulatory scheme that will include a pre-market approval process is under development and planned for implementation in mid-2005. This work is occurring as part of the planned trans-Tasman Therapeutic Products Regulatory Scheme.

For further information go to www.medsafe.govt.nz

[a] A person who exports, imports, manufactures or arranges for the manufacture of a medical device for supply in New Zealand.

OESOPHAGITIS WITH DOXYCYCLINE AND OTHERS

ADR UPDATE

Medsafe Editorial Team

This article was published on the Medsafe web site and e-mailed to electronic *Prescriber Update* subscribers in October 2003.

Oesophagitis is a well-documented consequence of doxycycline therapy. A number of other medicines are similarly implicated. Taking doses at bedtime or without fluids is a common cause of the oesophagitis. This adverse effect can be prevented by advising patients to take doxycycline with food or a large glass of water, and to sit upright or stand for at least 30 minutes afterwards.

Dose form may not be a contributing factor

CARM has received a total of 56 reports of oesophagitis associated with antibiotics; of these, 46 were for doxycycline. In Australia, there have been 46 reports of oesophagitis and 49 reports of oesophageal ulceration received in total, all with doxycycline. It is unclear whether these events are more likely to occur with a particular dose form (i.e. tablets or capsules), as the brands most commonly used in Australia are available only in tablet formulations.[1] However, doxycycline capsules frequently remain in contact with the oesophagus for longer periods than the tablet form.[2]

Many other medicines are known to cause oesophagitis

Oesophageal damage occurs when a medicine lingers in the oesophagus long enough to cause mucosal lesions. This can arise when little or no fluid is taken to assist swallowing of the medicine and facilitation of its subsequent passage through the oesophagus into the stomach. Damage can also occur, probably from reflux, if the patient lies down soon after taking the medicine. Ulcers may be seen endoscopically. At least 70 different medicines have been reported to cause oesophageal disorders. Antibacterials such as clindamycin, doxycycline, minocycline and tetracycline are the most commonly implicated agents. Other medicines include alendronate, aspirin, ferrous sulphate, non-steroidal anti-inflammatory agents, potassium chloride and quinidine.[2]

Symptoms are often acute and severe

In most cases, there are no patient-related predisposing factors other than poor swallowing technique (i.e. insufficient fluid intake or not remaining upright). The symptoms of doxycycline-induced oesophagitis include sudden onset of pain on swallowing and often very severe chest pain. A temporal relationship between onset of symptoms and ingestion of doxycycline should be considered as part of the diagnosis. In most cases, cessation of the causative agent is sufficient for symptoms to resolve.[2] Recovery may take longer than two weeks in severe cases.[3] Symptomatic use of a proton pump inhibitor for 1-2 weeks may be required. However, endoscopy is not usually necessary and can be extremely uncomfortable for the patient.

Oesophageal damage can be prevented

Prescribers and pharmacists are reminded that the risk of this adverse effect can be minimised, or even avoided, by advising patients to take every dose of doxycycline (and other implicated medicines) either with food or a large glass of water, and to remain sitting upright or standing for at least 30 minutes (and up to 2 hours[4]) afterwards.[3]

Competing interests (authors): none declared.

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IMMP INSERTION STUDIES OF THE MULTILOAD® INTRAUTERINE DEVICE

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This article was published on the Medsafe web site and e-mailed to electronic *Prescriber Update* subscribers in October 2003.

Intensive Medicines Monitoring Programme (IMMP) data on over 16,000 New Zealand women using the intrauterine contraceptive device, Multiload® Cu375, have now been analysed and published. The studies showed that general practitioners performed 92% of the reported insertions during the 10-year monitoring period. Whilst insertion problems occurred more often in nulliparous women, incidence rates were reassuringly low. An incidence of 1.6 uterine perforations per 1000 insertions was observed, with 46% of cases not diagnosed until more than one year after insertion.

