RGH E-Bulletin Digest Number 73

The next in our 2014 series of continuing professional development activities is the RGH E-Bulletin Digest No. 73 – edited by Associate Professor Chris Alderman.

This CPD activity assesses your understanding of four recent RGH Pharmacy E-Bulletins, Volumes 54-9→55-1 (May/June 2014).

Learning Objectives:

After completing this activity, pharmacists should be able to:

- Discuss the nature and treatment of myelofibrosis
- Discuss the use of Garcinia cambogia as a complementary medicine
- Specify the medications that can be used in the management of high output GI stoma
- Describe the nature and treatment of akathisia.

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: A1409AP0**.

Chris Alderman B Pharm, FSHP, BCPP (USA), CGP

Chris Alderman is the Director of Pharmacy at the Repatriation General Hospital in Daw Park, South Australia, and also holds a dual appointment as Associate Professor, Pharmacy Practice at the Quality Use of Medicines and Pharmacy Research Centre, University of South Australia.

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.

AusPharm gratefully acknowledges the financial support provided by the sponsors of our CPD program, **MIMS**

RGH Pharmacy E-Bulletin

Volume 54 (9): May 26, 2014

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

Ruxolitinib for the treatment of myelofibrosis

Myelofibrosis is a disorder of bone marrow. Also known as chronic idiopathic myelofibrosis or primary myelofibrosis, it is classified as a myeloproliferative disease and causes proliferation of an abnormal clone of haematopoietic progenitor cells within the bone marrow and at other sites, resulting in fibrosis. This in turn impairs the ability to generate new red blood cells, eventually resulting in progressive pancytopenia. The proliferation of fibroblasts and deposition of collagen within the bone marrow is a secondary phenomenon. An enlarged spleen (hypersplenism) also contributes to the pancytopenia and in particular thrombocytopenia and anaemia. Other myeloproliferative disorders such as polycythaemia vera and essential thrombocytosis can progress to myelofibrosis.

Migration of haemopoetic cells away from the bone marrow to the liver and the spleen causes hepatomegaly, massive splenomegaly and poikilocytosis. The spleen is usually markedly enlarged, sometimes weighing as much as 4kg. Myelofibrosis causes death via bone marrow failure, cachexia and development of acute myeloid leukaemia. Features include pain and anorexia from an enlarged spleen, and potential for dependency on frequent blood transfusions which can affect quality of life. This is a rare chronic disorder affecting approximately 1 in 100,000 people, and can occur at any age (but is usually diagnosed later in life in people over 60). Average survival ranges from 2 to 11 years.

Conventional treatments include splenectomy, hydroxyurea, and thalidomide. For a minority of younger patients, allogenic stem cell transplant could be considered as an option but this carries significant risks.

Ruxolitinib is a JAK 1 and JAK 2 inhibitor which has been approved by the Australian Therapeutic Goods Administration for the treatment of disease-related splenomegaly or symptoms in patients with primary myelofibrosis related to polycythaemia vera myelofibrosis or essential thrombocytopenia myelofibrosis. It inhibits Janus Associated Kinases (JAKs) JAK1 and JAK2 which mediate the signalling of a number of cytokines and growth factors that are important for haematopoiesis and immune function. Although approximately 50 % of patients with myelofibrosis have this gene mutation other mechanisms of direct or indirect activation of the intracellular JAK signal transducer and activation of transcription pathways are known. These pathways are central to the pathogenic competent of myelofibrosis regardless of the mutational status of JAK2.

The COMFORT1 trial was a randomised, double blind, placebo-controlled phase 3 trial conducted across the US, Canada and Australia. The trial involved 309 patients with intermediate or high rick myelofibrosis who were randomly assigned to receive twice daily ruxolitinib (155) or placebo (154). The primary end point was the proportion of patients with a reduction in spleen volume of greater than or equal to 35 % after 24 weeks. This endpoint was reached in 41 .9% of patients in the ruxolitinib group compared to 0.7% in the placebo group. The COMFORT II trial compared ruxolitinib with best available treatment (BAT) and was an open label, randomised controlled trial. The primary outcome was reduction in spleen volume the same as for COMFORT 1, measured after 48 weeks. In COMFORT 11 there was a 28.5% reduction in ruxolitinib treated compared to BAT (0%). Ruxolitinib caused anaemia and thrombocytopenia in a significant minority of trial participants. Elevation in ALT and AST were reported and also increased risk of infection.

Ruxolitinib is not currently listed for subsidised supply through the Pharmaceutical Benefits Scheme, but is available in Australia through a sponsor-funded compassionate access scheme.

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

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

RGH Pharmacy E-Bulletin

Volume 54 (10): June 2, 2014

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

Garcinia cambogia for weight loss

Garcinia cambogia is a herbal product that in recent times appears to be promoted heavily for weight loss via the Internet, social media and television.

Hydroxycitric acid is the active ingredient of the Malabar tamarind (garcinia cambogia), a tropical fruit found in South East Asia. In cookery, garcinia cambogia is used as a condiment in Thai and Indian cuisine. Information published over the Internet promotes that this product 'reduces appetite, stops carbohydrates converting to fat, elevates the metabolism and helps people lose weight without dieting or exercise.'

