# RGH E-Bulletin Digest Number 80

The next in our 2015 series of continuing professional development activities is the RGH E-Bulletin Digest No. 80 – edited by Associate Professor Chris Alderman.

This CPD activity assesses your understanding of four recent RGH Pharmacy E-Bulletins, Volumes 57-4→ 57-7 (January/February 2015).

**Learning Objectives:**

After completing this activity, pharmacists should be able to:

- Describe drug treatments that have been used as a means to prevent non-melanoma skin cancer
- Outline new knowledge relating to the treatment of Clostridium Difficile infection
- Discuss various electrolyte abnormalities that may relate to drug therapy.

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: A1505AP1**.

---

**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**

# RGH Pharmacy E-Bulletin

**Volume 57 (4): January 19, 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



## Chemoprevention and Non-melanoma Skin Cancer

Non-melanoma Skin Cancer (NMSC) is the most common cancer worldwide and accounts for 96% of all skin cancers, of which basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) are the vast majority, in a ratio of 4:1. In organ transplant recipients, immunosuppression inverts this proportion and the incidence of SCC risk can increase by 60 to 100 times. Surgery is the most common form of therapy for NMSC and sun protection measures should be recommended to all patients, but for those deemed to be high-risk, additional preventative measures may be warranted.

Vitamin A analogues (retinoids) are the most researched chemopreventative agents that have been shown to be efficacious. The basis for the chemopreventative action of retinoids remains largely unknown, but may include immunomodulation, inhibition of cell proliferation and keratinisation, promotion of cellular differentiation and induction of apoptosis. It is recognised that it is important that chemoprevention must be used in conjunction with standard NMSC treatments.

Retinoid chemoprevention should only be used in those deemed to be high risk, including groups such as those with NMSC who are chronically immunosuppressed, those with psoriasis and PUVA treatment presenting with NMSC, patients with radiation induced NMSC, people with Xeroderma Pigmentosum (XP) and nevoid BCC sufferers, those developing five or more NMSCs per year, those affected by metastatic or aggressive NMSCs or those with multiple NMSCs on the head or neck area.

Both isotretinoin and acitretin are effective chemoprevention for NMSCs, but in general istotretinoin is used primarily in patients with XP and nevoid BCC syndrome, whilst acitretin is largely use in organ transplant recipients, psoriasis and those with severe sun damage. Retinoids must be used continuously in order to maintain their protective action, and discontinuation has actually been shown to result in a rebound of the number of NMSCs.

The utility of the long-term use of retinoids can, however, be compromised by their side-effects, some of which include mucocutaneous reactions (xerosis, photosensitivity, chelitis and alopecia), headaches, dyslipidaemia, hepatotoxicity and skeletal changes.

Teratogenicty is commonly known and female patients must utilise two forms of contraception and remain pregnancy free for two months prior to, and up to two years after treatment (depending upon which retinoid is used). Pregnancy testing, liver function tests, complete blood count, renal function, fasting lipid profile and skeletal radiologic profile should all be tested before, and on a regular basis throughout treatment.

It is thought that treatment-limiting side effects can be reduced by a stepped approach to dosing: i.e. 10 mg/day of acitretin for 4 weeks followed by 20 mg/day for 4 weeks then a maintenance dose of 25 mg/day. For isotretinoin, initial treatment is started at around 0.25 mg/kg/day for two months followed by 0.5 mg/kg/day. Regular patient evaluation is paramount throughout treatment.

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

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

# RGH Pharmacy E-Bulletin

**Volume 57 (5): January 26 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


# Clostridium difficile management options

Clostridium difficile infection (CDI), mainly precipitated by the use of broad spectrum antibiotics, has increased in incidence and severity over the last decade and currently ranks as the third most common nosocomial infection. Until recently treatment options for CDI have been limited to oral metronidazole and vancomycin, however due to the emergence of a hypervirulent C. difficile strain known as NAP1/BI/027, CDI has become increasingly difficult to treat with recurrence rates reported as 20-30%. Given that CDI has a 30 day mortality rate of up to 38.1%, recurrent infection represents a major treatment challenge for which new therapeutic options are urgently needed. In May 2011, the FDA approved the use of fidaxomicin, a first-in-class oral macrocyclic antibiotic for the treatment of CDI in adults.

