RGH E-Bulletin Digest Number 77

The first in our 2015 series of continuing professional development activities is the RGH E-Bulletin Digest No. 77 – edited by Associate Professor Chris Alderman.

This CPD activity assesses your understanding of four recent RGH Pharmacy E-Bulletins, Volumes 56-3→56-6 (September/October 2014).

Learning Objectives:

After completing this activity, pharmacists should be able to:

- Understand the potential causative contribution of medications to the development of urinary retention
- List important adverse effects of the cholinesterase inhibitors
- Discuss the clinical pharmacology of anidulafungin and mirabegron.

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: A1502AP0.

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.

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RGH Pharmacy E-Bulletin

Volume 56 (3): September 29, 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

Anidulafungin

Anidulafungin is an echinocandin antifungal recommended for the treatment of invasive candidiasis (including candidaemia) in adults. Currently there are three antifungals in this class - caspofungin, micafungin (not marketed in Australia) & anidulafungin. These drugs exert antifungal activity by inhibiting 1-3-β-D-glucan synthetase. As 1-3-β-D-glucan is an integral part of the fungal cell wall, inhibition of synthesis leads to fungal cell death. Beta-glucans account for a major proportion of cell wall mass in yeasts such as Candida species and thus echinocandins have a fungicidal effect. Beta-glucan synthesis is concentrated in apical tips of the hyphae of Aspergillus species and echinocandins exert only fungistatic effect resulting in abnormally branched hyphae. Differential features of echinocandins are listed below:

Feature	Anidulafungin	Caspofungin	Micafungin
Volume of distribution	30-50L	-	0.39 ± 0.11 l kg^{-1}
Protein binding (%)	>99	>97	>99
Metabolism	Degradation	Hepatic (hydrolysis, N-acetylation)	Hepatic (non-oxidative)
T1/2 (h)	26.5	~10	11-17
Loading dose	+	+	-
Renal disease adjustment	-	-	-
Hepatic disease adjustment	-	+ (Moderate)	-
Cyp substrate	-	Weak	Weak
Drug interactions	Nil clinically significant	Cyclosporin, tacrolimus, dexamethasone, rifampicin, other inducers of drug clearance	Sirolimus, itraconazole, nifedipine

Adapted from George et al; Mycoses 2011;55:36-44

Anidulafungin is active against most Candida species but *C.parapsilosis* and *C. guilliermondii* are reported to have decreased susceptibility to all echinocandins. Anidulafungin is not active against *Cryptococcus neoformans* or *Zygomycetes* spp.

Anidulafungin is minimally absorbed after oral administration and is only available in IV preparations. The drug exhibits linear pharmacokinetics, is highly protein bound and distributes minimally to cerebrospinal fluid, urine and the eye. Anidulafungin is not metabolised but eliminated by chemical degradation to an inactive open ring peptide. 30% is eliminated in the faeces of which 10% is excreted as unchanged drug, and only 1% is eliminated into urine. For oesophageal candidiasis and candidaemia, the recommended dose of anidulafungin is a 200 mg IV loading dose on day 1 followed by 100 mg IV daily for at least 14 days (no adjustment required for weight). Common adverse effects are hyperkalaemia, thrombocytopenia, increased bilirubin and infusion reactions.

The azole drugs (e.g. fluconazole) remain as antifungals of choice for candidiasis/candidaemia, but the choice of therapy depends on various factors such as recent azole exposure, antifungal susceptibility data, history of drug intolerance & severity of illness (including co-morbidities). Anidulafungin is advantageous in that it has minimal drug interactions, and is well-tolerated in terms of renal and hepatic insufficiency, but the drug must be administered by the IV route.

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.

RGH Pharmacy E-Bulletin

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

Drug-induced urinary retention

Urinary retention is defined as the inability to empty the bladder completely. Urinary retention can be chronic (developing over a long period of time) or acute (sudden inability to micturate). Risk factors for acute urinary retention include increasing age, male gender, conditions such as Benign Prostatic Hypertrophy (BPH), prostate cancer, diabetes mellitus & constipation, surgery use of certain medications. As micturition is so complex, many drugs can interact with the micturition pathway via different modes of action. Observational data suggest that up to 10% cases of acute urinary retention may relate to medication use. Provided below is a summary drugs that are most commonly associated with urinary retention, but there are many reports of urinary retention caused by a variety of other medication classes.

Anticholinergics
There are many drug classes that have anticholinergic properties. Anticholinergics block the parasympathetic pathway, resulting in reduced contractions of the detrusor muscle of the bladder. Anticholinergic drugs include but are not limited to antihistamines, antidepressants (in particular tricyclic antidepressants), antipsychotics, benztropine, oxybutynin, hyoscine butylbromide, tiotropium and ipratropium.

α-Adrenoreceptor agonists
Adrenergic drugs bind to α receptors in the internal sphincter of the urethra, constricting bladder outlet and resulting in voiding difficulty. Phenylephrine and pseudoephedrine can particularly increase the risk of urinary retention when used in combination with antihistamines in over the counter cough and cold preparations.

