RGH E-Bulletin Digest Number 72

The next in our 2014 series of continuing professional development activities is the RGH E-Bulletin Digest No. 72 – edited by Associate Professor Chris Alderman.

This CPD activity assesses your understanding of four recent RGH Pharmacy E-Bulletins, Volumes 54-5→54-8 (April/May 2014).

Learning Objectives:

After completing this activity, pharmacists should be able to:

- Describe the nature and prevalence of drug-related QT interval prolongation
- •Discuss the clinical pharmacology of infliximab and glycopyrronium
- •Discuss the place of drug therapy in the management of venous thromboembolism.

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: A1408AP1**.

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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

QT interval prolongation and drugs

The QT interval reflects the measurement of the duration of ventricular depolarization and repolarization and is measured in milliseconds (ms) on an electrocardiogram (ECG) from the Q-top (the beginning of the QRS complex) to the end of the T wave. The QT interval is dependent on heart rate, gender and age. Prolongation of the QT interval can result in a life threatening arrhythmia called Torsade de Pointes (TdP). Usually TdP is self-terminating but it can cause ventricular fibrillation or rarely sustained ventricular tachycardia, resulting in dizziness, syncope, cardiac arrest and sometimes death.

QT prolongation can be defined as more than 450ms in men and over 470ms in women and may be a congenital or acquired disorder.

There are many factors that predispose to QT prolongation including: age, female gender, left ventricular hypertrophy, heart failure, myocardial ischaemia, hypertension, diabetes mellitus, increased thyroid hormone concentrations, elevated serum cholesterol, high body mass index, slow heart rate and electrolyte abnormalities (including hypokalaemia and hypomagnesaemia). However, one of the most common causes of acquired QT prolongation is the use of specific drugs. The mechanism of drug induced QT prolongation is postulated to be due to blockade of cardiac potassium channels. The prolongation of the QT interval by drugs is usually seen within several days of commencing treatment. Listed below are some of the drugs associated with QT prolongation:

Antibiotics:	Azithromycin, clarithromycin, erythromycin, roxithromycin, moxifloxacin
Antifungals:	Fluconazole, voriconazole, ketoconazole
Antidepressants:	Amitriptyline, clomipramine, imipramine, dothiepin, doxepin, citalopram, escitalopram
Antipsychotics:	Risperidone, fluphenazine, haloperidol, clozapine, amisulpride, zisprasidone, droperidol
Antiarrhythmics:	Sotalol, amiodarone, disopyramide, quinidine,
Antineoplastics:	Arsenic trioxide, dasatinib, lapatininb, nilotinib, pazopanib, sorafenib, sunitinib, toremifene, veramurafenib
Antimalarials:	Chloroquine, mefloquine, quinine
Antivirals:	Nelfinavir
Other:	Cisapride, cocaine, dextropropoxyphene, domperidone, methadone, solifenacin, tacrolimus, vardenafil

Both pharmacokinetic and pharmacodynamic drug interactions can significantly increase the risk of QT prolongation. Many drugs that can potentially prolong the QT interval are hepatically metabolized via the cytochrome isoenzymes CPY3A4, 1A2 and 2D6 and because most drugs that prolong the QT interval do so in a concentration-dependent manner, if their metabolism is inhibited then the likelihood of QT prolongation or TdP significantly increases. Caution must be taken to avoid concomitant administration of more than one drug that prolongs the QT interval as the potential risk increases when these drugs are used in combination.

Although QT prolongation is associated with certain drugs it remains difficult to predict the relative risk associated with their administration. Drugs that have the potential to prolong the QT interval should not be used at doses that exceed the recommended range, and these medications should be prescribed with particular caution for patients with underlying risk factors, such as cardiac disorders. Close monitoring of electrolytes and an ECG is recommended within the first few days of therapy in high risk patients.

Further information regarding drugs that prolong the QT interval can be found at www.crediblemeds.org and www.qtdrugs.org

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

Inhaled Glycopyrronium Bromide for COPD

Chronic obstructive pulmonary Disease (COPD) is a progressive, chronic inflammatory disease of the lung: smoking is the most common risk factor. Common symptoms include dyspnoea, cough, increased sputum production, emphysema and comorbidities (cardiovascular disease, lung cancer and osteoporosis). It is a leading cause of mortality and morbidity worldwide. Given that symptoms are due to increased airway resistance, treatment relies on the use of bronchodilators which influence the activity of β_2 and muscarinic receptors for maintenance therapy.

Tiotropium Bromide was the first long-acting muscarinic antagonist (LAMA) to be approved for the management of COPD and more recently Glycopyyronium Bromide (Seebri®,Breezhaler®) has been developed. Glycopyrronium Bromide acts as a bronchodilator in the airways by inhibiting acetylcholine induced bronchoconstriction in bronchial smooth muscle cells.

