RGH E-Bulletin Digest Number 71

The next in our 2014 series of continuing professional development activities is the RGH E-Bulletin Digest No. 71 – edited by Associate Professor Chris Alderman.

This CPD activity assesses your understanding of four recent RGH Pharmacy E-Bulletins, Volumes 54-1→54-4 (March/April 2014).

Learning Objectives:

After completing this activity, pharmacists should be able to:

- Discuss the various elements of the recently produced evidence-based Cancer Council Australia clinical practice guidelines for the management of cancer pain in adults
- Identify causes of drug-induced and other forms of parotitis
- Outline the clinical pharmacology of pimavanserin and droxidopa.

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

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

This activity has been accredited for 0.5 hr of Group One CPD (0.5 CPD Credits) that may be converted to 1 Group Two CPD Credit upon successful completion of the corresponding assessment for inclusion on an individual pharmacist's CPD Record. **Accreditation number: A1407AP0**.

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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

Cancer pain management guidelines

The Cancer Council Australia has recently produced evidence-based clinical practice guidelines for the management of cancer pain in adults, available online at
http://wiki.cancer.org.au/australia/Guidelines:Cancer_pain_management

These are intended to guide community prescribers in the rational management of pain, and as such, have advice on assessment and non-pharmacological management of pain. The interactive sections address a range of areas:

- Patient–centred care
- Screening
- Assessment
- Patient communication & self-management
- Pharmacological management
- Non-pharmacological management
- Practice improvement & quality control
- Resources
- Opioid formulations
- References

The section on pharmacological management guides prescribers through choice of opioid and other therapies; it has subheadings including:

- Regular analgesia
- Renal impairment
- Additional analgesics for breakthrough pain
- Adjuvants
- Anti-cancer treatment
- Interventional therapy
- Preventing, monitoring, managing opioid adverse effects
- Assessment/management of opioid toxicity/adverse effects
- Opioid rotation
- Preventing misuse of opioids
- Assessing capacity to drive a vehicle
- Review and referral

There are 43 recommendations in this section, ranging from use of paracetamol and NSAIDS for mild pain, to advice on regular and breakthrough dosing of opioids and recommendations for conversion from other opioids to a transdermal patch, plus suggestions for adjuvant analgesia. Clinical footnotes are included, explaining to the prescriber the background behind the recommendations and the level of consensus or evidence.

A reference list of equivalent potencies or conversions between opioids is not provided, however the user is directed to the EviQ Opioid Conversion Calculator provided by the NSW Cancer Institute:
www.eviq.org.au/opioidcalculator.aspx

Use of this calculator requires the user to first register on the EviQ website with a password and then log in; it is free of charge.

Anti-cancer treatment in this context refers to use of bisphosphonates, denosumab or radiotherapy in patients with pain from bone metastases. The section dealing with interventional therapy mentions nerve blocks and intrathecal administration of drugs. The adverse effects which prescribers are advised to consider include constipation, nausea, drowsiness, pruritis, myoclonus, respiratory depression and CNS toxicity. Advice is given on management of delirium, and this takes into account the life expectancy of a cancer patient. Opioid rotation is advised in situations of intolerable side effects or inadequate analgesia despite adequate doses of opioids, e.g. when patients develop hyperalgesia. In unfamiliar situations, prescribers are always advised to seek specialist advice: "If the prescribing clinician or other staff are unfamiliar with any agent under consideration, consult a specialist pain medicine physician, palliative medicine physician, clinical pharmacist or clinical pharmacologist who are familiar with the agent".

Acknowledgment – This E-Bulletin is based on work by Jenny Casanova, Senior Clinical Pharmacist, RGH.

