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Medicines that prolong the QT interval – www.torsades.org

This web site of the University of Arizona's Center for Education and Research on Therapeutics provides listings of medicines that prolong the QT interval and/or induce torsades de pointes (TdP) ventricular arrhythmia. There are four lists according to the evidence supporting the association between medicine use and induction of TdP or prolonged QT:

- Drugs with risk of TdP
- Drugs with possible risk of TdP
- Drugs to be avoided by patients with congenital long QT syndrome
- Drugs unlikely to cause TdP.

MeNZB adverse events

From 19 July 2004 to 16 September 2005, over 2.48 million doses of MeNZB™ vaccine were administered, and 1695 reports of adverse events were received by CARM. The relative proportions of each of the reactions have remained consistent as the vaccination campaign has expanded across the country. For the full safety monitoring reports which detail the types and numbers of reactions reported see www.immunise.moh.govt.nz/safety.html

Herbal medicines and health supplements

Please report suspected adverse reactions or interactions involving complementary and alternative medicines to the Centre for Adverse Reactions Monitoring in Dunedin (see back cover for reporting details). These products include herbal medicines, bee products, homoeopathic products, dietary supplements, minerals, and any other medicines containing animal or plant extracts. Your reports will assist in both identifying potential reactions and developing safety advice to minimise the risk of harm to consumers. 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. There have been recent instances in New Zealand where health supplements and traditional Chinese or Chinese-sourced medicines have been found to illegally contain corticosteroids, frusemide, piroxicam, sibutramine or medicines to treat erectile dysfunction. If you have concerns about the therapeutic efficacy or pattern of side effects in consumers using these types of products, please contact the Compliance Team at Medsafe (ph 04 496 2176).

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.

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

WATCHING BRIEFS

Quick updates and short reminders about medicine safety issues.

Update on COX-2 inhibitors

Medsafe has recently concluded the updating of the data sheets for the following COX-2 inhibitors: Arcoxia® (etoricoxib), Celebrex® (celecoxib), Dynastat® (parecoxib), Mobic® (meloxicam) and Prexige® (lumiracoxib). These changes were recommended by the Medicines Adverse Reactions Committee (MARC), and are intended to best manage the cardiovascular risks of the COX-2 inhibitors and to identify those select patients in whom appropriate use may be warranted. Key points for prescribers are:

- The decision to prescribe a selective COX-2 inhibitor should only be made if non-pharmacological interventions and simple analgesic therapies have been tried and found to lack analgesic efficacy or have unacceptable adverse effects in the individual patient; and after assessment of the individual patient's overall risks.
- As the cardiovascular risks of the selective COX-2 inhibitors may increase with dose and duration of exposure, the shortest duration possible and the lowest effective daily dose should be used.
- Patients on long-term treatment should be reviewed regularly, such as every three months, with regards to efficacy, risk factors and ongoing need for treatment.
- Use in the peri-operative period is contraindicated in patients undergoing cardiac or major vascular surgery; and contraindicated in patients who have previously had a myocardial infarction or stroke.
- Patients with significant risk factors for cardiovascular events should only be treated with a COX-2 inhibitor after careful consideration of the patient's overall risk and the potential risks and benefits of alternative analgesic therapies.
- Prescribers should inform the individual patient of the possible increased risks when prescribing a COX-2 inhibitor for patients at high risk of cardiovascular adverse events.

Prescribers are additionally encouraged to continue reporting any suspect adverse reaction of clinical concern relating to the use of COX-2 inhibitors. These reports will assist Medsafe and MARC in the ongoing safety monitoring of these medicines.

Leflunomide – watch for respiratory symptoms

Leflunomide (Arava®) is a disease-modifying anti-rheumatic agent indicated for the treatment of rheumatoid arthritis. It is often used in conjunction with methotrexate. The Centre for Adverse Reactions Monitoring (CARM) has received seven reports of pneumonitis occurring in patients taking leflunomide together with methotrexate. Clinical trial data indicate that pneumonitis can also occur with leflunomide alone. This disorder is characterised by dyspnoea, hypoxia and lung infiltrates. Initial symptoms in the CARM reports were various combinations of dyspnoea, cough, fever, lethargy, weight loss and influenza-like symptoms followed by rapid progression to acute respiratory compromise. Early recognition is important as pneumonitis can be life-threatening or lead to persistent disability. Patients should be informed about initial warning symptoms so that these can be investigated immediately and the suspect medicines discontinued.

Isotretinoin – contraception is critical

Isotretinoin is highly teratogenic, which means that effective contraception is essential for all women of childbearing age (including those with a history of infertility) for whom isotretinoin is a treatment option. Women should be counselled about the risk of teratogenicity so they know it is critical that they not become pregnant while on isotretinoin. Prescribers must also exclude pregnancy prior to starting isotretinoin, and inform women to continue using contraception for one month after stopping isotretinoin.

Reminder about obtaining patient consent

Prescribers are reminded of their obligation to obtain informed consent from patients when making treatment decisions. This requirement forms part of the *Code of Health and Disability Services Consumers' Rights 1996*, which states that every consumer has the right to be fully informed of the risks and benefits of the proposed treatment. The Code also states that consumers have the right to receive the information they need to make an informed choice or give informed consent.