In the human lung, three muscarinic receptor types are thought to be of relevance (M_1 - M_3). M_3 receptors are thought to be the prime mediators of bronchoconstriction, while M_2 receptors are thought to protect against bronchoconstriction – in addition, blockade of M_2 receptors may increase heart rate. As such, ideal bronchodilators would have a relatively higher affinity for M_3 (and M_1) receptors. Glycopyrronium has a 4 to 5 fold higher selectivity for M_1 and M_3 receptors and in addition is known to dissociate more slowly from these receptors than is the case for other muscarinic receptor antagonist agents.

There have been two pivotal phase 3 trials which have provided the clinical evidence for the efficacy of glycopyrronium in the management of COPD: the GLOW1 study (glycopyrronium bromide in COPD airways clinical study 1) and the GLOW2 study (study 2).

In the GLOW1 study, 822 patients were randomised to receive treatment with glycopyrronium, or placebo. Of those enrolled, approximately 20 per cent in each arm discontinued treatment early. The mean FEV_1 value for those receiving active treatment was significantly higher when measured after 12 weeks and six months, with significant improvement in breathlessness and a lower incidence of moderate to severe COPD exacerbations and reduced admissions due to severe exacerbations.

In the GLOW2 study, 1066 patients were randomised to receive one year of treatment with glycopyrronium, or placebo, or open-label tiotropium (this study was not powered to demonstrate glycopyrronium superiority relative to tiotropium). Active treatment was discontinued in approximately 22-23 per cent of those receiving the active treatment, as opposed to 28 per cent in the placebo group). After 12 weeks, FEV_1 was significantly higher in the glycopyrronium and tiotropium groups and this difference was maintained at 12 months. Likewise, the rate of moderate to severe exacerbations was significantly lower in both the glycopyrronium and tiotropium groups.

In a shorter GLOW3 trial, exercise tolerance was significantly improved at day 1 and after 3 weeks.

In summary, glycopyrronium bromide proved to be well tolerated in trials of up to 52 weeks with most side-effects being mild to moderate in severity.

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

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

P-glycoprotein drug interactions

Infliximab – a brief review

Infliximab (Remicade®) is an immunoglobulin G1 (IgG1) human monoclonal antibody produced from human and mouse proteins, and has affinity to human tumour necrosis factor alpha (TNF-α), a pro-inflammatory and immunoregulatory cytokine. Infliximab neutralises the biological activity of TNF-α by binding to the transmembrane forms of TNF-α, which in turn inhibits TNF-α from binding to its receptors. Responses to TNF-α at a cellular level include:

- Chemokine up regulation, e.g. interleukin-8 (IL-8)
- Pro-inflammatory cytokine up regulation, e.g. IL-1
- Priming and activation of neutrophils
- Up regulation of adhesion molecules and tissue factors by endothelial cells

Biological responses linked to TNF-α include:

- Induction of pro-inflammatory cytokines
- Increase in endothelial layer permeability and expression of adhesion molecules by endothelial cells and leukocytes, which then enhances leukocyte migration
- Activation of neutrophils and eosinophils
- Induces acute phase and other liver proteins

Cells which express the infliximab-TNF-α bound complex can then be lysed by complement or effector cells. As an overexpression of TNF-α mediates chronic inflammation in diseases, neutralisation of TNF-α through the use of an agent such as infliximab plays a key role in the management of a range of serious inflammatory diseases. This is evident by the number of indications currently approved by the Pharmaceutical Benefits Scheme (PBS) in Australia for infliximab, which include:

- Ankylosing spondylitis
- Crohn's disease
- Plaque psoriasis
- Psoriatic arthritis
- Rheumatoid arthritis
- Ulcerative colitis

The PBS website lists specific criteria that must be addressed to allow patients to qualify for subsidised supply of infliximab under the PBS scheme in Australia. However, due to the positive outcomes associated with the inactivation of TNF-α in other situations, there is an increase in off-label use of infliximab in conditions such as Behçet's disease (the drug is already approved in Japan for Behçet's disease-related uveoretinitis not responding to conventional treatments), sarcoidosis (with infliximab producing improvements in articular, cardiac, hepatic, neurologic, renal, ocular , parotid gland, vertebral and/or skin involvement) and non-infectious uveitis (effective in treatment of ocular inflammation). The increasing off-label use of infliximab is reflected in experiences that are documented in case reports and case series, even when the extent of trial-based evidence to support the use of the drugs for these indications is limited.

Acknowledgment – This E-Bulletin is based on work by Allen Lau, Utility Pharmacist, RGH.