Two phase III randomized, double-blind, multinational, non-inferiority trials OPT-80-003 and OPT-80-004 have compared the safety and efficacy of a 10 day course of oral fidaxomicin 200 mg twice daily against oral vancomycin 125 mg four times daily in adults with active CDI. Analysis in the modified intention to treat populations in both trials demonstrated fidaxomicin to be non-inferior to vancomycin for curing CDI (87.7% with fidaxomicin vs 86.8% with vancomycin in one study, and 88.2% vs 85.8% in the other. In both cases, fidaxomicin was associated with lower CDI recurrence rates within 4 weeks following clinical cure (12.7% vs 26.9%, $p < 0.001$ and 15.4% vs 25.3%, $p = 0.005$)
.
Unlike current antibiotics used for CDI, fidaxomicin displays narrow spectrum bactericidal activity against C. difficile with minimal effect on the normal colonic microflora, thereby decreasing the risk of further colonization, proliferation and reinfection. Fidaxomicin is also less likely to promote acquisition of vancomycin resistant enterococci (VRE) and candida species when compared to vancomycin, a potential benefit in terms of infection control. Fidaxomicin inhibits RNA polymerase activity of Gram positive bacteria at a very early stage of transcription. As it blocks gene transcription, fidaxomicin has the potential to inhibit sporulation and toxin production which may explain its superiority over vancomycin in reducing CDI recurrence. Fidaxomicin has lower MICs against C. difficile when compared to vancomycin, and has a prolonged post-antibiotic effect ranging from 9.5-12.5 hours, allowing for twice daily dosing. Due to its low systemic absorption following oral dosing, fidaxomicin and its active metabolite achieve faecal concentrations approximately 5000 times above the MIC90 of 0.25mcg/mL, giving fidaxomicin maximal opportunity to exert its bactericidal activity against C. difficile with minimal systemic adverse effects.

In the OPT-80-003 trial, among patients evaluated for safety there were no significant differences in adverse events reported with fidaxomicin and vancomycin (62.3% vs 60.4% respectively). The most common adverse events reported with fidaxomicin include nausea, vomiting, GI haemorrhage, anaemia and neutropenia. Fidaxomicin undergoes esterase dependent metabolism to the active metabolite OP-1118. No dose adjustment is necessary in patients with renal or hepatic impairment. The metabolism is not mediated via cytochrome P450 pathways, which means there is a low risk of interaction with co-administered drugs. Fidaxomicin has also demonstrated a low propensity to develop resistance and cross resistance with other antibiotics.

> Currently a 10 day course of fidaxomicin costs $4677.06 in Australia, and the supply is not subsidised through the Australian Pharmaceutical Benefits Scheme (PBS). Despite its high cost, two cost-analysis studies comparing oral vancomycin (including extemporaneously compounded oral vancomycin) and fidaxomicin found that the latter agents was cost effective in terms of recurrences and clinical cure rates, based upon a 9.8% difference in recurrences as reported in the two major pivotal trials. Cost effective use of fidaxomicin necessitates its targeted use in populations at highest risk of relapse and recurrent CDI in particular the elderly, those receiving concomitant antibiotics, those with first relapse and those with renal impairment or cancer.

Acknowledgment – This E-Bulletin is based on work by Claire Higgins, Clinical Pharmacist, RGH

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

# RGH Pharmacy E-Bulletin

**Volume 57 (6): February 2 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



# Drug-related electrolyte abnormalities (part one)

There are many medications that can cause abnormalities in the serum electrolyte profile – in some cases these disturbances can be mild, transient and relatively insignificant, but in others there may be potentially serious symptoms or complications that can contribute to morbidity or mortality. In this E-Bulletin a range of potentially iatrogenic cases of electrolyte disturbance are discussed.

*Serum Sodium*

Medications may contribute to both hyponatremia and hyperkalaemia, most commonly the former of these. Hypovolemic hyponatremia may arise from drug-induced diarrhoea and vomiting or from diminished water intake. These situations may be related to the use of medicines that cause nausea and/or diarrhoea, with implicated agents potentially including chemotherapy drugs, SSRIs and many antibiotics. The Syndrome of Inappropriate Secretion of Anti-Diuretic Hormone (SIADH) is another potential cause for a low serum sodium – many agents are potentially implicated as causes, including antidepressants (especially TCAs, SSRIs and venlafaxine), as well as carbamazepine, opioids such as morphine, some chemotherapy agents (especially vincristine, vinblastine and cyclophosphamide) and some antipsychotic agents. Hyponatraemia is also prominently associated with the use of diuretics through other mechanisms – thiazides and indapamide are thought to be more likely to be implicated than loop diuretics, and the effect is most likely to be seen in the early phase of treatment. Incidentally, a mild hypochloraemic alkalosis is a relatively common finding amongst people treated with loop diuretic agents.

