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Origin of *Prescriber Update* articles

Most articles in *Prescriber Update* orginate from recommendations made by the Medicines Adverse Reactions Committee (MARC). These articles can be classified as Adverse Drug Reaction Updates or MARC Prescribing Advice.

Adverse Drug Reaction Update articles are written in response to adverse reaction reports lodged with the Centre for Adverse Reactions Monitoring (CARM) and 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 MARC in response to medicine safety issues and overseas experiences.

Prescriber Update articles are usually authored by the Medsafe Editorial Team, MARC members or New Zealand health professionals. During the editorial process, articles are peer reviewed by at least two individuals or professional groups with current, practical experience of the subject matter.

To assist readers in knowing the origin of articles published by Medsafe, the above symbols will appear next to the article title, where relevant.

Articles are also on the Medsafe web site

Remember that *Prescriber Update* articles are also available on the Medsafe web site and can be freely accessed at any time. Go to **www.medsafe.govt.nz** then to the *Health Professionals* section and click on *Prescriber Update Articles* in the menu displayed. Articles are listed chronologically in the order they are published on the web site, or grouped by subject if they are related. Alternatively you can use the *Search* function (click on the oval icon with the magnifying glass) and enter a keyword to locate the information on the Medsafe web site.

Prescribing Medicines In Pregnancy – an Australian categorisation of risk of drug use in pregnancy

Medsafe is supplying a complimentary copy of the fourth edition of this booklet with this issue of *Prescriber Update*. Additional copies of *Prescribing Medicines in Pregnancy* may be requested from Wickliffe: phone 04-496-2277, fax 03-479-0979, email pubs@moh.govt.nz or post an order to the Ministry of Health, c/- Wickliffe Ltd. PO Box 932, Dunedin. Alternatively visit http://www.health.gov.au:80/tga/docs/html/mip/medicine.htm to download the text of this reference.

Medicine Information For Consumers

The Medsafe web site contains consumer medicine information (CMI) for more than 270 medicines. CMI is written by pharmaceutical companies and follows guidelines set by Medsafe. The purpose of CMI is to provide written information for consumers, to help them use their medicine more safely and effectively. Please inform your patients about the CMI available (at no charge) on the Medsafe web site. You can either direct patients to www.medsafe.govt.nz/consumers/cmi/cmiform.asp or access the CMIs yourself at this web address.

Medsafe is distributing a CMI poster with this issue of *Prescriber Update*. The poster is directed at consumers, explaining what CMI is and how to obtain it. Please display the poster in your waiting room or pharmacy so patients can read it.

Additional copies of the CMI poster may be requested from Wickliffe: phone 04-496-2277, fax 03-479-0979, email pubs@moh.govt.nz or post an order to the Ministry of Health, c/- Wickliffe Ltd. PO Box 932, Dunedin.

Important
Please read

THIORIDAZINE AND ARRHYTHMIA: PRESCRIBING CHANGES

MARC Rx ADVICE

Medsafe Editorial Team

This article was published on the Medsafe web site and e-mailed to electronic *Prescriber Update* subscribers in June 2001.

Thioridazine (Melleril™, Aldazine™) increases the risk of arrhythmia from QT-prolongation. Consequently, the Medicines Adverse Reactions Committee has recommended the following changes to how thioridazine is prescribed in New Zealand.

Thioridazine is now contraindicated in the following circumstances, all of which are risk factors for arrhythmia:

- use with medicines which inhibit the metabolism of thioridazine (cimetidine, most antidepressants, pindolol, propranolol)
- use with medicines which prolong the QT-interval (some antiarrhythmics, most antipsychotics, cisapride)
- use in patients with predisposing factors for arrhythmia or pre-existing QT-prolongation ($QT_c \geq 500$ms).

Thioridazine should be initiated only by a specialist and only as third line therapy. In addition, the following precautions should be observed for new patients:

- assess for risk factors for arrhythmia
- check the QT_c-interval and serum potassium
- use the minimum effective dose
- observe a maximum of 200mg daily ordinarily
- use dosages above 200mg daily up to a maximum of 600mg daily only under specialist supervision and only with QT_c-interval monitoring following each increase.

For all patients currently taking thioridazine:

- assess for risk factors for arrhythmia
- check the QT_c-interval and serum potassium
- doses above 200mg daily require review by a specialist
- reduce the dose if QT_c-interval $\geq$ 500ms
- withdraw thioridazine if QT_c-interval is persistently $\geq$ 500ms, or in the presence of any contraindication.

Any children taking thioridazine should also have their therapy reviewed by a specialist.

If thioridazine discontinuation is necessary, gradually reduce the dose over a period of one month and concurrently introduce alternative medication. Specialist supervision may be advisable for the withdrawal process.

MARC review resulted in changes to reduce risk of arrhythmia

The Medicines Adverse Reactions Committee (MARC) has reviewed data on the risk of QT-prolongation with thioridazine, a Medsafe-commissioned expert report and regulatory action taken by authorities overseas. The Committee noted that anecdotal evidence and CARM data suggested thioridazine was well tolerated by the overwhelming majority of patients using it in New Zealand. The Committee observed that the data on QT-prolongation were sparse, but considered it prudent to take steps to reduce the risk of arrhythmia from QT-prolongation in patients prescribed thioridazine.

Avoid thioridazine with interacting medicines or predisposing conditions

Thioridazine is now contraindicated in the following circumstances, all of which are **risk factors** for arrhythmia:

- A history of QT-prolongation, ventricular arrhythmia, torsade de pointes, and risk factors for arrhythmia, such as second or third degree atrioventricular block, clinically significant heart disease and congenital long QT-syndrome.
- Baseline QT_c-interval $\geq$ 500ms.
- Abnormal serum potassium.
- Concomitant use of medicines which inhibit CYP 2D6 (e.g. cimetidine, fluoxetine, paroxetine, moclobemide, tricyclic antidepressants) or inhibit thioridazine metabolism by another mechanism (e.g. fluvoxamine, pindolol, propranolol).

- Concomitant use of medicines which may prolong the QT-interval including quinine, cisapride, some antiarrhythmic medicines (e.g. amiodarone, quinidine, flecainide, sotalol), tricyclic antidepressants and some other antipsychotic agents (e.g. droperidol, haloperidol, risperidone).

New patients to be initiated by a specialist

Thioridazine therapy should be initiated only by a specialist and only after the patient has failed to respond adequately to treatment with appropriate courses of at least two other suitable medicines. The patient should first be assessed for risk factors for arrhythmia (see above), and undergo an ECG to determine the QT_c-interval and a check of serum potassium. Abnormal potassium levels should be corrected. If the patient is on interacting medicines, therapy must be adjusted to avoid these medicines or an alternative to thioridazine prescribed instead. Do not use thioridazine in patients with predisposing factors for arrhythmia or pre-existing QT-prolongation ($QT_c \geq 500$ms).

It is recommended that the initial dose of thioridazine be at the lower end of the range and be gradually increased until the desired effect is achieved or a maximum of 200mg daily is reached. Dosages above 200mg daily should be prescribed by a specialist and only in exceptional circumstances. The maximum dose of 600mg daily should be observed. Two weeks after every increase in dose, the QT_c-interval should be measured with an ECG taken 12 hours after or immediately prior to a dose. The dosage should be reduced if the QT_c-interval is ≥ 500ms and the patient re-assessed for risk factors.

Patients on a maintenance dose of greater than 200mg daily need to be **monitored**. This involves repeating an ECG if the patient develops a disease state, or commences medication, that may increase the risk of QT-prolongation either directly or indirectly (e.g. by causing hypokalaemia). In all cases, if the QT_c-interval is persistently ≥ 500ms, or if the patient now has a contraindication, thioridazine should be discontinued gradually (see below).

Review all patients currently taking thioridazine

Patients who are taking thioridazine at daily doses of more than 200mg should be evaluated by a specialist for their need to continue at high doses. These patients and all others already taking thioridazine should be reviewed for risk factors for arrhythmia (outlined above), undergo an ECG to determine the QT_c-interval and a check of serum potassium. Conduct the ECG 12 hours after or immediately before a dose. Abnormal potassium levels should be

corrected. If the patient is on interacting medicines, adjust therapy to avoid these medicines, or switch to an alternative to thioridazine.

Patients with QT_c-interval ≥ 500ms should have their dose reduced and continuing use of thioridazine evaluated. If the QT_c-interval is persistently ≥ 500ms thioridazine should be discontinued gradually (see below).

