

AUSTRALIAN ADVERSE DRUG REACTIONS BULLETIN

Volume 28, Number 3, June 2009

- ☆ Drug-associated macular oedema - latanoprost and rosiglitazone
 - ☆ Drug-induced lupus erythematosus: An emerging association with TNF inhibitors
 - ☆ Metformin, dehydration and lactic acidosis
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Please report **all** suspected reactions to these **Drugs of Current Interest**

Duloxetine (Cymbalta)
Dabigatran (Pradaxa)
Paliperidone (Invega)
Pramipexole (Sifrol)
Pregabalin (Lyrica)
Rosuvastatin (Crestor or Visacor)

Ranibizumab (Lucentis)
Rivaroxaban (Xarelto)
Sitagliptin (Januvia)
Strontium ranelate (Protos)
Varenicline (Champix)

1. Drug associated macular oedema – latanoprost and rosiglitazone

Macular oedema causes blurred or distorted vision due to painless swelling of the macula. The condition is relatively common and is frequently associated with various ocular conditions including cataract surgery and age-related macular degeneration; and, rarely, drug toxicity. Chronic macular oedema or multiple recurrences may result in macular photoreceptor damage with permanent impairment of central vision.¹

To date, we have received 25 adverse drug reaction (ADR) reports of drug-associated macular oedema. Most have implicated latanoprost (7 reports from a total of 216 for this drug) or rosiglitazone (9 reports from a total of 344), and 3 each have reported use of an NSAID or a bisphosphonate.

Latanoprost is a prostaglandin F_{2α} analogue used as eye drops for the treatment of open angle glaucoma or ocular hypertension either alone (Xalatan) or in combination with the beta-blocker timolol (Xalacom). It reduces intraocular pressure by decreasing resistance and thereby increasing uveoscleral outflow of aqueous humour. It has not been found to have significant systemic pharmacological effects.

Macular oedema is identified in the latanoprost Product Information (PI) as a potential adverse effect, more commonly occurring in patients with aphakia or pseudophakia with anterior chamber lenses and/or torn posterior lens capsule, or in patients with known risk factors for macular oedema such as diabetic retinopathy and retinal vein occlusion.

Macular oedema is also a risk with other prostaglandin F_{2α} analogues but we have received only one report with bimatoprost (from a total of 18) and none with travoprost (from 17 reports). This may reflect lower usage of these drugs when compared with latanoprost.

The association between the hypoglycaemic agent rosiglitazone and macular oedema is also known and is described in the Avandia or Avandamet PI: *“Very rare postmarketing reports of new onset or worsening diabetic macular oedema with decreased visual acuity have been reported with rosiglitazone. Many of these patients reported concurrent peripheral oedema. In some cases the visual events resolved or improved following discontinuation of the drug. Prescribers should be alert to the possibility of macular oedema if patients report disturbances in visual acuity.”*

There is evidence that withdrawal of rosiglitazone is followed by resolution of macular oedema.^{2,3}

Macular oedema should be suspected with any loss of visual acuity not correctible by pin-hole refraction, and requires prompt specialist evaluation for confirmation of diagnosis and further measures as appropriate.

References:

1. Telander DG & Cessna CT. Macular edema, Irvine-Gass. <http://emedicine.medscape.com/article/1224224>
2. Ryan E, Han D, Ramsay R, Cantrill H, Bennett S, Dev S, Williams D. Diabetic macular edema associated with glitazone use. *Retina* 2006; 26: 562-570
3. Liazos E, Broadbent, D, Kumar N. Spontaneous resolution of diabetic macular oedema after discontinuation of thiazolidinediones. *Diabet Med* 2008; 5: 860-862.

2. Drug-induced lupus erythematosus: An emerging association with TNF inhibitors

Systemic lupus erythematosus (SLE) is considered drug-induced when, in relation to a suspect drug, both of the following apply:

- Idiopathic lupus features or antibodies are absent prior to treatment.
- Recovery occurs within one year of withdrawal of treatment.

Clinically, drug-induced lupus erythematosus (DILE) tends to be similar to, and less severe than, idiopathic SLE: arthralgia, myalgia and skin rash (not the classic malar rash) are prominent, renal or neurological involvement is rare. Management requires withdrawal of the suspect

drug, after which improvement begins, generally within weeks. Arthralgia/arthritis may call for treatment with an NSAID, and severe symptoms may require short courses of steroids.¹

Tumour necrosis factor (TNF) inhibitors (infliximab, adalimumab, etanercept) are powerful immunosuppressants approved for indications including rheumatoid and psoriatic arthritis, ankylosing spondylitis, and Crohn's disease. However, the deficiency of TNF caused by these drugs is known to predispose some patients to TNF inhibitor-induced SLE.

