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The Renal Pharmacist

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View from the Chair

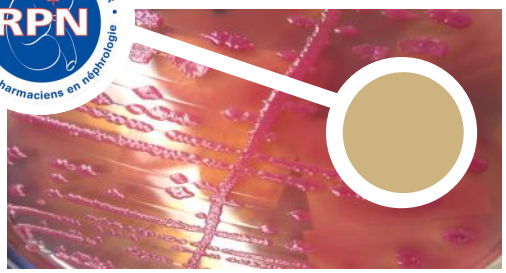
2016 marked 20 years since the founding of our network and so much progress has been made in *enhancing the quality of pharmacy and interdisciplinary patient care along the continuum of renal insufficiency*.

As we start 2017, the world suddenly feels different – less friendly, less tolerant and less secure. I wonder if any previous chair felt the need to overtly state that the Renal Pharmacists Network was built on inclusiveness, equality and diversity. In 2017, not only will we expand our network southwards by exploring a new partnership with the American College of Clinical Pharmacists, but also we will expand our influence globally. I imagine videos of our lectures being shared thousands of times around the world, watched alike by students in university lecture halls and seasoned practitioners in hospital conference rooms.

...the Renal Pharmacists Network was built on inclusiveness, equality and diversity

More than ever, bringing together providers to better heal those who are sick, feels significant. 20 years on, there remains so much more to do.

Clifford Lo,
BSc(Pharm), PharmD, MHA, BCPS
Chair, Renal Pharmacists Network 2017-2018



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The Renal Pharmacists Network Nephrology Education Day took place September 30th 2016, at the Intercontinental Hotel Yorkville in Toronto. Included in this issue are summaries of the presentations at this event.

The slides for these presentations can also be accessed on the RPN website:
http://renalpharmacists.net/category/presentations/

Novel Oral Anticoagulants in CKD

Presented by: Dr. Mark Crowther, MD, MSc, FRCPC, Chair and Professor – Department of Pathology and Molecular Medicine, and Professor – Department of Medicine, McMaster University.
Author: Jennifer Wichart, BScPharm, ACPR, Pharmacy Clinical Practice Leader for Solid organ transplant, Nephrology and Ambulatory paediatrics, Foothills Medical Centre Alberta Health Services, Calgary Alberta.

At the 2016 RPN Education Day, Dr. Mark Crowther delivered an informative and entertaining session on direct oral anticoagulants or DOACs. The presentation started with a review of why we like vitamin K antagonists: we can monitor them, they are highly effective, low cost and have a strong brand recognition. This was contrasted with why we don't like them: they require intensive monitoring, have wide inter- and intra-patient variability, can cause bleeding and probably cause enhanced vascular disease in patients with CKD. He then introduced the DOACs starting with the two oral direct factor Xa inhibitors, apixaban and rivaroxaban as well as the direct thrombin inhibitor, dabigatran.

Information about use of DOAC therapy in patients with CKD is limited and it is generally suggested to avoid all DOACs if CrCl < 30 ml/minute. Further discussion can be found in the systematic review by Harel et al. (J Am Soc Nephrol. 2014 Mar;25(3):431-42). As always, more research is required in this population and we anxiously await the results of the VERDICT trial, a non-inferiority trial comparing reduced doses of DOACs (rivaroxaban or apixaban) with standard of care in patients with renal impairment who are experiencing an acute venous thromboembolism. This trial will include patients with a CrCl as low as 15 ml/min and has an estimated study completion date of March 2019.

Dr. Crowther reviewed the risk of bleeding complications in patients with a focus on the results of a systematic review and meta-analysis that included > 100,000 patients (Chai-Adisaksopha C et al. Blood 2014 Oct 9;124(15):2450-8). He presented an algorithm with general suggestions of what to do to manage bleeding: (1) stop the drug, (2) investigate and treat the cause, (3) administer an antidote, (4) test the integrity of the coagulation system, (5) use non-specific blood "thickeners", (6) transfuse to replace deficient factors or transfuse if it will reverse the drug, (7) consider dialysis or other maneuvers to remove the drug, (8) by the time this is complete, most of the drug will have been cleared.