Patients who are at high risk of arrhythmias through either intrinsic (e.g. disease states) or extrinsic (e.g. concomitant medication) factors should be switched to an alternative to thioridazine. **Discontinuation** of thioridazine should be done by gradually reducing the dose over a period of one month and concurrently introducing the new medication. Depending on the severity of the patient's condition, it may be advisable to have the change in medication supervised by a psychiatrist.

Abrupt withdrawal of thioridazine may be associated with symptoms such as nausea, vomiting, gastric upset, trembling, dizziness, anxiety, agitation and insomnia, as well as transient dyskinesia or the re-emergence of psychotic symptoms. Patients on high doses or who have received long term therapy are particularly at risk for these symptoms.

Specialist involvement required for all paediatric patients

The same checks for contraindications, QT-prolongation and abnormal serum potassium should be conducted for new and existing paediatric patients, as for adults. The initiation of thioridazine for children should be by a specialist and only as third line therapy. Children who are currently taking thioridazine should have their therapy reviewed by a specialist (paediatrician or child psychiatrist). The maximum dose of 4 mg/kg/day should be observed (upper limit 200mg). Doses above 200mg daily should be used only in exceptional circumstances, under specialist supervision, and the patient monitored as outlined above.

Consult the data sheets for all details of the changes

The above changes have been incorporated into the data sheets for thioridazine (Melleril™, Aldazine™). It is recommended that prescribers of thioridazine read the data sheets for these products to familiarise themselves with all the details of the changes (see www.medsafe.govt.nz/Profs.htm).

VIAGRA REMINDER: ASK! DON'T BE SHY!

Medsafe Editorial Team

This article was published on the Medsafe web site and e-mailed to electronic *Prescriber Update* subscribers in May 2001.

Sildenafil (Viagra™) plus nitrates may result in a precipitous fall in blood pressure. Do not use nitrates to relieve an angina attack if the patient has recently taken sildenafil - use other angina treatments instead. Doctors and nurses must ask about Viagra use before administering glyceryl trinitrate (GTN) spray or any other nitrate preparation.

Sildenafil should not be prescribed if there is regular or intermittent nitrate use

Sildenafil is contraindicated in patients taking nitrates for cardiovascular disease. This includes all dose forms such as oral (e.g. GTN spray, sublingual tablets, slow release preparations), injectable (e.g. sodium nitroprusside) and topical (e.g. transdermal patches) nitrates. Remember to ask patients about nitrates used recreationally, e.g. amyl nitrate. Also remind patients who are using nitrates, that they must not take sildenafil.

Sildenafil, through inhibition of phosphodiesterase type 5, enhances the effect of local nitric oxide release in the corpus cavernosum during sexual stimulation. This results in arterial and venous dilation and inflow of blood. If exogenous nitrates are given, there will be a systemic rise in nitric oxide concentrations, which in combination with sildenafil, potentiates the vasodilatory effect of nitrates. This can cause a significant drop in blood pressure (BP) and may be life threatening.

Doctors, nurses and paramedics must ask patients (men and women[a]) about recent Viagra™ use before administering GTN spray or any other nitrate.

If the patient has taken sildenafil, give analgesia - NOT nitrates - to relieve angina pain

When a patient who has taken sildenafil develops acute angina, other anti-angina treatments must be used instead of nitrates, for example: aspirin, morphine, oxygen, ß-adrenergic blockers (note: the potentiating effect on BP

reduction is not observed with sildenafil when used in combination with non-nitrate vasodilators), and heparin. In serious or complicated cases of angina or chest pain, advice should be sought from a cardiologist, and transfer of the patient to hospital in an ambulance is recommended.

It is unknown when nitrates can be safely administered to patients who have taken sildenafil.[1] The risk of an exaggerated BP response with nitrates decreases with time from the dose of sildenafil. Based on pharmacokinetics, plasma levels of sildenafil are low at 24 hours[1] and some authors suggest that after 24 hours the administration of a nitrate may be considered.[2] However some conditions such as age over 65 years, hepatic impairment, severe renal impairment or use of cytochrome P450 3A4 inhibitors (including erythromycin, ketoconazole, diltiazem and HIV protease inhibitors) can result in reduced clearance of sildenafil. In such patients, the time frame for withholding nitrates will be longer.[1] The advice of a cardiologist or emergency physician should be sought in situations of doubt. *If the decision is made to administer nitrates, close monitoring must be provided with proper facilities available for fluid and vasopressor support,[2] and emergency resuscitation.*

Inadvertent co-administration of nitrates and sildenafil can cause severe hypotension

In the event of inadvertent co-administration of nitrates and sildenafil, close monitoring must be undertaken in an environment where fluid replacement, vasopressor support and emergency resuscitation can be provided (usually in hospital). With significant hypotension, place the patient in the Trendelenburg position, administer intravenous fluid and consider using alpha-agonists in severe cases (bearing in mind that these may exacerbate any coronary ischaemia present).

Please refer to the full data sheet[1] (available on the Medsafe web site: www.medsafe.govt.nz) before prescribing Viagra™.

[a] Sildenafil is approved only for use in men, but unapproved use by women may occur.

References

1. Pfizer Pty Ltd. *Viagra data sheet*. February 2001. http://www.medsafe.govt.nz/Profs/Datasheet/v/viagratab.htm
2. Cheitlin MD, Hutter AM, Brindis RG et al. *ACC/AHA Expert Consensus Document.* Use of sildenafil (Viagra) in patients with cardiovascular disease. 1999. http://circ.ahajournals.org/cgi/content/full/99/1/168

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Many mothers are required to use drugs during breastfeeding. Almost all drugs transfer into breast milk and this may carry a risk to a breastfed infant. Factors such as the dose received via breast milk, and the pharmacokinetics and effect of the drug in the infant need to be taken into consideration. Problems should not be overstated however, as many drugs are considered 'safe' during breastfeeding.

Transfer of drugs into breast milk is influenced by protein binding, lipid solubility and ionisation

Nearly all drugs transfer into breast milk to some extent. Notable exceptions are heparin and insulin which are too large to cross biological membranes. The infant almost invariably receives no benefit from this form of exposure and is considered to be an 'innocent bystander'. Drug transfer from maternal plasma to milk is, with rare exceptions, by passive diffusion across biological membranes. Transfer is greatest in the presence of low maternal plasma protein binding and high lipid solubility. In addition, milk is slightly more acidic than plasma (pH of milk is approximately 7.2 and plasma is 7.4) allowing weakly basic drugs to transfer more readily into breast milk and become trapped secondary to ionisation. Milk composition varies within and between feeds and this may also affect transfer of drugs into breast milk. For example, milk at the end of a feed (hindmilk) contains considerably more fat than foremilk and may concentrate fat-soluble drugs.

Transfer of drugs into breast milk is most commonly described quantitatively using the milk to plasma (M/P) concentration ratio. The accuracy of this value is improved if it is based on the area under the concentration-time curves (AUC) of the drug in maternal milk and plasma (M/P_{AUC}).

Calculation of infant exposure to drugs can be used to help guide safe use

The infant's dose (D_{infant}) received via milk can be calculated using the maternal plasma concentration ($C_{maternal}$), M/P_{AUC} ratio and the volume of milk ingested by the infant (V_{infant}):

$$D_{infant}\ (mg/kg/day) = C_{maternal}\ (mg/L) \times M/P_{AUC} \times V_{infant}\ (L/kg/day)$$

The volume of milk ingested by infants is commonly estimated as 0.15L/kg/day. The infant dose (mg/kg) can then be expressed as a percentage of the maternal dose (mg/kg). An arbitrary cut-off of 10% has been selected as a guide to the safe use of drugs during lactation. Drugs such as lithium (infant dose as high as 80% of the weight-adjusted maternal dose) and amiodarone (infant dose up to 50%) should be avoided due to high infant exposure and potential for significant toxicity. For drugs with greater inherent toxicity such as cytotoxic agents, ergotamine, gold salts, immunosuppressives and isotretinoin, the cut-off of 10% is too high and breastfeeding is contraindicated.

As a general rule, maternal use of topical preparations such as creams, nasal sprays or inhalers would be expected to carry less risk to a breastfed infant than systemically administered drugs. This is due to lower maternal concentrations and therefore lower transfer into breast milk. However, the risk to the infant must be considered in relation to the toxicity of the drug used, the dosage regimen and the area of application. For example, use of corticosteroids nasal sprays or inhalers in standard doses would be considered compatible with breastfeeding.

Other factors to consider in conjunction with the infant's dose include the pharmacokinetics of the drug in the infant. Generally, drugs that are poorly absorbed or have high first-pass metabolism are less likely to be problematical during breastfeeding. For example, gentamicin is highly hydrophilic and is very poorly absorbed when administered orally. Should any gentamicin be ingested via breast milk, it is unlikely to be absorbed.