Large New Zealand cohort for Multiload

The IMMP has collected data on 16,159 New Zealand women who have used the copper intrauterine contraceptive device (IUD) Multiload Cu375 between 1991 and 2001. This cohort is thought to be the largest for any one type of IUD in the world. The database includes records of over 17,400 insertions throughout New Zealand. The median age of the women was 32 years (range 14-56 years) and 40% of insertions were performed in women who had delivered two babies (range 0-11). Approximately 9% of insertions were performed in nulliparous women – a group previously excluded from many clinical trials of IUDs.

General practitioners reported the majority (92%) of the insertions. For about 73% (1,244) of all doctors, the number of reported Multiload Cu375 insertions during the ten-year study period was less than ten; 24% (400) of doctors reported 10-50 insertions; 2% (35) between 50 and 100 insertions; and 1% (20) reported inserting more than 100 devices. These numbers were calculated from Multiload Cu375 insertion forms sent in by 1,699 participating New Zealand doctors. Based on these IMMP data, two large studies[1,2] looking at the insertion of Multiload Cu375 have been published internationally. The findings of these studies are summarised here.

Low rate of insertion problems found

The first study[1] was a detailed analysis of the insertion procedure for Multiload Cu375. Problems fitting the device occurred at a low rate – about 2% of all insertions (1.35% difficult insertion and 0.44% failed insertion). More difficulties were reported for insertions in nulliparous women (3.9%) compared to those in parous women (1.95%).

Adverse reactions occurring at the time of insertion, such as pain, bleeding or vaso-vagal episode, were reported in 1.2% of all insertions. Again, nulliparous women had a greater risk of adverse reactions – 3.5% compared with 1.1% in parous women. However, this risk may be acceptable in nulliparous women if they are unable to use other contraceptive methods.

Experience of doctor correlates with insertion problem incidence

Doctors who reported inserting less than ten devices noted an insertion problem incidence of 2.5%, compared to 2.1% for doctors who inserted either 10-49 or 50-99 devices, and 1.3% for doctors who reported 100 or more insertions. The difference between low (<10 devices) and moderate (10-99) rate inserters was not statistically significant (RR= 1.2; 95% CI = 0.9-1.5). However, the difference between low rate inserters and high (≥ 100) rate inserters was statistically significant (RR = 1.9; 95% CI = 1.3-2.8). There are potential service provision implications of this finding, although the absolute risk of insertion problems occurring with either low or high rate inserters was low, i.e. about one extra woman in every 100 insertions will have an insertion-related problem if the device is put in by a low-rate inserter

compared to a high-rate one. In New Zealand there are many other factors, including the availability of IUD insertion in rural areas, which must be taken into account when considering contraception choice for each woman.

Incidence of uterine perforation higher than previously reported

The second study[2] was performed to determine the rate of uterine perforation on Multiload Cu375 insertion. A review[3] of eight previous studies reported no uterine perforations in over 5,000 IUD insertions. Analysis of the IMMP database identified 28 reports in 17,469 insertions (1.6 per 1000) suggesting that uterine perforation had occurred. Of these reports, 14 cases had been termed "IUD embedded". These were included as 'partial perforations' in the analysis, as it was considered that for an IUD to become embedded, some degree of uterine wall damage must have occurred at the time of insertion. Review of the individual case reports supported this interpretation.

The results suggested that uterine perforation was not suspected at the time of IUD insertion in many women. Only seven of the 28 (25%) uterine perforations were diagnosed immediately or within one week. For 13 cases (46%) the diagnosis was not made until more than one year after insertion. The clinical consequences of uterine perforation included pain, bleeding, pregnancy and surgical removal of the IUD from the pelvic cavity. Whilst this study[2] reported a higher incidence than other studies,[3] this may still be an underestimate due to undiagnosed cases of perforation, or cases not reported to the IMMP.

Findings of insertion studies reassuring

These two large studies,[1,2] based on IMMP data, have provided useful information about the insertion of Multiload Cu375 in both parous and nulliparous women. The results of both studies are reassuring, showing that in clinical practice the insertion of Multiload Cu375 is associated with few complications.