Considering DOACs, idarucizumab is the specific reversal agent for dabigatran (Pollack CV Jr et al. N Engl J Med 2015 Aug 6;373(6):511-20). Dosing suggestions are to administer 2 of the 2.5 gram doses by IV infusion. Andexanet is a reversal agent for both direct and indirect Xa inhibitors (Connolly SJ et al. N Engl J Med. 2016 Sep 22;375(12):1131-41) and is currently not on the market in Canada or the USA.

Low Molecular Weight Heparins and Circuit Anticoagulation in Hemodialysis

Presented by: Seadna Ledger, BScPhm, ACPR, Clinical Pharmacist – Nephrology, London Health Sciences Centre.
Author: William Nevers, BSc(Pharm), ACPR, PharmD, Clinical Pharmacy Specialist – Nephrology, Kelowna General Hospital, British Columbia.

During the Fall RPN education event held in Toronto, Seadna Ledger presented on the use of Low Molecular Weight Heparins (LMWH) for circuit anticoagulation in hemodialysis (HD). The focus of the presentation was to provide information on guideline recommendations, best available evidence, dosing, safety and use in different modalities. It was emphasised throughout the presentation that when deciding on circuit anticoagulation, there needs to be a balance between clotting and bleeding to account for HD efficiency, blood loss, workload and treatment cost.

LMWHs for anticoagulation of circuit HD offers many advantages for both the patient and healthcare provider, these include convenience, reduced risk of heparin-induced thrombocytopenia, less osteoporosis and hyperkalemia and lower triglyceride levels. These advantages need to be weighed against the potential pitfalls of using LMWHs in patients with end stage renal disease, such as accumulation and only partial reversal with protamine (may be used to reverse major bleeding, but may only reverse up to 60% of anti-Xa activity).

Some of the Nephrology Societies (The European Renal Association-European Dialysis and Transplant Association

(ERA-EDTA), British Renal Association) have updated their recommendations to use LMWH or to use unfractionated heparin (UFH) for circuit anticoagulation. Other Societies such as The National Kidney Foundation (NKF) still have UFH as their primary recommendation with LMWH as an alternative, while The Canadian Society of Nephrology (CSN) and the Caring for Australians with Renal Impairment (CARI) Society do not provide specific recommendations. For patients that have higher risk of bleeding, the ERA-EDTA, British and NKF Societies state that systemic anticoagulation should be avoided and that regular flushing (every 15-30min) needs to occur.

An evaluation of the literature shows evidence for circuit anticoagulation with enoxaparin, tinzaparin and dalteparin. The evidence for enoxaparin demonstrates that by using either a bolus of 0.7-1mg/kg or a dose of 40mg, that there was not an increase in bleeding and minimal clotting in HD patients. These trials show promise for enoxaparin but have small patient populations (50-100 patients) and are short in duration (1 session to 6 months). The evidence for dalteparin shows doses from 2,500 – 5,000 units per HD session with no increase in bleeding or thrombotic events over multiple runs. As with enoxaparin, these trials were small (12-55 patients) and short duration (4 weeks-200 sessions). Tinzaparin has more extensive literature compared to the other two agents and has demonstrated similar clotting rates and bleeding rates vs. UFH. The doses that were used for tinzaparin ranged from 2,500 – 5,000 units and had similar patient numbers (12-108 patients), however, used much more extensive duration of treatments. The most recent study by Al-Saran et al (2010) had 23 patients with over 1600 HD sessions with tinzaparin and Braham et al (2008) had 108 patients with over 1800 HD sessions. There have been two studies that have compared LMWH vs. another LMWH; Beijering 2003 had ~ 75 patients in both the tinzaparin and dalteparin arms (median doses 4,500 and 5,000 units respectively) which showed no difference in bleeding or clotting after 40 HD sessions. Chuang 2011 compared 62 nadroparin patients to 14 enoxaparin patients over 12,000 consecutive sessions and found nadroparin had 23% clotting vs 14% in the enoxaparin group. There was no difference in bleeding. Two meta-analyses (Lim 2004 and Shantha 2015) both showed that LMWH are as safe and effective as UFH in terms of bleeding risks and for preventing circuit thrombosis.