If a clinician is considering prescribing an unapproved medicine (i.e. a medicine that has not been assessed by Medsafe against regulatory standards for safety, efficacy and quality), the onus is on the prescriber to satisfy themself that the medicine is of appropriate safety, quality and efficacy before deciding to prescribe it.

Medsafe considers that, in order for clinicians to comply with the Code, during the consultation the patient should be advised about 1) the unapproved status of the medicine; and 2) the information that led the clinician to decide why that particular unapproved medicine is the most appropriate treatment for the patient. It is only after this information has been communicated that the patient's informed consent for treatment with an unapproved medicine is considered to have been obtained.

Miconazole oral gel interaction with warfarin

Prescribers are reminded of the potentially severe interaction between miconazole oral gel (Daktarin® oral gel) and warfarin. Clinically significant increases in the international normalised ratio (INR) of patients stabilised on warfarin have been reported following concomitant use of miconazole oral gel, due to systemic absorption. Warfarin patients who are given miconazole oral gel should be monitored for change in anticoagulant effect and the dose of warfarin adjusted, if necessary. As miconazole oral gel can be purchased without a prescription, both pharmacists and prescribers should inform patients taking warfarin of the potential for this interaction.

Update on Salamol inhalers

Testing of the Salamol® brand of salbutamol inhalers has shown that blockages can be prevented by washing the device once every week. Remove the metal canister and rinse the plastic mouthpiece under warm water for 30 seconds, shake to remove excess water then leave it to air dry (overnight if possible). Reassemble the inhaler device once dry. Patients may wish to keep a spare inhaler handy for use while the cleaned inhaler is drying.

CARDIAC VIGILANCE RECOMMENDED FOR METHADONE

ADR UPDATE

Medsafe Pharmacovigilance Team

This article was published on the Medsafe web site and e-mailed to electronic *Prescriber Update* subscribers in November 2005.

Methadone may cause QT prolongation and torsades de pointes. Higher doses, concomitant QT interval-prolonging agents and the presence of other risk factors for QT prolongation may predispose patients to the development of potentially fatal arrhythmias with methadone. Prescribers are advised to evaluate their patients for modifiable risk factors prior to initiating methadone. ECG monitoring is recommended with methadone doses >150mg/day and in patients with either risk factors for QT prolongation or symptoms that may be attributable to arrhythmia.

Methadone is used for analgesia and opioid dependence

Methadone is a synthetic opioid analgesic indicated for the treatment of opioid dependence and moderate to severe pain. It is estimated that 60% of patients treated for opioid dependence in New Zealand receive doses of <100mg per day and approximately 10% of patients receive >200mg per day.[1] Most patients with chronic pain require methadone to be administered twice daily, although total daily doses are usually <100mg per day.[2]

Prolongation of the QT interval is used as a surrogate marker for the risk of developing potentially fatal arrhythmias such as torsades de pointes (TdP).[3,4] The QT_c* interval is considered to be prolonged if it is >450ms in men or >460ms in women.[4] A QT_c of >500ms,[4] or an increase of >40ms,[5] is generally accepted to confer a high risk of TdP.

Local and international reports of methadone-associated QT prolongation

There have been two New Zealand reports of arrhythmia in patients taking methadone for opioid dependence. One patient was taking methadone 150mg/day and experienced recurrent syncopal episodes before he collapsed and died suddenly at home. The other patient was taking methadone 120mg/day and was admitted to hospital after experiencing two syncopal episodes. ECG monitoring revealed episodes of self-limiting TdP with prolonged QT_c. The methadone dose was reduced to 60mg/day and the QT_c interval returned to normal.

In June 2004, the Swedish Medical Products Agency reported on 32 cases of QT prolongation, arrhythmia or sudden death in patients taking methadone.[6] As of April 2005, the World Health Organisation's adverse reactions data base included 255 reports of heart rate and rhythm disorders associated with methadone. These included 24 reports of TdP, 26 reports of QT prolongation and 117 reports of cardiac arrest.

Biologically plausible mechanism and risk factors identified

In vitro studies have demonstrated that, as with the majority of non-cardiac medicines that cause QT prolongation, methadone prolongs the cardiac action potential by inhibiting cardiac potassium channels.[7] In addition, a prospective study in opioid-dependent patients demonstrated a statistically significant increase in the QT_c interval after two months of methadone treatment.[5] In a review of 17 cases of TdP with methadone, the majority of patients were taking very high doses (mean 400mg/day) or had at least one other risk factor for QT prolongation.[8]

* QT_c = corrected QT interval; often derived using Bazett's formula (QT_c = QT interval/√ R-R interval), which corrects for the heart rate.[4]

The presence of other risk factors for QT prolongation increases the risk of developing QT prolongation or TdP with a medicine.[3] Risk factors include[3,4]:

- advanced age
- female gender
- electrolyte abnormalities e.g. hypokalaemia or severe hypomagnesaemia
- bradycardia
- heart disease (e.g. heart failure or ischaemia)
- congenital long QT syndrome or pre-existing QT prolongation
- concomitant use of other QT prolonging medicines (e.g. tricyclic antidepressants, some antipsychotics and antibiotics[9] – see www.torsades.org/medical-pros/drug-lists/drug-lists.htm for a more comprehensive listing)
- concomitant use of medicines that may inhibit the metabolism of methadone (e.g. fluconazole and some SSRI antidepressants[10]).