Acknowledgements

The IMMP staff would like to thank all the doctors who submitted IMMP notification forms and follow-up forms for Multiload Cu375. Without your co-operation these studies would not have been possible.

Competing interests (author): none declared.

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ADVERSE REACTIONS OF CURRENT CONCERN

MARC Rx ADVICE

The Medicines Adverse Reactions Committee (MARC) initiated the list of *adverse reactions of current concern* to bring particular medicine adverse reactions to the attention of prescribers. The purpose of the list is also to encourage prescribers to report these reactions to the Centre for Adverse Reactions Monitoring (CARM) so that more information can be gathered, and further action taken if necessary. The reports provide a New Zealand perspective on emerging medicine safety issues.

As with any adverse reactions monitoring scheme, analysis can only be based on reports that are received. Prescribers are therefore encouraged to continue reporting adverse reactions to CARM so that the MARC can make the best possible recommendations based on information reflecting the New Zealand situation.

Regular amendments to the list of reactions are made either in response to adverse events reported in New Zealand or international pharmacovigilance issues.

Please report **all cases** of the following adverse reactions (no changes since the June 2003 issue of *Prescriber Update*) to: CARM, PO Box 913, Dunedin. Use the reporting form inside the back cover of *Prescriber Update*, or download the form from the CARM or Medsafe web sites: www.otago.ac.nz/carm or www.medsafe.govt.nz/Profs/adverse.htm

Medicine/s	Adverse reactions of current concern	*Prescriber Update* reference
Atypical antipsychotics	hyperglycaemia	Vol.23(1), Apr 2002 & No.18, Jun 1999
Celecoxib	cardiovascular events	Vol.23(1), Apr 2002
Complementary and alternative medicines*	all adverse reactions	Vol.23(2), July 2002 & No.13, Oct 1996
Diane 35® and 35 ED®	venous thromboembolism	Vol.23(1), Apr 2002 & No.20, Feb 2001
Estelle 35® and 35 ED®	venous thromboembolism	Vol.23(1), Apr 2002 & No.22, Oct 2001
Fluticasone (inhaled)	adrenal insufficiency, hypoglycaemia, or seizure	Vol.24(1), June 2003
Hormone replacement therapy	venous thromboembolism	Vol.23(3), Nov 2002 & No.16, Apr 1998
Rofecoxib	cardiovascular events	Vol.23(1), Apr 2002
SSRIs	severe agitation, severe restlessness/akathisia, and/or increased suicidality	Vol.23(3), Nov 2002

* includes herbal medicines, bee products, homoeopathic products, dietary supplements, minerals, and any other medicines containing animal or plant extracts.

INTENSIVE MEDICINES MONITORING PROGRAMME

About the IMMP

The purpose of the Intensive Medicines Monitoring Programme (IMMP) is to identify previously unrecognised adverse reactions to new medicines. It also develops adverse reaction profiles for these medicines, as well as measuring incidence and characterising reactions of clinical concern. In addition, the IMMP is able to identify any high-risk groups amongst the patients being treated. The results of IMMP findings are used to enhance the safe use of medicines.

Which medicines are monitored?

Medicines of a new class are added to the IMMP so that unknown adverse effects can be identified as soon as possible. Medicines may also be included in the programme if they are similar to other medicines for which safety concerns exist. The medicines currently being monitored are listed in the following table.

What to report

Successful assessment of the significance of events depends on prescribers and pharmacists reporting all events occurring with IMMP medicines, including adverse reactions and random clinical incidents. Please report:

- all new events including common minor ones
- any change in a pre-existing condition
- abnormal changes in laboratory test results
- accidents
- all deaths and causes
- possible interactions.

