RGH E-Bulletin Digest Number 81

The next in our 2015 series of continuing professional development activities is the RGH E-Bulletin Digest No. 81 – edited by Associate Professor Chris Alderman.

This CPD activity assesses your understanding of four recent RGH Pharmacy E-Bulletins, Volumes 57-8→57-11 (February/March 2015).

Learning Objectives:

After completing this activity, pharmacists should be able to:

- Discuss the clinical pharmacology of patiromer and aclidinium
- Outline the key findings of the CitAD trial
- Describe new insights relating to the optimal duration of dual antiplatelet therapy after placement of coronary stents.

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.

This activity has been accredited for 0.5 hrs of Group 1 CPD (or 0.5 CPD credits) suitable for inclusion in an individual pharmacist's CPD plan which can be converted to 1 hr of Group 2 CPD (or 1 CPD credit) upon successful completion of relevant assessment activities.
Accreditation number: A1506AP0.

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He has over 25 years' experience as a specialist clinical pharmacist in psychiatry, and holds specialist qualifications in psychiatry and geriatric pharmacy with the US Board of Pharmaceutical Specialties.

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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A joint initiative of the Patient Services Section and the Drug and Therapeutics Information Service of the Pharmacy Department, Repatriation General Hospital, Daw Park, South Australia. The RGH Pharmacy E-Bulletin is distributed in electronic format on a weekly basis, and aims to present concise, factual information on issues of current interest in therapeutics, drug safety and cost-effective use of medications.
Editor: Assoc. Prof. Chris Alderman, University of South Australia – Director of Pharmacy, RGH

Patiromer – a new treatment for chronic hyperkalaemia

Hyperkalaemia is an electrolyte disturbance commonly seen amongst patients with chronic kidney disease (CKD) and those with heart failure. The reasons for high serum potassium concentrations in these patients include a combination of aldosterone resistance leading to decreased potassium excretion in the distal tubule, acidosis, and increased potassium intake. These patients also commonly require treatment with medications that can further increase serum potassium concentrations: these include Renin Angiotensin Aldosterone System (RAAS) inhibitors, spironolactone or eplerenone and potassium supplements.

Management of hyperkalaemia in patients with CKD and heart failure is often challenging. The strategies include dietary restriction, loop diuretic therapy, sodium bicarbonate to combat acidosis, and dose reduction or withdrawal of agents that retain/increase potassium. However, these treatment approaches have limited success.

Potassium biding resins, such as Resonium A® (sodium polystyrene sulfonate) and Calcium Resonium® (calcium polystyrene sulfonate) are commonly used in management of chronic hyperkalaemia. However, there is a lack of high quality evidence of effectiveness of these agents. Furthermore, they can cause serious or intolerable gastrointestinal adverse events ranging from gastric irritation to (rarely) ischaemic colitis, gastrointestinal obstruction, ulceration, perforation or necrosis.

Patiromer is a non-absorbable dry powder given as oral suspension when mixed in small amount of water. It predominantly binds to potassium in the colon. Patiromer exchanges potassium for calcium. Weir et al conducted a study of the effectiveness of this agent for patients with CKD who were taking RAAS inhibitors and whose serum potassium concentrations were in the range of 5.1 - 6.5 mmol per litre. All eligible patients participated in a single blind treatment phase and received patiromer (initially 4.2 g or 8.4 g twice a week) for 4 weeks. A total of 76% of the patients achieved normal potassium levels at the end of this phase; 107 of these patients entered an 8-week placebo controlled, randomised withdrawal phase, in which the primary outcome was the median change in potassium level after 4 weeks. 60% of patients who were switched to placebo had recurrent hyperkalaemia, as compared to 15% of those who continued patiromer.

The most common adverse effects observed in the trial were constipation (11%) and hypokalaemia (3%). However, it is noteworthy that the study duration was not longer than 12 weeks. It may be that the adverse events such as constipation and hypokalaemia would be more bothersome if the treatment is continued for a longer term.

Despite the evidence that patiromer appears promising as a new treatment of hyperkalaemia, the decrease in potassium with patiromer therapy appears to be gradual. It is uncertain how effective patiromer will be in an acute situation.