Opioids
Opioids can cause urinary retention by a number of mechanisms. Inhibition of the parasympathetic nerves of the bladder decreases the sensation of bladder fullness and increased tone of the sphincter increases outflow resistance. Confusion and constipation may also contribute to urinary retention.

Calcium channel blockers
Diltiazem and verapamil reduce bladder contractions by inhibiting calcium influx in the smooth muscle.

Antipsychotics
First generation drugs such as chlorpromazine and the second generation antipsychotic clozapine have strong anticholinergic effects which can cause urinary retention. Risperidone and ziprasidone have also been reported to cause retention through central serotonergic and D2 blocking effect, & stimulation of peripheral α1adrenoreceptors in the urinary tract.

Antidepressants
Besides tricyclic antidepressants, other antidepressants including SSRIs, SNRIs and reboxetine have been associated with urinary retention. Both serotonin and noradrenaline are involved in control of micturition. The mechanism by which urinary retention is caused is likely to be central and peripheral activation of adrenoreceptors and 5-HT2 receptors.

Acute urinary retention is painful and requires prompt catheterisation to provide relief. If the retention is suspected to be drug induced, cessation or dose reduction of the offending agent should be considered. In patients with risk factors, particularly older men, careful review of concomitant medications and using the lowest effective dose is important to help prevent drug induced urinary retention.

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

Mirabegron

Mirabegron (Betmiga®) is beta 3 adrenergic agonist - a new class of agent that induces detrusor muscle relaxation resulting in increased bladder storage capacity. This product was registered with the Australian Therapeutic Goods Administration in October 2013 for the symptomatic treatment of urgency, increased micturition frequency and/or urgency incontinence as may occur in patients with overactive bladder (OAB) syndrome
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Overactive bladder (OAB) can result from the dysfunction of nerves or muscles in the bladder, most commonly the dysfunction of the detrusor muscle. In OAB the detrusor muscle contracts inappropriately regardless of how much urine is stored in the bladder, hence the term detrusor overactivity. OAB is characterised by urgency, frequency or nocturia with or without urge incontinence. It is a common and distressing condition that affects 20-30% of the population over 75 years although it can also affect children and young adults. It is more prevalent in women, the overweight, and the elderly.

Treatment often starts with bladder training and lifestyle modifications, followed by pharmacological treatment which until recently consisted of the use of antimuscarinics including oxybutynin, tolterodine, solifenacin and darifenacin. Unfortunately many patients discontinue therapy with these agents due to lack of efficacy or debilitating side effects such as dry mouth, constipation, sedation, cognitive decline or dry eyes.

Mirabegron offers an additional pharmacologic treatment option for patients with OAB with a different mechanism of action and safety profile from antimuscarinic agents. Three placebo controlled trials have evaluated the safety and efficacy of Mirabegron. The most common adverse effects of mirabegron include hypertension, nasopharyngitis, urinary tract infection and headache. Palpitations and tachycardia have been reported in people taking mirabegron and patients with uncontrolled hypertension should not be prescribed the drug. Caution is recommended if using mirabegron for patients who have a prolonged QT interval or for those taking concurrent medications that prolong the QT interval. Blood pressure monitoring is recommended when commencing mirabegron.

The recommended starting dose of mirabegron is 25mg, and dependant on response and tolerability the dose may be increased to 50mg once daily.

Mirabegron is eliminated in the urine (55%) and in the faeces (34%) and has a terminal half-life of approximately 50 hours. Use for patients with end stage renal disease or severe hepatic disease in not recommended. The lower dosage of 25mg is recommended in patients with severe renal impairment, with no dosage adjustments required in patients with mild to moderate renal impairment. The 25mg daily dose also recommended in patients with moderate hepatic impairment. Mirabegron is a moderate CYP2D6 inhibitor thus monitoring and dose adjustment may be required if co-administered with imipramine, desipramine, flecainide, metoprolol and perhexiline, and other drugs that are extensively metabolised by CYP2D6. Mirabegron also increases exposure to digoxin, so this drug should be commenced at a low dose and titrated based on therapeutic monitoring.

As there is limited comparative and long-term efficacy data currently available for mirabegron, this agent should be used when antimuscarinic drugs are contraindicated, ineffective or not tolerated. Current phase 2 trials are being conducted both here at RGH and overseas, looking at the use of mirabegron in combination with solifenacin in patients with OAB: in the future, it may be that this agent is used more often in combination than alone.

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

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

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

Adverse effects of cholinesterase inhibitors

Cholinesterase inhibitors are used in patients with mild to moderately severe Alzheimer's disease to improve dementia symptoms. In Australia, donepezil, rivastigmine and galantamine are subsidised for supply through the Pharmaceutical Benefits Scheme (PBS), based on the results of a Mini-Mental State Examination (MMSE) or Standardised Mini-Mental State Examination (SMMSE). Ongoing funding is based on whether or not the patient has had a clinically meaningful response to treatment after six months (see http://www.pbs.gov.au/pbs/home) for full details). These drugs have been shown to improve symptoms but are not disease modifying, and can have significant side effects, and therefore the benefits of therapy need to be carefully weighed against adverse drug reactions.

