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Therapeutic Goods Administration

Medicines Safety Update

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In this issue

Pioglitazone risk–benefit review

A recently completed TGA review of pioglitazone (Actos and generics) has found that the drug has a favourable long-term risk–benefit balance. However, health professionals should weigh the known risks against the benefits of pioglitazone therapy and discuss these with patients.

The TGA's review was prompted by the identification of an increased risk of bladder cancer with long-term use of pioglitazone.[1,2] In light of ongoing safety concerns with rosiglitazone, another drug in the same class, the TGA conducted a full risk–benefit review of pioglitazone.

Pioglitazone is a thiazolidinedione (TZD) oral antidiabetic drug that has been registered in Australia since 2001.

To 1 September 2013, the TGA has received 212 adverse event reports involving pioglitazone. The most commonly reported events were cardiac failure, oedema and weight gain, but there were also 11 reports of bladder cancer. Before June 2011, no such cases had been identified.

Risk–benefit evaluation

The TGA review found that pioglitazone lowers HbA1c by a similar amount to that seen with other classes of oral antidiabetic drugs. Where pioglitazone was added to current therapy, HbA1c was lowered by 0.8–1.3% after 16 weeks.

In the PROspective pioglitAzone Clinical Trial In macroVascular Events (PROactive) study, risk was reduced from 13.6% over three years with placebo to 11.6% with pioglitazone, equating to a 16% reduction of the risk of a combined end point of death, myocardial infarction and stroke.[3]

In terms of risks, the TGA found the potential for bladder cancer increased by 40% (3 in 10 000 person-years) after two years of use. The risk appears to increase with duration of use.

Other identified risks associated with pioglitazone therapy included:

- the fracture risk for women is doubled (from 0.5 to 1.0 per 100 patient years) when weighed against non-TZD comparators
- compared to placebo there is an increased incidence of heart failure (11% vs 7.5%) and oedema (22% vs 13%), as well as dose-related weight gain.

Information for health professionals

The existing evidence shows pioglitazone has a favourable long-term risk–benefit balance. The absolute risks are likely to vary with age. Take these factors into account when considering treatment with pioglitazone.

REFERENCES

1. FDA Drug Safety Communication. Update to ongoing safety review of Actos (pioglitazone) and increased risk of bladder cancer. US Food and Drug Administration; 2011.
2. Therapeutic Goods Administration. Pioglitazone and risk of bladder cancer. Med Saf Update 2011;5.
3. Dormandy JA, Charbonnel B, Eckland DJ, Erdmann E, Massi-Benedetti M, Moules IK, et al. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study. Lancet 2005;366:1279-89.

Medicines Safety Update is the medicines safety bulletin of the Therapeutic Goods Administration (TGA)

TGA Health Safety Regulation

5-alpha reductase inhibitors and risk of high-grade prostate cancer

New warnings regarding the risk of high-grade prostate cancer have been added to the Product Information documents for the 5-alpha reductase inhibitors finasteride and dutasteride.

5-alpha reductase inhibitors (5ARIs) are a class of drug primarily used to treat symptomatic benign prostatic hyperplasia (BPH) in men.

The two 5ARIs registered in Australia are finasteride (Proscar [5 mg] and Propecia [1 mg]) and dutasteride (Avodart [0.5 mg] and Duodart [0.5 mg in combination with 0.4 mg tamsulosin]). Propecia is only indicated for the treatment of male pattern hair loss.

The TGA has reviewed a US Food and Drug Administration (FDA) assessment of two large trials that evaluated the use of finasteride or dutasteride daily versus placebo for the reduction in risk of prostate cancer.

The FDA found that, while the trials demonstrated an overall reduction in prostate cancer diagnoses due to a decreased incidence of lower risk forms of prostate cancer, both trials showed an increased incidence of high-grade prostate cancer.[1]

The TGA has since worked with the sponsors of finasteride and dutasteride to update the Australian Product Information (PI) documents to include a new precaution regarding the risk of patients developing high-grade prostate cancer.

