RGH E-Bulletin Digest Number 79

The next in our 2015 series of continuing professional development activities is the RGH E-Bulletin Digest No. 79 – edited by Associate Professor Chris Alderman.

This CPD activity assesses your understanding of four recent RGH Pharmacy E-Bulletins, Volumes 56-11→ 57-2 (November/December 2014).

Learning Objectives:

After completing this activity, pharmacists should be able to:

- Outline novel drug treatment options that have been assessed for the management of resistant schizophrenia
- Discuss the clinical features of anaphylaxis
- Discuss the clinical pharmacology or praculopride
- Discuss the potential clinical applications of neprilysin inhibitors.

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: A1504AP0.

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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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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

Novel alternatives for treatment-resistant schizophrenia

Schizophrenia is a complex brain disorder characterised by abnormal social behaviour and a distorted perception of reality. Many patients continue to be symptomatic despite receiving recommended treatment, including clozapine (which is generally reserved for refractory schizophrenia). A number of unconventional therapies have been studied for treatment-resistant schizophrenia, including adjunct allopurinol, minocycline, omega-3 fatty acids and other therapies.

Allopurinol
Allopurinol inhibits purine degradation and enhances adenosinergic activity. This produces effects similar to dopamine antagonists, a mechanism for antipsychotic action in schizophrenia. There have been multiple studies and case reports investigating the addition of allopurinol (300 mg daily or twice daily) to antipsychotics for the treatment of refractory schizophrenia. In particular, a double-blind, placebo-controlled, crossover trial involving 22 patients explored the addition of allopurinol (300 mg twice daily) to an antipsychotic for poorly responsive schizophrenia or schizoaffective disorder. Allopurinol was found to be well tolerated and produced significant improvement in Positive and Negative Syndrome Scale (PANSS) scores. Another double-blind, placebo-controlled trial involving 46 patients over eight weeks assessed the addition of allopurinol (300 mg daily) or placebo to haloperidol (15 mg daily). The researchers concluded that allopurinol may be an effective adjuvant agent in chronic schizophrenia. A review article addressing available literature concluded that allopurinol in doses of 300 mg once or twice daily may improve psychotic symptoms, especially refractory positive symptoms. However, the authors suggest the need for larger, randomized clinical trials for more conclusive data.

Minocycline
Studies evaluating the use of minocycline in neurological disorders suggest benefit associated with anti-inflammatory and neuro-protective properties. While a study is currently being undertaken to investigate the role of minocycline in treatment resistant schizophrenia, the current place in therapy of minocycline is unclear.

Omega-3 fatty acids
Omega-3 fatty acids may have a role in the management of a range of psychiatric conditions. This may involve various biological mechanisms, including alterations in dopaminergic function, which is of particular interest in schizophrenia. A double-blind, placebo-controlled trial assessing 87 patients concluded that the augmentation of neuroleptics with ethyl eicosapentaenoic acid (EPA) 3000 mg daily, did not result in significant changes in symptoms of schizophrenia.

Others
Other ‘unconventional’ therapies for treatment resistant schizophrenia include the complementary medicine ginkgo biloba, and also ondansetron. It has been proposed that Ginkgo biloba (which may act as a free radical scavenger), may be effective in schizophrenia. Serotonin (5-HT3) receptors are involved in the pathogenesis of schizophrenia: ondansetron, which is a serotonin (5-HT3) antagonist, has been studied in schizophrenia. However, the role of either one of these agents in refractory schizophrenia remains unclear.

Clozapine remains the treatment of choice in refractory schizophrenia. While several alternatives to clozapine have been studied, larger, randomized trials are required to determine the magnitude of benefit from alternative agents in treatment resistant schizophrenia.

Acknowledgment – This E-Bulletin is based on work by Nashwa Masnoon, Pharmacy Intern, RGH

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Don't miss anaphylaxis

Allergy and risk of anaphylaxis has become an increasing health burden. Common causes of anaphylaxis include exposure to foods, insect stings and medications. Anaphylaxis requires immediate recognition, early use of adrenaline and other life support measures. Optimal management involves the systematic use of strategies to avoid exposure to the causative factors whenever possible.

Anaphylaxis is the most severe form of allergic reaction, requiring urgent medical treatment. The Australasian Society of Clinical Immunology and Allergy (ASCIA) defines anaphylaxis as:

> "Any acute onset illness with typical skin features (urticarial rash or erythema/flushing, and/or angioedema), PLUS involvement of respiratory and/or cardiovascular and/or persistent severe gastrointestinal symptoms.
>
> OR
>
> Any acute onset of hypotension or bronchospasm or upper airway obstruction where anaphylaxis is considered possible, even if typical skin features are not present."