Infants have lower drug clearance than adults

Drug clearance in the infant is a particularly important consideration and premature infants have a severely limited ability to clear drugs. Within a few days of delivery, term infants have glomerular filtration rates approximately one-third of adult values after adjusting for difference in body surface area, and premature infants have even more impaired clearance (see Table 1).

Generally, adult glomerular filtration rates (adjusted for the difference in surface area) are attained by five to six months of age. Metabolic processes such as phase 1 oxidation and phase 2 glucuronidation are also impaired in the neonate. Drugs subject to high first-pass metabolism may have higher oral availability in premature or term infants due to impaired ability to metabolise on first-pass. Adult metabolic capacity is attained towards the latter part of the infant's first year of life. The following table is useful for estimating infant clearance.

Table 1: Approximate clearance values at different ages

Post-conceptual age	Clearance of drug (compared with adults)
24-28 weeks	5%
28-34 weeks	10%
34-40 weeks	33%
40-44 weeks	50%
44-68 weeks	66%
> 68 weeks	100%

Minimise risk to the breastfed infant by reducing drug exposure

The overall risk of a drug to a breastfed infant depends on the concentration in the infant's blood and the effects of the drug in the infant. If, after assessment of the risks and benefits, the decision is made to breastfeed while the mother is using a drug, the infant should be monitored for adverse effects such as failure to thrive, irritability and sedation. However, it is difficult to identify adverse reactions occurring in neonates. Feeding immediately prior to a dose may help to minimise infant exposure as concentrations in milk are likely to be lowest towards the end of a dosing interval. However, for some drugs, milk concentrations lag behind plasma concentrations.

For drugs that have an infant dose greater than the arbitrary cut-off of 10% of the weight-adjusted maternal dose, it may be reasonable to reduce infant exposure by alternating breast and bottle-feeding. For drugs that are not considered safe in breastfeeding, breast milk may be expressed and discarded for the treatment duration. Breastfeeding may be resumed after the drug has been eliminated from the maternal blood stream. A period of approximately four half-lives will reduce maternal concentrations to around 10% of steady-state concentrations.

Safety assessment of some frequently used drugs

A discussion of the safety of the more commonly used drugs is provided below. The data must be assessed in conjunction with information on the maternal dose and therefore probable maternal concentrations, the age of the infant and their likely ability to eliminate the drug. In general, if the infant dose as a percentage of the maternal dose (corrected for weight) is close to 1%, the drug can be considered 'safe' regardless of infant age. For drugs where the weight-adjusted dose is closer to 10%, the infant clearance should also be taken into account (see Table 1). For example, if the weight-adjusted infant dose is 10% but the infant is premature, the lower clearance will mean that the infant concentrations may be well above those expected.

Analgesics:
Analgesics such as paracetamol, ibuprofen, naproxen and codeine are considered to be 'safe', due to low transfer into breast milk and few problems with extensive usage. Transfer of aspirin into breast milk appears to be low but it is best avoided due to the theoretical risk of Reye's syndrome. Sumatriptan has a short half-life of approximately two hours and infant exposure can be almost completely avoided by expressing and discarding breast milk for approximately eight hours after dosing. Limited data on tramadol suggest low transfer into breast milk although where possible, it would be preferable to use agents which are more established such as codeine and paracetamol. Morphine is usually considered 'safe' because of low transfer into milk, and high first-pass metabolism.

Anthelminthics:
There does not appear to be any data on the transfer of mebendazole or pyrantel embonate into human breast milk although these agents are generally considered to be 'safe' due to poor absorption from the gastrointestinal tract.

Antibiotics:
Antibiotics such as penicillins, cephalosporins and macrolides are considered to be compatible with breastfeeding although there are theoretical risks of alterations to infant bowel flora and allergic sensitisation.

The safety of metronidazole is controversial due to the possibility of high transfer into breast milk. The weight-adjusted infant dose may be as high as 36% of the maternal dose indicating that infant exposure may be higher than the arbitrary cut-off of 10%. Techniques that may be considered for minimising infant exposure include choosing an alternative antibiotic such as amoxycillin/clavulanic acid (if appropriate), alternating breast and bottle feeding, or

withholding breastfeeding during the treatment course. If breastfeeding is to be withheld, the mother should be encouraged to continue to express breast milk while on the antibiotic course but to discard the milk. This will help to maintain lactation and enable the mother to resume breastfeeding at the end of the course.

The transfer of tetracyclines into breast milk is low but they are usually avoided due to the possible risks of inhibiting bone growth or causing dental staining. Fluoroquinolones should also be avoided in breastfeeding as they have been reported to cause arthropathies in immature animals. Sulphonamides such as sulphamethoxazole are unlikely to be problematical in most situations but are best avoided in infants with hyperbilirubinaemia or glucose-6-phosphate dehydrogenase deficiency.

Anticoagulants:
Heparins (unfractionated and low molecular weight) are considered 'safe' since these agents have a large molecular weight and do not cross into breast milk to a significant extent. They are also poorly absorbed. Warfarin is also considered to be compatible with breastfeeding as transfer is low, and adverse effects and changes in prothrombin time have not been detected in breastfed infants. However, it would be prudent to monitor the infant's prothrombin time during treatment.

Anticonvulsants:
Carbamazepine, phenytoin and sodium valproate are generally considered to be compatible with breastfeeding although the infant should be observed for evidence of central nervous system depression. Available data on the safety of lamotrigine in breastfeeding suggest that transfer into breast milk may be considerable and therapeutic concentrations have been detected in breastfed infants. There are insufficient published data to comment on the safety of gabapentin in breastfeeding.

Antidepressants:
Selective serotonin reuptake inhibitors (SSRIs) transfer into breast milk to varying extents. Paroxetine is reported to have the lowest transfer into breast milk (weight-adjusted infant dose 1-3%). Fluoxetine transfers to a greater extent (weight-adjusted infant dose ≤ 14%) and its active metabolite, norfluoxetine, has a long half-life of one to two weeks and may accumulate in a breastfed infant. Data on citalopram (weight-adjusted infant dose approximately 5%) suggest that the relative infant dose of citalopram is intermediate between paroxetine and fluoxetine. Based on these data, paroxetine is the preferred SSRI in breastfeeding women.

Most tricyclic antidepressants are considered to be compatible with breastfeeding due to low transfer into breast milk and this is supported by extensive usage data. Moclobemide has low-transfer into breast milk and is considered compatible with breastfeeding.

Antihistamines:
Agents such as promethazine, dexchlorpheniramine and diphenhydramine are considered to be safe through extensive usage, although it would be prudent to monitor for evidence of sedation or irritability in the infant. There is less data on the non-sedating antihistamines, although loratadine and fexofenadine are likely to be safe due to low transfer into milk.

Benzodiazepines:
Sporadic use of benzodiazepines with a short plasma half-life such as midazolam and temazepam is unlikely to be problematical due to low quantities transferred into breast milk. Agents with a long half-life such as diazepam may accumulate in the infant with prolonged exposure and may be associated with lethargy, poor suckling and reduced weight gain.

Decongestants:
A short course of pseudoephedrine (weight-adjusted dose < 4%) is unlikely to be problematical. However, topical decongestant nasal sprays or drops are usually preferred due to lower infant exposure.

Social drugs:
These have particular problems because the dose and pattern of usage are uncontrolled. In addition most have relatively high infant doses. Infant exposure following maternal ethanol ingestion may be as high as 20% and has been associated with impaired psychomotor development. Alcohol consumption should be minimised during lactation (e.g. by withholding breastfeeding for about two hours after ingestion of a standard alcoholic drink).

Caffeine exposure may be as high as 34% of the weight-adjusted maternal dose and side effects such as restlessness and irritability have been reported in infants exposed via breast milk.

Nicotine has been detected in the plasma of breastfed infants, and smoking is best avoided by breastfeeding mothers. The use of nicotine replacement therapy (e.g. transdermal delivery systems) in breastfeeding mothers should be considered in terms of risks and benefits. However, as a general rule, the short-term use of nicotine replacement therapy is far preferable than continued smoking.

Drugs affecting milk:
Drugs can affect milk secretion or composition by affecting factors such as mammary gland development, milk secretion and hormonal regulation of lactation. Prolactin is necessary for human milk secretion and may be affected by drug use. Dopamine agonists such as cabergoline reduce prolactin and are sometimes used therapeutically to stop lactation. Dopamine antagonists such as metoclopramide and most antipsychotics may increase prolactin (see article on page 28) and milk production. Other drugs that have been associated with causing hyperprolactinaemia include SSRIs and opioids.