Conversely, vigorous diuresis is also sometimes associated with a high serum sodium, or hypernatraemia. Other drugs that may cause hypernatraemia include corticosteroids, anabolic steroids, androgens and oestrogens. Another potentially iatrogenic cause for hypernatraemia is an inappropriately high sodium load, which may be delivered inadvertently in association with some antibiotics and other agents such as sodium bicarbonate.

*Serum Magnesium*

Primary hypermagnesaemia is relatively rare, but medications may contribute through contributions to indirect mechanisms such as renal failure, diabetic ketoacidosis, haemolysis and adrenal insufficiency. Hypomagnesaemia is relatively more common, and is estimated to occur in up to 12% of hospitalised adults. Drugs associated with significant hypomagnesaemia include platinum-based chemotherapy agents, amphotericin B and cyclosporine. Other agents implicated include aminoglycoside antibiotics, pentamidine, tobramycin, tacrolimus and diuretics.

Recent evidence suggests that Proton Pump Inhibitors (PPIs) may also be associated with hypomagnesaemia, especially when prescribed at a high dose or for extended duration (refer E-Bulletin 53(5) from February 2014). The effect appears to be associated with all drugs in the PPI class, and clinical manifestations of this effect have included muscle cramps and even arrhythmias.

It is also important to note that magnesium deficiency is frequently associated with hypokalaemia, and in the presence of hypomagnesaemia hypokalaemia becomes relatively refractory to treatment with potassium supplements. It is thought that magnesium deficiency exacerbates potassium wasting by increasing distal potassium secretion. Both hypokalaemia and hypomagnesaemia exacerbate the effects of digoxin on the myocardium in the context of digoxin toxicity.

Acknowledgment – This E-Bulletin is based on work by Chris Alderman, Senior Clinical Pharmacist, SA Pharmacy

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

# RGH Pharmacy E-Bulletin

**Volume 57 (7): February 9 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



# Drug-related electrolyte abnormalities (part two)

This E-Bulletin continues discussion of common and clinically important electrolyte abnormalities. The information provided is not intended to be exhaustive, but instead provides a range of examples where electrolyte disturbances are associated with medications.

*Serum Potassium*
Abnormalities in the serum potassium are amongst the most common of all medication-related electrolyte disturbances, and can have profound clinical consequences.

Hypokalaemia is prominently associated with a range of commonly used medications. Potassium-wasting diuretics that block sodium reabsorption proximal to the distal nephron are implicated, and include thiazide agents and indapamide, loop diuretics such as frusemide, and osmotic diuretics such as mannitol. The prevalence of hypokalaemia is so substantial with these agents, concurrent potassium supplementation or potassium-sparing agents are frequently prescribed, particularly for older people. Some laxatives can cause hypokalaemia by inducing diarrhoea, especially when abused. Diuretics and/or laxatives may be abused by some people with eating disorders, and hypokalaemia in this context warrants careful assessment. Other agents implicated as a potential cause of hypokalaemia include amphotericin, some penicillins and theophylline. As previously noted, there is a prominent association between hypokalaemia and hypomagnesaemia.

Hyperkalaemia is arguably the most dangerous of electrolyte abnormalities. Significantly elevated serum potassium can cause arrhythmias and increase the risk of sudden cardia death. Potassium homeostasis is profoundly influenced by renal function, and in the context of renal impairment, hyperkalaemia is a common manifestation. In this circumstance, elevation of serum potassium may reflect both compromised elimination and also the intake of potassium from various sources. Foods that are rich in potassium citrus juices and fruits, bananas, tomatoes, honeydew melon, potatoes, cantaloupe, peaches, and salt substitutes. Herbal products may be a source of exogenous potassium source – for example Morindia citrifolia (Noni juice), some forms of Ginseng, Red Sqill, Yew Berry and Dogbane. Oher sources can include protein-calorie supplements, potassium supplements, some penicillin products and stored blood (the concentration of potassium in the serum stored blood rises by up to 1 mmol/L per day).

Drugs known to be associated with hyperkalaemia include potassium-sparing diuretics (including eplerenone, spironolactone, amiloride, and triamterene), NSAIDs, ACE inhibitors, ARBs (Angiotensin Receptor Blockers), and immunosuppressants such as cyclosporine and tacrolimus. Less well-known associations include heparin, trimethoprim, penicillin G and beta blockers.

