RGH E-Bulletin Digest Number 85

The next in our 2015 series of continuing professional development activities is the RGH E-Bulletin Digest No. 85 – edited by Associate Professor Chris Alderman.

This CPD activity assesses your understanding of four recent RGH Pharmacy E-Bulletins, Volumes 58-12→59-3 (June 2015).

Learning Objectives:

After completing this activity, pharmacists should be able to:

- Identify common causes of drug-induced hypertension
- Discuss the clinical pharmacology of lorcanserin and sodium oxybate
- Discuss the implications of the current literature relating to home BP monitoring and self-titration of antihypertensive treatment.

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: A1509AP1.
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.

apc ACCREDITED CPD

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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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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

Drug-induced hypertension

Many therapeutic agents can cause either a transient or persistent increase in blood pressure. This secondary hypertension (HT) may present as new onset HT or exacerbation of existing HT, or as difficult to treat HT.

While the drugs discussed below have been found to increase BP in some patients, it is important to assess the risk for each patient on an individual basis. Some factors that might increase a patient's risk for these drugs to increase their BP include: the dose of the drug taken, the patient's current blood pressure control, their co-morbidities, other medicines and the individual risk of each drug.

*Non-steroidal anti-inflammitories (NSAIDs) including cyclooxygenase 2 inhibitors (**Regular use**)*
Meta-analysis shows an average increase in systolic blood pressure (SBP) of 5 mm Hg in patients without HT and up to 14 mm Hg in those with existing HT. Inhibited of prostaglandin synthesis by NSAIDs reduces vasodilatory & natriuretic effects. Increased sodium & water retention activates the renin-angiotensin-aldosterone system (RAAS), increasing BP & attenuating antihypertensive effects of ACE inhibitors, angiotensin receptor blockers (ARBs), beta-blockers and diuretics.

Corticosteroids
Mineralocorticoid receptor stimulation results in sodium and fluid retention. Cortisone and hydrocortisone, which have the highest activity, cause the greatest fluid retention.

Hormones
Combined oral contraceptives and hormone replacement therapy increase BP through oestrogen activation of RAAS causing volume retention. Avoid the use of combined oral contraceptive if HT is not controlled.

Calcineurin Inhibitors
Cyclosporin and tacrolimus demonstrate a dose dependent increase in SBP of about 5-11 mmHg through vasoconstriction and increased sodium retention by activation of the kidney sodium chloride transporter.

Antidepressants
Venlafaxine, desvenlafaxine and reboxetine commonly cause HT through increased synaptic levels of serotonin and/or noradrenaline. HT related to monoamine oxidase inhibitors is usually associated with ingestion of tyrosine rich foods

Stimulants
Cocaine, amphetamines, caffeine, nicotine, alcohol, pseudoephedrine, phenylephrine (oral, nasal and ophthalmic instillations), modenafil, methylphenidate, and atomoxetine exert hypertensive effects through noradrenaline and or dopaminergic stimulation .

Other agents
Humanized monoclonal antibodies for VEGF and receptor tyrosine kinase inhibitors - HT is a dose limiting toxicity and may occur in up to 60% of patients. Erythropoiesis stimulating agents cause HT mainly through vasoconstriction. Typically, HT is associated with higher doses and possibly a higher mean haemoglobin rise. Complementary therapies are also implicated. Liquorice, which may be present in tobaccoless smoke, increases cortisol and fluid retention. Ephedra alkaloids and yohimbine are adrenergic stimulants. Others agents that have been reported to increase HT include coenzyme Q10, olive leaf, ginger, and Ma huang. Ginseng has been reported to cause both increased and reduced blood pressure.

Considering the high prevalence of polypharmacy, an awareness of the possibility of drug induced HT is prudent. Appropriate management is to select a different agent, reduce the dose or cease the offending agent for a limited duration. If discontinuation is not possible agents that counteract the mechanism of drug induced HT may be trialled.

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

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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

Sodium oxybate for excessive day time sleepiness in narcolepsy

Narcolepsy is an uncommon and complex neurological disorder that affects sleep control and wakefulness. People diagnosed with narcolepsy experience varied symptoms but excessive day time sleepiness is universal. Other symptoms can include cataplexy, which is described as a sudden loss of muscle tone, which leads to feelings of weakness and loss of voluntary muscle tone. Hypnagogic hallucinations are described as delusional experiences which are vivid and often frightening and which occur during sleep onset. Hynopompic hallucinations occur during awakening. Sleep paralysis is also a symptom of narcolepsy, as well as disruption to nocturnal sleep patterns and interrupted sleep. Apart from a physical examination and exhaustive medical history there are two tests which are considered essential in the diagnosis of narcolepsy. A polysomonogram (PSG) is performed over night to document abnormalities in the sleep cycle, and the multiple sleep latency test (MSLT) should be performed during the day to measure daytime sleepiness and to determine if isolated REM sleep occurs inappropriately during waking hours. Current therapy for the treatment of narcolepsy includes the use of stimulants such as dexamphetamine and modafanil. Abnormal symptoms of REM sleep are treated with antidepressant drugs.