When determining the appropriate dose, initial dosing can be found in the product monograph for dalteparin and tinzaparin (2,500-5,000 units and 2,500-4500 units respectively). Many health authorities have dose escalation charts depending on the grade of the clot. To switch from UFH to LMWH, sources base it on 40-50% of former heparin dose.

Some precautions and contraindications to take into account prior to using LMWHs for circuit anticoagulation include whether the patient has acute gastroduodenal ulcers or cerebral hemorrhage, septic endocarditis, any uncontrolled bleeding or spinal anesthesia. With regards to anti-Xa monitoring, it is not routinely done at all sites and the efficacy is based on clotting scales. Anti-Xa levels can be very costly and subtherapeutic levels can still end up causing bleeding and therapeutic levels may still result in clotting. The TRIVET study showed that out of 148 patients with chronic kidney disease, 18 had bleeding events (6 in the HD arm). Anti-Xa levels greater than 0.5IU/mL did not appear to correlate with bleeding events.

LMWHs use is not limited to intermittent HD patients only; they can also be used in patients undergoing daily and nocturnal dialysis. When administering for daily dialysis, there is concern of accumulation and there is limited evidence and dosing guidelines. A literature review showed that doses of 2,500 units of

dalteparin per 48 hours can be used safely and can increase the dose by 2,500 unit increments if clotting occurs. Grade 4 clotting only occurred in 1/260 HD daily dialysis patients and only 3% had clotting scores above 2. No bioaccumulation occurred with all pre-dialysis anti-Xa levels less than 0.4U/mL. There is an ongoing study at London Health Sciences Centre to determine dosing, safety and efficacy of LMWHs in nocturnal dialysis which hopes to be completed in September 2017.

In summary, LMWHs appear to be both safe and effective for HD circuit anticoagulation. Even though there are limitations to the literature, compared to UFH they do not increase the risk of bleeding or thrombosis and there is very little head to head data to choose among agents. LMWHs are more convenient than UFH but will result in significant cost and there is still some uncertainty in terms of dosing and safety in special populations (nocturnal HD, high risk bleeding).

Can an APP a Day Keep the Med Errors Away?

Presented by: Stephanie Ong, BScPhm, MSc, Clinical Pharmacist – Nephrology, University Health Network Toronto.
Author: Aflora Huen, BScPhm, Clinical Pharmacist, Trillium Health Partners, Mississauga Ontario.

Mobile apps are a modern day upgrade to previous adherence aides. Several have been developed to study medication management in renal patients.

Apps have been developed to improve adherence rates (iNephro in Germany); to improve adherence rates and prevent medication errors (ALICE app in Spain); to aid in medication error prevention and detect drug interactions ("Safe Kidney Cohort" study in US).

Patients with kidney disease are complex, as they usually have more than two comorbidities, use multiple medications, have several different providers and visit various levels of health care and transition points.

One potential solution from UHN is a "Mobile based self-management system for patients with advanced chronic kidney disease". There are four behavioural elements targeted: monitoring BP, medication management, symptom assessment, tracking laboratory results. The mobile platform is supported by two key foundational elements: Care Team and Knowledge. The BP transferred seamlessly to the mobile device via Bluetooth, triggering automatic feedback messages from pre-programmed algorithms. For the Medication element, there is an active interface with the pharmacy record system, allowing real time updates of medication list. There are prompts for regular reviews of medications to notify team of changes to medications or problems. For Symptoms, there is an assessment of five directed symptoms with action messages for patient to monitor symptoms. Lab results are interfaced with clinical laboratory systems allowing for real time update of lab results and personalized action messages and feedback for patients.

Once this was developed, it was trialled in the UHN Renal Clinic patients who fit the criteria of complex disease with multiple medications, who spoke English and who were not dependent nor residents of long-term care facilities. Patients starting dialysis, or having a kidney transplant were excluded. Forty-seven patients were recruited.

