RGH E-Bulletin Digest Number 78

The next in our 2015 series of continuing professional development activities is the RGH E-Bulletin Digest No. 78 – edited by Associate Professor Chris Alderman.

This CPD activity assesses your understanding of four recent RGH Pharmacy E-Bulletins, Volumes 56-7→56-10 (October/November 2014).

Learning Objectives:

After completing this activity, pharmacists should be able to:

- Describe aspects of the recently updated Australian Asthma Handbook
- Discuss the clinical pharmacology of tolvaptan
- List some of the medications than can cause neuropathyList important adverse effects of the cholinesterase 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: A1503AP0.

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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

Neuropathy and drugs

Neuropathy is a general term that has been used in relation to pathology involving damage or disease affecting nerves. There are many causes, including systemic illnesses such as diabetes, nutritional deficits, trauma, alcoholism, or infection. A neuropathy affecting a single nerve is referred to as a mononeuropathy, and if multiple nerves are affected the term polyneuropathy is applied. Various manifestations of neuropathy can be associated with a range of symptoms – for example, sensory neuropathy may be associated with numbness, compromised proprioception, and decreased perception of temperature or pain. Motor neuropathy can impair balance and coordination, whereas autonomic neuropathy may affect continence, or regulation of blood pressure or heart rate.

Many types of peripheral neuropathy are amenable to therapeutic intervention with pharmacotherapy. For example, neuropathic pain may be responsive interventions based upon the use of agents such as amitriptyline, duloxetine, carbamazepine, pregabalin and other agents. Some features of autonomic neuropathy may be responsive to medications – examples include the use of pro-kinetic agents in the context of gastrointestinal dysmotility, or the use of agents to assist with BP regulation and to reduce the impact of orthostasis.

Although medications may be helpful in addressing the symptoms of neuropathy, it is also important to recognise that drugs can also cause or exacerbate neuropathies through a range of mechanisms. Drugs that have been implicated as causes of iatrogenic neuropathy are listed below:

Drugs used in oncology:
Cytarabine, carboplatin, cisplatin, etoposide, docetaxol, etoposide, paclitaxel, thalidomide, vincristine.

Anti-infective agents:
Dapsone, ethambutol and isoniazid (antitubercular agents), gentamicin (particularly affecting nerves in the ear), metronidazole and nitrofurantoin (especially when used for extended treatment courses) and medications such as antiretroviral agents used in the management if HIV infection.

Drugs used for rheumatology, or immunosuppression:
Gold derivatives, colchicine, indomethacin, TNF-alpha blockers such as infliximab or etanacept, tacrolimus (and possibly other agents used in the context of solid organ transplantation).

Miscellaneous agents:
Amiodarone and perhexiline (especially in the context of toxicity), nitrous oxide (chronic use/misuse), phenytoin, pyridoxine (in excess), statins, disulfiram, metformin (associated with vitamin B12 deficiency).

It also important to acknowledge that there is potential for confounding by associated diagnosis – for example, although metformin may be associated with vitamin B12 deficiency and peripheral neuropathy, it is equally possible that long-term sub-optimal control of diabetes may also contribute to peripheral neuropathy.

Evidence for the concurrent prescribing of agents intended to protect against drug-induced neuropathy has been equivocal. Even so, agents such as vitamin E are sometimes used with this intention.

Acknowledgment – This E-Bulletin is based on work by Chris Alderman, Director of Teaching Training & Research, SA Pharmacy, RGH

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

Contemporary asthma: combination fluticasone/vilanterol

In the contemporary approach to asthma management, where does the combination product based upon the drugs fluticasone furoate/vilanterol fit?

The Australian Asthma Handbook (AAH, asthmahandbook.org.au) provides evidence-based and consensus guidance on the diagnosis and management of asthma. It includes a number of clinically important changes since the previous guidance; these were summarised in a previously published E-bulletin from early September 2014.

For adults with asthma requiring preventer therapy the AAH recommends low dose inhaled corticosteroids (ICS) as first line treatment. This is based upon clinical trials demonstrating that most people gain good control of asthma symptoms with low dose ICS. In adults, a low dose ICS is defined as a daily dose of beclomethasone 100 - 200 mcg, budesonide 200 - 400 mcg, ciclesonide 80 - 160 mcg or fluticasone proprionate (FP) 100 - 200 mcg. These dose ranges can be facilitated through the prescription of the lower strength inhaler of each ICS (e.g. beclomethasone 50 mcg pMDI or Autohaler, budesonide 100 and 200 mcg Turbuhaler (daily doses of budesonide < 400 mcg can be given once a day), ciclesonide 80 or 160 mcg pMDI and FP 50 mcg pMDI or 100 mcg Accuhaler.

The AAH states if a patient gains good control of asthma symptoms by using a low dose of ICS, then this person would be categorised as having mild asthma. If the patient requires combination therapy with a low dose ICS plus long acting beta-agonist (LABA) to achieve good control, they are considered to have moderate asthma, and if a high dose ICS is required (with a LABA) for good control the patient has severe asthma.

