RGH E-Bulletin Digest Number 84

The next in our 2015 series of continuing professional development activities is the RGH E-Bulletin Digest No. 84 – edited by Associate Professor Chris Alderman.

This CPD activity assesses your understanding of four recent RGH Pharmacy E-Bulletins, Volumes 58-8→58-11 (May/June 2015).

Learning Objectives:

After completing this activity, pharmacists should be able to:

- Describe issues related to the use of statins after haemorrhagic stroke
- Discuss the clinical features of neuroleptic malignant syndrome
- Describe features and management of angioedema associated with ACE Inhibitors
- Discuss aspects of the clinical pharmacology of thalidomide.

Information in this E-Bulletin Digest is derived from critical analysis of available evidence – individual clinical circumstances should be considered when making treatment decisions.

Competencies addressed by this activity include: 4.1, 4.2, 4.3, 6.1, 6.2, 7.1, 7.2.

Successful completion of this activity is demonstrated by answering seven of the eight multiple choice questions correctly.

Accreditation number: A1509AP0.
This activity has been accredited for 0.5 hours of Group 1 CPD (or 0.5 CPD credits) suitable for inclusion in an individual pharmacist's CPD plan which can be converted to 0.5 hours of Group 2 CPD (or 1 CPD credit) upon successful completion of relevant assessment activities.

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He is a past president of the Society of Hospital Pharmacists of Australia and achieved admission as a Fellow of SHPA in 1993. He is the author of over 80 peer-reviewed publications and several book chapters, and his research interests focus upon strategies to achieve safe and effective use of psychotropic drugs. He has a special interest in veteran psychiatry, in particular in the management of post-traumatic stress disorder.

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RGH Pharmacy E-Bulletin

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Editor: Assoc. Prof. Chris Alderman, University of South Australia – Director of Pharmacy, RGH

Statin use after intracerebral haemorrhage

Statins (HMG Co-A reductase inhibitors) are widely prescribed for primary and secondary prevention of ischaemic cardiac and cerebrovascular disease, with evidence from randomised controlled trials validating their benefit. The situation has not been as clear for haemorrhagic stroke prevention. Results of the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial published in 2006 showed that patients taking a statin who had a history of a haemorrhagic stroke had a higher incidence of subsequent haemorrhagic stroke. As survivors of intracerebral haemorrhage (ICH) commonly have co-morbid cardiovascular risk factors that would usually warrant statin therapy, the question of whether statins should be prescribed after an ICH often arises, with the answer not necessarily straightforward. The risks and the benefits of statin therapy post ICH must be weighed up and, often in clinical practice, if patients were on a statin at the time of ICH it is ceased. Consideration must be given to whether it is safe to restart the statin after the acute haemorrhagic stage, depending on the patient's general cardiovascular risks.

The location of the ICH is an important factor to consider when assessing the risk of another haemorrhagic stroke when restarting the statin. Lobar intracerebral haemorrhage (bleeding into the cerebrum) has a substantially higher rate of recurrence than does deep intracerebral haemorrhage. In one study, where a Markov decision model was used to evaluate the risks and benefit of statins, it was predicted that statin therapy would increase the baseline annual probability of recurrence of ICH in a patient who had experienced a lobar ICH from approximately 14% to approximately 22%, offsetting the cardiovascular benefit for both primary and secondary cardiovascular prevention. Lifelong avoidance of statins in this patient population is recommended.

Lobar ICH is usually caused by cerebral amyloid angiopathy (CAA), which presently doesn't have any established preventative treatment. Patients with CAA are at risk of both symptomatic ICH and accumulation of clinically silent microhaemorrhages which may precipitate larger ICH events and explain why the risk of lobar ICH is lifelong.

Deep ICH is predominantly caused by hypertensive vascular disease with the risk of recurrence able to be reduced with antihypertensive therapy.

Newer research in an observational study investigating the outcome of patients after ICH who received a statin while in hospital found that these people had better survival rates and were more likely to go home or to a rehabilitation centre than those who didn't get a statin. The trial also reported that the patients who were previously on a statin and had the drug discontinued while in hospital did worse than those who continued the statin. Other studies have also identified that patients on a statin at the time of ICH have better outcomes than those not on a statin. It may be that the timing of statin use is an important factor and that if the risk is smaller soon after ICH (as some trials have indicated) then statins may be potentially beneficial for a short duration post ICH but should then be stopped.

