RGH E-Bulletin Digest Number 83

The next in our 2015 series of continuing professional development activities is the RGH E-Bulletin Digest No. 83 – edited by Associate Professor Chris Alderman.

This CPD activity assesses your understanding of four recent RGH Pharmacy E-Bulletins, Volumes 58-4→58-7 (April/May 2015).

Learning Objectives:

After completing this activity, pharmacists should be able to:

- Recognise serious opioid-related toxicities
- Provide information about the use of denosumab for malignancy-related hypercalcaemia
- Outline the clinical pharmacology of alemtuzumab and suvorexant.

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.

Accreditation number: A1508AP0.
This activity has been accredited for 0.5 hours of Group 1 CPD (or 0.5 CPD credits) suitable for inclusion in an individual pharmacist's CPD plan which can be converted to 0.5 hours of Group 2 CPD (or 1 CPD credit) upon successful completion of relevant assessment activities.

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

Monitoring for and prevention of acute opioid toxicities

In the acute setting, especially post-operatively, patients may be at risk of toxicity from opioids. Elderly patients in particular may need to be started on low doses of opioids which are titrated gently upwards to desired benefit. Numerous side effects can occur and while it is often presumed that opioid-naïve patients will be more sensitive, those patients who are already taking opioids have not necessarily developed tolerance to these effects. Some anaesthetists prefer that patients do not use long-acting opioids in the acute post-operative setting; however, there are differing approaches to the management of chronic pain patients already on long term opioids prior to surgery.

Adverse effects resulting from short-term use of opioids include:

- Respiratory: respiratory depression, apnoea, bronchospasm
- Cardiovascular: bradycardia, vasodilation, hypotension, especially during intravenous administration
- Neurological: sedation, confusion, delirium, dysphoria/euphoria, miosis (constriction of pupils), impaired cognition. All patients should be cautioned not to drive.
- Dermatological: sweating, flushing, urticaria, pruritis
- Gastrointestinal: nausea & vomiting, decreased gastric motility/delayed gastric emptying, constipation. Laxatives should always be prescribed and antiemetics made available.
- Musculoskeletal: myoclonus – more likely with high doses, impaired renal excretion & prolonged therapy
- Urinary: urinary retention & difficulty with micturition

Opiate toxicity is classically defined as a triad of respiratory depression, central nervous system depression, and miosis. In severe cases, hypotension is also present. Fatalities due to opioid toxicity most commonly result from respiratory arrest, even in young healthy adults. It should never be assumed that prior exposure to opioids negates the risk of respiratory depression. Respiratory depression, leading to high blood levels of carbon dioxide, can in fact coexist with a normal respiratory rate. Therefore a decrease in respiratory rate is an unreliable indicator of respiratory depression; sedation is a more sensitive indicator. Apnoea can also occur, particularly during sleep or in the context of concomitant sedatives and general anaesthetics (also alcohol & cannabis). Respiratory rate less than 8 breaths/min (usual rate ranges from 12-20) is a cause for concern, as is sedation score greater than 2.Nursing staff are advised to monitor sedation scores both before and after administration of opioids, however, there is variability in sedation score classification used by different institutions.

Sedation score example

0	awake, alert
1	mild sedation – easy to rouse
2	moderate sedation; easy to rouse but unable to remain awake
3	difficult to rouse

An order for naloxone should always be available for immediate administration, but does not need to be given in the absence of respiratory depression; precipitation of opioid withdrawal and/or pain crisis is potentially an issue. Note also that the duration of action is 90 minutes for naloxone and that the duration of effect of the opioid still in the patient's system may be greater than this.

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

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Denosumab for hypercalcaemia of malignancy

Hypercalcaemia of malignancy (HCM) is a common paraneoplastic syndrome, reported in up to 20% of cancer patients. Compared to non-malignant causes of hypercalcaemia, HCM tends to have a rapid onset and is more severe. Manifestations include skeletal pain, nephrolithiasis (the process of forming a kidney stone), abdominal discomfort, dehydration and altered mental state. Untreated, HCM can lead to renal impairment, coma and death. The presentation of HCM often translates to poor prognosis, despite strategies to reduce serum calcium levels. HCM primarily results from tumour-driven increases in bone resorption. Treatments for hypercalcaemia are therefore aimed at reducing serum calcium levels by inhibiting bone resorption, increasing urinary calcium excretion or decreasing intestinal calcium absorption.