Fluticasone furoate (FF) is the ICS in combination with vilanterol (a LABA) in the recently TGA approved product (Breo®). FF/vilanterol is available in 100/25 mcg and 200/25 mcg combination products, administered as a once a day inhalation via a dry powder inhaler (Ellipta®). During clinical trials, the most commonly reported adverse reactions associated with these products were headache and nasopharyngitis. Co-administration with strong inhibitors of CYP3A4 (e.g. clarithromycin, ketoconazole, ritonavir) increases systemic exposure to both FF and vilanterol and may result in increased potential for adverse effects.

It is important to note that 100 mcg/day of fluticasone furoate is regarded as equivalent to fluticasone propionate 250 mcg twice a day (500 mcg/day) – that is to say, FF is five times the potency of FP. Hence, the lowest strength of FF/vilanterol is above the threshold defining a low dose ICS. Based on the AAH guidance, FF/vilanterol is only suitable for those patients categorised as having moderate to severe asthma, and the current available strengths do not allow for back titration to the equivalent of a low dose ICS. For this reason, in accordance with the latest Australian guidance, the FF/vilanterol product would not be regarded as ideal for use as first line preventer therapy for most adults who are affected by asthma.

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

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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

Tolvaptan for the treatment of hyponatremia

Tolvaptan is a selective vasopressin V 2 receptor antagonist and is the first vaptan agent to be approved by the Therapeutic Goods Administration for use in Australia in July 2014.

Hyponatremia is a common electrolyte abnormality and is manifested by a reduction in serum sodium levels with symptoms ranging from nausea to coma and seizures. The reference range for normal serum sodium normal values is between 135 and 145 mmol/l. Mild to moderate hyponatremia has been defined as serum sodium levels between 120 to 135mmol/L and severe hyponatraemia as 120mmol/L or less. Hyponatremia is not a primary diagnosis and is commonly associated with the Syndrome of Inappropriate Antidiuretic Hormone (SIADH) or other syndromes such as excessive water intake during exercise, heart failure, cirrhosis of the liver, renal failure and nephritic syndrome. The use of certain drugs can also cause hyponatremia, especially diuretics, selective serotonin reuptake inhibitors, and noradrenaline re-uptake inhibitors, and carbamazepine.

Tolvaptan is a vasopressin antagonist which has affinity and selectivity for the V2 receptor, primarily located in the kidney. Antagonism at the V2 receptor causes a decrease in the number of aquaporin-2 channels in the renal collecting tubules, which results in decreased water reabsorption, a net increase in free water excretion (aquaresis) and an increase in serum sodium concentration. This aquaresis is not associated with an increased excretion of sodium or potassium ions.

Tolvaptan is primarily metabolised in the liver almost entirely by CYP 34A and it is a substrate and inhibitor of p-glycoprotein. Terminal elimination half-life is around 8 hours and a steady state serum concentration is reached after the first dose. Current prescribing information states tolvaptan should be avoided in patients with underlying liver disease. Adverse effects include thirst, dry mouth, constipation, polyuria and pollakiuria and hyperglycaemia.

Tolvaptan has been evaluated in 2 clinical trials. SALT 1 and 2- Study of Ascending Levels of Tolvaptan in Hyponatremia and the EVEREST programme –Efficacy of Vasopressin Antagonists in Heart Failure Outcome Study with Tolvaptan - which was designed to evaluate the long term effects of tolvaptan therapy and included all patients in the SALT trials. 424 patients were enrolled in SALT 1 and 2 with a diagnosis of euvolaemic or hypervolemic hyponatremia resulting from heart failure, SIADH, liver cirrhosis and other causes. They were treated for 30 days with tolvaptan or placebo and followed for 7 days after withdrawal. Treatment was initiated in hospital. Patients were randomly assigned to receive tolvaptan at 15 mg per day or placebo. Initial mean sodium concentration was 129 mmol/L. The primary end point for both studies was the change in serum sodium from baseline to day 4 and baseline to day 30 in patients with a serum sodium less than 135 mmol/L. In comparison to placebo tolvaptan was associated with a statistically significant increase in serum sodium ($p < 0.0001$).

Initiation of treatment with tolvaptan should occur in hospitals to ensure appropriate therapeutic monitoring and should not be used to raise serum sodium levels in an emergency. The starting dose is 15 mg once a day and can be titrated up to 60 mg per day with or without food. Tolvaptan is contraindicated with strong CYP 3A4 inhibitors and it may be less effective when used with potent CYP3A4 inducers such as rifampicin, phenytoin, carbamazepine and St John's Wort.

Tolvaptan has been approved in Australia for the treatment of clinically significant hypervolemic or euvolaemic hyponatremia including those patients with heart failure and SIADH. It is also approved for those patients with less marked hyponatremia which is symptomatic and has resisted correction with fluid restriction. Tolvaptan is available in Australia as a 15 mg tablet but its current cost may prove prohibitive for wide spread use.

