RGH E-Bulletin Digest Number 91

The next in our 2016 series of continuing professional development activities is the RGH E-Bulletin Digest No. 91 – edited by Associate Professor Chris Alderman.

This CPD activity assesses your understanding of four recent RGH Pharmacy E-Bulletins, Volumes 60-12 → 61-3 (November 23 → December 14, 2015).

Learning Objectives:

After completing this activity, pharmacists should be able to:

- Describe the nature of the potential relationship between pholcodine exposure and adverse reactions to neuromuscular blocking agents
- Discuss the potential role of nicotinamide in the prevention of non-melanoma skin cancer
- Describe the possible effects of vitamin K derivatives in the maintenance of bone health
- Discuss the clinical pharmacology of lurasidone.

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: A1603AP1.
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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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

Pholcodine and neuromuscular blockade

Pholcodine is an over the counter medicine in Australia that is used for the relief of dry cough. Pholcodine (3-(2-morpholinoethyl) morphine is a morphine molecule derivative with a morpholino side-chain. Unlike morphine, pholcodine does not relieve pain, or cause significant respiratory depression or CNS excitation. It is thought to have no euphoric properties and there is no apparent significant risk of addiction. Pholcodine is available in products as a single ingredient, but is also present as an ingredient in various cough and cold preparations that include multiple active ingredients.

There is an apparent link between pholcodine exposure and anaphylactic reactions associated with neuromuscular blocking agents (NMBA), which can lead to perioperative morbidity and mortality. Pholcodine is a strong inducer of the Immunoglobulin E (IgE) antibody response. Scandinavian data suggests that susceptible people (about 20 to 25% of the population examined in this research) taking pholcodine may become IgE sensitized - once sensitized, pholcodine re-exposure will boost IgE antibody levels and IgE by around a 100-fold. The main allergenic determinant of NMBA sensitivity is the quaternary ammonium ion (QAI) epitope which is also found in pholcodine (and various other chemicals and drugs). Anaphylaxis occurring with NMBA is thought to be primarily mediated through IgE antibodies that bind QAI epitopes.

Research from Norway found that there was a 10 fold higher incidence of anaphylactic reactions to NMBA in this country compared to that observed in Sweden. It is noteworthy that pholcodine use in Norway was widespread compared to Sweden where the drug was not available.

A small randomized trial examined 17 patients with a history of NMBA anaphylaxis who were randomised to receive a cough syrup containing either pholcodine or guaiphenesin for one week. Serum IgE and IgE antibodies were measured before the drug exposure, and the measurement was repeated at endpoints 4 and 8 weeks after exposure. Patients exposed to pholcodine had a sharp rise in levels of IgE antibodies to suxamethonium, morphine and pholcodine. There was no change in the guaiphenesin group. This study showed that serum levels of IgE antibodies associated with allergy towards NMBA increased significantly in sensitized patients after exposure to cough medicine containing pholcodine.

In 2007, based on data supporting an association between pholcodine exposure and rates of NMBA anaphylaxis, pholcodine was withdrawn from the Norwegian market. Three years after withdrawal, there was a significant reduction in anaphylactic reactions to NMBA in Norway.

The European Medicines Agency (EMA) in 2011 has concluded that the benefits of pholcodine outweigh its risks, and although a cross-sensitization between pholcodine and NMBA is biologically plausible, the available data is weak and not fully consistent. Whilst the data from Sweden and Norway seem credible, the epidemiological evidence from a small geographical region is not sufficient to prove a causal link between NMBA anaphylaxis and pholcodine. Whether the QAI mechanism or another mechanism exists, the exact mechanism is unclear. Continued monitoring and reporting of this interaction remain important.

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

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

Nicotinamide for skin cancer prevention

A recent study published in the New England Journal of medicine (ONTRAC) was conducted at the Royal Prince Alfred and Westmead Hospitals in Sydney, investigating the use of nicotinamide for non-melanoma skin cancers and actinic keratosis.

It is well known that non melanoma skin cancers such as basal cell carcinomas (BCC) and squamous cell carcinomas (SCC) are the most common cancers in white populations and in Australia are four times more common as all other cancers combined.

Nicotinamide is the amide of nicotinic acid (vitamin B3 / niacin). In cells, niacin is incorporated into nicotinamide adenine dinucleotide (NAD) and nicotinamide adenine dinucleotide phosphate (NADP), although the pathways for nicotinic acid amide and nicotinic acid are very similar. NAD+ and NADP+ are coenzymes in a wide variety of enzymatic oxidation-reduction reactions. Nicotinamide prevents ATP depletion and glycolytic blockade induced by UV radiation and as a consequence improves cell energy and repair. It also reduces immunosuppression induced by exposure to UV radiation. UV radiation and exposure to UV light is the primary cause of non-malignant skin cancers and actinic keratosis. Reducing skin exposure and sunscreen application is primarily aimed to reduce the incidence but application and adherence of sunscreens can be less than satisfactory.

