RGH E-Bulletin Digest Number 86

The next in our 2015 series of continuing professional development activities is the RGH E-Bulletin Digest No. 86 – edited by Associate Professor Chris Alderman.

This CPD activity assesses your understanding of four recent RGH Pharmacy E-Bulletins, Volumes 59-4→59-7 (July 2015).

Learning Objectives:

After completing this activity, pharmacists should be able to:

- Understand patterns and causes of medication errors that occur in institutional settings
- Discuss the clinical pharmacology of vortioxetine
- Describe the basis of allergy to latex used in medical products, including drug products
- Outline recent advances announced in releases by the US Food and Drug Administration.

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: A1510AP1.
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

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.

AusPharm gratefully acknowledges the financial support provided by the sponsors of our CPD program, **MIMS**

MIMS 100% pure knowledge

RGH Pharmacy E-Bulletin

Volume 59 (4): July 6 2015

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

Medication safety principles

Despite the best efforts of people working in the various settings where patient care is delivered, it is well known that medical error is common, spans the various disciplines involved in delivering health care, and has serious adverse impacts upon the lives of patients and staff. The issue is not new: the Latin phrase *Primum non nocere* has often been attributed to Hippocrates, and alternatively the Greek physician Galen of Pergamon, but in all likelihood found its first application but the English physician Thomas Sydenham (1624-1689). In modern day time, the imperative to ensure that patient care should not cause harm has gathered impetus through the findings of research that has provided introspection upon the work of those working in the provision of patient care - for example the famous Harvard Medical Practice Study involved review of the medical charts of 30,121 patients admitted to 51 acute care hospitals in New York state in year 1984. In 3.7% of cases an adverse event led to prolonged admission or produced disability at the time of discharge – 69% of injuries were caused by errors. Similarly, The Quality in Australian Health Care Study (1995) examined the medical records of over 14,000 admissions to 28 hospitals in New South Wales and South Australia and found that 16.6% of these admissions were associated with an "adverse event", which resulted in disability or a longer hospital stay for the patient and was caused by health care. In this study, 13.7% of cases were associated with permanent disability and in 4.9% of cases the patient died.

Adverse events in health care arise from many sources - issues include surgical errors, falls in health care, nosocomial infection and others. There can be no doubt that medication errors can make a major contribution to harm arising from health care. Issues that contribute to medication-related harm include, but are not limited to:

- Wrong drug selected for administration
- Wrong dose administered
- Dose given when order held, or held in error
- Medication given to the wrong patient (especially in hospitals & nursing homes)
- Wrong route of administration
- Misinterpretation of orders
- Dispensing errors

Research in hospitals shows that medication errors are most likely for those undergoing complex surgery, for people with complex conditions, people treated in the emergency room, those treated by less experienced doctors, and for the elderly. The reality is that most of medicine is complex and uncertain. Most errors result from systems-related issues, such as a failure in training, working long hours, using products that have a physical similarity to others, and a lack of systemic checking procedures. The approaches that have been proven to be most effective in reducing error include those that reduce the complexity of processes, the deployment of checklists, reminders, protocols, automation and electronic systems, and the delivery of targeted training.

Dr James Reason, regarded by many as a leading founder in the movement to make health care safer, advanced the proposition that approaches in the prevention of human error can fall into two classes: person and system approaches. The person approach focuses on the errors of individuals (blaming for forgetfulness, inattention, or moral weakness etc.), whereas system approaches concentrate on the conditions under which individuals work and tries to build defenses to avert errors or mitigate their effects. Reliable organisations recognise that human variability is inevitable and that humans are fallible and errors expected, even in the best organisations, and that countermeasures should be based on the assumption that though we cannot change the human condition, we can change the conditions under which humans work. System defenses are important, in that all hazardous technologies involve barriers and safeguards. When a mistake happens, the important issue is not to attribute blame, but to find how and why the defenses against the error did not prevent it.