Evidence of risk – dutasteride

The Reduction by Dutasteride of Prostate Cancer Events (REDUCE) trial was a four-year study of 8231 men aged 50–75, with a prior negative biopsy for prostate cancer and baseline prostate-specific antigen (PSA) between 2.5 and 10.0 ng/mL. The men received either placebo (n=4126) or dutasteride 0.5 mg (n=4105) once daily for a total of four years.

Prostate biopsies were performed at two years and four years, with 1517 men being diagnosed with prostate cancer. There was a higher incidence of Gleason 8–10 prostate cancer in the dutasteride group (n=29, 0.9%) compared to the placebo group (n=19, 0.6%). There was no increased incidence in Gleason 5–6 or 7–10 prostate cancer.

Evidence of risk – finasteride

The Prostate Cancer Prevention Trial was a seven-year randomised, double-blind, placebo-controlled trial that enrolled 18 882 men aged 55 years or older, with a normal digital rectal examination and a PSA ≤3.0 ng/mL. The men received either finasteride 5 mg or placebo daily. Patients were evaluated annually with PSA and digital rectal exams.

Biopsies were performed for elevated PSA or an abnormal digital rectal exam. The incidence of Gleason 8–10 prostate cancer was higher in men treated with finasteride than in those treated with placebo (1.8% vs 1.1% respectively).

Information for health professionals

5ARIs are not approved for the treatment of prostate cancer and no clinical benefit has yet been demonstrated in patients with prostate cancer treated with 5ARIs.

Before making a decision to prescribe a 5ARI, the known risks should be weighed against the benefits of 5ARI therapy and discussed with the patient.

Evaluations for prostate cancer, including digital rectal examination and serum PSA screening, should be performed on patients with BPH before initiating therapy with a 5ARI and periodically thereafter.

Serum PSA concentration is an important component of the screening process to detect prostate cancer. Use of 5ARIs causes a decrease in serum PSA levels by approximately 50%.

Guidance on how to monitor and interpret PSA levels in patients taking a 5ARI can be found in the PIs.

REFERENCE

1. FDA Drug Safety Communication. 5-alpha reductase inhibitors (5-ARIs) may increase the risk of a more serious form of prostate cancer. US Food and Drug Administration; 2011.

MEDICINES SAFETY UPDATE

Duloxetine and serotonin syndrome

While serotonin syndrome is commonly associated with concomitant use of two or more serotonergic drugs, it can occur with a single drug. The TGA has received 21 reports of serotonin syndrome in which duloxetine (Cymbalta and generics) is the sole suspected drug.

Duloxetine is a serotonin and noradrenaline reuptake inhibitor indicated for the treatment of major depressive disorder, generalised anxiety disorder and diabetic peripheral neuropathic pain.

Serotonin syndrome is a known risk associated with duloxetine therapy and is listed as a precaution in the Product Information (PI).

To reduce the risk of serotonin syndrome, duloxetine should be used with caution with other serotonergic drugs, including selective serotonin reuptake inhibitors, tricyclic antidepressants, opioids, tryptophan and St John's wort.

Serotonin syndrome is characterised by:

- altered mental state, e.g. confusion and agitation
- autonomic dysfunction, e.g. tachycardia and sweating
- neuromuscular excitation, e.g. hyperreflexia, tremor.

The TGA has previously published an article regarding serotonin syndrome, including information about diagnosis and treatment of this potentially life-threatening condition.[1]

Adverse event reports

To 1 September 2013, the TGA has received 31 reports of serotonin syndrome in patients taking duloxetine. Co-suspected drugs were present in 10 reports, including fentanyl (two reports), amitriptyline (two reports), oxycodone, alfentanil, fluoxetine, dexamphetamine, tramadol, mirtazapine and ziprasidone. Duloxetine was the sole suspected drug in the other 21 reports.

The dose of duloxetine used was most commonly 60 mg daily (16 reports), while a dose of 30 mg daily was noted in five reports, and 90 mg or 120 mg daily in two reports each. The time to onset of serotonin syndrome was not generally available, but was within two days of starting duloxetine in five reports.