Tabulated summary of drug distribution into breast milk

Table 2 shows published M/P ratios from the literature and provides an estimate of the weight-adjusted infant dose. Interpretation of these requires an understanding of the limitations associated with published data, such as the availability of only single pairs of plasma and milk concentrations. Infant clearance (related to post-conceptual age) should always be considered.

Table 2: Summary of distribution of drugs into breast milk

ID = insufficient data

Drug	M/P_{AUC}	% maternal dose	Comments
Acid-suppressants:			
Cimetidine	1.7-5.8	5.4-6.7	Avoid in favour of safer alternatives with lower potential for side effects. May accumulate in milk due to active transport.
Famotidine	1.5	1.6	Probably safe.
Ranitidine	2.8	5.0-7.8	Probably safe when restricted to sporadic doses or a single dose at night-time. May accumulate in milk due to active transport.

Drug	M/P_{AUC}	% maternal dose	Comments
Analgesics:			
Aspirin	0.06	3.2	Avoid due to possible association with Reye's syndrome.
Codeine	2.16	6.8	Considered safe.
Ibuprofen	0	< 0.6	Considered safe. Not detected in milk.
Indomethacin	0.37	< 1.0	Considered safe. One case of seizures (causality questionable).
Mefenamic acid	ID	0.3	Probably safe.
Methadone	0.47	2.2	Considered safe in methadone maintenance as 60% of infants born to mothers in maintenance programmes develop symptoms of withdrawal.
Morphine	2.46	0.4	Considered safe.
Naproxen	ID	1.1	Probably safe.
Nefopam	ID	0.4	Probably safe.
Piroxicam	ID	5-10	Use a NSAID with a shorter half-life where possible.
Paracetamol	0.8	2.9-7.9	Considered safe.
Sumatriptan	4.1-5.7	0.3-6.7	Exposure limited by low oral availability in term infants. Expressing for 8 hours post-dose will almost completely avoid exposure.
Antibiotics:			
Aminoglycosides			
Gentamicin	0.17	2.2	Considered compatible with breastfeeding due to low transfer and low oral availability.

Drug	M/P_{AUC}	% maternal dose	Comments
Cephalosporins			
Cefaclor	ID	0.7	Considered safe. Low transfer into milk. Third generation cephalosporins have greater potential to alter bowel flora.
Cefalexin	0.09	0.5-1.2	
Cefotaxime	ID	0.3	
Ceftriaxone	0.04	0.7-4.7	
Fluoroquinolones			
Ciprofloxacin	2.17	4.8	Avoid fluoroquinolones due to theoretical risk of arthropathies.
Macrolides			
Clarithromycin	0.25	1.8	Considered safe. May alter bowel flora.
Erythromycin	0.41	2.1	
Penicillins			
Amoxycillin	ID	0.7	Considered safe. Note: although amoxycillin/clavulanic acid combination is used extensively in lactation, there are no published data on the safety of clavulanic acid.
Benzylpenicillin	0.37	0.8	
Phenoxymethyl-penicillin	ID	0.25	
Tetracyclines			
Minocycline	ID	3.6	Avoid tetracyclines where feasible due to the possible risks of dental staining and adverse effects on bone development.
Tetracycline	0.58	4.8	
Others			
Aciclovir	ID	1.1-1.2	Considered safe. No adverse effects noted in breastfed infants.
Fluconazole	0.75	11	Potential for accumulation particularly in premature infants.
Metronidazole	0.9-1.1	0.1-36.0	Controversial as exposure may be high. With high doses consider expressing and discarding milk.

Drug	M/P_{AUC}	% maternal dose	Comments
Others			
Nitrofurantoin	ID	0.6-6.0	Avoid in G6PD-deficient infants (due to the risk of haemolysis).
Sulphamethoxazole & Trimethoprim (i.e. co-trimoxazole)	0.1 1.26	2-2.5 3.8-5.5	Avoid sulphamethoxazole in infants with hyperbilirubinaemia and G6PD deficiency.
Anticoagulants:			
Warfarin	0	< 4.4	Probably safe. No changes in prothrombin times detected in breastfeeding infants. Monitor prothrombin time.
Anticonvulsants:			
Carbamazepine	0.36-0.39	2.8-7.3	Considered safe. Monitor for sedation, poor suckling.
Lamotrigine	ID	10-22	Concentrations in breastfed infants have been consistent with those expected to produce clinical effect. Best to avoid.
Phenobarbitone	ID	23-156	Avoid due to high infant exposure.
Phenytoin	0.13-0.18	3.0-7.2	Considered safe. Observe for sedation, poor suckling. One report of methaemoglobinaemia, poor suckling and sedation.
Sodium valproate	0.05	1.8	Considered safe at low doses. High doses may increase the risk of hepatitis.
Vigabatrin	ID	<1%	Avoid until further data are available.
Antidepressants:			
Tricyclics			
Amitriptyline	0.83	0.6-0.9	Probably safe. Negligible or no concentrations detected in breastfed infants.
Desipramine	ID	0.5-1.0	

Drug	M/P_{AUC}	% maternal dose	Comments
Tricyclics			
Dothiepin	0.8-1.6	0.2-1.5	Probably safe. Negligible or no concentrations detected in breastfed infants.
Doxepin	ID	0.01	
Imipramine	ID	0.13	
Nortriptyline	ID	0.53	
SSRIs			
See text			
Others			
Moclobemide	0.72	1.6	Probably safe.
Antiemetics:			
Domperidone	ID	0.05	Probably safe. May increase milk secretion.
Metoclopramide	ID	4.7-11.3	Low dose or sporadic use probably safe. May increase milk secretion.
Antihistamines:			
Loratadine	1.2	0.7	Probably safe. No adverse effects reported in infants.
Triprolidine	0.53	0.9	Considered safe.
Antipsychotics:			
Chlorpromazine	ID	0.2	Probably safe. May increase milk secretion. Monitor infant for sedation, irritability etc.
Flupenthixol	ID	0.5-0.8	
Haloperidol	ID	0.15-2.0	
Cardiovascular:			
Amiodarone	ID	37	Avoid in breastfeeding.
Atenolol	2.3-4.5	5.7-19.2	Avoid in favour of antihypertensives with lower infant exposure.
Captopril	0.03	0.014	Considered safe.
Digoxin	0.6-0.9	2.3-5.6	Considered safe.

Drug	M/P_{AUC}	% maternal dose	Comments
Cardiovascular:			
Diltiazem	0.98	0.9	Unlikely to be problematical in breastfeeding.
Enalapril	0.02	< 0.1	Considered safe.
Metoprolol	2.8-3.6	1.7-3.3	Probably safe.
Nadolol	4.6	5.1	Consider choosing a beta-blocker with a lower infant dose, if feasible.
Propranolol	0.32-0.76	0.2-0.9	Probably safe.
Quinapril	0.12	1.6	Considered safe.
Verapamil	0.6	0.14-0.84	Considered safe.
Sedatives/ hypnotics:			
Clonazepam	ID	1.5-3.0	Short-term use of low doses is probably safe.
Diazepam	0.16	2.0-2.3	Reasonable to breastfeed after a low single dose but potential for accumulation with prolonged use. Sedation has been reported in breastfed infants.
Lorazepam	ID	2.2	Short-term use of low doses is probably safe.
Midazolam	0.16	0.7	Short-term use of low doses is probably safe.
Nitrazepam	ID	ID	Short-term use of low doses is probably safe. Potential for accumulation with prolonged administration.
Zopiclone	0.5	4.1	Short-term use of low doses is probably safe.
Social Drugs:			
Cannabis (THC)	ID	ID	Avoid as long-term effects are unknown.

Drug	M/P_{AUC}	% maternal dose	Comments
Social Drugs:			
Caffeine	0.5-0.8	0.6-21.0	Low intake probably safe. Restlessness and irritability documented. Prolonged half-life (80-100 hours) in neonates.
Ethanol	0.9	3-4	Occasional low usage probably safe. Chronic intake may be associated with impairment of psychomotor development. Consider withholding breastfeeding for 1-2 hours per standard drink.
Nicotine	2.92	ID	Cigarette smoking should be avoided due to health hazards associated with smoking. Use of nicotine patches may be considered compatible with breastfeeding and is favoured over smoking.
Miscellaneous:			
Ethinyloestradiol	ID	0.3	May suppress lactation.
Levonorgestrel	ID	1.1	Considered safe.
Medroxy-progesterone	ID-0.72	3.4-5.0	Considered safe.
Norethisterone	ID-0.26	0.02-1.9	Considered safe.
Prednisone	ID	0.26	Short courses of low doses (≤ 20mg daily) are probably safe. Note: there are insufficient data on other systemic corticosteroids(e.g. betamethasone, dexamethasone).
Pseudoephedrine	2.5	4.0	Low doses or sporadic use probably safe.
Sulphasalazine	ID	1.2-7.0	Avoid in infants with hyperbilirubinaemia or G6PD deficiency.