Conflicting trial results render it difficult to make definitive recommendations regarding long-term therapy, and while the Australian National Stroke Guidelines currently recommend avoiding statin use post ICH, as more research results become available, this may change.

Acknowledgment – This E-Bulletin is based on work by Annabel Calder, Senior Clinical Pharmacist, RGH

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Editor: Assoc. Prof. Chris Alderman, University of South Australia

Neuroleptic malignant syndrome update

The Neuroleptic Malignant Syndrome (NMS) is a rare but potentially lethal complication associated with the use of antipsychotic (neuroleptic) drugs. The incidence of NMS is estimated at 0.01%-0.02% of patients treated. The syndrome is also associated with the use of other drugs that block dopaminergic transmission in the CNS, including metoclopramide and domperidone. Abrupt withdrawal of dopaminergic drugs has also been implicated in precipitating NMS. Lithium and antidepressants have also been reported to cause NMS. The syndrome has an unpredictable occurrence but most often occurs within two weeks of starting an antipsychotic or of changing the dose.

Characteristics of NMS?
Four key elements have been described: fever, autonomic instability (significant variability in blood pressure and pulse rate), extrapyramidal symptoms (especially severe muscular rigidity, tremor) and altered mental state (confusion or delirium). NMS is often accompanied by a raised creatinine kinase (CK). Raised white blood cell count, impaired LFTs, renal deterioration, altered coagulation studies and ECG abnormalities have also been reported.

Implications for patient management
Patients with chronic psychotic illnesses such as schizophrenia are at risk of NMS as a result of their need for ongoing antipsychotic drug therapy to control debilitating symptoms. Other patient populations can also be affected as a consequence of the widespread use of haloperidol, olanzapine and risperidone to manage behavioural issues both within hospitals and community facilities.

Unfortunately, the presentation of NMS is highly variable, sometimes occurring within hours of the first dose of antipsychotic, or sometimes after some months of uneventful treatment. Management involves discontinuing the anti-psychotic, giving IV hydration, DVT prophylaxis and cooling the patient. Pharmacological treatments that have been suggested include benzodiazepines (e.g. lorazepam orally or parenterally) which may ameliorate symptoms of catatonia (rigidity, mutism and stupor). Dopaminergic drugs such as bromocriptine and amantadine may assist with rigidity and tremor. Dantrolene is reserved for severe NMS characterised by severe rigidity, catatonia or coma, temperature $\geq 40^{\circ}$, and heart rate $\geq$ 120bpm.

The current Australian Psychotropic Therapeutic Guidelines suggest that 30% of patients develop the NMS again on rechallenge. Psychiatrist input should be sought and if ongoing treatment with an antipsychotic is considered necessary: wait at least 5 days before the antipsychotic rechallenge or use an alternative antipsychotic (preferably one chemically unrelated to the antipsychotic which was initially implicated). Start treatment with low doses, increasing slowly and closely monitor the patient.

Early detection should be regarded as key to the management of NMS. While drugs have been used with variable success in the management of NMS, the most important benefits come from prompt discontinuation of antipsychotic drug therapy and the implementation of intensive and appropriate supportive care.

Acknowledgment – This E-Bulletin is based on work by Lenore Jansen, Senior Clinical Pharmacist, RGH

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Editor: Assoc. Prof. Chris Alderman, University of South Australia

Icatibant in ACE-Inhibitor-induced angioedema

Angioedema, a potentially life-threatening condition, can be induced by Angiotensin Converting Enzyme (ACE) inhibitors. In the United States, ACE-inhibitors are the leading cause of medication-induced angioedema as they are widely prescribed. The onset of angioedema can begin during the first week of therapy however it may not present until after a month or, in several reported cases, has occurred several years into therapy. The pathogenesis of angioedema occurring without urticaria is generally the same as when urticaria is present. In ACE-inhibitor-induced angioedema, this is caused by raised levels of bradykinin rather than histamine. ACE inhibitors inhibit the effects of ACE which in turn impacts both the renin-angiotensin-aldosterone (RAA) pathway and the degradation of bradykinin. Angiotensinogen (produced in liver) is converted by renin in the kidney to produce angiotensin I, which is then metabolised to angiotensin II in the lungs by ACE. Angiotensin II then acts as a vasoconstrictor through the stimulation of both angiotensin I and II receptors; it is also responsible for inactivating bradykinin (whereas ACE is involved in the degradation of bradykinin).