In one report, a patient with back pain and depression commenced duloxetine 30 mg daily. After three weeks, the dose was increased to 60 mg daily and fentanyl patches were commenced. That same day the patient developed tremor, ataxia and sweating. Serotonin syndrome was diagnosed, requiring hospitalisation for further management.

Information for health professionals

Health professionals are reminded that, while serotonin syndrome most commonly occurs when serotonergic drugs are used in combination, it can be caused by a single drug.

Be cognisant of the risk of serotonin syndrome in patients being treated with duloxetine, even in the absence of a second serotonergic drug.

Duloxetine should be used with caution with other serotonergic drugs, and concomitant treatment with monoamine oxidase inhibitors (MAOIs), including moclobemide, is contraindicated. Duloxetine should not be used within 14 days of discontinuing treatment with an MAOI, and at least five days should be allowed after stopping duloxetine before starting an MAOI.

Similarly, as duloxetine is metabolised by both CYP1A2 and CYP2D6, it should not be used in combination with potent inhibitors of CYP1A2 (such as fluvoxamine).

Treatment with duloxetine should be discontinued if signs or symptoms of serotonin syndrome are identified.

Duloxetine should also not be used in patients with hepatic impairment, and use of a lower dose is recommended in patients with end-stage renal disease (creatinine clearance <30 mL/min).

Refer to the PI for further information regarding contraindications and precautions.

Please report adverse events involving duloxetine and serotonin syndrome to the TGA.

REFERENCE

1. Therapeutic Goods Administration. Serotonin syndrome: a reminder. Med Saf Update 2010;6.

MEDICINES SAFETY UPDATE

Minocycline and intracranial hypertension

A recent report has prompted the TGA to remind health professionals to consider the possibility of benign intracranial hypertension in patients being treated with minocycline if signs and symptoms consistent with that diagnosis are identified. Health professionals should advise patients being treated with minocycline of the signs of benign intracranial hypertension and consider recommending that they read the Consumer Medicine Information.

Minocycline belongs to the tetracycline group of antibiotics and is used to treat acne that is resistant to other antibiotics, as well as various other infections.

While rare, benign intracranial hypertension, also known as pseudotumour cerebri, is a known adverse event associated with tetracyclines, and minocycline treatment in particular.

Benign intracranial hypertension involves a persistent rise in cerebrospinal fluid pressure and is characterised by headache, nausea, vomiting and vision disturbances, including papilloedema with occasional sixth-nerve palsy.

From 1981 to 1 September 2013, the TGA received 43 reports of benign intracranial hypertension in people being treated with minocycline. In 39 of those reports, minocycline was the sole suspected drug. The most recent report was in November 2012. Prior to that, there had been no reports since 2006.

To reduce the risk of benign intracranial hypertension, concomitant treatment with tetracyclines and vitamin A or retinoids, such as isotretinoin, is contraindicated.

Visit the NPS MedicineWise website for further information about the risks associated with treatment of acne with oral antibiotics.[1]

REFERENCE

1. NPS MedicineWise. Oral antibiotics: an option in acne but consider the risks. 2013.

What to report? You don't need to be certain, just suspicious!

The TGA encourages the reporting of all **suspected** adverse reactions to medicines, including vaccines, over-the-counter medicines, and herbal, traditional or alternative remedies. We particularly request reports of:

- all suspected reactions to new medicines
- all suspected medicines interactions
- suspected reactions causing death, admission to hospital or prolongation of hospitalisation, increased investigations or treatment, or birth defects.

Reports may be submitted:

- **using the 'blue card'** available from the TGA website and with the October issue of *Australian Prescriber*
- **online** at www.tga.gov.au
- **by fax** to (02) 6232 8392
- **by email** to ADR.Reports@tga.gov.au

For more information about reporting, visit www.tga.gov.au or contact the TGA's Office of Product Review on 1800 044 114.

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