Efficacy for the treatment of obesity
The Natural Medicines Comprehensive Database (NMCDB) states that there is "insufficient reliable evidence to rate" for garcinia cambogia in the treatment of obesity. An ideal weight reduction product must achieve a reduction in weight and cardiovascular risk.

Two recent review articles have evaluated the efficacy and safety of garcinia cambogia. These reviews state that there have been conflicting reports with regards to the benefits of garcinia cambogia for weight loss. The studies that have been conducted to date are of limited value because of small sample sizes, short duration and the confounding influences of other strategies that were also incorporated in the trials (these included lifestyle recommendations, low calorie diets and the use of other ingredients claimed to be of benefit for weight loss). The reviews conclude that there is little evidence to support the long term use and benefits of garcinia cambogia for weight loss.

Safety of Garcinia cambogia
The NMCDB state that when used orally for 12 weeks or less this product possibly safe. However, there is insufficient reliable information about the safety of the long term use of garcinia cambogia. The product has been reported to cause various non-specific adverse effects including nausea, gastrointestinal discomfort and headache. There are reports of possible hepatitis associated with the use of a preparation which contained garcinia cambogia. There is currently information to suggest that there are clinically significant interactions between garcinia and medications, but again, objective information is lacking.

Summary
There are many and varied weight loss products available to purchase via the Internet, but the quality and safety of these is of potential concern, as quality assurance processes are not transparent The NMCDB state that for weight loss, an extract containing 50% hydroxycitric acid, at a dose of 1000 mg three times daily has been used. Hydroxycitric acid, at a dose of 500 mg four times daily has also been used for weight loss.

Despite the claims published via the Internet for the efficacy of garcinia cambogia in treating obesity, definitive conclusions remain to be proven in large scale long term clinical trials. As there is little evidence to support the efficacy and safety for the use of garcinia cambogia for weight loss, further research into the long term efficacy and safety in humans is needed.

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

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

RGH Pharmacy E-Bulletin

Volume 54 (11): June 9, 2014

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

Medications used in high-output stoma

A stoma has been defined as an artificial opening in the abdominal wall created after small bowel surgery involving partial or full removal of the small intestine. High output stomas (HOS) may arise as a consequence of the surgery. Pharmacological therapies to control HOS include anti-motility, anti-secretory and other agents.

Anti-motility agents
Opioids decrease intestinal motility, which is useful in HOS. Opioids commonly used for this purpose include loperamide, codeine and diphenoxylate/atropine. Loperamide enters the enterohepatic circulation, but is important to note that this may be severely disrupted following small bowel surgery and thus higher doses may be warranted. As a starting point, a dose of 2-10 mg four times a day of loperamide may be used, typically administered 30 minutes before food. Doses of codeine may range from 30-60 mg 30 minutes before food, up to four times daily. A double-blind crossover study comparing loperamide (4 mg three times daily) to codeine (60 mg three times daily) found that both the drugs were effective in significantly reducing ileostomy output. Loperamide was, however, considered to be the preferred option on the basis that it is not addictive, is non-sedating and does not cause fat malabsorption. In very high output stomas, the combination of agents may be used. The clinical utility of diphenoxylate products is limited by anticholinergic side effects of atropine that is included in the formulation.

Anti-secretory agents
Proton pump inhibitors (PPIs) and Histamine 2 (H2) antagonists are used in HOS due to their anti-secretory effect on gastric juices. The guidelines from the British Society of Gastroenterology state that the H2 antagonists cimetidine (400 mg four times daily orally) and ranitidine (300 mg twice daily orally) and the PPI omeprazole (40 mg once daily orally) decrease jejunostomy output, especially in patients with a net secretory output and those with output exceeding two litre daily. If less than 50 cm of jejunum remains, intravenous administration of omeprazole may be required, as the drug is absorbed in the duodenum and upper part of the small bowel.

Other agents
Another agent used in HOS is octreotide, a somatostatin analogue, which can promote intestinal reabsorption and inhibit gastric secretion. However, anti-secretory drugs (refer above) have been found to be as effective as intravenous octreotide if at least 50 cm of jejunum remains. Additionally, the use of octreotide is limited by high cost, the inconvenience of administration and adverse effects.

Clonidine, an alpha2-adrenergic receptor agonist, inhibits gastrointestinal motility, increases intestinal sodium and water absorption and reduces bicarbonate secretion. An approach involving the addition of clonidine 100 mcg orally twice daily to conventional therapy (anti-diarrhoeal and anti-secretory agents) resulting in decreased colostomy output in patients who are refractory to conventional treatment alone have been described in case reports. However, results from other research are conflicting.

Management of diarrhoea after small bowel surgery can require aggressive pharmacological treatment. The number of medications and the dosages used should be slowly increased to achieve the desired effect while minimizing adverse effects.