Acknowledgment - This E-Bulletin is based on work by Chris Alderman, Director of Teaching, Training and Research, SA Pharmacy

RGH Pharmacy E-Bulletin

Volume 59 (5): July 13 2015

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

Vortioxetine

Vortioxetine is a new antidepressant drug with a multimodal action. Although its mode of action is not understood with certainty, it exerts its effect through enhancement of serotonergic activity. It inhibits the reuptake of serotonin by binding with high affinity to serotonin transporter but lower affinity to noradrenaline and dopamine transporters. It may have affinity for 5-HT1A, 5-HT1B, 5-HT 1D, 5-HT3 and 5-HT7 receptors but whether there is beneficial clinical effect associated with effects at these receptors remains to be established.

Ten short-term, placebo-controlled clinical trials (including one for elderly patients) and one maintenance trial (recurrence prevention) have been conducted over 6-8 weeks duration (subjects aged 18 to <75 years, and in the elderly study ≥ 64 years) assessing this drug for the treatment of major depressive disorder. The primary efficacy endpoints in the short term studies were the change from baseline on either Montgomery Asberg Depression Rating Scale or the Hamilton Depression Rating Scale. Study populations across the nine short term studies (not including the study focusing on the elderly population) were similar in terms of disease characteristics and demographics, but there were differences in racial distribution. Most subjects were Caucasian (79%), followed by those who were black (18%) and Asian (1%). The mean ages of the patients were between 42 and 47 years; 34% males and 66% females. In the elderly study, the mean age of patients was 71 years. There were seven positive outcomes, and of the remaining four studies, three produced negative results and one was described as a failed study. The maintenance study was conducted in 396 patients who were treated with vortioxetine 5 mg or 10 mg daily for 12 weeks, and then randomised to continue treatment or to receive placebo. After 24 weeks, the rate of relapse was lower in the Vortioxetine group (13%) then in the placebo group (26%).

Vortioxetine has a linear, dose proportional pharmacokinetic profile. The half-life is approximately 66 hours and steady state plasma concentrations are reached within 2 weeks. The drug does not have an active metabolite. Moderate hepatic impairment and renal impairment do not appear to affect the clearance of Vortioxetine, but this agent has not been studied in patients with severe hepatic impairment. It is extensively metabolised primarily via CYP2D6 and poor metabolisers of CYP2D6 have twice the Vortioxetine plasma concentration of extensive metabolisers. Caution is suggested if he drug is coadministered with CYP 2D6 inhibitors (e.g. bupropion, fluoxetine, paroxetine and quinidine,) and in the situation a recommended maximum dose of 10 mg is suggested. If CYP2D6 inducers are used concurrently (e.g. rifampicin), a higher dose may be required.

Nausea is the most common side effect and is dose related. Others adverse effects include constipation, vomiting and sexual dysfunction. Vortioxetine was not associated with clinically important changes in laboratory tests but hyponatraemia has been reported and may be more common in the elderly.

The dose of vortioxetine ranges from 10 mg to 20 mg daily. A recommended starting dose in the elderly is 5 mg. Because of its long half-life, vortioxetine can be discontinued abruptly, but it is recommended that with doses of 15-20 mg daily, the dose be reduced to 10 mg daily for one week then ceased to avoid withdrawal effects. Risk of serotonin syndrome is elevated with concurrent serotonergic drugs.

Vortioxetine is not currently marketed in Australia but it has been approved by the United States FDA in September 2013.

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

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

RGH Pharmacy E-Bulletin

Volume 59 (6): July 20 2015

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

Latex allergy and injectable products

Natural latex is harvested from rubber trees and is the raw material that is used to make rubber products: natural rubber latex products and dry natural rubber products. Products that use natural rubber include medical gloves, some catheters and condoms. Dry natural rubber products include vial stoppers, dry rubber plungers for syringes and some ports used for IV injections. The process for manufacturing these two products is different – whereas the natural rubber latex manufacturing processes involve dipping, extruding or coating, dry natural rubber manufacturing processes involve compression, moulding or extrusion. The composition of natural rubber content and protein content of a rubber product depend upon the manufacturing process. Medication vial stoppers contain denatured latex proteins (as a result of the dry moulding process) and are less antigenic than natural rubber latex products. Even so, some of the proteins remain in finished products regardless. The protein content may also vary from batch to batch.