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UPDATED HRT PRESCRIBING GUIDELINE RELEASED

This article was published on the Medsafe web site and e-mailed to electronic *Prescriber Update* subscribers in June 2001.

In May 2001, the New Zealand Guidelines Group (NZGG) launched a new guideline called *The Appropriate Prescribing of Hormone Replacement Therapy.* It has an evidence-based approach and the key messages are presented below. The NZGG is distributing the Guideline to all prescribers over June/July 2001.

Medsafe would like to reinforce the warning in the Guideline that hormone replacement therapy (HRT) is contraindicated in existing coronary artery disease. This is a required statement in data sheets for HRT medicines. However, at present, some HRT products are indicated for reduction in risk of coronary heart disease (CHD) in women with *no current or prior* evidence of CHD. In light of the Guideline's advice that HRT is not recommended for the primary prevention of cardiovascular disease, Medsafe will be asking the Medicines Adverse Reactions Committee to comment on the appropriateness of this indication.

The Guideline has received endorsement by the NZGG and the following organisations: The Effective Practice Institute, The Royal NZ College of General Practice, Women's Health Action, NZ Heart Foundation, Australasian Menopause Society, The Cardiac Society of Australia and NZ, Family Planning Association, Osteoporosis NZ, The Royal Australian and New Zealand College of Obstetricians and Gynaecologists, and the College of Nurses Aotearoa NZ.

Key messages of the new HRT Guideline

- HRT is not recommended for routine use in the menopause.
- Decisions about the short-term (<5 years) use of HRT for the treatment of climacteric symptoms should be made separately from decisions about the long term use of HRT for the prevention of osteoporotic fractures.
- HRT is the single most effective therapy for the management of troublesome hot flushes and other menopausal symptoms.
- HRT prevents postmenopausal bone loss and is an effective therapy for established osteoporosis. Bone mineral density measurement can be used to assess bone density before treatment is offered. The optimum timing for osteoporosis prevention may be when a woman is in her 60s and 70s when fracture risk is rapidly increasing rather than in her 50s when fracture risk is relatively low.
- Estrogen replacement therapy or oral estriol should not be given without a progestogen for women with a uterus.
- There is insufficient evidence that HRT improves cognition or prevents or delays Alzheimer's disease.
- HRT is contraindicated for the secondary prevention of coronary artery disease. There is insufficient evidence at present of benefit or harm from HRT for the primary prevention of coronary artery disease.
- Short term HRT use (<5 years) does not increase the risk of breast cancer diagnosis. Longer term HRT use (>5 years) may be associated with an increase in breast cancer diagnosis but it remains uncertain if mortality from breast cancer is affected.
- Two very large randomised controlled trials are currently underway which may clarify the benefits and risks of HRT over the next 5 to 10 years.

Contact NZGG for further information

Full details of the evidence found to support the new HRT Guideline are freely available on the NZGG web site http://www.nzgg.org.nz. A detailed printed report is also available for purchase for $40 plus post and packaging from info@nzgg.org.nz or ph 04 471 4180.

NSAIAs CAN CAUSE LOWER GIT DAMAGE

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Two recent reports to the Centre for Adverse Reactions Monitoring (CARM) are a reminder that non-steroidal anti-inflammatory agents (NSAIAs) can cause damage to the mucosa of the distal small intestine and large intestine, as well as their more commonly known effects on the stomach and duodenum. Damage to the intestinal mucosa can lead to ulceration, bleeding, perforation and obstruction with the formation of diaphragm strictures. Presenting symptoms are similar to those of many bowel disorders, and serious complications may occur unless the possibility of NSAIAs as a cause is recognised. Immediate investigation is recommended with referral to a specialist and discontinuation of all NSAIAs.

Low incidence may hinder recognition of NSAIAs as cause

Minor damage from NSAIAs can occur to the mucosa of the distal small intestine and large intestine as well as the stomach and duodenum. This damage is common but more serious complications are thought to occur rarely. Gastroduodenal events causing hospitalisation are estimated to occur in between 1 in 500 and 1 in 50 patients taking NSAIAs for a year depending on predisposing factors.[1] In comparison, haemorrhage and perforation in the more distal intestine has been estimated to occur in about 1 in 5000 NSAIA-users a year.[2] This low incidence may contribute to the association not being recognised.

Recent cases of intestinal ulcers reported to CARM

Case 1: A 39 year old woman had been taking slow-release ketoprofen for many years. She had recurrent episodes of intestinal obstruction and iron deficiency anaemia over a five year period. Laparotomy revealed multiple intestinal ulcers on the mucosal surface and diaphragm strictures.

Case 2: A 73 year old woman had taken slow-release diclofenac for several months for a shoulder injury. She had a massive gastrointestinal haemorrhage, and was found to have colonic and ileal ulcers. She recovered after withdrawal of diclofenac and blood transfusion.

Multiple diaphragm strictures pathognomonic of NSAIA-induced damage

As well as haemorrhage, ulceration and perforation, NSAIAs can cause obstruction due to the formation of diaphragm strictures. These are thin septate narrowings, usually of the small intestinal mucosa and are thought to arise from circumferential ulcers. Multiple diaphragm strictures are pathognomonic of NSAIA-induced intestinal damage.[3]

Case series and case reports have now described diaphragm strictures in the large intestine and most have been associated with slow-release or enteric-coated NSAIA preparations.[4] Epidemiological studies are needed to confirm whether the risk to the large intestine is greater with altered release than with standard release NSAIA preparations.

Symptoms of complications due to mucosal damage can differ between the small and large intestine as described below.

Blood loss, obstruction and anaemia are suggestive of small intestine damage

Case 1 illustrates the diagnostic difficulty with intestinal lesions and this is particularly so for the small intestine. It is estimated that 20-65% of long-term NSAIA-users have NSAIA enteropathy, i.e. small bowel inflammation.[3] This is usually asymptomatic but clinical problems can arise from associated complications. These include blood loss, protein loss, ulceration and obstruction due to diaphragm stricture formation.[3]

Iron deficiency anaemia in a patient taking NSAIAs with a normal endoscopy and colonoscopy may be due to blood loss from the small intestine. Intermittent postprandial colicky pain (subacute obstruction) often with a history of iron deficiency and hypoalbuminaemia is suggestive of diaphragm strictures in the small intestine. Radiological findings may resemble malignancy or Crohn's disease, or can be normal. Enteroscopy can be helpful but is not always available.[3]

Diarrhoea, anaemia and weight loss may indicate large intestine damage

Colonic ulceration, perforation and haemorrhage have been associated with NSAIAs in one epidemiological study[2] and in many published case reports. NSAIA-induced diaphragm strictures are usually found in the ascending colon.[5] Symptoms suggestive of ulceration and diaphragm strictures in the large intestine are chronic diarrhoea, iron deficiency anaemia and weight loss, rather

than pain and subacute obstruction.[6] Major haemorrhage may occur as in Case 2. Colonoscopy, rather than x-ray, will help to ensure the correct diagnosis.[6]

NSAIAs can complicate existing bowel disease

NSAIAs may also cause relapse of Crohn's disease and ulcerative colitis, and diverticular perforation, fistulae and abscesses.[3] Due to similar presentations, it may be difficult to distinguish between relapses and NSAIA-induced exacerbations.

Early referral to a specialist is recommended when NSAIA complications are suspected. All NSAIAs should be stopped while investigation is undertaken. Patients should also be asked about any other medicines they may be taking, especially as some NSAIAs can be purchased over-the-counter.

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HYPERPROLACTINAEMIA WITH ANTIPSYCHOTICS

Medsafe Editorial Team

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Dopamine acts on the pituitary as an inhibitor of prolactin secretion. Blockade of dopamine D2 receptors by typical antipsychotics and risperidone can cause hyperprolactinaemia in males and females. Other atypical antipsychotics do not cause sustained hyperprolactinaemia because of their lower affinity for D2 receptors. Symptoms of hyperprolactinaemia include amenorrhoea, galactorrhoea, infertility, loss of libido and erectile dysfunction. Resulting hypogonadism may cause osteoporosis.