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

RGH Pharmacy E-Bulletin

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

Drugs and parotitis

Parotitis is defined as inflammation of the parotid glands, and can be unilateral or bilateral. Symptoms range from mild to severe, and include pain, erythema, swelling, dehydration and fever. Common causes of parotitis include bacterial (usually staphylococcus aureus) and viral (e.g. mumps, HIV) infections, the presence of salivary stones within the parotid duct system and also autoimmune disorders. Although drug-induced parotitis is a rare adverse reaction and case reports are limited, a number of agents have been implicated. Therefore, if bacterial and viral etiologies have been ruled out and the absence of stones has been confirmed by ultrasound, a thorough review of the medication received prior to development of the gland swelling is warranted.

The drugs most commonly reported to cause parotitis are the iodine- containing drugs such as contrast media. This type of parotitis is often referred to as “iodide-mumps” and occurs particularly when media are used for patients with renal impairment.

Many antipsychotics have been reported to contribute to parotitis, by various mechanisms. Use of phenothiazine antipsychotics commonly results in a dry mouth secondary to the anticholinergic effects of these agents. Hyposalivation can predispose patients to infection in the parotid glands, especially when patients have poor dental hygiene. Clozapine, which unlike many other antipsychotics is associated with hypersalivation, has been reported to be involved in parotitis in a number of cases. It has been suggested that the sustained hypersalivation may lead to inflammation within the salivary glands with subsequent stone formation. This reaction has also been seen as a result of exposure to other agents that cause hypersalivation, such as organophosphate insecticides.

Since the introduction of highly active antiretroviral therapy (HAART), a decrease in the overall incidence of oral manifestations of HIV infection has been reported. The incidence of HIV associated salivary gland-disease has however, increased significantly and this rise has been attributed to the use of HAART. Protease-inhibitor based HAART has been shown to decrease salivary gland flow rates and to significantly increase salivary gland size, thereby increasing the risk of parotid gland enlargement.

A number of other agents have been associated with parotitis, however, the mechanisms by which these agents may cause parotitis is currently unknown. Several reports have implicated antineoplastic agents, particularly L-asparaginase, but also cytarabine, as causative agents for parotitis. Angiotensin Converting Enzyme (ACE) inhibitors such as ramipril, enalapril and captopril, and calcium channel blockers including nifedipine have also been reported to cause parotid swelling. Several antibiotics have been linked to parotitis; cefuroxime, doxycycline, minocycline and nitrofurantoin are some of the antibiotics reported in case studies.

Many cases of drug induced-parotitis are bilateral, most likely due to the systemic nature of the reaction. However, unilateral cases have also been reported and these may be secondary to duct obstruction. In most cases, the parotitis will resolve on withdrawal of the offending drug.

Acknowledgment – This E-Bulletin is based on work by Dr Ivanka Hendrix, Senior Clinical Pharmacist, RGH.

FOR FURTHER INFORMATION – CONTACT PHARMACY DEPARTMENT ON 82751763 or email: chris.alderman@health.sa.gov.au. Information in this E-Bulletin is derived from critical analysis of available evidence – individual clinical circumstances should be considered when making treatment decisions. You are welcome to forward this E-bulletin by email to others you might feel would be interested, or to print the E-Bulletin for wider distribution. Reproduction of this material is permissible for purposes of individual study or research.

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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

Pimavanserin & treatment of psychosis in Parkinson's disease

Psychotic symptoms, especially visual hallucinations and paranoid delusions, are said to affect up to 40% of patients with Parkinson's disease at some stage. Management approaches for these symptoms should include consideration of other co-morbid states such as delirium (especially that associated with infections), reduction of dopaminergic agents and the use of antipsychotic agents. The atypical antipsychotic agents most commonly used in the treatment of Parkinson's Disease Psychosis (PDP) are clozapine and quetiapine. Quetiapine is usually the treatment of first choice as clozapine requires strict monitoring protocols. Risperidone and olanzapine are not as well tolerated and may worsen PD compared to quetiapine and clozapine.

It has been suggested that because lower plasma levels of clozapine (and hence lower doses than those used for schizophrenia) are sufficient to treat PDP, this is not associated with sufficient blockade of limbic dopamine D2 receptors to achieve antipsychotic effect purely through dopamine receptor blockade. A more likely mechanism of action is via the 5HT2A receptor blockade rather than simply via dopamine D2 receptor blockade. In Parkinson's disease, the binding of 5HT2A receptors is increased in the neocortex, and in addition, visual hallucinations are associated with increased numbers of 5HT2A receptors in visual processing areas.