At present it is not known how often QT prolongation occurs with methadone use, although it appears to be reported infrequently. This may be due to under-recognition, particularly in patients being treated for opioid dependence where sudden death may be attributed to either narcotic overdose or complications arising from long-term narcotic abuse.[8] Although in-vitro studies, spontaneous reports and case studies provide clinical evidence for an association between methadone use and QT prolongation, further studies are required to more clearly define this risk.

The risk of methadone-induced QT prolongation can be managed

Based on current evidence Medsafe offers the following advice to prescribers when using methadone for any indication. However, the use of methadone should not be precluded in opioid-dependent patients who would otherwise benefit from treatment.

- All patients should be evaluated for the presence of risk factors for QT prolongation prior to initiating methadone treatment. Modifiable risk factors should be corrected.
- Maintain patients on the lowest effective dose of methadone. Careful dose titration is required due to methadone's long half-life and pharmacokinetic variability.[10]
- For patients with chronic pain, the potential for QT prolongation should be considered before prescribing methadone. Morphine and codeine appear to have little effect on cardiac potassium channels in vitro,[7] so may be more appropriate choices particularly in patients with other risk factors for QT prolongation.
- For patients being treated for opioid dependence, methadone remains the most effective funded treatment available, although it is noted that buprenorphine may have less effect on cardiac potassium channels in vitro.[7] Specialist advice should be sought for patients who, despite elimination of all modifiable risk factors, have a persistently prolonged QT_c interval.
- Patients should be informed of the symptoms of arrhythmia and be advised to promptly seek medical advice if symptoms such as palpitations and syncope develop.
- ECG monitoring should be considered for methadone doses >150mg/day and in patients with risk factors for QT prolongation, or symptoms that may be attributable to arrhythmia.[6]
- Serum electrolytes should be measured regularly, particularly in patients with vomiting or diarrhoea, or those taking diuretics.
- If QT prolongation occurs (i.e. QT_c >500ms or an increase in the QT_c of >40ms), specialist advice should be obtained regarding discontinuing or reducing the dose of methadone.

Please report all cases of suspected QT prolongation, arrhythmia or death associated with methadone to the Centre for Adverse Reactions Monitoring (see back cover for details).

Competing interests (authors): none declared.

References

1. Personal correspondence, 7 April 2005. Drug dependency specialist, Wellington Hospital.
2. Personal communication, June 2005. Chronic pain specialist, Wellington Hospital.
3. Roden DM. Drug-induced prolongation of the QT interval. *New England Journal of Medicine* 2004;350(10):1013-1022.
4. Al-Khatib SM, LaPointe NM, Kramer JM, et al. What clinicians should know about the QT interval. *Journal of the American Medical Association* 2003; 289(16): 2120-2127.
5. Martell BA, Arnsten JH, Ray B, et al. The impact of methadone induction on cardiac conduction in opiate users [Letter]. *Annals of Internal Medicine* 2003;139(2):154-155.
6. Swedish update on methadone: QT prolongation, testosterone. *Reactions Weekly* 2004;No.1006 (19 June):2.
7. Katchman AN, McGroary KA, Kilborn MJ, et al. Influence of opioid agonists on cardiac human ether-a-go-go-related gene K+ currents. *Journal of Pharmacology and Experimental Therapeutics* 2002; 303(2): 688-694.
8. Krantz MJ, Lewkowiez L, Hays H, et al. Torsades de pointes associated with very-high-dose methadone. *Annals of Internal Medicine* 2002:137(6): 501-504.
9. Woosley RL. Drugs that prolong the QT interval and/or induce torsades de pointes. University of Arizona Health Sciences Centre. www.torsades.org/medical-pros/drug-lists/drug-lists.htm
10. Brown R, Kraus C, Fleming M, et al. Methadone: Applied pharmacology and use as adjunctive treatment in chronic pain. *Postgraduate Medical Journal* 2004;80:654-659.

COLCHICINE: LOWER DOSES FOR GREATER SAFETY

MARC Rx ADVICE

Medsafe Pharmacovigilance Team

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The dosage advice for colchicine has been revised, coinciding with the introduction of a 0.5mg strength tablet. Colchicine is now indicated as second-line therapy for acute gout. For healthy adults the dosing interval has been increased to six hourly, with a maximum dose of 2.5mg in the first 24 hours and a maximum cumulative dose of 6mg over four days. In elderly patients, patients with renal or hepatic impairment, and patients weighing less than 50kg other treatments should be considered or lower doses of colchicine used. Patients should be warned of the symptoms of colchicine toxicity and advised to discontinue therapy immediately if they occur.

High doses no longer appropriate

A new 0.5mg strength of colchicine tablets is now available in New Zealand, under the brand name of Colgout®, with revised dosage advice.[1] While colchicine is effective for treating acute gout it has a slow onset of action, with limited effectiveness if treatment is delayed and a narrow therapeutic index.[2] Due to the risk of dose-related serious adverse effects the use of high doses of colchicine to treat acute gout is no longer appropriate, especially in elderly patients,[3] patients with impaired hepatic or renal function,[1] and patients who weigh less than 50kg.[4]

Indications limited to second-line

Colchicine is now indicated as second-line therapy in the treatment of acute gout. Colchicine should not be used unless non-steroidal anti-inflammatories are contraindicated, or have been used and found to lack analgesic efficacy or to have unacceptable side effects in the individual patient.[1]

Dosing interval increased to six hourly

The dosing interval for colchicine has been increased from 2-3 hourly to six hourly. The dose for otherwise healthy adults is 1mg initially, then 0.5mg every six hours until pain relief is obtained.[1] From a safety perspective, it is no longer acceptable to continue dosing until gastrointestinal adverse effects occur.