Treat symptomatic antipsychotic-induced hyperprolactinaemia by dose reduction or change to an antipsychotic with less effect on prolactin. Also consider endocrinological consultation. Warn women that menstruation and fertility will return as their prolactin levels normalise, therefore contraceptive advice may be needed.

Prolactin is secreted by the pituitary gland. It influences gonadal function in both sexes, initiates and sustains lactation in females, and controls libido in males. Normal prolactin levels are slightly higher in women than men. Physiological rises in prolactin level occur during pregnancy, reaching a maximum at the time of delivery, falling postpartum and rising transiently with each suckling episode. Prolactin levels also rise within an hour after eating and after generalised seizures.[1] To accurately measure prolactin, check serum levels fasting or at least one hour after food.

Typical antipsychotics block dopamine inhibition of the pituitary and cause prolactin rise

Secretion of prolactin by the pituitary is under inhibitory control via dopamine from the hypothalamus. Interference with dopamine secretion or action leads to an increase in serum prolactin. Some medicines can do this by blocking dopamine's action on the pituitary (e.g. phenothiazines, butyrophenones, metoclopramide, risperidone) or by depleting dopamine (e.g. methyldopa, reserpine).[1] Opiates can stimulate prolactin release.[2] Other causes of

hyperprolactinaemia include diseases of the pituitary (e.g. prolactin secreting pituitary adenomas) or hypothalamus, severe primary hypothyroidism, liver cirrhosis, end stage renal disease, stress, high dose oestrogens and chronic cocaine use.[1]

Dopamine receptor dysfunction is thought to be part of the pathophysiology of schizophrenia.[3] There are four major dopaminergic pathways (mesolimbic, mesocortical, nigrostriatal, tuberoinfundibular) and five types of dopamine receptors (D1-5). D2 receptors are found in all the pathways.

In addition, serotonin receptors are believed to play a role in psychosis.[3] Serotonin is a modulator of dopamine; if the $5HT_{2A}$ serotonin receptor is blocked, this leads to an increase in dopamine concentration. The action of antipsychotics depends on their relative affinities for receptors of dopamine and serotonin.

Typical antipsychotics, such as haloperidol, act by blocking D2 receptors in a non-specific fashion. This results in different effects on the four dopaminergic pathways: in the limbic system, it decreases positive psychotic symptoms; in the tuberoinfundibular system, it causes hyperprolactinaemia; and in the nigrostriatal system, it can result in extrapyramidal symptoms (EPS). The effects on the mesocortical pathway are less clear, and may be a combination of therapeutic benefits and drug-induced 'negative' symptoms.[3]

Atypical antipsychotics act on serotonin receptors and have a lower incidence of EPS and negative symptoms

The first available atypical antipsychotic was clozapine. Over the last ten years it has been joined by risperidone, olanzapine and quetiapine. Atypical antipsychotics can be defined as "those that are effective against psychotic symptoms with a reduced tendency to induce neurologic movement disorders".[4] The definition may be expanded to include efficacy against negative symptoms and a wider spectrum of co-morbid symptoms. A prolactin-sparing effect is sometimes included in the definition, but risperidone would then be excluded.

Atypical antipsychotics have a higher affinity for $5HT_{2A}$ compared to D2 receptors. Clozapine, olanzapine, and quetiapine also show "limbic-specific" D2 receptor binding,[3] and hence treat psychosis with less of the negative side effects of dopamine blockade on the other dopamine pathways. Furthermore, serotonin blockade in the nigrostriatal pathways will increase dopamine and thus lower the incidence of EPS.

Risperidone can cause sustained hyperprolactinaemia

In contrast to the other atypicals, treatment with risperidone can result in a sustained elevated prolactin level. It causes a rapid,[5] dose-dependent rise in prolactin[3] similar to that observed with haloperidol.[6] However, an analysis of randomised double-blind studies of risperidone found the level of prolactin did not correlate with the incidence of clinically detected prolactin-related adverse effects in either sex at usual doses.[6] Sustained hyperprolactinaemia is less frequent with the other atypicals. Although olanzapine causes an early dose-related rise in prolactin, this is less frequent and less marked than that seen with haloperidol, and is usually transient.[7] A rise in prolactin is seen in about half of patients on olanzapine compared to over 90% of those taking risperidone, and enduring increases were less frequent in those taking olanzapine.[8]

Why the difference? Risperidone has a high affinity for D2 as well as serotonin receptors.[3] It is not "limbic specific" for the mesolimbic over the nigrostriatal tract like the other atypicals.[9] Risperidone antagonises dopamine in the tuberoinfundibular system causing a rise in prolactin. However, its antagonist action at $5HT_{2A}$ receptors in the nigrostriatal pathways may partially explain why risperidone has a low propensity to cause EPS despite its blockade of D2 receptors.

Hyperprolactinaemia results in hypogonadism and may cause osteoporosis

Hyperprolactinaemia is associated with hypogonadism due to inhibition of hypothalamic release of LHRH. The resulting low levels of oestrogen and testosterone may have long-term consequences. Some advocate screening for hyperprolactinaemia in all antipsychotic treated patients.

In premenopausal women, high prolactin will lower oestrogen levels. This may contribute to the development of reduced bone mineral density, although a causal association between antipsychotics and osteoporosis has not been established.[10] Menopausal women may need to be assessed for hormone replacement therapy (HRT), however this will need to be weighed up against the risks of HRT, such as venous thromboembolism in a group among whom smoking and obesity are common. High prolactin may also cause male hypogonadism through lowering of testosterone levels. Testosterone in men is important for improving lean body mass and reducing fat mass.[6] When prescribing antipsychotics, consider the significance of other risk factors for osteoporosis such as age, menopause, glucocorticoid use, hyperthyroidism,

calcium imbalance, polydipsia, alcoholism, smoking, amenorrhoea, anorexia nervosa, use of medicines such as lithium, dietary deficiency, lack of sun, and immobility.[11]

There has also been concern regarding hyperprolactinaemia and an increased risk of breast cancer. Although there is evidence in *in vitro* and animal studies, there are no supporting human data.[6,9]

Consider hyperprolactinaemia in a woman presenting with amenorrhoea while taking antipsychotics

In any woman presenting with secondary amenorrhoea on antipsychotics, hyperprolactinaemia must be considered in the differential diagnosis (remember to exclude pregnancy). Women with hyperprolactinaemia may present with irregular menses, galactorrhoea, decreased libido and even infertility despite regular menses. Men may present with reduction in libido, impotence, infertility, and rarely galactorrhoea and gynaecomastia. Other causes of hyperprolactinaemia should be investigated if the prolactin level is raised. The patient should be examined for chest wall irritation (which can promote galactorrhoea and raise prolactin), signs of a sellar mass (including assessment of visual fields), and blood tests done for TSH[12] (exclude hypothyroidism) and creatinine (exclude renal failure as a cause of hyperprolactinaemia). Referral for CT or MRI or an endocrinology consultation may be considered.

Consider changing the antipsychotic in symptomatic hyperprolactinaemia

Treatment of symptomatic hyperprolactinaemia in a patient on antipsychotics firstly involves exclusion of other aetiologies, followed by consideration of a change of medication to a prolactin-sparing antipsychotic or reduction in dose if the patient's mental state is stable. If this proves difficult, then an endocrinologist should be consulted and the risks and benefits of hormone replacement considered. Monitoring the patient's psychiatric status closely is essential if changing regimens. Asymptomatic hyperprolactinaemia in itself should not be an indication for changes to medication.

For all treatment changes, women must be warned that menses may resume along with fertility. Contraceptive advice may need to be given. With the resumption of normal cycles, there is also the risk that premenstrual exacerbation of schizophrenic symptoms may occur, requiring doses of antipsychotics to be adjusted over the cycle.

In order to adequately monitor for hyperprolactinaemia, a menstrual history should be taken prior to commencing a premenopausal woman on antipsychotics. When choosing an antipsychotic, it is important to weigh the overall risks and benefits for the individual patient (male or female). The atypical antipsychotics, while having a better side effect profile than the older agents, still carry a significant burden of treatment which varies between the atypicals. Attention has been drawn to some of these in recent *Prescriber Update* articles.[13,14]

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TETRACYCLINES AND BENIGN INTRACRANIAL HYPERTENSION - A HEADACHE RARE BUT REAL

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Benign intracranial hypertension (BIH) is a rare but potentially serious condition. BIH has been documented in association with a variety of medicines, particularly the tetracyclines. A case has been reported to CARM of benign intracranial hypertension with minocycline, recurring on rechallenge. The common presenting feature of BIH is headache. The signs are papilloedema and sometimes sixth nerve palsy. Raised intracranial pressure confirms the diagnosis. If associated with a medicine, the condition may resolve totally on stopping it. Treatment includes therapeutic lumbar punctures and acetazolamide. Complications of BIH can be lasting visual defects or even blindness, so discontinue the medicine and refer promptly if suspected. Doctors should regularly enquire about headache when prescribing a tetracycline, even for a short period. The combination of a tetracycline and isotretinoin should be avoided.