Bisphosphonates, such as intravenous zoledronic acid and pamidronate, have been proven to be effective in the treatment of HCM, and are generally considered first-line medications for this indication. These are non-hydrolyzable analogs of inorganic pyrophosphate and through their interference with osteoclast-mediated bone resorption, effectively reduce serum calcium, with peak effects occurring in 2-4 days. However, not all patients have durable responses to bisphosphonate therapy, with a reported relapse rate to pamidronate or zoledronic acid of 24% and incomplete treatment response of 22%. Furthermore, for people with impaired renal function, there is a greater risk for nephrotoxicity.

Denosumab is currently registered for the treatment of osteoporosis and prevention of skeletal related events due to bone metastases from solid tumours. It is a human monoclonal antibody directed against the receptor activator of nuclear factor-κB ligand (RANKL), the molecular pathway leading to osteoclast recruitment and differentiation and bone resorption. Denosumab interferes with this process by binding with high affinity and specificity to RANKL. It prevents RANKL from binding to its receptor, thereby inhibiting the development, activation and survival of osteoclasts, leading to reduced bone resorption and cancer-induced bone destruction. Following a dose of denosumab, bone turnover decreases within 24 hours, with maximal effects after 2-4 weeks, and duration lasting up to several months. Case reports have demonstrated effectiveness of reduced serum calcium within 2-4 days following denosumab treatment. In a proof-of-concept study of advanced cancer patients with bisphosphonate-refractory HCM, denosumab (administered at doses of 120 mg weekly for 4 weeks then monthly), was shown to effectively lower serum calcium levels to ≤11.5 mg/dL (2.9 mmol/L) in 70% of patients. The median time and duration of response was 9 days and 104 days, respectively.

Other clinical trials have demonstrated superiority to zoledronic acid in delaying time to first-on-study skeletal-related events. It has also been shown to prevent HCM more effectively than zoledronic acid. Unlike bisphosphonates, denosumab is cleared by the reticulo-endothelial system, and is not reliant on the kidneys. Therefore, adjustment of dosing in renal impairment is not required. It also has the advantage of ease of administration as a subcutaneous injection. However, studies have reported an increased risk of hypocalcaemia with denosumab compared to bisphosphonates, (3.1-10.8% versus 1.3-5.8%, respectively). While sporadic cases of osteonecrosis of the jaw have been reported, the main adverse effect of denosumab treatment that has emerged is hypocalcaemia, suggesting a potentially greater potency in HCM.

Although the literature on the use of denosumab for HCM is scarce, this approach offers an alternative treatment option in the treatment of HCM, particularly in renal insufficiency or bisphosphonate-refractory cases. Nevertheless, providers should be aware of its propensity to cause significant hypocalcaemia, and patients receiving denosumab should have calcium levels monitored closely.

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

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Alemtuzumab

In April 2015, alemtuzumab (Lemtrada®) was approved for reimbursement via the Pharmaceutical Benefits Scheme (PBS) for first & second line treatment of adults with active relapsing/remitting multiple sclerosis (RRMS). Alemtuzumab is a humanised anti-CD52 monoclonal antibody acting by depletion/subsequent repopulation of circulating T & B lymphocytes, & has demonstrated superiority over interferon beta 1a in a phase II RCT (CAMMS-223) & two phase III RCTs (CARE-MS I/CARE-MS II) in both treatment naive & treatment failure patients with early active RRMS.