This study was a phase 3 double blind randomised controlled trial of 386 participants who had at least two non-melanoma skin cancers in the previous 5 years. Study participants were randomly assigned 500 mg of nicotinamide twice a day or placebo for a period of 12 months. Skin cancers checks were performed by dermatologists blinded to treatment groups at baseline and then 3 monthly for a total period of 18 months. Patient characteristics were similar in the 2 groups at each hospital and median rate of adherence to treatment in the placebo or nicotinamide groups was 96% in the placebo group and 94 % in the nicotinamide group.

The primary end point of this study was the number of new confirmed non melanoma skin cancers over the 12 month study period. Secondary end points included the number of new BCC's, SCC's and actinic keratosis during the study period and for 6 months after and the safety and efficacy of nicotinamide as assessed by adverse events. The rate of new non melanoma skin cancers was significantly lower in the nicotinamide group than in the placebo group by 23% at 12 months. The average number of actinic keratoses was 11% in the treatment group at 3 months, 14% at 6 months, 20 % at 9 months and 13% at 12 months compared to placebo. The number and type of adverse events reported between each group was similar but it was determined there was no clinically significant differences between each group.

This study demonstrates that nicotinamide is a safe and effective treatment in reducing the rates of new non-melanoma skin cancers and actinic keratoses in a group of high risk patients. Nicotinamide is available as an over the counter preparation vitamin supplement from pharmacies and is relatively inexpensive and provides a novel treatment choice for prevention of non-melanoma skin cancers is certain population groups.

Acknowledgment – This E-Bulletin based on work by Margie Harlow, Deputy Director, Distribution Services, RGH

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

Vitamin K2 in osteoporosis

The vitamin K (Vit K) group consists of a range of naphthoquinone compounds that includes phylloquinone or phytomenadione (Vit K1), menatetrenone or menaquinone (Vit K2), menadione (Vit K3), acetomenaphthone or menadiol (Vit K4) and 4-Amino-2-Methyl-1-Naphthol (Vit K5). Vit K2 is designated as MK-1 to MK-13 according to the length of the side chain and the forms that have been most studied are MK-4 and MK-7.

A number of findings have related Vit K status to bone health and as Vit K is a cofactor involved in the carboxylation of osteocalcin, a protein believed to be involved in bone mineralization, it has been suggested that supplementation with Vit K may reduce the risk of osteoporosis. However, evidence on the effects of Vit K on bone mineral density (BMD) and fracture risk in people with osteoporosis is conflicting.

A number of studies in postmenopausal women given 15–45 mg of Vit K2 MK-4 orally daily, reported improved BMD and reduced vertebral or non-vertebral fractures. However, the treatment differences were modest, studies were small, of short duration, were only in Japanese women, not blinded, were compared to placebo and doses of 45 mg are considered to be 500 fold higher than considered adequate for osteocalcin carboxylation. A larger Japanese study and a smaller study in elderly American women using the same supplement and dose found no effect. In 2006, Cockayne and colleagues conducted a systematic review and meta-analysis of randomized controlled trials that examined the effects of Vit K2 supplementation on BMD and bone fracture and reported that supplementation with Vit K1 or Vit K2 MK-4 improved BMD in 12 out of 13 trials. Again, trials were of poor quality, used high doses of Vit K2, lasted from 6 to 36 months and were mostly conducted in Japanese postmenopausal women. Reduction in fracture was reported, although this was not a primary outcome, so caution should also be taken when interpreting this finding. In addition, the prevailing Japanese diet might have confounded findings. A subsequent review in 2009 confirmed this uncertainty of effectiveness of Vit K in the treatment of osteoporosis.

A small trial investigating the effects of Vit K2 MK-7, which has a longer half-life and greater potency than Vit K2 MK-4, found that supplementation at a dose of 180 mcg/day for 3 years in postmenopausal women, decreased loss in vertebral height and slowed reduction of bone loss over 3 years at lumbar spine and femoral neck but not total hip. More recently (2015) a meta-analysis of 19 randomised controlled trials concluded that Vit K2 may play a role in the slowing of vertebral bone loss in postmenopausal women with osteoporosis, although no significant effect could be demonstrated for fractures. When administered orally, Vit K2 has been safely used in clinical trials lasting 1–3 years. All Vit K preparations antagonize the effects of oral anticoagulants such as warfarin. Antibiotics can destroy vitamin K-producing bacteria in the gut, potentially decreasing vitamin K status. Bile acid sequestrants, orlistat and any conditions reducing the body's absorption of dietary fat can also reduce the absorption of fat-soluble vitamins, such as vitamin K. Forty-nine different preparations containing Vit K2 MK-7, from 0.017 mcg to 180 mcg, have been listed with ARTG, as either single or multi-ingredient preparations. Preparations including VitK2 MK-4 are not available.

From the lack of good quality randomised controlled trials in sufficiently large numbers of patients, further studies are needed to understand the potential benefits of Vit K2 in the treatment of osteoporosis, and therefore routine supplementation is not currently recommended.