Outcomes measured included Acceptability and Clinical Measures. Adoption of the smartphone application was mostly better than 80% and this was sustained over the 6 month study period. By measurement of Clinical Measures, there was more effective control of BP; more ready detection of mediation errors, lab work showed slight improvement in hemoglobin but no changes in potassium and phosphate (likely due to short duration of study and not enough lab values to impact behavioural changes). Conclusions of this study suggest that mobile apps and integrated mobile app system for CKD patients are both acceptable and feasible. Early evidence of benefit is suggested by improvement of BP with the identification and reduction of medication errors.

Ongoing challenges include concerns with privacy and security, need for clinical validation through additional studies, as well as need for standards and regulation development and maintenance for these apps.

Intraperitoneal Magnesium Replacement in Peritoneal Dialysis

Presented by: Elaine Cheng, BSc(Pharm), ACPR, PharmD, Clinical Pharmacy Specialist – Nephrology at Vancouver General Hospital. Presented at RPN Education Day on Sept 30, 2016 – summarized by Jennifer Lowry, BScPhm, Clinical Pharmacist, Renal Program at Grand River Hospital in Kitchener.

Dr. Cheng presented a case of critical hypomagnesemia to the audience and thoroughly reviewed the literature with respect to replacing magnesium intraperitoneally.

Hypomagnesemia is defined as total serum magnesium (Mg) less than 0.7 mmol/L (normal 0.7-1.1 mmol/L).

It was interesting to note that the usual Mg content of peritoneal dialysis (PD) solutions is 0.25 mmol/L whereas in hemodialysis fluid baths it is 0.5 mmol/L. This patient experienced lower Mg levels while on peritoneal dialysis versus hemodialysis.

There are several causes of hypomagnesemia related to redistribution of Mg, gastrointestinal causes (celiac disease specifically in this patient case), renal losses and disease, endocrine causes, diabetes, alcoholism, and some drugs such as proton pump inhibitors (PPI). The case patient was on pantoprazole 40 mg po daily.

Serious sequelae of hypomagnesemia may include electrolyte imbalances, effects on the neuromuscular and central nervous system, and cardiovascular toxicity. The case patient had Mg as low as 0.36 mmol/L and multiple ER visits due to uncontrolled atrial fibrillation.

Treatment involves replenishing Mg and possibly other electrolytes, and adjusting diet and medications that may be contributing to the hypomagnesemia. Due to this case patient's history of acid reflux that was unresponsive to other therapies as well as history of upper gastric bleed, stopping the PPI was not an option.

Oral Mg replacement usually causes diarrhea and IV supplementation presents challenges with fluctuating levels, IV access, infections, decreased quality of life, and staffing costs and time (administration and travel). Thus, it was decided to look to intraperitoneal (IP) Mg replacement as a potential treatment option.

There is very little literature on the use of IP Mg replacement. Three papers, spanning from 2001 to 2014, have been published in the area, one in a patient not on PD1 and two in PD patients2,3. All three papers reported successful correction of hypomagnesemia with no to minimal adverse effect of abdominal pain once a correct IP Mg dose was established.

Since the case patient did not tolerate oral magnesium, had fluctuating serum magnesium levels and recurrent hypomagnesemia with 5 g $MgSO_4$ IV therapy every 2 weeks, her team decided to trial IP $MgSO_4$ 4 g weekly in a daytime dwell of Dianeal 2.5% 2 L for 6 hours. They monitored peak (1 day post-dose) and trough (4 days post dose) serum Mg levels until levels stabilized within normal range. From January 2015 for one year the patient's Mg levels generally ran within normal limits. Following a critical low Mg level of 0.50mmol/L in January 2016, the patient's team decided to increase her IP Mg dose and trial administration through the continuous cycler peritoneal dialysis (CCPD) machine for ease of administration. They trialed doses ranging from 2.5 to 5 g IP 2-3x/week although of note, the patient did not actually receive the full dose as only 4.4 out of a 5 L dialysate bag was used to fill the patient.

The patient stabilized on 4g IP 3x/week in 5 L dialysate bags and it was found to be an effective and safe method of magnesium replacement. The patient reported no adverse effects, i.e. abdominal pain, and has had no subsequent visits to ER for uncontrolled atrial fibrillation.

