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Therapeutic Goods Administration

Medicines Safety Update

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In this issue

Anticholinergics and cognitive impairment

Health professionals should be aware that anticholinergic drugs may cause cognitive impairment in older patients when used long term.

Anticholinergics are a class of drug that blocks muscarinic actions of acetylcholine and has a wide range of effects. Drugs with definite anticholinergic properties include antiemetics (promethazine), anti-Parkinson agents (benztropine), gastrointestinal spasmolytics (propantheline), bladder spasmolytics (oxybutinin, tolterodine) and antidepressants (imipramine).[1]

Precautions for anticholinergics include using with caution in elderly patients, who are more sensitive to adverse events associated with these drugs. In particular, confusion can be precipitated or worsened. When used in elderly patients, anticholinergics should be initiated at a low dose and increased slowly to the lowest effective dose.

Evidence in the literature

Two recent long-term studies examined cognitive impairment in older patients.

One of those studies followed 13 004 patients aged 65 and older for two years. At the commencement of the study, 4% of patients were using a drug with definite anticholinergic properties.[2] These patients experienced a 0.33 point greater decline in mini-mental state examination (MMSE) compared to patients not taking anticholinergics.

The other study followed 1652 African American subjects over 70 years of age, for six years. At the commencement of this study, 11% of patients were using a drug with definite anticholinergic properties.[3] These patients experienced a 1.43 times increased risk of developing cognitive impairment compared to patients not taking a drug with definite anticholinergic properties. Also, the risk increased with the number of anticholinergics being used.

Information for health professionals

Health professionals are advised that anticholinergics should be used with caution in elderly patients due to a risk of cognitive impairment.

Consideration should be given to routine measurement of cognitive function in older patients taking drugs with anticholinergic properties for any indication, including non-nervous system indications.

It may be possible to lower the anticholinergic burden by replacing such drugs with alternatives that do not have anticholinergic properties.

REFERENCES

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2. Fox C, Richardson K, Maidment ID, Savva GM, Matthews FE, Smithard D, et al. Anticholinergic medication use and cognitive impairment in the older population: the medical research council cognitive function and ageing study. J Am Geriatr Soc 2011;59:1477-83.
3. Campbell NL, Boustani MA, Lane KA, Gao S, Hendrie H, Khan BA, et al. Use of anticholinergics and the risk of cognitive impairment in an African American population. Neurology 2010;75:152-9.

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

TGA Health Safety Regulation

System for Australian Recall Actions

The TGA recently launched the System for Australian Recall Actions (SARA) – an online, searchable database of recall actions for therapeutic goods undertaken in Australia.

Health professionals are encouraged to use SARA, along with other resources on the TGA website, such as the Database of Adverse Event Notifications and the alerts webpage, to access valuable information on medicine safety.

A recall action is a regulatory action taken for a therapeutic good supplied in Australia to resolve issues or deficiencies relating to safety, quality, efficacy or performance. Recall actions can be recalls, recalls for product correction or hazard alerts. Not all recall actions result in a product being removed from the market, for example hazard alerts may be issued in cases involving implantable devices, and corrections may be undertaken for products that have software issues.

SARA includes recall actions for a range of therapeutic goods including prescription medicines, over-the-counter medicines, complementary medicines, medical devices including in vitro diagnostic medical devices, and biologicals.

The database holds information on all recall actions that have been undertaken in Australia since 1 July 2012.

SARA has been launched as part of the TGA's commitment to improve transparency, as well as trust and confidence in the safety and quality of therapeutic goods and regulatory processes.

Changes to cough and cold medicines for use in children

With the arrival of winter, health professionals are reminded that cough and cold medicines should not be given to children under 6 years of age and only to children aged 6 to 11 years on the advice of a doctor, pharmacist or nurse practitioner.

These changes – and others relating to labelling and packaging – were made in 2012 as a result of a review of safety and efficacy for over-the-counter cough and cold medicines used in children (for further details visit www.tga.gov.au/industry/otc-notices-cough-cold-review-outcomes.htm).

The review found there was evidence that these medicines may cause harm to children, while the benefits of using them in children had not been proven. No changes were made to the scheduling of these medicines. Use of these medicines for a child under 6 years of age constitutes off-label use.

See also: Cranswick N. Cough and cold remedies for children. Aust Prescr 2013;36:e1.

Update - Progressive multifocal leukoencephalopathy (PML)

Following the publication of the article titled 'Progressive multifocal leukoencephalopathy – a rare but serious disease' (Medicines Safety Update Vol 4; No 1, 2013), the cases of PML in the TGA's database have been updated with new information which changes the final diagnosis for multiple cases. This update has occurred as part of the TGA's routine pharmacovigilance processes. The number of Australian reports of PML associated with immunomodulatory medicines, to 1 March 2013, is now:

- Rituximab – 12
- Natalizumab – 7
- Leflunomide – 1
- Alemtuzumab – 1.

Note: in many of these cases the patient had a history of chemotherapy and/or co-suspected immunosuppressant medicines such as nucleoside analogues, fingolimod, prednisolone and methotrexate.

The TGA's Database of Adverse Event Notifications has been updated to reflect the new diagnoses.