Patiromer has not yet been approved by the Food and Drug Administration for the treatment of hyperkalaemia and is currently unavailable in Australia.

Acknowledgment – This E-Bulletin is based on work by Wassana Sorich, Clinical Pharmacy Coordinator, RGH

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Aclidinium

Aclidinium is the newest addition to the range of available medicines for the treatment of airway disease. This drug is a competitive muscarinic receptor antagonist (anticholinergic). It is has been recently approved for subsidised supply through the Australian Pharmaceutical Benefits Scheme (PBS) - approved as of March 2014 and indicated as a long-term maintenance bronchodilator for the treatment of moderate to severe Chronic Obstructive Pulmonary Disease (COPD) in adult patients.

Early phase 2 trials showed advantages of twice daily dosing with aclidinium relative to once daily tiotropium. The mean baseline FEV1 for patients in the trial was 1.5L. On day 15, pre-dose FEV1 had increased by 143 mL with aclidinium compared to 107 mL with tiotropium, and decreased by 43 mL with placebo.

A larger randomised trial of 561 patients compared aclidinium to placebo twice daily for 12 weeks. At the start of this trial the mean FEV1 was 1.36 L, with the primary outcomes focusing on the change in FEV1 measured just before the morning dose, at trough. At 12 weeks trough FEV1 had increased by 62 mL and 99 mL using doses of 200 microgram and 400 microgram twice daily respectively.

A final trial compared 200 microgram and 400 microgram twice daily with placebo over 24 weeks in 828 smokers and ex-smokers. At 24 weeks the increase in FEV1 was 99 mL with 200 microgram and 128 mL with 400 microgram of aclidinium twice daily. This trial also assessed the peak FEV1 with both strengths of aclidinium and found an increase of 185 mL (200 microgram twice daily) and 209 mL (400 microgram twice daily) respectively.

Data is still lacking with regards to the side effects associated with aclidinium relative to the main comparator, tiotropium. Given the anticholinergic pharmacological mechanism, side effects such as dry mouth are expected. Contraindications are expected to be similar - i.e. narrow angle glaucoma, bladder outflow obstruction, or unstable cardiac disease. Trials involving patients using aclidinium saw in some cases a prolongation of the QTc interval on ECG, and hence patients with cardiac complications should use aclidinium with caution.

Aclidinium is rapidly absorbed from the lungs achieving maximal plasma concentration within 15 minutes of inhalation in patients with COPD. Given it is highly protein bound drug, it has a relatively low volume of distribution. It undergoes extensive hydrolysis and has a low absolute bioavailability, predominantly being renally cleared (65%) with no dose reductions required in renally impaired patients.

In summary, the research to date comparing aclidinium twice daily it appears to have revealed modest advantages over its comparator tiotropium, primarily reflected in improvements in trough FEV1 and peaks FEV1 improvements. However, studies were too small and short to show that one drug was convincingly better than the other.

Acknowledgment – This E-Bulletin is based on work by Fares Al-Sarawi, Pharmacy Intern, RGH

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Antiplatelet therapy beyond 12 months after drug-eluting stent

Percutaneous coronary intervention with either a bare metal stent or drug-eluting stent is a mainstay of treatment for myocardial infarction (MI). Drug-eluting stents have a reduced rate of stenosis when compared to bare metal stents, but a stent may re-thrombose beyond a year after insertion. This re-thrombosis is relatively rare event, but can be associated with MI and may be fatal. Current practice to protect against stent re-thrombosis involves the use of dual antiplatelet therapy (DEPT) that includes both aspirin and a thienopyridine medication such as clopidogrel or prasugrel.

The optimal duration of DEPT treatment after placement of a drug–eluting stent is still in question. According to American, European, Australian and New Zealand cardiac societies, the current recommendations are for 6-12 months of DEPT treatment. A recently published study in the New England Journal of Medicine is the first adequately powered, randomised, controlled trial that assesses benefit and risk beyond of this approach extended beyond one year after the placement of the stent. The trial compared one year of DEPT, followed by aspirin alone to an endpoint of 30 months against 30 months of DEPT after the placement of a drug-eluting stent.