References:

1. Bastani B, Pandurangan G. Intraperitoneal route of magnesium sulphate supplementation in a patient with severe renal magnesium wasting. Nephrol Dial Transplant 2001;16:2086-9.
2. Amirmokri P, Morgan P, Bastani B. Intra-peritoneal administration of potassium and magnesium: A practical method to supplement these electrolytes in peritoneal dialysis patients. Ren Fail 2007;29:603-5.
3. Egan G, Lange DB, Messenger S, et al. Intermittent intraperitoneal administration of magnesium sulphate in an elderly patient undergoing dialysis. Can J Hosp Pharm 2014;67:157-9.

Management of Pregnancy in Dialysis

Presented by: Dr. Michelle Hladunewich, MD, FRCPC, MSc, Division Director – Nephrology and Obstetrical Medicine at Sunnybrook Health Sciences Centre, Associate Professor at University of Toronto.
Author: Amanda Suarez, BScPharm, ACPR, Victoria Hospital, London Ontario.

Dr. Hladunewich gave an engaging and informative presentation on pregnancy in dialysis patients. She discussed the incidence and outcomes of pregnancy among women with ESRD, pregnancy management of women with ESRD, and potential long term issues following pregnancy in patients with ESRD.

The incidence of pregnancy in women with ESRD is very low, owing to a multitude of factors. ESRD impairs fertility by causing menstrual irregularities, amenorrhea, anovulation and early menopause. A large proportion of these patients also report experiencing sexual dysfunction, pain, depression, fatigue, medication side effects, and altered body image, all of which further impair pregnancy rates in this population. The first reported case of a pregnancy in a patient on HD occurred in 1970 in Italy, and the first case in a patient on PD occurred in 1983. Pregnancy complications in this population can include pregnancy loss, preterm delivery, low birth weight, shortened cervix, and pre-eclampsia. Historically, it was observed that residual renal function predicted better pregnancy outcomes, and because PD patients usually have better preserved residual renal function, it was thought that PD may be an optimal dialysis modality in these patients. However a case series showed that pregnancy outcomes were actually worse with PD compared to HD, as PD introduced new complications such as peritonitis, exit site infections, and restricted fetal growth owing to the volume of the PD fluid in the abdomen. It is now understood that HD is the preferred dialysis modality in this population. Furthermore, intensified HD has shown to have many benefits in improving pregnancy outcomes, such as better blood pressure control, better arterial compliance and endothelial function, and improved cardiac autonomic systems. Fetal mortality has been found to be proportional to BUN, and dialysis dose is highly correlated with gestational age. An intensified HD schedule not only optimizes pregnancy outcomes, it can also restore fertility in this patient population.

Dr. Hladunewich recommends a multimodal management strategy for pregnancy in the ESRD patient population, which includes pre-conception counselling, optimal medical and obstetrical care, and neonatal care. Prior to conception, patients should have a thorough medication review to reassess all medications for safety in pregnancy. ACEIs/ARBs should be discontinued, patients should be started on a maternal multivitamin with folic acid, and anemia management optimized. Diabetic medications may need to be reassessed and blood sugar control should be well maintained. Patients should be given the information and time needed to mentally prepare for a pregnancy, as intensified HD is a significant burden – it essentially becomes a full-time job. Dr. Hiladunewich recommends that a pregnant patient receive an intensified hemodialysis schedule of at least 36 hours a week. Electrolytes should be monitored very carefully, and many patients will need magnesium and phosphate supplementation. Vitamin D analogues and calcium carbonate are safe to use, however lanthanum should be avoided. Both erythropoetin and darbepoetin are safe, and usually need to be used in much higher doses than usual in order to maintain hemoglobin levels, as pregnancy causes EPO resistance. It is important to monitor and maintain good iron stores, and iron sucrose is the preferred IV iron preparation as it does not contain a preservative. Intradialytic hypotension should be avoided. Post-partum, breast-feeding can be an option, although it may be difficult to achieved due to scheduling dialysis as well as fluid fluctuations. For moms wishing to breastfeed, medications should be reviewed again for safety.