Immediate hypersensitivity reactions have been associated with exposure to rubber gloves, condoms, catheters, and even sporting equipment. Clinical features include urticaria, rhinitis, conjunctivitis, bronchospasm and anaphylaxis. These immediate hypersensitivity effects (Type 1) are IgE mediated and are nearly always elicited by proteins present in natural rubber. The proteins may cause antibody production that increases with each subsequent exposure. These reactions are associated with genetic factors that render some people more sensitive. It has been suggested that about 1% of the population of the USA is affected by allergy to natural rubber. The highest prevalence is seen amongst those with occupationally exposure (e.g. hospital staff, who have the highest at prevalence 5-15%.)

Rubber antigen exposure can occur by cutaneous, percutaneous, mucosal and parenteral exposure. The antigen can also be transferred by direct contact and aerosol transmission. Although severe systemic reactions have occurred after cutaneous and respiratory exposure, direct mucosal and parenteral exposure are associated the greatest risk of anaphylaxis. Deaths caused by rubber allergy reported to the FDA have been associated with rubber-containing enema catheters. Over 90% of all reactions reported are due to products produced by the dipping – e.g. rubber gloves and catheters.

It is possible that antigens may be released from medication stoppers and injection ports of intravenous tubing, and this has been suggested as the cause of otherwise unexplained anaphylaxis in patients with natural rubber allergy. One study has demonstrated that natural rubber vial stoppers release sufficient latex protein to elicit positive intradermal skin reactions.

Guidelines for avoidance have been published by the American College of Allergy, Asthma and Immunology (ACAAI) and recommend that 'latex' free medical products should be available on hospital wards. If a product free of natural rubber is not available, one approach involves the removal of the stopper and the drug being drawn directly into a syringe from the open vial. Even so, removal of the dry natural rubber stopper from vials does not necessarily yield solutions with less latex allergen than solutions prepared conventionally.

Manufacturers of pharmaceuticals cannot exclude the use of latex gloves during the manufacturing process. Also, it is possible that information can change on a year to year basis, depending supply sources for medicines, which can vary. It is recommended that those with a latex allergy to always check prior to the administration of the product and not to rely on previous recommendations. The only way to determine whether the product is latex free is to contact the sponsor company supplying the product directly.

Acknowledgment – This E-Bulletin based on work by Chris Alderman, Director of Teaching, Training & Research, SA Pharmacy, help from Tricia Warrick, DATIS, RGH

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

RGH Pharmacy E-Bulletin

Volume 59 (7): July 27 2015

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

FDA update – July 2015

The US Food and Drug Administration (FDA or USFDA) is a well known agency of the United States Department of Health and Human Services. The FDA serves in the interests of public health, principally regulating food safety, tobacco products, dietary supplements, medications, vaccines, blood products, medical devices, cosmetics, and veterinary products. The scope of the work of the FDA is huge. Noteworthy news announcements are issued on a regular basis and address a range of clinical issues relating to therapeutics, drug safety and cost-effective use of medications. This E-Bulletin summarises some recent media releases from the FDA:

On 24 July 2015, US FDA approved alirocumab injection, the first of a new class of drugs known as proprotein convertase subtilisin kexin type 9 (PCSK9) inhibitors, used as a treatment for lowering serum cholesterol. This drug is an antibody that targets a specific protein (PCSK9): this protein works by reducing the number of hepatic receptors that remove LDL cholesterol from the blood. By blocking the effects of the enzyme, there is a greater activity to remove LDL cholesterol from the blood. Common adverse effects include injection site reactions, nasopharyngitis, and flu-like symptoms.

Also on 24 July, the FDA approved sonidegib to treat locally advanced basal cell carcinoma that has recurred following surgery or radiation. Administered orally, the drug inhibits a key enzyme pathway that is active in basal cell cancers. At the recommended dose of 200 mg daily, sonidegib is associated with side effects including muscle spasms, alopecia, dysgeusia, fatigue, nausea, musculoskeletal pain, diarrhoea, myalgia and pruritus. The drug is associated with foetal death and major foetal malformations and thus should not be administered to pregnant women.