*Serum Calcium*
Both hypercalcaemia and hypocalcaemia can be related to drug therapy. Elevation of the serum calcium may be observed in association with excessive vitamin D or Vitamin A, as well as treatment with thiazide diuretics, oestrogens, androgens and lithium.

Hypocalcaemia has been observed with anticonvulsant drug, aminoglycosides, and proton pump inhibitors. Although used therapeutically for the treatment of hypercalcaemia, denosumab and bisphosphonates may actually induce hypocalcaemia.

Acknowledgment – This E-Bulletin is based on work by Chris Alderman, Senior Clinical Pharmacist, SA Pharmacy

**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:

Lens M, Lens & Medenica L. Systemic retinoids in chemoprevention of non-melanoma skin cancer. Expert Opin Pharmacother, 2008; Jun9(8):1363-74

Vincenzo Bettoli, Stefania Zauli and Anna Virgili. Retinoids in the chemoprevention of non-melanoma skin cancers: why, when and how. Journal of Dermatological Treatment, 2013; 24: 235 – 237

Prado R, Franics SO, Mason NM, Wing G, Gamble RG, Dellavale R. Nonmelanoma skin cancer chemoprevention. Dermatol Surg 2011 Nov(11);37:1566-1578.

J.Hardin, BSc, MSc abd P. R. Mydlarski, MD, FRC. Systemic Retinoids: Chemoprevention of Skin Cancer in Transplant Recipients. Xxx.skintherapyletter.com/2010/15.7/1

Comely, O. A., D. W. Crook, and R. Esposito. "Fidaxomicin versus vancomycin for infection with Clostridium dificile in Europe, Canada, and the USA: a double-blind, non-inferiority, randomised controlled trial IJ." Lancet Infect Dis 12.4 (2012): 281-289.

Louie, Thomas J., et al. "Fidaxomicin versus vancomycin for Clostridium difficile infection." New England Journal of Medicine 364.5 (2011): 422-431

PARADIGM-HF — The Experts' Discussion. Mariell Jessup, M.D., Keith A.A. Fox, M.B., Ch.B., Michel Komajda, M.D., John J.V. McMurray, M.D., and Milton Packer, M.D. N Engl J Med 2014; 371:e15 September 11, 2014DOI: 10.1056/NEJMp1410203

Stiles, S 2014, After Sinking in, PARADIGM-HF Critiqued at HFSA Sessions, Medscape September 25, viewed 22/11/14, http://www.medscape.com/viewarticle/832290#vp_1

Vardeny O, Miller R, Solomon SD, Combined Neprilysin and Renin-Angiotensin System Inhibition for the Treatment of Heart Failure,JACC: Heart Failure(2014), doi:10.1016/j.jchf.2014.09.001.

BPAC A primary care approach to sodium and potassium imbalance www.bpac.org.nz/BT/2011/September/imbalance.aspx.

# 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**

For people who are not organ transplant recipients, the most common form of skin cancer is:
a) basal cell carcinoma
b) melanoma
c) squamous cell carcinoma
d) dermatological adenoma

The most researched chemopreventative agents shown to be efficacious in preventing non-melanoma skin cancer are:
a) vitamin A analogues
b) vitamin B analogues
c) vitamin C analogues
d) vitamin D analogues

Clostridium Difficile infections have become increasingly difficult to treat with recurrence rates reported as high as:
a) 1 - 2%
b) 5 – 10%
c) 10 – 20%
d) 20 - 30%

Which of the following statements is true with respect to dosing of fidaxomicin?
a) 50% dosage reduction is needed for those with severe hepatic impairment
b) 50% dosage reduction is needed for those with severe renal impairment
c) no dosage reduction is needed for those with severe renal impairment
d) none of these statements are true

Which of the following drugs is associated with hyponatraemia?
a) fluvoxamine
b) hydrochlorothiazide
c) carbamazepine
d) all of the above

In the presence of hypomagnesaemia, which electrolyte disturbance is generally more refractory to treatment?
a) hypernatraemia
b) hyponatraemia
c) hyperkalaemia
d) hypokalaemia

An example of a herbal products which may be a source of exogenous potassium is:
a) Garlic extract
b) Morindia citrifolia (Noni juice)
c) Ginkgo Biloba
d) Black cohosh

Treatment with denosumab has been known to cause:
a) hypocalcaemia
b) hypontraemia
c) hypokalaemia
d) hypochloraemia