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

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

Lurasidone – a new antipsychotic

Lurasidone (Latuda®) is a newly registered antipsychotic drug. As with other antipsychotics, the mechanism of action of the drug is not fully understood. However it is believed that the effects of lurasidone are mediated through blockade of dopaminergic transmission through antagonist activity at the D2 receptor. Lurasidone also antagonises 5HT7 and 5HT2A receptors and is a partial agonist of 5HT1A.

Lurasidone is indicated for schizophrenia and is available in Australia as 40 mg and 80 mg tablets, which can be subsidised under the PBS with a streamlined authority. The lurasidone product information recommends a starting dose of 40 mg once daily with a maximum daily dose of 160 mg. The peak plasma concentration of lurasidone is reached 1-3 hours after oral administration, with steady state concentration taking approximately seven days to attain and an elimination half-life of 18 hours. Lurasidone is mainly excreted by the kidneys.

The efficacy of lurasidone has been established at doses of 40 mg, 80 mg, 120 mg and 160 mg once daily in several short-term, placebo-controlled trials. Five trials have assessed the efficacy of lurasidone based on Positive and Negative Syndrome Scale (PANSS) or Brief Psychiatric Rating Scale derived from PANSS scale (BPRSd) over six-weeks. All five trials found lurasidone at the various strengths listed above to be significantly more effective than placebo as measured using the PANSS or BPRSd. One trial was extended to assess the long-term efficacy of lurasidone compared to quetiapine. At 12 months, the estimated probability of relapse in people receiving lurasidone was 23.7% compared with 33.6% in those receiving quetiapine. In another comparative study that enrolled patients with stable schizophrenia, this time comparing with risperidone, it was found that after 12 months 20% of people receiving lurasidone had relapsed compared with 16% receiving risperidone.

In common with other antipsychotics, adverse effects can differ depending on duration of treatment. Based on the short-term trials referred to above, the most common adverse effects were somnolence, extrapyramidal symptoms, akathisia, insomnia and nausea. In terms of longer-term metabolic adverse effects with relation to weight gain, it was found in longer-term comparative studies that people taking lurasidone were less likely to have gained weight than those taking risperidone.

As reflected in the approved product information, consideration of dose modification needs to be taken into account for patients with moderate to severe renal impairment or moderate hepatic impairment, in which the recommended starting dose is 20 mg. Lurasidone should not be used in patients with severe hepatic impairment. Lurasidone is metabolized by CYP3A4. Concomitant use of strong CYP3A4 inhibitors or inducers is contraindicated with lurasidone, however dose reductions can be made if a patient is taking a moderate CYP3A4 inhibitor. This course of action is dependent on individualised clinical judgement.

Schizophrenia is a mental illness that is often difficult to treat, even with optimized antipsychotic drug therapies. While evidence is lacking with regards to comparative efficacy data between lurasidone and other antipsychotics, this novel antipsychotic may be able to assist patients who have experienced treatment failure with other agents in the past.

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

FOR FURTHER INFORMATION – CONTACT PHARMACY DEPARTMENT ON 08 7425 0040 or email: chris.alderman@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

Pholcodine is an over the counter medicine chemically related to which of the following?

a) aspirin
b) tramadol
c) diclofenac
d) morphine

Research suggests that amongst people previously exposed to pholcodine, the incidence of anaphylactic reactions to neuromuscular blocking agents such as suxamethonium may be increased by a factor of

a) two-fold
b) five-fold
c) ten-fold
d) one hundred-fold

Nicotinamide is structurally related to:

a) vitamin B1
b) vitamin B3
c) vitamin B6
d) vitamin B12

Research suggests that when administered to at-risk people, nicotinamide can help to prevent:

a) malignant melanoma
b) plantar warts
c) actinic keratoses
d) dysplastic naevi

The possible role for vitamin K in the preservation of bone health may be related to:

a) the actions of vitamin K as a cofactor involved in the carboxylation of osteocalcin
b) the potentiation of the actions of parathyroid hormone
c) induction of the metabolism of vitamin D2
d) decreased gastrointestinal absorption of free calcium

The administration of vitamin K2:

a) has no effect upon the efficacy of warfarin
b) increases the efficacy of warfarin
c) reduces the efficacy of warfarin
d) none of the above

As well as exerting antagonist activity at the Dopamine D2 receptor, lurasidone also

a) antagonises 5HT7 and 5HT2A receptors and is a partial agonist of 5HT1A
b) acts as an agonist at 5HT7 and 5HT2A receptors and is a partial agonist of 5HT1A
c) acts as an agonist 5HT7 and 5HT2A receptors and an antagonist of 5HT1A
d) antagonises 5HT7 and 5HT2A receptors and is also an antagonist of 5HT1A

The usual starting dose of lurasidone is:

a) 20 mg once daily
b) 40 mg once daily
c) 20 mg twice daily
d) 40 mg twice daily