Intensified hemodialysis can produce better pregnancy outcomes, however it can also have other important consequences. Intensified hemodialysis can cause a significant amount of maternal stress as a result of the large time commitment required. Patients who undertake such a rigorous dialysis regimen usually end up losing any residual renal function that they previously had. This can actually make subsequent pregnancies more difficult to achieve, and affect long-term morbidity and mortality. A pregnancy can also affect future options for the patient to receive a kidney transplant, as pregnancy is a very sensitizing event. Future studies are needed to further evaluate and describe long term OB and fertility outcomes, effects on transplant and sensitization, as well as looking at newborn and child development.

Please send any articles of interest to
renalpharmacistsnetwork@gmail.com

Recent Publications

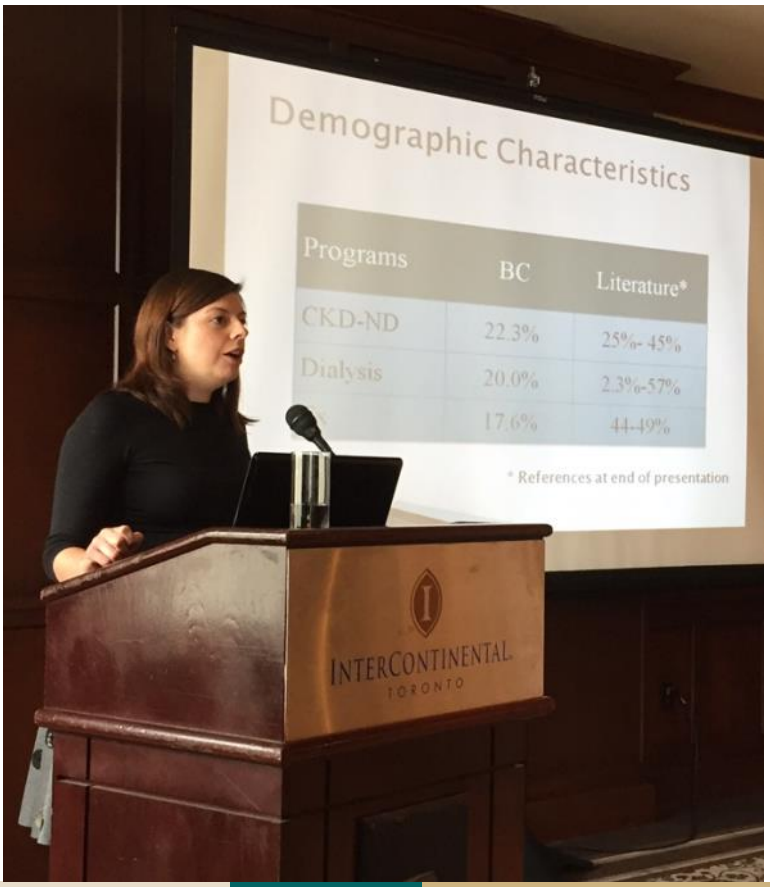
Jeremiah, S et al. **Risk of Acute Kidney Injury After Intravenous Contrast Media Administration**. *Annals of Emergency Medicine*, 2017; DOI: 10.1016/j.annemergmed.2016.11.021

Hladunewich**,** M.A. et al. **Managing glomerular disease in pregnancy.** Nephrol Dial Transplant (2017) 32 (suppl_1): i48-i56.

Ribic, CM et al. **Intermittent HEMOdialysis Anticoagulation with TINzaparin versus Unfractionated Heparin (HEMO-TIN): A Multicentre Randomized Control Trial.** Abstract presented at the Annual meeting of the American Society of Nephrology 2016 https://ajkdblog.org/2016/11/20/kidneywk-2016-the-poster-sessions/

Lim, W et al. **Assessment of Low Molecular Weight Heparin Accumulation in Patients with Chronic Kidney Disease: Results from the TRIVET Study.** Abstract presented at the Annual meeting of the International Society on Thrombosis and Hemostasis 2016 https://www.mdlinx.com/oncology/conference-abstract.cfm/57899/?conf_id=231425&searchstring=&coverage_day=0&nonus=0&page=1

The Annual meeting of the American Society of Hematology https://ash.confex.com/ash/2016/webprogram/Paper98396.html



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