The Database of Adverse Event Notifications (DAEN) developed by the Therapeutic Goods Administration of Australia (http://www.tga.gov.au/safety/daen.htm) records case reports that have been submitted in association with donepezil, rivastigmine and galantamine. Gastrointestinal symptoms have been the most commonly reported adverse effects, followed by psychiatric disorders, nervous symptom issues and cardiac disorders.

Gastrointestinal effects:
Nausea is significant, occurring in up to 47% of subjects in controlled trials, and is observed to be dose related. Vomiting, diarrhoea and anorexia are very common, reported in more than 10% of patients. Abdominal pain, dyspepsia, and weight loss also occur. Patients with low body weight (i.e. < 55kg) may experience more gastrointestinal side effects. Cholinesterase inhibitors are contraindicated in patients with gastrointestinal obstruction or in patients with active peptic ulcer disease as these agents increase gastric acid secretion and can aggravate existing peptic ulcer disease.

Psychiatric disorders and nervous system:
Confusion and agitation are common (more than 1% of patients). Hallucinations, headache, insomnia, vivid dreams, depression, fatigue, drowsiness, dizziness and tremor are also observed. There have also been reports of seizures, loss of consciousness and coma. Caution is required in patients with a history of seizure activity.

Cardiovascular:
The increased cholinergic activity with cholinesterase inhibitors may exert vagotonic effects on heart rate and bradycardia has been reported. Hypertension, hypotension, and fainting can occur. Cholinesterase inhibitors need to be used cautiously with patients already treated with other medicines that can cause bradycardia, of for those who have experienced heart block or brady-arrhythmias.

Other adverse reactions:
Muscle cramps, urinary incontinence (1% to 10% of patients), and increased sweating. Cholinomimetics can worsen symptoms of prostatic hyperplasia. Bronchoconstriction has been reported and application site reactions can occur with topical rivastigmine.

Cholinesterase inhibitors offer modest benefit in the management of dementia: the use of these agents needs to be considered in the context of the patients' other disease states as well as monitoring for side effects, allowing for consideration of both potential risks and benefits.

Acknowledgment – This E-Bulletin is based on work by Lenore Jansen, 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:

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Verhamme KMC et al Drug –induced urinary retention: Incidence, management and prevention. Drug Safety 2008; 31: 373 - 88

Veterans' MATES Therapeutic Brief 26; The impact of commonly used medicines on urinary incontinence. Mar 2011

TGA, Database of Adverse Event Notifications (DAEN) - medicines between 01/01/1971 to 21/05/2014, report generated on 12/9/14 for donepezil, galantamine, and rivastigmine. http://www.tga.gov.au/safety/daen.htm

Kaviranjan H and Schneider L S, Efficacy and adverse effects of cholinesterase inhibitors and memantine in vascular dementia: a meta-analysis of randomised controlled trials. Lancet Neurology 2007; 6: 782 - 92

Sobow T and Kloszewska I, Cholinesterase inhibitors in the "real world" setting: rivastigmine versus donepezil tolerability and effectiveness study. Arch Med Sci 2006; 2.3: 194- 8

Australian Public Assessment Report for Mirabegron TGA January 2014

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

Anidulafungin is a new antifungal agent most closely related to:

a) amphotericin
b) fluconazole
c) nystatin
d) caspofungin

Anidulafungin is not active against which of the following species?

a) Candida albicans
b) Cryptococcus neoformans
c) Aspergillus niger
d) None of the above

Which of the following may contribute to urinary retention?

a) phenylephrine
b) morphine
c) diltiazem
d) all of the above

Medications have been estimated to contribute to urinary retention in approximately what percentage of cases?

a) 1%
b) 2%
c) 10%
d) 20%

The mechanism of action of mirabegron is mediated through its effects as a:

a) beta 2 adrenergic agonist
b) beta 2 adrenergic antagonist
c) beta 3 adrenergic agonist
d) beta 3 adrenergic antagonist

The recommended starting dose of mirabegron is:

a) 2.5 mg daily
b) 25 mg daily
c) 5.0 mg daily
d) 50 mg daily

With respect to the adverse effects of cholinesterase inhibitors, which of the following statements is most accurate?

a) in clinical trials, nausea has been reported at a frequency of nearly 50%
b) constipation is relatively common
c) patients with larger body weight and BMI experience more gastrointestinal symptoms
d) kidney stones are frequently associated with rivastigmine treatment but not with other drugs from the class

Which of the following adverse effects are important to consider in relation to cholinesterase inhibitor treatment?

a) bradycardia
b) urinary incontinence
c) muscle cramps
d) all of the above