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

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

RGH Pharmacy E-Bulletin

Volume 55 (1): June 23, 2014

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

Antipsychotic-induced akathisia

Akathisia is one of the most commonly experienced extrapyramidal adverse effects associated with antipsychotic medication. It is characterised by feelings of inner restlessness with a compelling urge to keep moving, and patients may present with frequent pacing, a continual shifting of weight or an inability to sit still. Depending upon severity this can impact upon medication adherence, or may contribute to aggression or an increased risk for suicide. Symptoms of akathisia may also be misinterpreted as signs of agitation associated with psychosis and treatment inefficacy.

The exact pathophysiology of akathisia is unknown however it has been suggested that it may involve dopamine receptor blockade in the mesocortical and mesolimbic regions of the brain. It has also been hypothesised that serotonin receptor activity may be implicated; in particular the 5-HT2A/2C receptors where antagonism is thought to result in anti-akathisia activity.

Risk factors which may increase the incidence of akathisia include receiving treatment with conventional antipsychotics, high potency antipsychotics, treatment at a high dose and concurrent use of other psychotropic substances. Studies have reported differing rates of akathisia comparatively between atypical antipsychotics. Akathisia may be more commonly experienced in patients treated with aripiprazole, risperidone or ziprasidone compared to those treated with olanzapine, and less frequently associated with quetiapine or clozapine.

Treatment strategies for akathisia can include reducing the dose of antipsychotic, changing to an alternative antipsychotic associated with a lower incidence of akathisia or trialling additional medication for symptom management. Anticholinergic agents may be useful for other extrapyramidal effects but their effectiveness for akathisia is less well defined and side effects such as urinary retention, constipation and memory impairment can be problematic.

Benzodiazepines have been used for anxiolytic and muscle relaxant effects however their use can be limited by sedation and issues with drug dependence and tolerance. Beta-blockers, in particular propranolol, have been found to be effective but can be poorly tolerated due to hypotension and bradycardia.

There is limited evidence supporting the use of low dose mirtazapine (15mg), potentially due to its antagonism at the 5-HT2A receptor. A randomised controlled study of 90 patients comparing mirtazapine 15mg, propranolol 80mg and placebo for antipsychotic-induced akathisia reported a response rate of 43.3% for patients taking mirtazapine, 30% for those taking propranolol and 6.7% for placebo, however 26% of patients dropped out of the study due to adverse events or a lack of response, and the study was not powered adequately to compare mirtazapine and propranolol.

Other alternative treatment options of cyproheptadine, mianserin, clonidine or amantadine have also been trialled with variable success.

Further large-scale randomised controlled trials are required to gain a better understanding of antipsychotic-induced akathisia and how best to approach management.

Acknowledgment – This E-Bulletin is based on work by Ellise Liew, 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:

Chuah LO et al. Updates on antiobesity effect of garcinia origine (-) HCA. Evidence –based complementary and alternative medicine 2013:2013:1-17

Poyurovsky, M. Acute antipsychotic-induced akathisia revisited. The British Journal of Psychiatriy (2010) 196, 89-91.

Ranjan, S et al. Atypical antipsychotic-induced akathisia with depression: therapeutic role of mirtazapine. The Annals of Pharmacotherapy (2006) 40, 771-4

Hieber, R et al. Role of mirtazapine in the treatment of antipsychotic-induced akathisia. The Annals of Pharmacotherapy (2008) 42, 841-6

Kumar, R and Sachdev, P. Akathisia and second-generation antipsychotic drugs. Current opinion in psychiatry (2009) 22:293-299

Merck Manual: Professional Edition: Primary Myelofibrosis: www.merckmanuals.com/professional/hematology_and_oncology/myeloproliferative_disorders/primary_myelofibrosis.html

NCBI: Gut journal: Guidelines for management of patients with a short bowel: www.ncbi.nlm.nih.gov/pmc/articles/PMC2806687/

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

Which of the following is a condition that is commonly associated with myelofibrosis?

a) hypersplenism
b) aplastic anaemia
c) throbocytosis
d) osteoporosis

Which of the following agents has been assessed in clinical trials as a potential treatment for myelofibrosis?

a) ruxolitinib
b) infliximab
c) etanercpt
d) abciximab

Garcinia cambogia is a complementary medicine derived from a plant related to which of the following, used in cookery?

a) cumin
b) tumeric
c) tamarind
d) cardamom

The putative active ingredient of Garcinia cambogia when used to aid weight loss is:

a) ethyl acetic acid
b) alpha hydroxyl butyric acid
c) tauric acid
d) hydroxycitric acid

Which of the flowing agents has been used for management of high-output GI stoma?

a) proton pump inhibitors
b) loperamide
c) octreotide
d) all of the above

Which of the following has been used in the management of GI stoma to increase intestinal sodium and water absorption and reduces bicarbonate secretion?

a) prazosin
b) hydrallazine
c) clonidine
d) amlodipine

It has been suggested that the pathophysiology of akathisia is involves dopamine receptor blockade:

a) in the mesocortical and mesolimbic regions of the brain
b) in the brainstem
c) in the substantia nigra
d) in skeletal muscle

Which of the following has been trialled as a treatment for akathisia?

a) lithium
b) mirtazapine
c) sertraline
d) venlafaxine