The CAMMS223 trial compared annual IV cycles of alemtuzumab (12 mg/day and 24 mg/day over 36 months) to SC interferon beta (44 mcg three times weekly) in previously untreated patients with RRMS. Alemtuzumab was found to reduce the risk of sustained accumulation of disability by 71% and the risk of relapse by 74% ($P < 0.001$) when compared to interferon beta 1a.There were no significant differences in safety or efficacy between the 12 mg and 24 mg alemtuzumab doses or between two versus three cycles. The CARE-MS I trial was a phase III replication of the CAMMS-223 study and compared annual IV alemtuzumab 12 mg/day to SC interferon beta 1a over two years in treatment-naive patients. Similar to the CAMM-223 trial, alemtuzumab reduced the rate of relapse by 54.9% compared to interferon beta 1a, however there was no significant difference between the groups in terms of rates of sustained accumulation of disability. CARE-MS II recruited patients with RRMS who had relapsed at least once on either interferon beta 1a or glatiramer. Escalation to alemtuzumab (12 mg/day for 2 cycles) resulted in a risk reduction of 49% for relapse and 42% for 6-month disability progression when compared to interferon beta 1a. In both CARE-MS I and CARE-MS II, alemtuzumab patients had fewer new or enlarging T2 lesions and contrast enhancing lesions on MRI but no significant advantage in the volume of T2 lesions. The rate of reduction of brain parenchymal fraction (a measure of brain atrophy) was also notably decreased with alemtuzumab treatment.

Adverse events with alemtuzumab were similar across all trials. Most had mild to moderate infusion reactions (commonly headache, rash, nausea and pyrexia) with 3% experiencing serious infusion associated events. Infections (especially herpes and UTIs) were more common with alemtuzumab than with interferon (77% vs 66%) but were predominantly of mild or moderate severity. In clinical trials, prophylactic aciclovir (200 mg orally, twice daily) for one month starting on day 1 of each treatment cycle reduced the incidence of herpes complications from 2.8% to 0.5% and is now routinely used in the alemtuzumab treatment protocol. Alemtuzumab was associated with the formation of autoantibodies & increased risk of secondary autoimmunity including ITP, thyroid disorders & rarely nephropathies (anti-glomerular basement membrane disease), occurring up to five years after treatment. To minimise risk of serious adverse effects complete blood counts, creatinine measurements and urinalysis should be taken before treatment and monthly afterwards, and thyroid function tests should be performed every three months for 48 months after the last treatment. Caution should be exercised in patients with previous autoimmune conditions, although available data suggest that alemtuzumab does not worsen pre-existing autoimmune conditions. The only contraindication to alemtuzumab treatment is HIV infection.

The introduction of effective therapies for MS over the past 20 years has brought positive change for those with MS. Despite these new therapies, some people continue to relapse or cannot receive natalizumab (patients positive for John Cunningham virus). Those with RRMS that remains active after first line disease modifying therapy have a poor prognosis. The addition of alemtuzumab further improves the outlook for patients with aggressive MS. No clinical trials to date have compared the safety and efficacy of alemtuzumab to any MS treatment other than interferon beta 1a. There is also a lack of valid criteria to select patients requiring early aggressive treatment to prevent progression of disability. As long as this crucial information is missing, at a cost of over $100,000 per treatment course many physicians might be reluctant to use alemtuzumab in early RRMS.

Acknowledgment – This E-Bulletin is based on work by Claire Higgins, Clinical Pharmacist, RGH

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Suvorexant – a preliminary overview.

Insomnia is common, particularly amongst the elderly, and has been described in terms of symptoms such as difficulty getting to asleep, staying asleep, or waking after sleep but not feeling refreshed (non-restorative sleep). Commonly seen in the context of comorbid issues including a variety of psychiatric illnesses (mood disorders, anxiety disorders and substance misuse), chronic insomnia is associated with compromised quality of life and an increased risk of substance use disorders. Many authorities advocate non-pharmacological approaches to treatment – these may include relaxation techniques, yoga, and various meditation techniques.