Stent thrombosis, major cardiovascular/cerebrovascular events and MI were all significantly reduced when 30 months of DEPT were used relative to the shorter period of 12 months of DEPT (0.4% vs 1.4% for stent thrombosis, 4.3% vs 5.9% for cumulative incidence of major cardiovascular/cerebrovascular events and 2.1% vs 4.1% for MI). However, the rates of moderate to severe bleeding were increased with the longer duration of DEPT (2.5% vs 1.6%). All events were rare, and the numbers need to treat were large.

It is worth noting all patients were excluded from extending from one year of DEPT to 30 months if they suffered adverse cardiovascular or cerebrovascular events, or stent thrombosis in the first year after the placement of the stent. It is precisely these patients that tend to be considered at high risk and therefore who may benefit the most from extended DEPT. Patients were also excluded from extended DEPT if they had suffered moderate to severe bleeding in the first year of treatment.

The rates for death associated with cardiac causes, vascular causes and stroke were found to be similar in both groups. Death from any cause was greater in the 30 months DEPT group when compared to those receiving 12 months DEPT (2% vs 1.5%). Although this has partly been attributed to an imbalance in the prevalence of pre-existing cancer in the tow groups, it is nevertheless of concern that there was no demonstrable overall mortality benefit.

It appears that extending DEPT beyond a period of year may be beneficial for some patients, but that this approach does come at the expense of an apparently increased bleeding risk. The age range of the patients included in the study was from 51.8yrs to 72 years, so questions do remain about the overall risk: benefit relationship in the older population of people undergoing stenting.

In summary, it appears that on the basis of evidence currently to hand, decision regarding the nature and duration of treatment with DEPT for longer than a period 12 months after the placement of a drug-eluting stent must be individualised.

Acknowledgment – This E-Bulletin is based on work by Nicky Gordon, Senior Pharmacist, RGH

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CitAD (Citalopram on Agitation in Alzheimer Disease) Trial

Behavioural and psychological symptoms of dementia (BPSD) occur in the majority of patients with AD. Agitation is common, can be persistent, and is difficult to treat and costly to society. First line treatment is non-pharmacological with an emphasis on supporting families and carers, but instances may arise where pharmacological therapy is sought. To date there is very little evidence to support the use of any pharmacological agent in BPSD, but atypical antipsychotics, antidepressants, benzodiazepines, mood stabilisers, cholinesterase inhibitors and memantine may be seen in clinical practice. These medications are not without adverse effects. Atypical antipsychotics have been demonstrated to increase mortality and cerebrovascular adverse effects in patients with dementia and each is associated with increased falls risk.

Citalopram, an SSRI, has been suggested as alternative to atypical antipsychotics for agitation and aggression in dementia. The primary objective of the Citalopram on Agitation in Alzheimer Disease (CitAD) Randomised Clinical Trial (RCT) was undertaken to evaluate the efficacy of citalopram for agitation in patients with Alzheimer's Disease (AD), but without major depression. The study was a randomised, placebo-controlled, double blind, parallel group trial that enrolled 186 patients with probable AD (MMSE scores ranged from 5-28) and clinically significant agitation (physician determined) from eight academic centres in the United States and Canada, from August 2009 to January 2013. Exclusion criteria included those who had a major depressive episode or psychosis requiring antipsychotic treatment. Prolonged QT interval on ECG was later added an exclusion criteria. Medications for the treatment of AD including cholinesterase inhibitors and memantine at stable doses within the month preceding randomisation were permitted. Participants were randomised to receive psychosocial intervention and either citalopram (n=94) or placebo (n=92) for a period of nine weeks. Doses of citalopram commenced at 10 mg per day with a planned titration to 30 mg per day over three weeks, based on tolerability and response.