Sodium oxybate has FDA approval in the USA for use to treat cataplexy in narcolepsy and for the treatment of excessive day time sleepiness (EDS) observed in narcolepsy. This agent is the sodium salt of gamma hydroxybutyrate (GHB), which is a known illicit intoxicant and a CNS depressant which is subject to abuse and misuse. Sodium oxybate is a CNS depressant but the mechanism of action in the treatment of narcolepsy is poorly understood. It is thought that sodium oxybate action is mediated through $GABA_B$ agonist action and at noradrenergic and dopaminergic neurons as well as thalamocortical neurons.

A systematic review and meta- analysis has been recently published; pooling data from 6 randomised controlled trials. This research found that treatment with sodium oxybate (in all of the trials) resulted in a significant reduction in cataplexy and EDS. The limitations of the meta analysis were a relative short follow up period and small sample sizes.

Sodium oxybate is an oral solution administered in two equal divided doses at night. The starting dose is 4.5g – with 2.25 g taken at bedtime and 2.25g taken up to 4 hours later. The dose can be titrated up to 6 - 9 g at night. This agent should be taken at least two hours after food as its bioavailability is significantly reduced. Each dose needs to be prepared and diluted prior to getting in to bed as sodium oxybate will cause abrupt sleep onset without first feeling drowsy. An alarm will need to be set to awaken for the second dose.

Sodium oxybate is a CNS depressant and in combination with other CNS depressants may increase the risk of respiratory depression, sedation, coma and death. Sleep-disordered breathing, depression and suicide risk, psychiatric adverse reactions, parasomnias, increased serum sodium levels, nausea, dizziness, vomiting, somnolence, enuresis and tremor have all been reported.

The Australasian Sleep Association guidelines recommends sodium oxybate as a second line treatment in the management of narcolepsy with and without cataplexy, and its use should be restricted to patients supervised by sleep physicians who actively manage patients with narcolepsy as regular clinical monitoring will be required.

The product is currently only available in Australia under auspices of the Special Access Scheme (SAS).

Acknowledgment – This E-Bulletin is based on work by Margie Harlow, Director of Pharmacy, 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

Lorcaserin – a new weight-loss drug

Rates of overweight and obesity have been increasing at an alarming rate in Australia over the last two decades. Obesity negatively affects quality of life in many ways, by increasing morbidity risk and reducing life expectancy. Despite being preventable, overweight and obesity continue to be major problems in the Australian population. Conventional lifestyle changes such as diet and exercise are first-line and effective in producing weight-loss; however without motivation and proper instruction these changes can revert back to old habits such as a sedentary lifestyle and a high-calorie intake diet. In Australia two widely used pharmacological treatments from obesity are orlistat (Xenical®) and phentermine (Duromine®). However recently in the US a new weight-loss drug – lorcaserin (Belviq®) – has come to market following FDA approval for long term weight management. Lorcaserin has not yet been approved in Australia by the Therapeutic Goods Administration, but with growing demand it may well make its way into the Australian market in the future.

Lorcaserin is a serotonin-2C agonist. Its mechanism is based on the principle that when the serotonin-2C receptor is activated in the hypothalamus, appetite and therefore food intake is reduced. It is dosed at 10 mg twice daily, and is indicated for patients with a BMI > 30kg/m2 or BMI > 27kg/m^2 with comorbidities.

Three clinical studies were used to provide evidence for FDA approval of lorcaserin: Behavioural Modification and Lorcaserin for Overweight and Obesity Management (BLOOM), Behavioural Modification and Lorcaserin Second Study for Obesity Management (BLOSSOM) and BLOOM-Diabetes Mellitus (BLOOM-MD). The BLOOM and BLOSSOM studies included volunteers with a BMI > 30kg/m^2 or a BMI > 27kg/m^2 with one comorbidity. The BLOOM study found that participants taking lorcaserin had an average weight loss of 5.8 ± 0.2kg after one year compared to 2.2 ± 0.1kg with placebo ($p < 0.001$). The BLOSSOM study had similar results. The BLOOM-MD study included diabetic patients with a BMI of 27-45 kg/m^2 and an HbA1C of 7-10%. This study produced similar results in terms of weight lost, and also showed a reduction in HbA1C of 0.9 ± 0.6 with lorcaserin compared to 0.4 ± 0.6 with placebo ($p < 0.001$). Energy intake and hunger ratings were also reduced. In all three studies, both the lorcaserin and placebo groups were counselled on diet and exercise.

In clinical trials the most common adverse effects were headache, nausea, dizziness, fatigue, dry mouth and constipation. These were generally mild and resolved quickly, and the drug was generally well tolerated. The main precaution with lorcaserin is that it should not be combined with SSRIs or MAOIs due to the risk of serotonin syndrome.

Issues have been raised surrounding two previously FDA approved serotonergic weight-loss drugs – fenfluramine and dexenfluramine – which were taken off the market as they were observed to cause cardiac valvulopathies. These drugs activate serotonin-2B receptors. Lorcaserin, however, selectively targets the serotonin-2C receptor and not the serotonin-2B receptor, so it is thought that damage to heart valves is not likely. This was confirmed during phase III trials, when the relative risk of FDA-defined valvulopathy in participants taking lorcaserin was reported to be 1.16 (95% CI 0.81-1.67), not statistically significant.