Case report: BIH recurred on rechallenge with minocycline

The New Zealand Centre for Adverse Reactions Monitoring (CARM) has received its second report of benign intracranial hypertension (BIH) related to minocycline. It involved a 14 year old female who was being treated with minocycline for acne. Other prescribed medicines were fluticasone and salbutamol inhalers. She presented with headache unrelieved by analgesics, and had intermittent vomiting. Her signs on admission to hospital included slurred speech, reduced sensation and left sided weakness, with mild lateral rectus palsy on the right. The minocycline, which she had taken for thirteen days, was discontinued. A diagnosis of hemiplegic migraine was made, and she recovered from this episode. The headache then recurred after restarting minocycline. Papilloedema was observed and the diagnosis of benign intracranial hypertension (with hemiplegic migraine) was made. Treatment included four lumbar punctures and acetazolamide. The patient had not yet fully recovered at the time of reporting.

BIH is associated with various medical conditions and medicines

Benign intracranial hypertension (also known as pseudotumor cerebri, or idiopathic intracranial hypertension) is a rare condition of unknown cause with an annual incidence of 0.9/100,000 in the general population. It is likely that there is a genetic predisposition.[1] It is significantly more common in adolescent and young adult women, but can occur in children. In case control studies, obesity and weight gain have been demonstrated as risk factors for BIH.[2] Other medical conditions linked to BIH include migraine, thyroid and parathyroid disorders, Addison's and Cushing's diseases, systemic lupus erythematosis, HIV/AIDS, and sarcoidosis.

Medicines reported to be associated with BIH include vitamin A analogues, tetracyclines, steroids (especially in withdrawal), nalidixic acid, sulphonamides, lithium, thyroxine, growth hormone, amiodarone and tamoxifen.[3]

Benign intracranial hypertension presents with headache

The predominant presenting symptom is daily headache (90% of cases), pulsatile in quality. Less frequent symptoms are visual disturbances and pulsatile tinnitus. BIH can be completely asymptomatic. The mechanism is not fully understood but current opinion favours impaired reabsorption of cerebrospinal fluid (CSF).

Papilloedema without lateralising signs is diagnostic

The diagnostic criteria are:

- Increased intracranial pressure (> 200 mm water)
- Normal neurological examination except for papilloedema and/or sixth nerve palsy
- No mass or ventricular enlargement on imaging
- Normal CSF protein and white cell count
- No clinical or imaging evidence of venous sinus thrombosis
- There may be decreased visual acuity and visual field defects.

BIH appears to occur most frequently with minocycline

Of the medicines associated with BIH, minocycline is most frequently reported in the literature. The WHO adverse reactions database documents 188 cases of intracranial hypertension with minocycline, 31 with tetracycline and 27 with doxycycline. One review of 162 cases of medicine-related BIH found that 9% were linked to minocycline, 5.5% to tetracycline and 1.2% to

isotretinoin.[4] The lipophilic properties of minocycline may be the explanation for the higher number of reported cases. It is possible that the incidence of BIH may increase if two or more drugs which might cause BIH are used together. For this reason tetracyclines should not be prescribed concomitantly with retinoids (e.g. isotretinoin).[4]

In contrast to the truly idiopathic cases, minocycline-related BIH occurs more often in patients of normal weight than in the obese. Minocycline-induced cases tend to resolve on stopping the medicine, without recurrence, strengthening the cause and effect hypothesis.[5]

The above case is the second report of benign intracranial hypertension from a total of 172 adverse reaction reports for minocycline on the CARM database. Australia's Adverse Drug Reactions Advisory Committee figures for minocycline are 463 (all adverse reactions) and 24 (cases of BIH) from 1974 to 1999. A prospective trial describes 14 probable cases out of 700 treated patients.[6] There was no association with dosage, so the effect is likely to be idiosyncratic. Most cases occurred in the first four weeks of treatment, but two happened after 6 and 12 months, respectively.[6]

It is not always benign

Active intervention may not be needed in the absence of visual defects and if there is an association with a medicine which has been discontinued. Treatment includes weight loss if indicated, repeated lumbar punctures until the intracranial pressure returns to normal, and oral acetazolamide. Short-term systemic steroids are advocated by some authorities. Neurosurgical decompression techniques are sometimes used for intractable headache or progressive visual field loss. Although most patients recover fully, the epithet "benign" is misleading as complications include irreversible visual field defects, and, occasionally, blindness.

Ask about headache when prescribing tetracyclines

Minocycline and other tetracyclines are commonly prescribed for acne. Prescribers should be aware that benign intracranial hypertension has been associated with their use, as delay in its diagnosis can lead to serious consequences. Acne treatment may not even be considered as a medicine by patients when asked what medicines they are taking.[7] Active enquiry about headache, visual disturbances and tinnitus is advised at each visit. Because the onset of BIH can be insidious or asymptomatic, some authorities also recommend regular fundoscopy of every person taking tetracyclines.

When BIH is suspected, the medicine must be stopped and a neurological opinion promptly sought. The same precautions should be observed when prescribing tetracyclines of any kind for malaria prophylaxis (an unapproved use in New Zealand).

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VITAMIN K PROPHYLAXIS IN THE NEWBORN

A consensus statement from:

Fetus and Newborn Committee of the Paediatric Society of New Zealand

The New Zealand College of Midwives (Inc.)

The New Zealand Nurses Organisation

The Royal New Zealand College of General Practitioners

The Royal Australian and New Zealand College of Obstetricians and Gynaecologists

This article was published on the Medsafe web site and e-mailed to electronic *Prescriber Update* subscribers in January 2001.

Current evidence supports the administration of vitamin K to all babies, to prevent vitamin K deficiency bleeding (VKDB). A new formulation of vitamin K is available, which can be given either intramuscularly (the preferred route) or orally.

Background

The Fetus and Newborn Committee of the Paediatric Society of New Zealand issued a statement on vitamin K prophylaxis for haemorrhagic disease of the newborn (now preferably called vitamin K deficiency bleeding: VKDB) in 1995[1]. In 1992, a British report had suggested a possible association between intramuscular vitamin K and an increased risk of childhood cancer. By 1995 several large epidemiological studies from North America and Europe had been published, none of which supported such an association. Evidence also suggested that the alternative oral route for vitamin K administration was not as successful at preventing the late form of VKDB. The 1995 statement, therefore, recommended that "all newborn infants should have vitamin K prophylaxis and that the preferred route of administration is intramuscular."

Since 1995 there has been continuing debate on this issue, a number of further studies published and, importantly, ongoing surveillance of cases of VKDB in several countries. In addition, the launch of a new vitamin K product (Konakion MM®, which will replace Konakion®) in New Zealand demands a review of previous recommendations.

As with earlier studies of a possible link between intramuscular vitamin K prophylaxis and childhood cancer, the most recent have been of variable design and not without methodological problems. Whilst most reviewers[2] have interpreted these studies as not demonstrating any such link at least one editorial[3] concluded a small risk of leukaemia (but not other cancers) could not be excluded, although "the potential risk … seems more hypothetical than real." The risk of leukaemia may be small but does nevertheless influence the decision making of some families.

Neonatal bleeding is not always due to vitamin K deficiency and vitamin K deficiency often occurs after the four week neonatal period, hence the specific term, vitamin K deficiency bleeding has been adopted internationally.[4] VKDB is bleeding due to inadequate activity of vitamin K dependent coagulation factors (II, VII, IX, X). In a bleeding infant, a prolonged prothrombin time (PT) together with normal fibrinogen level and platelet count is almost diagnostic and rapid correction of the PT and/or cessation of bleeding after vitamin K administration are confirmative.[4]

Three forms of VKDB

VKDB is an uncommon but potentially fatal disorder which presents with spontaneous bleeding, or bruising. Internal haemorrhage, including intracranial bleeding, may occur. There are three recognised forms:

Early: This is very rare, and occurs on the first day of life in infants whose mothers are taking anticonvulsants (particularly phenobarbitone or phenytoin), anti-tuberculous therapy or vitamin K antagonist anticoagulants. Consideration should be given to treating such mothers with oral vitamin K, 20mg/day, for 2 weeks prior to delivery.[2]

Classic: Bleeding occurs from the 2nd to 7th day of life. Older data suggest the incidence in babies who do not receive vitamin K prophylaxis is in the order of 400 to 1700 per 100,000 births.[2]

Late: This occurs between one week and six months of age, almost exclusively in breast fed babies, and often in association with unrecognised liver disease or malabsorption syndrome.