MEDICINES SAFETY UPDATE

Mitigating risks of dabigatran: right patient, right dose and careful clinical monitoring

A recent TGA safety review has found that careful patient and dose selection, along with careful clinical monitoring, are the keys to the safe use of dabigatran (Pradaxa).

Dabigatran is a direct thrombin inhibitor, indicated for the prevention of stroke in patients with non-valvular atrial fibrillation, and for the prevention of venous thromboembolism in patients undergoing total hip or knee arthroplasty.

Patient selection

As with all anticoagulants, bleeding is the major concern when using dabigatran. Age, renal function, comorbidities and concomitant drugs are the main determinants of bleeding risk. These risk factors are outlined in more detail in the table below. Health professionals should take these risk factors into consideration when selecting dabigatran for their patients.

Health professionals should carefully consider the risks and benefits of dabigatran compared with warfarin before switching patients who are well-controlled on warfarin. Additional information regarding patient selection and risk:benefit considerations for dabigatran can be found at www.nps.org.au.

Table
Factors known to increase haemorrhagic risk when taking dabigatran

Age	Being aged 75 years or over
Factors increasing dabigatran plasma levels	Moderate renal impairment (30–50 mL/min CrCL) Selected P-glycoprotein-inhibitor co-medication
Pharmacodynamic interactions	Acetylsalicylic acid (ASA; aspirin) Non-steroidal anti-inflammatory drugs (NSAIDs) Clopidogrel
Diseases/procedures with special haemorrhagic risks*	Congenital or acquired coagulation disorders Thrombocytopenia or functional platelet defects Active ulcerative gastrointestinal disease Recent gastrointestinal bleeding Recent biopsy or major trauma Recent intracranial haemorrhage Brain, spinal or ophthalmic surgery Bacterial endocarditis

* Prescribers should note that these are contraindications

Clinical studies have demonstrated a trend towards increased risk of myocardial infarction in patients taking dabigatran compared with warfarin, but the significance of this is uncertain. Health professionals should bear this in mind when making a decision to prescribe dabigatran.

Dose selection

Renal function testing should occur before commencement of dabigatran. Creatinine clearance should be estimated using the Cockcroft-Gault calculation.

The Cockcroft-Gault formula is:

$$\frac{1.23 \times (140 - \text{age[years]}) \times \text{weight[kg]} \ (\times 0.85 \text{ if female})}{\text{serum creatinine [micromol/L]}}$$

Health professionals are reminded that patients with a creatinine clearance of less than 30 mL/min should not be prescribed dabigatran. Patients with a creatinine clearance of 30–50 mL/min requiring dabigatran for stroke prevention should receive the reduced dose of 110 mg twice daily.

For patients with an increased haemorrhagic risk (see Table) the 110 mg twice-daily dose should be considered when prescribing dabigatran for the prevention of stroke in patients with non-valvular atrial fibrillation.

Clinical monitoring

- Clinical monitoring for early signs of bleeding is important in the management of patients taking dabigatran. Patients need to be informed of signs and symptoms to be aware of, and when to seek medical help.
- Renal function testing should be repeated at least annually, but more frequently in clinical situations where a decline in renal function may be expected, for example dehydration, shock or change in medications.
- Coagulation testing may be helpful in certain circumstances, such as in the event of bleeding, in emergency situations or a suspected overdose and in the perioperative setting. Refer to the Product Information (PI) for further information about coagulation testing. The clinical usefulness of routine testing as a risk stratification measure for dabigatran is unknown.

- There is currently no commercially available antidote. Surgical haemostasis and supportive therapies including the use of non-specific reversal agents are suggested when managing the bleeding patient. Clinical guidelines are available to assist health professionals manage the actively bleeding patient – see www.health.qld.gov.au/qhcss/mapsu/documents/dabigatran_info.pdf

New information about drug–drug interactions added to PI

The use of dronedarone has been added to the list of contraindications with dabigatran after a pharmacokinetic study showed a 2.4 fold increase in exposure to dabigatran when it is taken with dronedarone. More details regarding this interaction can be found in the Precautions section of the PI.

'Real world' experience

The 'real world experience' published to date indicates that dabigatran and warfarin share a similar overall bleeding risk.

The TGA continues to monitor reported adverse events for dabigatran and evaluate new information as it comes to hand.

New dabigatran contraindication

Dabigatran (Pradaxa) is now contraindicated in patients with prosthetic heart valves.

An interim analysis of the RE-ALIGN study – of dabigatran versus warfarin for thromboprophylaxis in patients with mechanical heart valves – found more frequent thromboembolic events and major bleeding in those patients taking dabigatran. Further information can be found in a US Food and Drug Administration safety announcement published on its website on 19 December 2012.

Patients with prosthetic valves taking dabigatran should be transitioned to warfarin. Suddenly stopping dabigatran is not recommended because of the risk of stroke. See the Product Information for guidance.

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.

For the latest safety information from the TGA, subscribe to the TGA Safety Information email list via the TGA website

For correspondence or further information about Medicines Safety Update, contact the TGA's Office of Product Review at ADR.Reports@tga.gov.au or 1800 044 114

Medicines Safety Update is written by staff from the Office of Product Review