In clinical studies of rheumatoid arthritis, two of 3,000 adalimumab-treated patients developed new-onset lupus-like syndrome, remitting on withdrawal of adalimumab.² There are also case reports of DILE in association with adalimumab, etanercept and infliximab.^{3,4}

TNF inhibitors account for 35 of the 87 ADR reports of DILE or DILE-like symptoms received by the TGA since 2003 when the first of these drugs was PBS-listed:

TNF inhibitor	Total ADR reports	SLE-related reports	PBS usage*
Infliximab	269	21	25,440
Adalimumab	144	10	112,776
Etanercept	220	5	142,459

*PBS/RPBS scripts to Jan 09

If DILE is suspected, patients should have measurement of antinuclear antibodies (ANA) and double stranded DNA (dsDNA) antibodies. If a patient on TNF inhibitors develops symptoms suggestive of a lupus-like syndrome and is positive for antibodies against dsDNA, treatment should be discontinued, as recommended in TNF inhibitor PI documents.

References:

1. Khanna D, McMahon M, Furst D. Safety of tumour necrosis factor- α antagonists. *Drug Safety* 2004; 27: 307-324
2. Adalimumab (Humira) PI (version dated 28/10/08)
3. Costa M, Said N, Zimmermann B. Drug-induced lupus due to anti-tumor necrosis factor agents. *Seminars in Arthritis and Rheumatism* 2008; 37: 381-387
4. Mañosa M, Domènech E, Marín L, Olivé A, Zabana Y, Cabré E, Gassull M. Adalimumab-induced lupus erythematosus in Crohn's disease patients previously treated with infliximab. *Gut* 2008; 57: 559

3. Metformin, dehydration and lactic acidosis

Lactic acidosis is a rare but extremely serious metabolic complication of metformin usage. The association has featured in two previous Bulletins^{1,2} and a boxed warning on this serious reaction appears in PI documents for metformin-containing products:

Life threatening lactic acidosis can occur due to accumulation of metformin. The main risk factor is renal impairment; other risk factors include old age associated with reduced renal function and high doses of metformin (> 2g/day).

Metformin is contraindicated in acute conditions with the potential to compromise renal function, such as dehydration. This highlights the importance of educating patients about how to manage their diabetes, including their medications, when they become acutely unwell.

Since 1985, we have received 141 reports of lactic acidosis associated with metformin, 25 of which described a fatal outcome. Many of the reports describe a recent history of diarrhoea, vomiting or gastrointestinal infection prior to the development of acidosis.

A recent report describes a 61 year old female on metformin, gliclazide, frusemide, quinapril and candesartan/hydrochlorothiazide who continued to take her medications during a five day period of nausea, vomiting and diarrhoea, with no accompanying food intake. She was admitted to

hospital with lactic acidosis, acute renal failure and shock, and died three days later. Clearly, the ongoing use of diuretics whilst severely dehydrated and ongoing exposure to metformin lead to the development of fatal acute renal failure and lactic acidosis.

Another recent case involved a 68 year old female who presented with acute anuric renal failure and lactic acidosis after a four day history of nausea and vomiting. During this period she continued her medications, which included metformin, glibenclamide, lercanidipine, telmisartan/hydrochlorothiazide and insulin glargine. This patient recovered after emergency dialysis.

Patients should be educated about managing their diabetes and their medications, particularly metformin, in the context of acute illness. If a patient on metformin develops vomiting and/or diarrhoea, especially when coupled with poor oral intake, they should see their doctor and consideration should be given to temporarily ceasing metformin until a normal dietary intake can be tolerated. Consideration should also be given to temporarily withholding any concomitant diuretic therapy, as this will exacerbate acute renal impairment in a dehydrated patient.

References:

1. Fatal lactic acidosis with metformin. *Aust Adv Drug Reactions Bull* 1995; 14 (2).
2. Metformin and lactic acidosis — a reminder. *Aust Adv Drug Reactions Bull* 2001; 20 (1).

WHAT TO REPORT? (you do not need to be certain, just suspicious!)

ADRAC encourages the reporting of all **suspected** adverse reactions to medicines, including vaccines, OTC medicines, herbal, traditional or alternative remedies. ADRAC particularly requests reports of:

- *ALL suspected reactions to **new drugs** (see **drugs of current interest**, front page)
- *ALL suspected drug interactions
- *Suspected reactions causing
 - Death
 - Admission to hospital or prolongation of hospitalisation
 - Increased investigations or treatment
 - Birth defects

For blue cards

Reports of suspected adverse drug reactions are best made by using a prepaid reporting form ("blue card") which is available from the website: <http://www.tga.gov.au/adr/bluecard.pdf> or from the Adverse Drug Reactions Unit ☎ 02-6232-8744.

Reports can also be submitted electronically, by going to the TGA website <http://www.tga.gov.au> and clicking on "report problems" on the left, by fax: 02-6232-8392, or email: ADR.Reports@tga.gov.au

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The Bulletin is also available on the Internet at: <http://www.tga.gov.au/adr/aadrb.htm>

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