Lorcaserin produced promising results in initial studies and may have a future as the next big weight-loss drug in Australia; however it is important for patients to realise that there is no ‘magic pill’ for overweight and obesity, and that a balanced diet and sufficient exercise are always important whether they are taking a weight-loss medication or not.

Acknowledgment – This E-Bulletin is based on work by Jasmine Peters, Pharmacy Intern, RGH

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Editor: Assoc. Prof. Chris Alderman, University of South Australia

Home BP self-monitoring & self-titration of antihypertensives

Elevated blood pressure is one of many cardiovascular risk factors. Self-management refers to an individual's ability to manage the symptoms, treatment, physical and psychosocial consequences and lifestyle changes associated with a chronic condition. Self-management of blood pressure has included home based monitoring and adherence to medication and lifestyle activities. Clinical studies compared the addition of self-titration of antihypertensive medication to home based monitoring with usual care for the management of elevated blood pressure.

Advantages of blood pressure home monitoring include patient engagement and responsibility, a truer reflection of a patient's underlying blood pressure including variability, assessment of white-coat and masked hypertension, and assessing response to management. Interventions using home based monitoring produce larger reductions in blood pressure than those using office based measurement.

A recent clinical trial has demonstrated home based monitoring combined with self-titration of medication produced greater systolic BP reductions than usual care over one year in primary care patients with BP >140/90. Reductions were 5.4 mm Hg greater. Self-titration was directed by a predetermined plan agreed upon with the patient's doctor. The dropout rate at the end of 12 months was about 30% and adherence to the treatment protocol diminished over time. A subsequent primary care trial assessing self-titration included patients with a history of stroke, coronary heart disease, diabetes, or chronic kidney disease and baseline BP of ≥ 130/80 mm Hg. Mean BP over the 12 month course of the study had declined to 128.2/73.8 mm Hg in the intervention group vs 137.8/76.3 mm Hg in the control group- a significant difference of 9.2/3.4 mm Hg. There was no excess of adverse events.

Attitudes of patients involved in the studies included positivity towards home monitoring and enthusiasm for the opportunity to manage their own medications. Conversely other patients required extra supervision in spite of training. A reported difficulty in decision making concerned borderline elevations where patients demonstrated inertia. Instruction and training of 2-3 hours were among identified key factors for success in the studies. Doctors were impressed at the ability of patients to self-manage; however, identifying training demands were challenging. Thorough training in home monitoring leads to confidence for both patients and professionals of the validity of readings fostering partnership to maximise the benefit of home measurement.

Research suggests that selected patients with elevated blood pressure requiring treatment, including those with high cardiovascular risk, can use home based self-monitoring and medication self-titration in line with an agreed individualised plan from their doctor to effectively lower blood pressure over a one year period. However, more research is required into performance and persistence with self-titration protocols before implementation into clinical practice is recommended.

Acknowledgment – This E-Bulletin is based on work by Dr Brian Simmons, DATIS, 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:

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

Which of the following agents is most prominently associated with drug-induced hypertension?

a) fluoxetine
b) mirtazapine
c) venlafaxine
d) doxepin

Which of the following complementary medicines has been reported to be associated with increased BP?

a) liquorice extract
b) ginseng
c) olive leaf extract
d) all of the above

People with narcolepsy may experience hypnagogic hallucinations, which are best described as:

a) vivid and often frightening delusional experiences which occur during sleep onset
b) vivid and often frightening delusional experiences which occur during awakening from sleep
c) disturbing conscious daydreams that happen during waking hours
d) severe nightmares that happen during the course of usual sleep

Sodium oxybate has a close structural relationship to which illegal intoxicant?

a) “ecstasy” or MDMA
b) gamma hydroxybutyrate or GHB
c) tetrahydrocannabinol or THC
d) phencyclidine or PCP

Lorcaserin is new agent that has been approved as a means to help with weight loss. The mechanism of action is as:

a) a serotonin-2C agonist
b) a serotonin-2C antagonist
c) a serotonin-1A agonist
d) a serotonin-1A antagonist

Previously FDA-approved serotonergic weight-loss drugs (fenfluramine & dexenfluramine) were withdrawn from the US market as they were observed to be associated with:

a) congestive cardiac failure
b) cardiac valvulopathies
c) mycocarditis
d) cardiac arrhythmias

Advantages of blood pressure home monitoring are thought to include:

a) greater patient engagement and responsibility
b) a truer reflection of blood pressure variability
c) less emphasis on elevated BP that might reflect “white coat hypertension”
d) all of the above

A recent clinical trial demonstrated home based blood pressure monitoring combined with self-titration of medication produced:

a) greater systolic BP reductions than usual care over one year in primary care patients with BP >140/90
b) greater diastolic BP reductions than usual care over one year in primary care patients with BP >140/90
c) greater systolic BP reductions than usual care over one month in primary care patients with BP >160/80
d) greater diastolic BP reductions than usual care over one month in primary care patients with BP >160/80