Various medication options have also been used for the treatment of insomnia, the most common of which involves the use of benzodiazepines such as temazepam, nitrazepam, oxazepam, lorazepam and triazolam. Alternative hypnosedatives are sometimes referred to as the "Z" drugs, and include zopiclone, zolpidem and zaleplon (not available in Australia). Various other medications have been used to promote sleep, including some antidepressants (notably amitriptyline, doxepin, mianserin and mirtazapine), melatonin and melatonin agonists (agomelatine), antihistamines such as promethazine, and others, even including low doses of antipsychotic agents such as quetiapine. Many of these approaches can afford some degree of assistance, but are associated with serious problems such as increased risk of falls/fractures, residual daytime sedation, and potential for dependence and withdrawal after the treatment has been discontinued.

In late 2014, the US Food and Drug Administration provided an approval for suvorexant, subsequently marketed as Belsomra® - this agent is an orexin receptor antagonist), the first in a new class of drugs for insomnia. The putative mechanism of action for this agent is to inhibit the effects wakefulness-promoting orexin neurons in the arousal system in the brain.

Suvorexant has an elimination half-life of approximately 12 hours, and is principally cleared via metabolism via CYP3A4. Care is required when coprescribing with drugs that influence CYP3A4 activity – for example azole antifungals and macrolide antibiotics. Dosage adjustment is not generally indicated in the presence of moderate renal of hepatic impairment. An important adverse effect to consider include significant residual drowsiness that may impair cognition and motor function the following day, meaning that the risk of falls may be increased, and the ability to safely operate machinery or drive a vehicle safely may be impaired. Notwithstanding this, it is important to note that these considerations are also relevant to currently employed strategies such as the use of benzodiazepines and sedating tricyclic antidepressants. Other dose related side effects that have been reported include muscle weakness, abnormal dreams and headache. Abrupt discontinuation of suvorexant does not appear to be associated with rebound insomnia or the appearance of withdrawal effects.

In Australia, The Therapeutic Goods Administration has approved suvorexant for inclusion in schedule 4 of the Standard for the Uniform Scheduling of Medicines and Poisons (Australia) as of February 2015. Although direct to consumer advertising of therapeutic goods is not allowed in Australia, the product is heavily promoted to consumers in the USA, raising concerns about the possible "medicalisation" of minor sleep disturbance. Suvorexant is not currently listed for subsidised supply under the auspices of the Australian Pharmaceutical Benefits Scheme.

Acknowledgment – This E-Bulletin is based on work by Claire Higgins, 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

The likelihood of myoclonus related to opioid use is increased with:

a) high dose treatment
b) impaired renal function
c) prolonged treatment
d) all of the above

With respect to opioid-related respiratory depression:

a) respiratory depression can exist with a normal respiratory rate
b) high respiratory rate is an indicator of respiratory depression
c) increase in respiratory rate is a reliable indicator of respiratory depression
d) sedation is a more sensitive indicator of respiratory depression heart rate

Compared to non-malignant causes of hypercalcaemia, hypercalcaemia related to malignancy tends to:

a) have a less rapid onset and is more severe
b) have a more rapid onset and is more severe
c) have a less rapid onset and is less severe
d) none of the above

If used for management of malignancy-related hypercalcaemia, the dosage of denosumab:

a) requires reduction in the presence of renal impairment
b) does not require reduction in the presence of renal impairment
c) need only be adjusted after intravenous administration
d) needs to be increased if the dose is administered subcutaneously

Alemtuzumab is approved for first & second line treatment of

a) motor neurone disease
b) muscular dystrophy
c) multiple sclerosis
d) tardive dyskinesia

In view of infections associated with alemtuzumab, treatment protocols now routinely include prophylaxis with:

a) fluoconazole
b) ribavirin
c) acyclovir
d) cotrimoxazole

Suvorexant is an example of a new class of drugs that are best described as:

a) orexin receptor agonists
b) orexin receptor antagonists
c) orexin anti-sense antagonists
d) orexin anti-sense agonists

Dose-related side effects of suvorexant have been reported to include:

a) nausea, diarrhoea, weight loss
b) rebound insomnia and the appearance of withdrawal effects
c) dry mouth, blurred vision and constipation
d) muscle weakness, abnormal dreams and headache