Recent surveillance in Australia[5] and Europe[2,6] gives the risk of late VKDB per 100,000 babies as being:

	Australia	Europe
No vitamin K	34.4[a]	
1 dose oral Konakion®	20	
2 doses oral Konakion MM®		5
3 doses oral Konakion®	4.1	2.6
I.M. Konakion® at birth	0.2	0

[a] "344" appears in reference but this was an estimate and "34.4" is likely to be more accurate and is closer to that in other studies (Dr P. Loughnan).

New formulation of vitamin K

Konakion®, the only form of vitamin K available in New Zealand for many years, has not been licensed for oral use (although practitioners may still prescribe it by that route). It contains phytomenadione (vitamin K_1) as the active ingredient but also polyethoxylated castor oil, propylene glycol and phenol, which some practitioners consider are mucosal irritants for the infant. The new Konakion MM® is designed specifically for oral as well as intramuscular use, and contains phytomenadione and the naturally occurring products, glycocholic acid and lecithin. The advent of this form of vitamin K should allay any concerns about oral administration related to the phenol content of the former preparation.

Current Recommendations

The international debate and uncertainties in the last decade over the safety of vitamin K administration to newborns requires maternity providers to ensure that patients have access to discussion and information that recognises the complexity around their decision making in newborn care. The following recommendations are based on current evidence, which supports the administration of vitamin K to prevent VKDB in susceptible babies.

1. It is the responsibility of the lead maternity carer (LMC) to discuss vitamin K prophylaxis and ensure that parents are aware of the recommendation that all babies should receive vitamin K prophylaxis.
2. The recommended route of administration is intramuscular; 1mg (of Konakion MM®, 2mg/0.2ml) being given at birth. Preterm infants may receive 0.5mg.
3. If parents do not agree to an intramuscular injection, the alternative is for the infant to receive Konakion MM®, 2mg orally at birth. These infants should then receive a repeat oral dose (2mg) at 3-5 days and at 4-6 weeks of age. If the infant vomits or regurgitates within 1 hour of an oral dose, this dose should be repeated.
4. The oral regime is not recommended in "high risk" situations, such as maternal anticonvulsant or anticoagulant therapy (warfarin or phenindione), tuberculostatic drugs (such as rifampicin and isoniazid), prematurity, birth asphyxia or other conditions which will delay oral feeding.
5. If the parents opt for repeat oral doses of vitamin K, both the LMC and the parents themselves carry responsibility to see that the infant receives these doses.
6. Most cases of severe VKDB are preceded by "warning bleeds" and it is important for practitioners and parents to be aware that spontaneous bleeding in the first six months of life may be caused by haemorrhagic disease. Examples of "warning bleeds" include bleeding from the nose or umbilicus, spontaneous bruising and black bowel motions. Parents who have opted for no vitamin K prophylaxis should particularly be made aware of these signs.
7. Many cases of late VKDB occur when there is liver dysfunction. Prolonged jaundice in the newborn needs to be investigated. In the event that the infant has conjugated hyperbilirubinaemia, the need for vitamin K administration should be considered and discussed with parents.
8. Infants who are suspected of having VKDB should normally be admitted

to hospital for investigation. Consideration should be given to intravenous vitamin K administration and fresh frozen plasma or other source of clotting factors.

9. A written record of the date, dose and method of administration of vitamin K should be kept in the Child Health Record Book.

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IMMP
INTENSIVE MEDICINES
MONITORING PROGRAMME

The medicines currently being monitored are (recent changes are in **bold**):

Medicine	Proprietary name	Indications/Action
Celecoxib	Celebrex	COX-2 inhibitor (selective NSAIA)
Clozapine	**Clozaril, Clopine, SBPA Clozapine, Zopine**	**atypical antipsychotic**
Copper IUCD *(follow-up only)*	Multiload Cu 375	intrauterine contraceptive device
Eformoterol ***(follow-up only)***	Foradil, Oxis	potent long-acting ß$_2$-agonist
Entacapone	Comtan	Parkinson's disease – adjunctive treatment only
Levonorgestrel intrauterine system	Mirena	progestogen-releasing intrauterine system
Montelukast	Singulair	anti-asthmatic/leukotriene inhibitor
Nefazodone	Serzone	antidepressant/5HT2 blocker
Olanzapine	Zyprexa	atypical antipsychotic
Quetiapine	Seroquel	atypical antipsychotic
Risperidone	**Risperdal**	**atypical antipsychotic**
Rofecoxib	Vioxx	COX-2 inhibitor (selective NSAIA)
Salmeterol ***(follow-up only)***	Serevent	potent long acting ß$_2$-agonist
Sibutramine	**Reductil**	**centrally acting anorexiant**
Tolcapone	Tasmar	Parkinson's disease – adjunctive treatment only
Zafirlukast	Accolate	anti-asthmatic/leukotriene inhibitor

Please report all cases of adverse events occurring with IMMP medicines to the Centre for Adverse Reactions Monitoring (CARM), PO Box 913, Dunedin. The reporting form enclosed can be used or it can be downloaded from the Medsafe web site: www.medsafe.govt.nz/Profs/adverse.htm

Recent IMMP changes

Clozapine (Clozaril™, Clopine™, SBPA Clozapine™, Zopine™) **and Risperidone** (Risperdal™)
While these two atypical antipsychotics are not new in New Zealand, the addition of clozapine and risperidone to the IMMP will allow the incidence of adverse reactions and clinical events of concern for all atypical antipsychotics to be assessed. It is particularly important to monitor the safety of these agents as they are often used long term in patients who are resistant to other treatments.

Sibutramine (Reductil™)
Sibutramine is a new centrally acting anti-obesity agent indicated for the management of obesity, including weight loss and maintenance of weight loss. It is postulated that sibutramine decreases food intake by enhancing central noradrenaline and 5-HT function, and increases metabolic rate by enhancing peripheral noradrenaline function. Following cardiovascular safety concerns about other centrally acting anorexiants, it is prudent to monitor sibutramine.

Eformoterol (Serevent™) **and Salmeterol** (Foradil™, Oxis™)
New patients are no longer being added to the cohorts for eformoterol and salmeterol but follow-up of existing patients is continuing.

ADVERSE REACTIONS OF CURRENT CONCERN

CARM
CENTRE FOR ADVERSE REACTIONS MONITORING

The purpose of the Medicines Adverse Reactions Committee's (MARC) list of Adverse Reactions of Current Concern is twofold: to raise the level of awareness of these adverse reactions and to evoke reports so that more information may be gathered and appropriate action taken. The current list is below (there have been no further changes since the February 2001 issue of *Prescriber Update*).

Medicine	Adverse reactions	*Prescriber Update* reference
Cisapride	cardiac arrhythmias	No.18, Jun 1999 & No.14, Feb 1997
Clozapine	hyperglycaemia	No.18, Jun 1999
Diane-35™	venous thromboembolism	No.20, Feb 2001
Herbal medicines	all adverse reactions	No.13, Oct 1996
Hormone replacement therapy	venous thromboembolism	No.16, Apr 1998
Nefazodone	hepatic reactions	No.19, Feb 2000
NSAIAs	serious soft-tissue infection	No.20, Feb 2001
Oral contraceptives	venous thromboembolism	No.17, Dec 1998 & No.11, Feb 1996
Ticlopidine	neutropenia and thrombocytopenia	No.17, Dec 1998 & No.14, Feb 1997

Please report all cases of adverse reactions of current concern to the Centre for Adverse Reactions Monitoring (CARM), PO Box 913, Dunedin. The reporting form enclosed can be used or it can be downloaded from the Medsafe web site: www.medsafe.govt.nz/Profs/adverse.htm

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CARM
CENTRE FOR ADVERSE REACTIONS MONITORING

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, traditional and alternative remedies

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

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

Report all adverse 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.

To report: Use the pre-addressed postage paid adverse reactions card supplied with *Prescriber Update* or *New Ethicals Catalogue.*

Or: Download the form from www.medsafe.govt.nz/profs.htm

Mail the report to: The Medical Assessor
Centre for Adverse Reactions Monitoring
PO Box 913, Dunedin

Or fax it to: (03) 477 7150

Phone: (03) 479 7497

Email: carmnz@stonebow.otago.ac.nz

1. The list of adverse reactions of current concern is on page 43.
2. The list of medicines in the Intensive Medicines Monitoring Programme (IMMP) is on page 41.