Where to report

Please report all adverse events occurring with IMMP medicines to: Centre for Adverse Reactions Monitoring (CARM), PO Box 913, Dunedin. Use the reporting form inside the back cover of *Prescriber Update*, or download the form from either the CARM or Medsafe web sites: www.otago.ac.nz/carm or www.medsafe.govt.nz/Profs/adverse.htm

Medicines on the IMMP

Medicine	Proprietary name/s	Indications/Action
Clozapine	Clozaril, Clopine	atypical antipsychotic
Entacapone	Comtan	Parkinson's disease – adjunctive treatment only
Etoricoxib	Arcoxia	COX-2 inhibitor (selective NSAIA)
Levonorgestrel intrauterine system	Mirena	progestogen-releasing intrauterine system
Montelukast	Singulair	anti-asthmatic / leukotriene inhibitor
Nefazodone	Serzone	antidepressant / 5HT2 blocker
Olanzapine	Zyprexa	atypical antipsychotic
Parecoxib	Dynastat	COX-2 inhibitor (selective NSAIA)
Quetiapine	Seroquel	atypical antipsychotic
Risperidone	Risperdal	atypical antipsychotic
Sibutramine	Reductil	centrally acting anorexiant
Tolcapone	Tasmar	Parkinson's disease – adjunctive treatment only
Valdecoxib	Bextra	COX-2 inhibitor (selective NSAIA)
Zafirlukast	Accolate	anti-asthmatic / leukotriene inhibitor

Follow-up only:

New patients are no longer being added to the cohorts for celecoxib (Celebrex®) and rofecoxib (Vioxx®). However, follow-up of existing patients is continuing.

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

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CARM
CENTRE FOR ADVERSE REACTIONS MONITORING

Fax: (03) 479 7150
Phone: (03) 479 7247

Reporting form for Adverse Reactions to Medicines, Vaccines and Devices and all Clinical Events for IMMP

PATIENT DETAILS

H1574

Surname:	First Name(s):	NHI No:
		Ethnicity:
Address:		Date of Birth:
		Sex: M ☐ F ☐

ALL MEDICINES IN USE – ASTERISK SUSPECT MEDICINE(S)

Medicine(s) / Vaccine(s)+ 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 ☐ Unknown ☐ Fatal ☐ Date of Death:

Severe? No ☐ Yes ☐ **Rechallenge?** No ☐ Yes ☐ Result:

OTHER FACTORS

Renal Disease ☐ Hepatic Disease ☐ Allergy ☐ Describe:

OTC Use? ☐ Industrial Chemicals ☐ Other Medical Conditions? ☐ Describe:

REPORTING DOCTOR/PHARMACIST/NURSE

Name:	Telephone:
Address:	Date:
Email address:	

Send completed form to CARM

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

ADVERSE REACTIONS REPORTING GUIDELINES

Please do not hesitate to report ***any suspect reaction of clinical concern***. The following general guidelines apply.

Report adverse reactions to:

- All medicines
- Vaccines
- "Over-the-counter" (OTC) medicines
- Herbal, complementary and alternative remedies.

Report **adverse reactions** and **interactions** that are:

- **serious**
- **adverse reactions of current concern**[1].

Report **all** reactions to **new medicines** and **all** events to **IMMP medicines**[2].

Report **serious allergic reactions** so that a danger or warning can be entered against the patient's name in the national health database.

If in doubt, report.

Reporting may be made on-line, by mail, fax, e-mail or phone

On-line reporting: Register and report on-line at www.otago.ac.nz/carm/report.asp

Reporting form: Use the form overleaf or the card supplied with *New Ethicals Catalogue*. The reporting form can also be downloaded from www.otago.ac.nz/carm/report.asp *or* www.medsafe.govt.nz/profs/adverse.htm

Mail the form to: Freepost 112002
The Medical Assessor
Centre for Adverse Reactions Monitoring
P O Box 913, Dunedin

Or fax it to: (03) 479 7150

Phone: (03) 479 7247

E-mail: carmnz@stonebow.otago.ac.nz

Web site: www.otago.ac.nz/carm

1. The list of *Adverse Reactions of Current Concern* is on page 33.
2. The list of medicines in the Intensive Medicines Monitoring Programme (IMMP) is on page 35.