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

Rivaroxaban for treatment of DVT and PE

Venous thromboembolism (VTE) is a collective term used to describe two disorders: deep-vein thrombosis (DVT) and pulmonary embolism (PE). Together DVT and PE have an annual incidence of approximately 1 to 2 cases per 1000 persons (0.1-0.2%). For several decades the standard therapy for most patients with acute VTE has included the use of a heparin/heparinoid product overlapped with and followed by a vitamin K antagonist (usually warfarin). Once a patient has experienced a first VTE event, they are subsequently at higher risk of recurrence, with 5-10% of patients experiencing a further VTE event within the first year after treatment ends.

The major risk associated with warfarin treatment for long-term prevention of VTE is major bleeding, and this occurs in 1-2% of patients annually who are treated with a vitamin K antagonist. Treatment with warfarin is complicated by the need for laboratory monitoring, as well as numerous drug-drug, drug-disease state, and drug-dietary interactions. Also, variable dosing with warfarin can present a challenge with respect to adherence.

Rivaroxaban is a fixed dose factor Xa inhibitor that is currently used in Australia for the prevention of stroke in patients with non-valvular atrial fibrillation as well as for postoperative VTE prophylaxis following knee and hip replacement surgeries. However, this drug is FDA approved in the United States for acute VTE treatment and secondary prophylaxis. The FDA approval of rivaroxaban for acute VTE treatment and secondary prophylaxis was largely based on the findings of the EINSTEIN program which consisted of three randomized trials.

The first clinical trial compared the efficacy and safety of rivaroxaban vs. heparin plus vitamin K antagonist for the acute treatment of DVT, and the second trial was similarly designed to compare efficacy and safety of rivaroxaban vs. a heparin plus vitamin K antagonist for the acute treatment of PE. The third randomized trial compared the long term efficacy and safety of rivaroxaban vs. placebo at endpoints of 6 to 12 months for patients who had already been taking rivaroxaban for treatment of acute VTE.

Both the acute DVT and PE treatment trials showed that rivaroxaban was non-inferior to standard therapy in preventing recurrent DVT and PE. After 12 months of treatment, the event rates for recurrent DVT were 2.1% vs. 3.0% in the rivaroxaban and standard therapy groups respectively. Recurrent PE occurred in 2.1% and 1.8% of patients in the rivaroxaban and standard therapy groups respectively at the 12 month endpoint after first incidence of PE. The percentage of patients experiencing major bleeding and clinically relevant non-major bleeding (the principal safety outcome) was similar in both studies comparing rivaroxaban vs. standard therapy for acute treatment of DVT and PE. In the long term study of rivaroxaban vs. placebo, rivaroxaban showed a reduction in the occurrence of VTE with 1.3% of patients experiencing VTE in the rivaroxaban group vs. 7.1% of patients in the placebo group. In this long term study of rivaroxaban 0.7% of patients experienced nonfatal major bleeding in the rivaroxaban group and none experienced nonfatal major bleeding in the placebo group.

If using rivaroxaban for treatment of VTE, the usual regimen involves initiation at a dose of 15 mg twice daily orally for the first 21 days, followed by 20 mg by once daily for the remainder of anticoagulant therapy. An advantage of rivaroxaban is that there is no need to overlap with a heparin when initiating therapy. However, the lack of an antidote to reverse the anticoagulant effect of rivaroxaban needs to be considered as a risk compared with traditional warfarin treatment.

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

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

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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

For adult males, an accepted definition of QT prolongation is when the interval exceeds:

a) 250 ms
b) 350 ms
c) 450 ms
d) 550 ms

Which of the following agents is been associated with QT interval prolongation

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

In the human lung, there are three muscarinic receptor types thought to be of relevance. Which muscarinic receptor is thought to be the most important mediator of bronchoconstriction, with blockade providing the basis for COPD treatment?

a) M_1
b) M_2
c) M_3
d) all of the above

In trials comparing glycopyrronium vs. placebo for COPD, which outcomes were observed with active drug intervention?

a) mean FEV_1 value was significantly higher when measured after 12 weeks and six months
b) significant improvement in breathlessness
c) lower incidence of moderate to severe COPD exacerbations
d) all of the above

Infliximab is a human monoclonal antibody produced from proteins derived from

a) humans and mice
b) humans and hampsters
c) humans and pigs
d) mice and hamsters

Indications currently approved by the Pharmaceutical Benefits Scheme (PBS) in Australia for infliximab

a) autoimmune hepatitis
b) systemic lupus
c) ulcerative colitis
d) erosive oesophagitis

After a first VTE, the approximate proportion of patients with a further VTE within the first year after treatment ends is:

a) 0.5-1.0%
b) 1-1.5%
c) 5-10%
d) >20%

Major bleeding during warfarin treatment for VTE occurs at an annual incidence of approximately

a) 1-2%
b) 2-3%
c) 3-4%
d) 5-5%