Pimavanserin is a selective 5HT2A inverse agonist, and in clinical research has been found to be well tolerated, reducing PDP without an association with worsening of motor symptoms or sedation. An inverse agonist binds to the same receptor as an agonist, but induces an opposite response. In a randomised, placebo-controlled trial of 199 patients aged 40 years and older, subjects were randomly allocated to receive pimavanserin 40 mg per day or matched placebo over a 6 week period. The primary analysis included 90 patients on placebo and 95 patients receiving pimavanserin.

Assessment using the Scale for the Assessment of Positive Symptoms adapted for Parkinson's Disease (SAPS-PD) at day 43 showed a significant improvement in delusions and hallucinations for pimavanserin group compared to those receiving placebo (-5.79 for Pimavanserin and -2.73 for placebo, p=0.001). Ten patients in the pimavanserin group discontinued treatment because of an adverse event, compared to four in the placebo group. Six discontinuations in the pimavanserin group were associated with psychosis. Overall there were three deaths (one sudden death in the placebo group, and two in the pimavanserin group from sepsis/septic shock); but the cause of death was not ascribed to study drug in any of these cases. There was a small but clear increase in QT interval with pimavanserin treatment, and this change was not detected in the placebo group. There were no cardiac adverse events noted for any subjects in the study. The most common adverse events observed were urinary tract infections and falls.

The limitation to this study is that there is no safety data and efficacy collected beyond the six week endpoint, and further studies are required to confirm this. Pimavanserin is currently being assessed as a potential treatment for PDP in a Phase III clinical trial.

Acknowledgment – This E-Bulletin is based on work by Irene Heng, Senior Clinical Pharmacist, RGH.

FOR FURTHER INFORMATION – CONTACT PHARMACY DEPARTMENT ON 82751763 or email: chris.alderman@health.sa.gov.au. Information in this E-Bulletin is derived from critical analysis of available evidence – individual clinical circumstances should be considered when making treatment decisions.

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

Droxidopa

Droxidopa (marketed as Northera®) has been recently approved by the US Food and Drug Administration for the treatment of orthostatic dizziness or light-headedness in patients with symptomatic neurogenic orthostatic hypotension caused by primary autonomic failure (associated with conditions such as Parkinson's disease, multiple system atrophy, and pure autonomic failure), as well as dopamine beta-hydroxylase deficiency, and non-diabetic autonomic neuropathy. Neurogenic orthostatic hypotension (NOH) is a rare, chronic but debilitating cause of orthostatic drop in blood pressure that occurs upon standing, and is associated with Parkinson's disease. Symptoms of NOH include dizziness, light-headedness, blurred vision, fatigue, and fainting upon standing, and may severely limit the patient's daily activities.

In clinical trials, patients treated with droxidopa reported a decrease in dizziness, light-headedness, and feeling faint, compared to those taking placebo. However, it should be noted that clinical effectiveness extending beyond a treatment period longer than two weeks has not yet been demonstrated, clinical assessment of benefit should be through if treatment is to extend beyond this duration.

While the exact mechanism of action of droxidopa is unknown, it is a synthetic amino acid analogue that is metabolized to norepinephrine. After metabolism and systemically distribution it is thought to exert its pharmacological effects via norepinephrine and not through the parent compound or other metabolites.

The metabolism of droxidopa is mediated by the catecholamine pathway via catechol-O-methyltransferase (COMT) and DOPA decarboxylase, and not through the CYP450 system. This may prove to be beneficial for patients taking multiple medications, reducing the potential for drug interactions. In Phase 3 clinical trials, patients concomitantly taking carbidopa, a peripheral dopa-decarboxylase inhibitor, had reduced clearance of droxidopa, and subsequent 100% increase in exposure to droxidopa (reflected by measurement of the Area Under the Curve). However, this reduced clearance and increased AUC was not associated with increased incidence of adverse effects.