Acknowledgment – This E-Bulletin is based on work by Margie Harlow, Drug Distribution Coordinator, RGH

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

Preventer therapy for asthma in children

Considerations regarding regular preventer treatment for children after the initial diagnosis of asthma are based on age and patterns of symptoms, according to the recently published Australian Asthma Handbook (asthmahandbook.org.au). A stepped approach to adjusting asthma medication is suggested in which all children will need a reliever for use 'as needed' (short acting beta2 agonist, SABA); some children will need a regular preventer such as a low dose inhaled corticosteroid (ICS), leukotriene receptor antagonist (montelukast), or a cromone; and very few children will require an increased dose of ICS or combination such as low dose ICS plus montelukast or ICS/long acting beta2 agonist (LABA) combination. The majority of children requiring preventers will be well controlled on low dose ICS or montelukast.

Summary of initial preventer therapy for children

Age	Pattern of Symptoms	Management (in addition to as needed SABA)
0-12 months	Intermittent asthma or viral-induced wheeze	Regular preventer NOT recommended.
	Multiple-trigger wheeze	Refer to specialist.
1-2 years	Intermittent asthma or viral-induced wheeze	Regular preventer NOT recommended.
	Persistent asthma or multiple-trigger wheeze	Consider trial with cromone. Review in 2-4 weeks. Consider trial with low dose ICS if symptoms are disrupting sleep, play, feeding. Review in 4 weeks.
2-5 years	Infrequent intermittent asthma or viral-induced wheeze	Regular preventer NOT recommended.
	Frequent intermittent or mild persistent asthma or episodic wheeze with frequent symptoms, or multiple-trigger wheeze	Consider montelukast 4 mg once daily. Review in 2-4 weeks. If no response, consider regular low dose ICS. Review in 4 weeks.
	Moderate to severe persistent asthma or moderate to severe multiple-trigger wheeze	Consider regular low dose ICS. Review in 4 weeks.
6 years	Frequent intermittent asthma	Consider montelukast 5 mg once daily, review in 2-4 weeks. Cromone is an alternative.
	Mild persistent asthma	Consider montelukast 5 mg once daily, review in 2-4 weeks. If no response, consider regular low dose ICS. Cromone is an alternative.
	Moderate to severe persistent asthma	Consider regular low dose ICS. Review in 4 weeks.

ICS = inhaled corticosteroid, SABA = short acting $beta_2$ agonist Adapted from the www.asthmahandbook.org.au

Evidence for the efficacy of LABAs in children is limited (esp. for children < five years of age. ICS/ LABA combinations are not indicated for children ≤ 5 years of age. A Cochrane Systematic Review assessing the addition of LABAs to ICS for persistent asthma in children concluded that although there was very small improvement in lung function it was probably not clinically important, and there was no significant reduction in flare-ups. In studies comparing the addition of LABAs with an increased dose of ICS, there was short-term improvement in lung function with LABAs, but again no significant difference in flare-ups. Current guidelines recommend the following options for children with asthma who are not well controlled on low dose ICS (after checking adherence and inhaler technique is correct, and diagnosis confirmed:

- increased dose of ICS;
- combined low dose ICS/LABA therapy; or
- the addition of montelukast to the low dose ICS (recognising this may not be PBS subsidised).

Acknowledgment – This E-Bulletin is based on work by Rose Allin, Senior Pharmacist, DATIS, 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:

Australian Asthma Handbook (asthmahandbook.org.au)

Schrier RW et all for the SALT Investigators .Tolvaptan , a selective oral vasopressin V2 receptor antagonist ,for hyponatremia N Engl J Med 2006 ;355:2099-2112

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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 antibiotics is a potential cause of drug-induced neuropathy?

a) metronidazole
b) trimethoprim
c) amoxycillin
d) erythromycin

Which of the following cardiovascular agents is a potential cause of drug-induced neuropathy?

a) ramipril
b) isosorbide mononitrate
c) perhexiline
d) atenolol

The Australian Asthma Handbook defines low-dose inhaled corticosteroid therapy as equivalent to what daily dose of inhaled fluticasone?

a) 50 - 100 mcg
b) 100 - 200 mcg
c) 200 - 400 mcg
d) none of the above

A dose of 100 mcg of fluticasone furoate is regarded as equivalent to what dose of fluticasone propionate?

a) 50 mcg
b) 100 mcg
c) 250 mcg
d) 500 mcg

Tolvaptan is used for the treatment of which electrolyte disturbance?

a) hyponatraemia
b) hypokalaemia
c) hyperkalaemia
d) hypercalcaemia

Tolvaptan exerts therapeutic effects by acting as:

a) a selective vasopressin V 1 receptor agonist
b) a selective vasopressin V 2 receptor agonist
c) a selective vasopressin V 1 receptor antagonist
d) a selective vasopressin V 2 receptor antagonist

According to the most recent edition of the Australian Asthma Handbook, a 4-year-old child with infrequent intermittent asthma or viral-induced wheeze:

a) would not usually require treatment with inhaled corticosteroid
b) should be treated with low dose inhaled corticosteroid
c) should be treated with high dose inhaled corticosteroid
d) should be treated with a long-acting beta agonist

According to the most recent edition of the Australian Asthma Handbook, a 6-year-old child with frequent intermittent asthma might be considered as a suitable candidate for treatment with montelukast at a daily dose of:

a) 5 mg
b) 10 mg
c) 20 mg
d) 50 mg