Maximum daily and cumulative doses updated

For otherwise healthy adults the maximum dose of colchicine in the first 24 hours is 2.5mg and the total dose given in an acute attack should not exceed 6mg over four days.[1]

Consider other treatments for the elderly

The elderly may be more susceptible to cumulative toxicity with colchicine,[5] and due to age-related renal function impairment, other treatments such as corticosteroids should be considered. If colchicine is used in the elderly lower doses should be given and a maximum cumulative dose of 3mg over four days should be observed.[1]

Reduce the dose in renal and hepatic impairment

Colchicine is contraindicated in severe renal impairment (creatinine clearance <10ml/min[1]) or hepatic impairment, and concomitant renal and hepatic disease. If colchicine is used in patients with less severe impairment a reduction in the individual doses, an increase in the interval between doses or a reduction in the total daily dose may be necessary. Specifically, the dose should be reduced by half if the patient's creatinine clearance is 50ml/min or less; and close monitoring is advised.[1]

Intensive regimen should not be repeated for at least three days

Prescribers are reminded that for all patients at least three days must elapse between courses of acute treatment with colchicine, in order to avoid the risk of toxicity due to colchicine accumulation.[1]

Warn patients of the symptoms of colchicine toxicity

Colchicine in overdose is extremely toxic and has resulted in fatalities.[6] Patients should be warned that the first signs of toxicity are nausea, vomiting and diarrhoea. A burning sensation of the throat, stomach or skin may also occur. Symptoms usually appear 2 to 12 hours post-ingestion and often before pain relief is obtained.[5] If symptoms of toxicity occur patients should immediately discontinue colchicine therapy and see their doctor. If toxicity is suspected, prompt hospital admission is essential.[4]

This revised dosage advice is consistent with that issued in the New Zealand Rheumatology Association's 2005 *Consensus Statement on the Use of Colchicine in the Treatment of Gout.*[3]

Competing interests (authors): none declared.

References

1. Anspec New Zealand Ltd. *Colgout tablets data sheet* 1 November 2005. www.medsafe.govt.nz/profs/Datasheet/c/Colgouttab.htm
2. Gow P. Gout – An update on a deadly disease. *NZ Pharmacy Journal* 2005;25(4):21-24.
3. New Zealand Rheumatology Association. NZRA *Consensus Statement on the Use of Colchicine in the Treatment of Gout.* November 2005. www.rheumatology.org.nz/colchicine.html
4. Medsafe Editorial Team. Colchicine toxicity prompts dosage change. *Prescriber Update* 1998;(17):9-11. www.medsafe.govt.nz/Profs/PUarticles/colchicinetoxicity.htm
5. Antigout Drugs. In Sweetman SC (Ed) *Martindale* 34th Edn. 2005: Great Britain, p.412-416.
6. Kubler P. Fatal colchicine toxicity. *MJA* 2000;172:498-499.

SEVERE CUTANEOUS ADVERSE REACTIONS: MORE THAN SKIN DEEP

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Allergic reactions to medicines frequently manifest as skin rashes. Many of these reactions are mild and self-limiting but the more severe reactions, including Stevens-Johnson syndrome and toxic epidermal necrolysis, are associated with significant morbidity and mortality. The majority of these severe cutaneous adverse reactions (SCARs) occur soon after commencement of therapy. Medicine classes most commonly associated with these reactions include antibiotics, anticonvulsants and non-steroidal anti-inflammatories. Newer medicines associated with SCARs include lamotrigine and valdecoxib. Prompt clinical recognition and cessation of suspected medicines helps to minimise morbidity and mortality.

SJS, TEN and erythema multiforme are the main players

The concept of Severe Cutaneous Adverse Reactions, or SCARs, has arisen because of difficulties surrounding the definition and differential diagnosis of erythema multiforme (EM), Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN).[1-5] The acronym SCARs encompasses the continuum between these three conditions, ranging from EM at the lower end of morbidity and mortality (mortality approximately 1%), to the much more severe TEN with a mortality of 30-35%.[6-8] SCARs are thought to be T-cell mediated delayed hypersensitivity reactions.[5,6,9] They can be caused by autoimmunity and a number of allergens, including bacteria and viruses. However, medicines are probably the most common cause, particularly of the more severe reactions such as TEN.[6-9]

Local case reports reflect the pattern seen internationally

From 1965 to 2004, the Centre for Adverse Reactions Monitoring (CARM) received 585 reports of SCARs causally linked to one or more medicine or vaccine.[10] Forty-three of these reports are of TEN, 135 are of SJS, and 306 are of EM. There are also 101 reports of bullous eruptions (BE), some of which may have actually been TEN, SJS or EM.

The medicines considered to be causally related in more than ten CARM reports of SCARs include cotrimoxazole (77 reports), cefaclor (38), amoxycillin/clavulanic acid (25), amoxycillin (24), carbamazepine (23), phenytoin (19), allopurinol (16), bupropion (11) and erythromycin (11).