Factors that increase the risks of fatal anaphylaxis include a history of asthma, initial misdiagnosis of the condition, and delayed or absent administration of adrenaline. The differential diagnosis of anaphylaxis includes acute generalized hives, acute asthma, syncope, panic attack, aspiration of foreign body, and cardiovascular or neurologic events.

It is likely anaphylaxis is underdiagnosed. Hypotension or shock is not necessarily required for anaphylaxis to be present. Skin and mucosal symptoms and signs are absent or unrecognised in 10-20% of episodes. Urticaria, erythema and angioedema may be transient, subtle and easily overlooked. Of reported episodes of anaphylaxis, 80-90% involve the skin, 70% the respiratory system, 45% the gastrointestinal tract, 45% the cardiovascular system (CVS) and 15% the central nervous system.

Adrenaline is the most important first-line drug in the treatment of anaphylaxis and is safe when administered correctly. It is common for food-related reactions to cause difficulty breathing, creating trouble deciding whether to use the protocol for anaphylaxis or for asthma. This can lead to delayed or inappropriate treatment that may contribute to fatalities. Bronchodilators do not prevent or relieve upper airway obstruction, hypotension or shock.

As part of the rapid primary assessment and initial treatment of acute asthma, the Australian Asthma Handbook (AAH) recommends identification and management of anaphylaxis. Clinicians should "consider the possibility of anaphylaxis for all patients, not just those with the most severe acute asthma." It is recommended to "give adrenaline if anaphylaxis is suspected or cannot be excluded". Importantly the AAH further states that "systemic adrenaline is indicated for patients with anaphylaxis and angioedema, but current evidence does not support its routine use in the management of acute asthma in the absence of anaphylaxis."

Further anaphylaxis information for health professionals is available from ASCIA. http://www.allergy.org.au/health-professionals/anaphylaxis-resources

Acknowledgment – This E-Bulletin is based on work by Brian Simmons, DATIS, RGH

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

Prucalopride for chronic constipation

Constipation can be a commonly experienced chronic condition. Recommendations for management include addressing reversible factors, lifestyle and dietary changes and the use of laxative agents such as bulking or osmotic agents, stool softeners and stimulants. Prucalopride is a selective 5-HT4 receptor agonist which has pro-kinetic effects, stimulating gastrointestinal motility via activation of intestinal 5-HT4 receptors. It has been marketed for use in the treatment of chronic constipation where treatment with laxatives has not been effective.

Three randomised controlled trials included patients with chronic constipation who had ≤ 2 bowel movements per week. Patients were randomised to receive prucalopride 2 mg or 4 mg daily or placebo over the 12 week study duration. The primary endpoint of the studies was the number of patients who reported an average of ≥3 spontaneous and complete bowel motions each week. The results from these trials showed a reported improvement in between 20-30% of patients receiving prucalopride, compared with 10-12% for placebo. There was no significant difference in the results achieved with the 2 mg and 4 mg doses.

An integrated analysis of three randomised, placebo-controlled trials of prucalopride in patients with chronic constipation found that prucalopride improved bowel function and colonic transit time. For the 98 patients treated with 2 mg prucalopride, colonic transit time was reduced by 12.0 hours (95% CI -18.9, -5.1) and for the 70 patients receiving 4 mg, colonic transit time was reduced by 13.9 hours (95% CI -20.5, -7.4). The placebo patients (n = 112) had a reported increase in colonic transit time by 0.5 hours (95% CI -4.5, 5.5).

Adverse effects reported most commonly with prucalopride include headache, dizziness and gastrointestinal disturbances such as nausea, abdominal pain and diarrhoea. These adverse effects were often transient and more common at the start of therapy. Potential adverse cardiovascular effects have been investigated due to the withdrawal from the market of cisapride and tegaserod (less specific 5-HT4 agonists). Results from studies conducted in healthy volunteers looking at patients taking up to 20 mg of prucalopride found no significant difference in QTc interval compared with placebo. The product information for prucalopride advises caution for use in patients prescribed other medication known to prolong the QTc interval.

For patients aged 18-65 years, 2 mg once daily is the recommended dose compared with 1 mg once daily initially for those >65 years and those with renal or hepatic impairment. Prucalopride has a high oral bioavailability with the majority of the dose excreted unchanged in the urine. It is rapidly absorbed with peak plasma concentrations after 2-3 hours and is extensively distributed with low protein binding. The elimination half-life of prucalopride is approximately 24 hours. Contraindications for use include patients with intestinal obstruction, perforation or ileus or active inflammatory bowel disease.

Prucalopride may be a treatment option in patients with chronic constipation; however therapy should be reviewed if there has been no evidence of effect after 4 weeks. The majority of trial participants were female, resulting in its approval for use only in women in a number of locations. However, its pharmacodynamic effects appear similar in men and women.

Prucalopride is approved by the Therapeutics Goods Administration for use in Australia but is currently not available for subsidised supply through the Australian Pharmaceutical Benefits Scheme (PBS).