The starting dose of droxidopa is 100 mg orally, three times daily and may be titrated up to a maximum dose of 600 mg three times a day. Although the drug is renally excreted, no dose adjustments are needed for people with mild to moderate renal impairment, and no recommendations are made concerning patients with severe renal disease. The capsules should be swallowed whole and may be taken with or without food.

In clinical trials, the most common adverse effects included headache, dizziness, nausea, hypertension, and fatigue. Droxidopa may also cause supine hypertension and exacerbate underlying existing ischemic heart disease, arrhythmias, and congestive heart failure. To reduce the incidence of supine hypertension, patients are encouraged to elevate the head of the bed and take the last dose at least three hours before bedtime. Also, patient's supine blood pressure should be monitored at baseline, during treatment, and when increasing the patient's dose.

Interestingly, the formulation for this medication currently also contains FD+C Yellow No. 5 (tartrazine), which may cause allergic type reactions in susceptible people. The incidence of this sensitivity is relatively low in the general population, but occurs more commonly in those who have aspirin hypersensitivity.

Droxidopa is not yet approved for use in Australia.

Acknowledgment – This E-Bulletin is based on work by Jennifer Whitesides, Pharm D Candidate, Mercer University and international clerkship candidate, Pharmacy Department, RGH.

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

http://wiki.cancer.org.au/australia/Guidelines:Cancer_pain_management

A review and assessment of drug-induced parotitis. Krista G Brooks and Dennis F Thompson, the annals of pharmacotherapy, 2012 DECEMBER, VOLUME 46, PAGE 1688-99

Drug-induced parotitis. DF Thompson, Journal of Clinical Pharmacy and Therapeutics (1993) 18, 255-258

Cummings J et al. Pimavanserin for patients with Parkinson's disease psychosis: a randomised, placebo-controlled phase 3 trial. Lancet 2014; 383: 533 – 40

FDA Clears Droxidopa for Neurogenic Orthostatic Hypotension
http://www.medscape.com/viewarticle/820786

AusPharm CPD MCQs

Questions based on the above articles:

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

The Cancer Council Australia has recently produced evidence-based clinical practice guidelines for the management of cancer pain in adults, available online. Issues addressed include:

a) disposal of unwanted narcotic drugs
b) how to avoid illegal diversion of opioids
c) assessing fitness to drive during treatment for cancer pain
d) management of depression and anxiety

The cancer pain treatment guidelines mentioned above advise consideration of analgesia-related adverse effects including:

a) pruritis
b) sedation
c) myoclonus
d) all of the above

The pharmacological agents most commonly implicated in the aetiology of parotitis are:

a) contrast media containing iodine
b) parenteral anticoagulants
c) selective serotonin reuptake inhibitors
d) thiazide diuretics

A common cause of parotitis that is not drug-related is:

a) staphylococcal infection
b) ground nut allergy
c) hypertension
d) none of the above

Which of the following agents is regarded as a first-line choice for management of psychosis in Parkinson's disease?

a) clozapine
b) olanazpine
c) amisulpride
d) quetiapine

Pimavanserin is thought to exert a therapeutic effect against psychosis in Parkinson's disease by acting as a:

a) dopamine D2 agonist
b) dopamine D2 inverse agonist
c) 5HT2A agonist
d) 5HT2A inverse agonist

The metabolism of droxidopa is primarily mediated by:

a) catechol-O-methyltransferase (COMT)
b) Cytochrome P4501A2
c) P-glycoprotein
d) none of the above

Droxidopa has been recently approved by the US FDA for treatment of orthostatic dizziness or light-headedness in patients with symptomatic neurogenic orthostatic hypotension. This condition may be caused by:

a) primary autonomic failure associated with conditions such as Parkinson's disease
b) antihypertensive medication
c) diabetic neuropathy
d) peripheral vascular disease