Worldwide, the incidence of SCARs from all causes ranges from 0.4 to 7.4 cases per million persons per year.[11,12] The medicines most commonly implicated in published case reports include sulphonamide antibiotics, anticonvulsants and non-steroidal anti-inflammatories (NSAIDs). The excess risk of developing SJS/TEN is estimated at 4.3 cases per million users per week for trimethoprim-sulphamethoxazole, 2.5 cases per million users per week for carbamazepine, and 2.0 cases per million users per week of oxicam NSAIDs.[11-15] Emerging new associations with SCARs include lamotrigine[16] (rate similar to carbamazepine), and the COX-2 inhibitor valdecoxib (rate similar to piroxicam[17]).

Recognising risk factors and manifestations can minimise harm

The majority of SCARs occur early in the course of treatment.[15,18] Risk factors for SCARs include both dosage and inherent patient factors. There appears to be an increased risk of SCARs with high dosages, particularly with anti-epileptics such as lamotrigine. Autoimmunity (including rheumatoid arthritis and lupus erythematosus) as well as viruses like Epstein Barr and HIV also increase the risk of SCARs.[6]

Treatment of SCARs involves early recognition of the adverse reaction and prompt cessation of all offending medicines.[6] Early discontinuation of the suspect medicine, especially if it has a short half-life, is associated with an improved prognosis (up to 5-fold reduction in mortality).[19] Patients with more severe reactions (i.e. SJS/TEN) may need early hospitalisation for cutaneous support (similar to extensive cutaneous burns). Mortality is often due to secondary sepsis with haemodynamic failure. There is ongoing controversy regarding the treatment of SCARs with systemic corticosteroids; there has been a general move away from their use. Newer treatments include cyclosporin and intravenous immunoglubulin,[6,20] but these have yet to be subjected to randomised clinical trials.

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References

1. Auquier-Dunant A, Mockenhaupt M, Naldi L, et al; SCAR Study Group. Severe Cutaneous Adverse Reactions. Correlations between clinical patterns and causes of erythema multiforme majus, Stevens-Johnson syndrome, and toxic epidermal necrolysis: results of an international prospective study. *Arch Dermatol* 2002;138(8):1019-1024.
2. Roujeau JC. Stevens-Johnson syndrome and toxic epidermal necrolysis are severity variants of the same disease which differs from erythema multiforme. *J Dermatol* 1997;24(11):726-729.
3. Roujeau JC. The spectrum of Stevens-Johnson syndrome and toxic epidermal necrolysis: a clinical classification. *J Invest Dermatol* 1994;102(6):28S-30S.
4. Bastuji-Garin S, Rzany B, Stern RS, et al. Clinical classification of cases of toxic epidermal necrolysis, Stevens-Johnson syndrome, and erythema multiforme. *Arch Dermatol* 1993;129(1):92-96.
5. Roujeau JC. Clinical heterogeneity of drug hypersensitivity. *Toxicology* 2005;209(2):123-129.
6. Ghislain PD, Roujeau JC. Treatment of severe drug reactions: Stevens-Johnson syndrome, toxic epidermal necrolysis and hypersensitivity syndrome. *Dermatol Online* J 2002;8(1):5.
7. Wolf R, Orion E, Marcos B, Matz H. Life-threatening acute adverse cutaneous drug reactions. *Clin Dermatol* 2005;23(2):171-181.
8. Bastuji-Garin S, Fouchard N, Bertocchi M, et al. SCORTEN: a severity-of-illness score for toxic epidermal necrolysis. *J Invest Dermatol* 2000;115(2):149-153.
9. Chave TA, Mortimer NJ, Sladden MJ, et al. Toxic epidermal necrolysis: current evidence, practical management and future directions. *Br J Dermatol* 2005;153(2):241-253.
10. Rademaker M, Tatley M, Ashton J. Spontaneous reporting of severe cutaneous adverse drug reaction in New Zealand. *Australas J Dermatol* 2002;43:A26 (and personal communication, New Zealand Pharmacovigilance Centre, August 2005).
11. Chan HL, Stern RS, Arndt KA, et al. The incidence of erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis. A population-based study with particular reference to reactions caused by drugs among outpatients. *Arch Dermatol* 1990;126(1):43-47.
12. Wolkenstein P, Revuz J. Drug-induced severe skin reactions. Incidence, management and prevention. *Drug Saf* 1995;13(1):56-68.
13. Schopf E, Stuhmer A, Rzany B, et al. Toxic epidermal necrolysis and Stevens-Johnson syndrome. An epidemiologic study from West Germany. *Arch Dermatol* 1991;127(6):839-842.
14. Roujeau JC, Kelly JP, Naldi L, et al. Medication use and the risk of Stevens-Johnson syndrome or toxic epidermal necrolysis. *N Engl J Med* 1995;333(24):1600-1607.
15. Mockenhaupt M, Kelly JP, Kaufman D, Stern RS; SCAR Study Group. The risk of Stevens-Johnson syndrome and toxic epidermal necrolysis associated with nonsteroidal antiinflammatory drugs: a multinational perspective. *J Rheumatol* 2003;30(10):2234-2240.
16. Schlienger RG, Shapiro LE, Shear NH. Lamotrigine-induced severe cutaneous adverse reactions. *Epilepsia* 1998;39(Suppl 7):S22-26.
17. Pfizer Inc. *Advisory Committee Briefing Document – Valdecoxib: Cardiovascular Safety, Skin Reactions, and Benefit/Risk Assessment*. Prepared for Health Canada's Public Forum on Selective COX-2 inhibitors held 9-10 June 2005 in Ottawa, Canada. www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/prodpharma/valdecoxib-06-2005_e.pdf
18. Rzany B, Correia O, Kelly JP, et al. Risk of Stevens-Johnson syndrome and toxic epidermal necrolysis during first weeks of antiepileptic therapy: a case-control study. Study Group of the International Case Control Study on Severe Cutaneous Adverse Reactions. *Lancet* 1999;353(9171):2190-2194.
19. Garcia-Doval I, LeCleach L, Bocquet H, et al. Toxic epidermal necrolysis and Stevens-Johnson syndrome: does early withdrawal of causative drugs decrease the risk of death? *Arch Dermatol* 2000;136(3):323-327.
20. Metry DW, Jung P, Levy ML. Use of intravenous immunoglobulin in children with Stevens-Johnson syndrome and toxic epidermal necrolysis: seven cases and review of the literature. *Pediatrics* 2003;112(6 Pt 1):1430-1436.