Earlier in July 2015, the FDA approved brexpiprazole for the treatment of schizophrenia, and as an add-on treatment to antidepressants to treat major depressive disorder. The most common side effects reported in clinical trials included weight gain and akathisia.

Another therapeutic agent recently approved for marketing by the FDA is a combination product that includes sacubitril (a neprilysin inhibitor) and valsartan (an angiotensin II receptor blocker), for the reduction of risk of cardiovascular death and hospitalization in patients with chronic heart failure (NYHA Class II-IV) and reduced ejection fraction.

Also in July 2015, the FDA strengthened an advisory statement regarding the risk of adverse cardiovascular events during treatment with NSAIDs. The advisory reports an increased risk of serious cardiovascular thrombotic events, including myocardial infarction and stroke, citing a “large number of studies that support this finding, with varying estimates of how much the risk is increased. Estimates of increased risk range from 10 percent to 50 percent or more, depending on the drugs and the doses studied.” The FDA notes that the increase in cardiovascular thrombotic risk has been observed most consistently at higher doses, and that the risk conferred by NSAID use appears to be similar in those with and without known cardiovascular disease or risk factors for cardiovascular disease. It also notes that some NSAIDs can interfere with the antiplatelet action of low dose aspirin.

Acknowledgment – This E-Bulletin based on work by Chris Alderman, Director of Teaching, Training & Research, SA Pharmacy.

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

References used in the preparation of the relevant E-Bulletins:

http://accesspharmacy.mhmedical.com/content.aspx?bookid=462&sectionid=41100771

http://www.health.gov.au/internet/main/publishing.nsf/content/nmp-pdf-resguide-cnt.htm

http://www.shpa.org.au/lib/pdf/positionstatement/Medication_safety_position_statement.pdf

The US Food and Drug Administration's Perspective on the new antidepressant Vortioxetine. J Clin Psychiatry 2015; 76(1): 8-14

Vortioxetine: A review of its use in Major Depressive Disorder. Drugs 2014; 28: 855-874

Smith CC. Risk of latex allergy from medication vial closures. Ann Pharmacother. 1999; 33: 373-4

Ask the Expert on . . . Latex Content in Medicines. http://www.medscape.com/viewarticle/506438

http://www.fda.gov/Drugs/default.htm

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

Regarding medication errors in institutional healthcare, which of the following causes are most commonly implicated?

a) systems errors – e.g. insufficient training, poor access to information resources
b) individual errors – e.g. inattention to detail, lack of regard for consequences
c) errors involving potentially criminal culpability – diversion of drugs, systematic cover-ups
d) errors directly generated by computers or other forms of information technology

Which of the following groups are known to be at increased risk for medication errors?

a) people undergoing complex surgery
b) those treated in the emergency room
c) those treated by less experienced doctors
d) all of the above

The recommended starting dose of vortioxetine for older people is:

a) 2.5 mg daily
b) 5 mg daily
c) 20 mg daily
d) 25 mg daily

The adverse effect most commonly associated with vortioxetine is?

a) hyponatraemia
b) erectile dysfunction
c) nausea
d) constipation

Hypersensitivity reactions to latex are most prominent amongst people with recurrent exposure. In hospitals, the prevalence may be as high as:

a) 1 – 2%
b) 2 -5 %
c) 5 – 15%
d) 25 – 30%

Immediate hypersensitivity reactions after latex exposure are thought to be:

a) related to effects mediated by IgE
b) caused by exposure to lipid complexes in latex
c) unrelated to underlying genetic factors
d) mostly related to dry natural rubber manufacturing processes involving compression, moulding or extrusion

Alirocumab is the first of a new class of drugs that can be used to manage some forms of:

a) heart failure
b) atrial fibrillation
c) hypertension
d) hyperlipidaemia

Administered orally, sonidegib is a new drug that can be used to treat:

a) malignant melanoma
b) locally advanced basal cell carcinoma
c) solar keratoses
d) strawberry naevi