The primary objective of the study was to assess the efficacy of citalopram for agitation in patients with AD but without major depression, with this achieved through the assessments using the Neurobehavioural Rating Scale (NBRS-A) and the modified AD Cooperative-Study Clinical Global Impression of Change (mADCS-CGIC). Results of the study demonstrated that participants who received citalopram showed significant improvement compared with those receiving placebo: (1) NBRS-A estimated treatment difference at week 9 (citalopram minus placebo) was −0.93 (95% CI, −1.80 to −0.06), p=0.04 and (2) mADCS-CGIC showed 40% of citalopram participants having moderate or marked improvement from baseline symptoms compared with 26% of placebo recipients, with estimated treatment effect (odds ratio [OR] of being at or better than a given CGIC category) of 2.13 (95% CI, 1.23-3.69), p = 0.01.

In terms of safety and adherence, anorexia, diarrhoea and fever were common in the citalopram group, and weight loss and insomnia in the placebo group. Those in the citalopram group also displayed greater cognitive deficits through a reduction in MMSE scores (clinical significance not known), more frequent falls, upper respiratory tract infections and gait impairment. Citalopram was also associated with a greater increase in QTc interval compared with placebo, with four participants showing QTc prolongation on ECG. Incidence of hyponatraemia was similar between groups. It is interesting to note that at 9 weeks, 78% of the sample were receiving 30mg of citalopram compared to 15% receiving 20mg. All participants also received extensive psychosocial intervention.

This study suggests that citalopram compared with placebo may reduce agitation and caregiver distress in patients with probable AD and agitation (without major depression) but given the majority of patients that responded were treated with citalopram 30 mg per day, the cognitive and cardiac adverse effects may limit its use in clinical practice. Citalopram may be a treatment to consider for patients with AD and agitation where the use of antipsychotics is not advisable.

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

FOR FURTHER INFORMATION – CONTACT PHARMACY DEPARTMENT ON 82751763 or email: chris.alderman@health.sa.gov.au.

References used in the preparation of the relevant E-Bulletins:

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www.australianprescriber.com/magazine/37/5/172/79/new-drugs/1065/aclidinium-bromide-for-chronic-obstructive-pulmonary-disease

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Sink KM, Holden KF, Yaffe K. Pharmacological Treatment of Neuropsychiatric Symptoms of Dementia A Review of the Evidence. JAMA 2005;293(5)596-608

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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

Reasons for high serum potassium for people with chronic kidney disease include:

a) aldosterone resistance
b) metabolic acidosis
c) increased potassium intake
d) all of the above

In a recent study examining utility of patiromer for chronic hyperkalaemia, the most common side effect encountered was:

a) diarrhoea
b) constipation
c) hypercalcaemia
d) hyponatraemia

Aclidinium is a recently released medicine for the treatment of airway disease. The proposed mechanism of action is as a:

a) competitive muscarinic receptor antagonist
b) non-competitive muscarinic receptor antagonist
c) competitive muscarinic receptor agonist
d) non-competitive muscarinic receptor antagonist

Which of the following statements is true with respect to aclidinium?

a) main route of elimination is renal clearance, dose reduction is needed for those with renal impairment
b) main route of elimination is renal clearance, dose reduction not needed for those with renal impairment
c) main route of elimination is hepatic clearance, dose reduction is needed for those with hepatic impairment
d) none of these statements are true

Dual Antiplatelet Therapy (DEPT) usually includes a regimen incorporating

a) aspirin and warfarin
b) aspirin and clopidogrel
c) clopidogrel and rivaroxaban
d) clopidogrel and warfarin

Recent research has demonstrated that extending the duration of dual antiplatelet therapy after placement of a drug-eluting stent to 30 months instead of a shorter period:

a) decreased stent restenosis
b) decreased deaths from MI
c) increased the incidence of moderate-major bleeding
d) all of the above

The results of the Citalopram on Agitation in Alzheimer Disease (CitAD) trial suggest that this approach:

a) reduced agitation for people with Alzheimer's disease, but only when there was comorbid depression
b) reduced agitation for people with Alzheimer's disease, even when there was no comorbid depression
c) did not reduce agitation for people with Alzheimer's disease, but helped comorbid depression
d) did not reduce agitation for people with Alzheimer's disease, and worsened comorbid depression

Adverse effects most frequently observed in the active treatment arm of the CitAD trial were:

a) headache, urinary tract infection and hyponatraemia
b) constipation, nausea and tremor
c) anorexia, diarrhoea and fever
d) drowsiness, myalgia and asthaenia