TOPICAL CORTICOSTEROIDS: FACE FACTS

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The use of topical corticosteroids on the face can result in harmful skin effects such as atrophy, telangiectasia and periorificial dermatitis. These adverse reactions are greater with the more potent steroids but can be minimised by limiting use on the face. The risks of facial use should be communicated to patients, along with clear directions about where to apply the topical steroid and for how long to continue treatment.

Topical steroids can cause unwanted skin effects

Whilst topical corticosteroids (creams, ointments and lotions) are helpful in the management of inflammatory skin disorders of the face, they can also cause a number of adverse skin effects. These include thinning or atrophy of the skin (due to reduction in collagen), opportunistic infection, telangiectasia, purpura, periorificial dermatitis and the worsening of rosacea.[1,2] Up to ten percent of women are prone to rosacea, which will be unmasked if they use steroids to treat other eczemas.[3] Periorificial (previously known as perioral) dermatitis is most commonly induced by inappropriate use of steroids on the face.[3,4] The risk of these adverse effects is greater with the more potent topical steroids, and is further increased when these preparations are applied under occlusion.[2]

New Zealand reports continue to be received

The Centre for Adverse Reactions Monitoring has received 14 reports, some recently, of facial skin damage attributed to the use of potent topical corticosteroids.

The adverse events included telangiectasia, abnormal pigmentation, periorificial dermatitis, rosacea, skin atrophy and striae. These reports were primarily for mometasone but all topical steroids carry this risk, especially the more potent ones.

Guide to potencies of topical corticosteroids available in New Zealand (brand names in brackets)[2]

Mildly Potent	Moderately potent	Potent	Very potent
Hydrocortisone 0.5% and 1%	Clobetasone butyrate 0.05% (Eumovate)	Betamethasone dipropionate 0.05% (Diprosone)	Clobetasol propionate 0.05% (Dermol)
	Triamcinolone acetonide 0.02% (Aristocort)	Betamethasone valerate 0.1% (Beta, Betnovate)	
		Diflucortolone valerate 0.1% (Nerisone)	
		Hydrocortisone butyrate 0.1% (Locoid)	
		Methylprednisolone aceponate 0.1% (Advantan)	
		Mometasone furoate 0.1% (Elocon)	

Minimise use on the face and inform patients of risks

While the reactions are well recognised, they are avoidable. Prescribers are reminded that topical corticosteroids should not be used on the face except for very short periods (i.e. less than two weeks) for inflammatory dermatoses such as psoriasis and eczema that are unresponsive to other treatments.[5] The use of topical corticosteroids on the eyelids or around the eyes should always be limited because the skin in this area is particularly thin.

Patients should be warned against using any steroid on their face unless advised to do so by their doctor, and that facial application should be limited to two weeks or less. The risks of facial use should be clearly explained to patients. The development or worsening of dermatitis around the mouth and eyes, or the development of erythema or prominent blood vessels on the cheeks, indicates that treatment should be discontinued.[1,3]

Provide patients with strict instructions for use

Prescriptions written for topical steroids should include explicit instructions about where and how often to apply the preparation, and the body areas where use must be avoided. Pharmacists should ensure these directions are included on the dispensing label. Prescribers should bear in mind that patients may keep unused or leftover corticosteroid skin preparations for some time after they are prescribed and thus forget the original indication or instructions for use. The prescribing of unnecessarily large quantities should be avoided. Patients should be warned not to share their topical steroid preparation with other people as this may result in unsafe application to unsuitable areas such as the face, as well as the potentially inappropriate treatment of undiagnosed skin conditions.

Competing interests (authors): none declared.

References

1. Skin Disorders. In Davies DM, Ferner RE, de Glanville H (Eds) *Davies's Textbook of Adverse Drug Reactions* 5th Edn. 1998: London, p 577.
2. Corticosteroids. In Sweetman SC (Ed) *Martindale* 34th Edn. 2005: Great Britain, p.1070-1075.
3. Personal communication, 24 October 2005. Dermatologist, Hamilton.
4. DermNet NZ – web site of the New Zealand Dermatological Society Incorporated. Perioral dermatitis. http://dermnetnz.org/acne/perioral-dermatitis.html
5. Rademaker M. Topical hydrocortisone. In Dollery CT (Ed) *Therapeutic drugs. A clinical pharmacopoeia* 2nd Edn. 1999: Edinburgh, p.H61-64.