Patients with ACE-inhibitor-induced angioedema have been known to have elevated bradykinin activity. High levels of bradykinin in turn stimulate vasodilation and increases vascular permeability which allows plasma extravasation into sub-mucosal tissue causing angioedema. Bradykinin itself is a potent vasodilator with a very short half-life (17 seconds). As mentioned, bradykinin is metabolised (inactivated) by ACE, but it is also metabolised by a variety of other enzymes (neutral endopeptidease, aminopeptidase P, dipeptidyl peptidase IV, kininase I). Therefore, in patients on ACE-inhibitor therapy, the other enzymes are more involved with the degradation of bradykinin and thus in theory a deficiency of these enzymes would predispose the patients to developing angioedema. There are currently no laboratory or genetic tests available to identify individual patients who are at an increased risk of developing ACE-inhibitor-induced angioedema. There is currently no approved treatment for angioedema secondary to ACE-inhibitor use. Current management involves discontinuation of the ACE-inhibitor and supportive measures such as airway management (includes intubation and mechanical ventilation if required) if the mouth or throat is involved, and the use of antihistamines, glucocorticoids and adrenaline. The use of fresh frozen plasma is another option since plasma contains the enzyme ACE, and therefore the administration of plasma could decrease the high levels of bradykinin thus shortening the duration of the angioedema attack and reducing the need for intubation (if the patient is not already intubated).

A recent small randomized, multicentre, double-blind trial compared icatibant (a selective bradykinin B2 receptor antagonist) or the current off-label standard therapy (which consistsed of intravenous prednisolone and clemastine) for ACE-Inhibitor-induced angioedema. All 27 patients had complete resolution of angioedema; however the median time to complete resolution with the use of icatibant was 8.0 hours which is significantly shorter than 27.1 hours with the use of standard therapy ($p = 0.002$). Icatibant (Firazyr©) is a synthetic bradykinin B2 receptor antagonist – there are several case reports discussing its effectiveness for the treatment of ACE-inhibitor angioedema. Experience to date suggests that this agent is most likely effective if given in the first few hours of the angioedema attack when the swelling is increasing. The dose of 30 mg (adults) is given as a slow subcutaneous injection (due to a large volume involved, i.e. 3 mL). Most patients would require only one dose for symptomatic management, but if symptoms continue to worsen after 6 hours, a second dose may be given (the half-life of the ACE-inhibitor needs to be taken into consideration). There has recently been a case of ACE-inhibitor-induced angioedema (affecting the tongue) at the Repatriation General Hospital where the patient was treated with a single-dose of icatibant with complete resolution (avoidance of intubation and mechanical ventilation) after the trial of adrenaline, glucocorticoids and antihistamine. There are many factors such as the legalities of “off-label” use, availability and cost (approximately AU$3000 per dose) which need to be considered before the use of icatibant in patients with ACE-inhibitor-induced angioedema.

Acknowledgment – This E-Bulletin is based on work by Annabel Calder, Senior Clinical Pharmacist, RGH

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Thalidomide-induced peripheral neuropathy

The outcomes of patients with multiple myeloma (MM) have significantly improved with the introduction of regimens incorporating the oral immunomodulators thalidomide and lenalidomide. In combination with other agents, thalidomide and lenalidomide have increased response rates and prolonged survival before and after autologous haematopoietic stem cell transplantation (ASCT), and are routinely incorporated into the treatment of those with newly diagnosed MM and at relapse for those not eligible for ASCT.

At the time of diagnosis of MM, more than 50% of patients are found to be suffering peripheral neuropathy (PN) and this is thought to be a consequence of the condition itself. A complicating factor is thalidomide (and less frequently lenalidomide) can induce PN and lead to significant impairment in function and quality of life. Since the introduction of these agents, immunomodulator-induced PN has become the leading cause of MM-associated PN, over and above PN inherent with MM.