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

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

Neprilysin inhibition in heart failure

Over the last decade, few changes have been made to heart failure guidelines and efforts towards the development of new agents with significant benefits have been unsuccessful.

Neprilysin, an enzyme that breaks down vasoactive peptides such as ANP, BNP, CNP, bradykinin and substance P, is a novel drug target of recent interest. The first drug developed to target Neprilysin was candoxatril. Candoxatril increases levels of ANP and natriuresis, but failed to show benefits in heart failure patients. This is likely a result of decreased breakdown of angiotensin II, and subsequent vasoconstriction, which counteracts the vasodilatory effects of ANP. In order to overcome this effect, omapratilat was developed as a combined ACEI and neutral endopeptidase inhibitor. After initial success in trials, a larger trial showed no benefit over enalapril, and also a high rate of angioedema. This was attributed to the combined action of omapratilat on ACE and neprilysin inhibition, resulting in high circulating levels of bradykinin.

Recent attention has been given to a new agent currently known as LCZ696. This is a combination of sacubitril, a neprilysin inhibitor, and valsartan. The investigators proposed that by using an ARB rather than an ACEI, high bradykinin levels could be avoided. The PARADIGM study included patients with NYHA class 2-4 heart failure with reduced ejection fraction (<40%), and assigned them to receive either LCZ696 200 mg twice daily or enalapril 10 mg twice daily. The primary outcome was a composite of cardiovascular mortality or hospitalization for heart failure. In March 2014 the study was stopped early due to clear superiority of LCZ696 over enalapril. Relative to Enalapril, the use of LCZ696 resulted in a 20% reduction in primary endpoint and cardiovascular death, and a 16% reduction in all-cause mortality. The incidence of hypotension was greater in the group assigned to LCZ696, however elevations in creatinine and potassium were lower; as was the incidence of cough. The rates of angioedema were low and not significantly different between groups.

The promising results from this study have been met with some criticism. Firstly, patients who were intolerant to either drug during a run in period were excluded from the trial. This may reduce the applicability of the results to clinical practice. There has also been debate around whether the target enalapril dose should have been 20 mg twice daily, which was the target dose in the CONSENSUS trial. However, the target dose in CONSENSUS was only reached in 22% of patients and the mean dose attained was 18.4 mg, which is comparable to the mean dose attained in PARADIGM (18.9 mg). Additionally, the SOLVD trial aimed for a lower target dose of 10 mg twice a day. Another criticism was that the target dose of LCZ696 was 200 mg twice daily, which delivers the maximum allowed daily dose of valsartan of 320 mg. This raised the question of whether the benefits of LCZ696 over enalapril were the result of non-equivalence in dosing between the ACEI and ARB. Another issue raised was whether the trial should have compared an ARB to LCZ696, rather than an ACEI to LCZ696, to improve comparability between the treatment groups.

Further studies will help to determine the role of LCZ696 in heart failure treatment, one of which is the PARAGON HF study. This is currently underway and will aim to determine the benefits of LCZ696 in patients with heart failure with preserved ejection fraction.

Acknowledgment – This E-Bulletin is based on work by Heather Forbes, Senior Clinical Pharmacist, 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

Which of the following drugs appears to offer potential benefit for the management of treatment-resistant schizophrenia?

a) colchicine
b) indomethacin
c) probenicid
d) allopurinol

Which of the following agents remains widely regarded as the agent of choice for drug-resistant schizophrenia?

a) clozapine
b) olanzapine
c) haloperidol
d) pimozide

With respect to anaphylaxis, skin & mucosal symptoms/signs are absent or unrecognised in approximately what proportion of cases?

a) 0.5 – 1%
b) 5 – 10%
c) 10 – 20%
d) up to 50%

Approximately what proportion of anaphylaxis cases include central nervous system involvement?

a) 1.5%
b) 15%
c) 3%
d) 30%

Which of the following best describes the mechanism of action of prucalopride?

a) selective 5-HT4 receptor agonism
b) selective 5-HT3 receptor agonism
c) selective 5-HT3 receptor antagonism
d) selective 5-HT4 receptor antagonism

For patients aged 18-65 years, what is the usual recommended dose of prucalopride?

a) 1 mg once daily
b) 2 mg once daily
c) 1 mg twice daily
d) 2 mg twice daily

Inhibitors of neprilysin have been studied as promising treatments for:

a) congestive heart failure
b) acute coronary syndrome
c) unstable angina
d) long QT syndrome

Recent research has assessed the effects of sacubitril (a neprilysin inhibitor) in combination with valsartan. The rationale for the combination with an angiotensin receptor blocker was based upon the objective of:

a) limiting higher levels of bradykinin
b) achieving higher levels of bradykinin
c) limiting higher levels of beta natriuretic peptide
d) achieving higher levels of beta natriuretic peptide