DRUG-INDUCED PANCREATITIS: AN UNLUCKY DIP

ADR UPDATE

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Medicines are amongst the common causes of acute pancreatitis, although they may not initially be thought of as an obvious causative factor. Those medicines more frequently implicated include anti-HIV agents, statins, tetracyclines and valproate. Prescribers should have a high index of suspicion in patients presenting with acute pancreatitis without an apparent cause, particularly if it is recurrent.

Consider medicines as a potential cause of acute pancreatitis

The causes of acute pancreatitis are varied but gallstones have been identified as the causative factor in 30-60% of published cases. Chronic alcohol consumption accounts for 15-30% of cases, with hypertriglyceridemia contributing to another 1.3-3.8%. Drug-induced pancreatitis (DIP) is thought to account for 2-5% of cases of acute pancreatitis.[1]

DIP can occur in both children and adults,[2,3] with as many as 13% of paediatric cases of acute pancreatitis being due to medicines.[2] Time to onset can be six (or even nine[2]) months after commencement of the suspect causative medicine.[3]

Local and international reports implicate a range of commonly used medicines

As at October 2005, the Centre for Adverse Reactions Monitoring had received 55 reports of DIP. In 23 of these cases, each patient was receiving only one suspect medicine. In 11 of the reports where outcomes were known, there had been improvement following de-challenge. The most frequently reported suspect agents were ACE inhibitors (n=6), valproate (n=4), tetracyclines (n=3), statins (n=3) and mesalazine (n=2). The Australian Adverse Drug Reactions Advisory Committee has received 379 reports of DIP. In approximately two-thirds of these cases patients were taking only one suspect medicine;[4] the medicines implicated were similar to those in New Zealand.

In the literature,[2,3,5] and the World Health Organisation's international database of adverse reactions, the most frequently reported medicines implicated in DIP are anti-HIV agents, atypical antipsychotics, azathioprine, mesalazine, oestrogens, statins, sulphonamides, tetracyclines, valproate and 6-mercaptopurine.

Well-recognised but under-reported

As is frequently the case in iatrogenic injury involving medicines, DIP is thought to be caused either by a hypersensitivity reaction or by the generation of a toxic metabolite. It is not always clear which of these mechanisms is operative.[1]

While medicines are regarded as a common cause of acute pancreatitis,[1] DIP is rarely reported. Prescribers should have a high index of suspicion for DIP in patients with acute pancreatitis without an obvious cause, particularly if it is recurrent. Where a medicine has been implicated in the aetiology of a patient's acute pancreatitis, the patient should not be re-exposed to that medicine.

Competing interests (author): none declared.

References

1. Greenberger NJ, Toskes PP. Acute and Chronic Pancreatitis. In Kasper DL, Braunwald E, Fauci AS, et al (Eds) *Harrison's Principles of Internal Medicine* 16th Edn. 2005: The McGraw-Hill Companies Inc, United States of America (on-line version accessed).
2. Pellock JM, Wilder BJ, Deaton R, Sommerville KW. Acute pancreatitis coincident with valproate use: A critical review. *Epilepsia* 2002;43(11):1421-1424.
3. Koller EA, Cross JT, Doraiswamy PM, Malozowski SN. Pancreatitis associated with atypical antipsychotics: From the Food and Drug Administration's MedWatch surveillance system and published reports. *Pharmacotherapy* 2003;23(9): 1123-1130.
4. Personal communication, 14 November 2005. Medical Officer, Adverse Drug Reactions Unit, Therapeutic Goods Administration, Australia.
5. Trivedi CD, Pitchumoni CS. Drug-induced pancreatitis: An update. *J Clin Gastroenterol* 2005;39(8):709-716.

CHANGES TO THE NATIONAL IMMUNISATION SCHEDULE EFFECTIVE FROM 1 FEBRUARY 2006

The Ministry of Health advises that from 1 February 2006 there will be changes to the National Immunisation Schedule (Schedule). The Schedule is reviewed every two years. The changes are:

1. National Immunisation Schedule changes

The changes to the Schedule for all children are:

1. *Haemophilius influenzae* type b (Hib)-only vaccine will be offered at 15 months with the MMR vaccine.
2. The combined adult diphtheria, tetanus, pertussis and inactivated polio (dTap-IPV) vaccine will be offered at 11 years.

Immunisation Schedule 2006
(Note: the changes have been highlighted in bold)

Age	DTaP-IPV	Hib-Hep B	Hep B	**Hib**	MMR	**dTap-IPV**	Td#	Influenza**
6 weeks	•	•						
3 months	•	•						
5 months	•		•					
15 months				•	•			
4 years	•				•			
11 years						•*		
45 years							•	
65 years							•	•

Key: D – diphtheria, d – adult diphtheria, T – tetanus, aP – acellular pertussis, ap – adult dose acellular pertussis, Hib – *Haemophilius influenzae* type b, Hep B – Hepatitis B, IPV – inactivated polio vaccine, MMR – measles, mumps, rubella.

* dTap-IPV will be given in 2006-7 so that children complete four doses of polio vaccine.

\# Note administration is not funded for these Td boosters.

** Influenza vaccine is also available for persons of all ages with certain chronic medical conditions as recommended in the *Immunisation Handbook*.

Note also that hepatitis B vaccine, hepatitis B immune globulin and BCG immunisation will continue to be offered to eligible babies as recommended in the *Immunisation Handbook*.