Common adverse effects of thalidomide are sedation (>75% of patients), PN, constipation and orthostatic hypotension (80-90% of patients and associated with autonomic neuropathy), cutaneous reactions, neutropenia (15-25%), peripheral oedema (15%) and deep venous thrombosis (DVT) (1-3% rising to > 10-12% when in combination with dexamethasone). The risk of PN with thalidomide increases with duration of treatment and cumulative dose however it may also occur early in the course of treatment. Thalidomide-induced PN is more common in the elderly, mainly affects the lower limbs and is characterised by stocking/glove distribution beginning in the fingers and toes and extending proximally. If detected early and not severe, thalidomide-induced PN may resolve within 3-4 weeks of ceasing therapy. More advanced PN improves more slowly and is reversible in only about 25% of patients, leading to permanent dysfunction in the remainder.

The most effective management of immunomodulator-induced PN is early detection and modification of therapy. It is recommended that all patients receive baseline neurotoxicity assessment prior to initiating thalidomide, then monthly for the first three months and periodically thereafter. In those who develop PN with thalidomide, an option may be to switch to lenalidomide, but lenalidomide is thought to be associated with a higher risk of DVT (when combined with dexamethasone) and neutropaenia.

Due to the improved response rates with thalidomide and lenalidomide, some patients may be unwilling to reveal the full extent of PN symptoms to their clinicians. Patients must receive clear advice to promptly report any symptoms indicative of PN, such as “pins and needles” sensations, numbness, tremor, muscle weakness and cramps, and pain and increased discomfort with certain sensations (especially in extremities). All members of the health care team need to be vigilant in asking about and detecting possible PN in order to ensure the full benefit of these agents are achieved.

Acknowledgment – This E-Bulletin is based on work by Joy Gailer, Senior Clinical Pharmacist, DATIS, RGH

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AusPharm CPD MCQs

Questions based on the above articles:

Successful completion of this activity is demonstrated by answering seven of the eight multiple choice questions correctly.

Select ONE alternative that best represents the correct answer to each of the following multiple choice questions

With respect to haemorrhagic stroke:

a) lobar intracerebral haemorrhage has a higher rate of recurrence than deep intracerebral haemorrhage
b) lobar intracerebral haemorrhage has a lower rate of recurrence than deep intracerebral haemorrhage
c) the rates for recurrence are not significantly different
d) recurrence of intracerebral haemorrhage is so rare the influence of the site cannot be quantified

Australian National Stroke Guidelines currently recommend:

a) avoiding statin use immediately after intracerebral haemorrhage
b) initiating statin use immediately after intracerebral haemorrhage
c) increasing statin dosage after intracerebral haemorrhage
d) decreasing statin dosage after intracerebral haemorrhage

Neuroleptic Malignant Syndrome (NMS) has been observed after:

a) introduction of atypical antipsychotics
b) treatment with metoclopramide or domperidone
c) abrupt withdrawal of dopaminergic drugs
d) all of the above

The current Australian Psychotropic Therapeutic Guidelines suggest that NMS will recur upon rechallenge in:

a) 0.3% of cases
b) 3% of cases
c) 30% of cases
d) nearly all cases

Current management of angioedema associated with ACE-inhibitors includes:

a) supportive measures such as airway management (intubation/mechanical ventilation if required)
b) antihistamines, steroids and adrenaline
c) fresh frozen plasma
d) all of the above

Icatibant is used for the treatment of angioedema associated with ACE-inhibitors. The mechanism of action is best described as:

a) selective bradykinin B2 receptor antagonism
b) non-selective bradykinin B2 receptor antagonism
c) selective bradykinin B1 receptor antagonism
d) non-selective bradykinin B1 receptor antagonism

The prevalence of thalidomide-induced peripheral oedema is estimated at approximately:

a) 1.5%
b) 2.5%
c) 15%
d) 25%

Relative to thalidomide, the risk of DVT associated with lenalidomide when combined with dexamethasone is thought to be:

a) higher
b) lower
c) lower, but only when combined with dexamethasone
d) none of the above