The Schedule for children at 11 years of age will be the adult dTap-IPV vaccine. The booster dose of pertussis vaccine has been added as children at this age have only received pertussis vaccine in their first year of life. The booster will provide protection during adolescence.

The Schedule change at 15 months is unlikely to have an adverse effect on disease control due to the DTaP dose offered at four years, and will also decrease the incidence of the localised swelling associated with increasing numbers of DTaP vaccine doses.

All Ministry of Health immunisation health education resources, including the *Immunisation Handbook 2002* are being amended.

2. Pneumococcal Immunisation Programme

A publicly funded Programme will be introduced for specific children at high risk of invasive pneumococcal disease.

3. Vaccines for children and adults pre- and post-splenectomy

Publicly funded pneumococcal polysaccharide, Hib and Meningococcal A, C Y, W135 vaccines will be available to children and adults pre- and post-splenectomy.

Additional information on these programmes will be sent to immunisation health professionals during December/January and will also be available on the Ministry of Health website (www.moh.govt.nz/immunisation), along with electronic copies of both the *Immunisation Handbook 2002*, and the 2006 edition when it is available.

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 intention is 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 to: CARM, NZ Pharmacovigilance Centre, 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
Complementary and alternative medicines*	all adverse reactions	Vol.23(2), July 2002 & No.13, Oct 1996
Leflunomide	all adverse reactions	Vol.25(1), May 2004
SSRI antidepressants	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 may be 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 table below.

Medicines currently monitored by the IMMP

Medicine	Brand name/s
Clozapine	Clozaril, Clopine
Levonorgestrel intrauterine system*	Mirena
Olanzapine	Zyprexa
Quetiapine	Seroquel
Risperidone	Risperdal
Sibutramine*	Reductil

* New patients are no longer being added to the cohorts for these medicines because sufficient numbers of patients have already been recruited. However, follow-up of existing patients is continuing so adverse event data are still being collected for these medicines.

What to report

Please report **all clinical events** in patients taking IMMP medicines, including:

- any suspected adverse reaction
- deaths (including cause if known)
- any new clinical events, even if minor or common
- accidents
- change in a pre-existing condition
- abnormal changes in laboratory test results
- possible interactions.

Where to report

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

What to tell patients prescribed IMMP medicines

Please remember to tell patients that they have been prescribed a monitored medicine. This means the IMMP receives details of their prescriptions and that their doctor may be asked for clinical information on the patient's experience whilst taking this medicine. If possible, an explanatory IMMP leaflet should be given to the patient (available from the IMMP, NZ Pharmacovigilance Centre, PO Box 913, Dunedin).

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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

HP3442

Surname:	First Name/s:	NHI No:	
Address:		Date of Birth:	Sex:
		Ethnicity:	

ALL MEDICINES IN USE *ASTERISK SUSPECT MEDICINE/S* Include over-the-counter (OTC) and alternative medicines

Medicine or Vaccine+batch no. (and brand name if known)	Daily Dose	Route	Date Started	Date Stopped	Reason for Use

DESCRIPTION OF ADVERSE REACTION OR EVENT

Date of onset: _____

Recovered ☐ Not yet recovered but improved ☐ Not yet recovered ☐ Unknown ☐ Fatal ☐ - Date of Death: _____

Severe? - Yes ☐ No ☐ Rechallenged? - No ☐ Yes ☐ Result: _____

OTHER FACTORS - Please tick or specify as appropriate

Renal disease ☐ Allergy ☐: _____ Other Medical Conditions: _____

Hepatic disease ☐ Nutritional Suppl or OTC use ☐: _____ Industrial Chemicals ☐: _____

REPORTER - Please tick as appropriate: Doctor ☐ Pharmacist ☐ Dentist ☐ Nurse ☐ Other ☐: _____

Name:

Address:

Signature: _____

Phone: _____ Date: _____

Send completed form to CARM

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

ADVERSE REACTIONS

What to report

Please report any suspect reaction of clinical concern. This includes adverse reactions involving:

- Prescription medicines
- Over-the-counter medicines (medicines purchased without a prescription)
- Complementary medicines (herbal medicines, naturopathic and/or homoeopathic medicines, and nutritional supplements such as vitamins and minerals)
- Vaccines.

In particular, please report the following:

- All suspected reactions to NEW medicines
- All Adverse Reactions of Current Concern[1]
- All events to IMMP medicines[2]
- All suspected drug INTERACTIONS
- UNEXPECTED or SERIOUS reactions (including those suspected of causing death, admission to hospital, prolongation of hospitalisation, or birth defects)
- Serious ALLERGIC reactions (to enable a danger or warning to be entered in the national health database so re-exposure can be avoided for that individual).

How to report

Fill in the reporting form, which is available:

- overleaf (inside the back cover of *Prescriber Update*)
- from the CARM web site: http://carm.otago.ac.nz/reporting.asp

On-line reporting is also available on the CARM web site.

Where to report

Send all adverse reaction reports to CARM (Centre for Adverse Reactions Monitoring) in Dunedin.

Post to: Freepost 112002
The Medical Assessor
CARM
University of Otago Medical School
P O Box 913
Dunedin

Fax: (03) 479 7150

Phone: (03) 479 7247

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

1. The list of *Adverse Reactions of Current Concern* is on page 36
2. The list of medicines in the Intensive Medicines Monitoring Programme (IMMP) is on page 37