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The Renal Pharmacist

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In this issue ...

A biannual Insight into the Renal Pharmacist Network

View from the Chair

This year has brought about some changes for the Renal Pharmacists Network, but as with most changes…change can be good. We were fortunate to add a Renal Pharmacists Education event in Calgary this year, which was a great success. We ran our usual Toronto, and Vancouver events that we also very well received. We saw Grace Leung, our treasurer move on to new opportunities and thank her for her years of service. But in her place we welcomed Julianne Kim from Sunnybrook in Toronto who has stepped into the role with ease. This year the CSN Education event went off without a hitch with a group of great presenters and productive round table discussions that followed. We are excited to be hosting an Education event in Winnipeg this year in the Fall, as we had Cali Orsulak from Winnipeg join our executive as our chair elect. This will be in addition to our Toronto, Calgary and Vancouver events. Next year the CSN AGM is to be held in Halifax, and since we are unsure of the attendance numbers there, we will be having our annual day long Education event in the new year in Toronto. We are looking forward to these and any other changes that are thrown our way. A big thanks the whole executive for all of their hard work in planning this year's events, so much hard work goes into the planning of the days and speakers and each of the events has gone off without a hitch. I am looking forward to an exciting year ahead!

…change can be good

Carlee Balint

RPN Chair 2015

Biography: Cali Orsulak

Cali Orsulak is the new chair elect for the Renal Pharmacists Network. She is from Winnipeg and has worked for the Health Sciences Centre since her graduation with a BSc. Pharm in 2000. She has been a pharmacist with the Manitoba Renal Program since 2003 where she has mainly worked as a hemodialysis pharmacist at the Sherbrook Dialysis Unit. She has also worked briefly in the Manitoba Renal Local Centre program and renal clinics.

Cali attained her certificate in diabetes education in 2004 and has a special interest in optimizing care in hemodialysis patients with diabetes. She has also done several presentations on this subject to nurses, pharmacists and other diabetes educators.

She also has a special interest in the "appropriate" prescribing of monitored drugs such as benzodiazepines and opioid medications. She is currently the pharmacist representative on the Manitoba Monitored Drugs Review Committee which monitors and identifies trends in monitored drug prescribing as well as providing education to optimize prescribing.

Cali has been involved in several pharmacy and hospital committees over the years. She was president of the CSHP Manitoba Branch and had also been a part of their education committee for several years as well as the newsletter editor. She had been a part of the MRP standards committee and most recently sits on the MRP patient safety committee.

She enjoys mentoring/teaching students and has precepted multiple pharmacy students, pharmacy residents and interns over the years. When Cali is not at work she enjoys outdoor activities such as hiking and swimming and loves travelling. Most recently she travelled to New Zealand where she did her first (and last) bungy jump at the world's first bungy site in Queenstown.

Welcome Cali!

Upcoming conferences:

BC Kidney Days 2015, Oct 1-2, 2015,
Pinnacle Hotel Vancouver Harbourfront
Theme: **Sharing our Success and Building our Future**
www.BCKidneyDays.ca

American Society of Nephrology Kidney Week 2015
San Diego, California Nov 3-8, 2016
www.asn-online.org

Highlights: Joint Session Between RPN and CSN, 2015, Montreal, QC

Submitted by Julianne Kim, BScPhm, Sunnybrook Health Sciences Centre, Toronto, ON

The Canadian Society of Nephrology Annual General Meeting was held on April 23-25th, 2015 in Montreal, Quebec. Dr. Danial Schecter was invited to speak on "Medical Marijuana, Cannabinoids and the Kidney: The Essentials" for the joint session between RPN and CSN.

In this presentation, Dr. Schecter reviewed the classification of cannabinoids (endocannabinoids, phytocannabinoids and synthetic cannabinoids) and the two subtypes of cannabinoid receptors, CB1 and CB2. CB1 receptors are mainly expressed in the central nervous system, kidneys, liver and the gut whereas CB2 is expressed in the immune system. The pharmacology of most of the cannabinoids is largely unknown but the most potent psychoactive agent, Delta-9-tetrahydrocannabinol (dronabinol or THC) has been isolated, synthesized and studied. Other cannabinoids that have been isolated are Delta-8-THC, cannabinol and cannabidiol (CBD) which have additive or antagonistic effects with THC.

Dr. Schecter discussed the *in vitro* effects of cannabinoids on inflammatory disease, metabolism, the cardiovascular system, liver and kidneys by attenuating oxidative stress. The best evidence to date is for symptom control, which includes nausea, vomiting, neuropathic pain, insomnia, anorexia and mood. He also reviewed the treatment options in Canada including dronabinol (no longer available), nabilone, Sativex® and herbal cannabis. Currently, patients can obtain a medical document from a physician and receive a mailed supply of herbal cannabis through a licensed producer (regulated by Health Canada). Physicians do not require a specific license to prescribe medical marijuana.

This topic was very interesting to the group and raised good discussion around our renal patients who are not managed well for symptom control.

Highlights: The Renal Pharmacists Network Nephrology Education Day 2015, Montreal, Quebec

The RPN Nephrology Education Day was held in Montreal on April 23rd, prior to the CSN conference. Many pharmacists across the country gathered to learn and network with renal colleagues. The day started off with Dr Jeffery Perl, a staff nephrologist at St Michael's Hospital in Toronto. As one of the primary investigators, he gave us an update on The Peritoneal Dialysis Outcomes and Practice Patterns Study (PDOPPS). He explained that differences in outcomes in PD are thought to be due variations in practice patterns. His research focusses on identifying optimal practice patterns and reducing variation in practice. Data collection is ongoing in multiple countries around the world. Great feedback was received and we look forward to seeing more data when available.

The next speaker, Katherine Desforges, a pharmacist from Montreal, gave us an update on agents for hyperkalemia management. This is a timely topic that was well received with the new agents on the horizon.

This year's short and snappy presentations were presented by our executive members. Derrick Soong did a quick journal club on a recently published article by Weir and colleagues on beta-blocker dialyzability and mortality in older patients receiving hemodialysis. Please see below for a summary and critique of this article. Carlee Balint gave us a brief update on ANCA vasculitis.

Finally, Karen Shalansky presented on intravenous iron chelation therapy and Marisa Batistella finished off with an update on drug dosing in SLEDD and nocturnal dialysis.
Our round table discussions were a success again this year giving attendees the opportunity to discuss common challenges and issues. This was a chance to get to know other renal pharmacists across Canada.

Overall, the day was a great success and provided opportunities for pharmacists from various institutions to network and discuss the latest topics. Special thanks to Jenny Ng and Judith Marin for organizing another successful event! Our next RPN day will be held in Toronto so please stay tuned for more information in 2016.

Short and Snappy: Journal Club

Submitted by Derrick Soong, PharmD, Windsor Regional Hospital, Ontario

β-Blocker Dialyzability and Mortality in Older Patients Receiving Hemodialysis.

Weir MA, Dixon SN, Fleet JL et al. J Am Soc Nephrol. 2015;26(4): 987-996.

Weir and colleagues conducted a one-to-one propensity matched, population based retrospective cohort study, using the Ontario Drug Benefit (ODB) database looking at patients receiving hemodialysis between 2002-2011. From this database, the investigators wanted to see if there was a higher risk of death and cardiovascular events initiating a 'high dialyzable' β-blocker among chronic hemodialysis patients over the age of 65 within the first 180 days of starting a β-blocker. The authors defined acebutolol, atenolol and metoprolol as high dialyzable β-blockers whereas bisoprolol and propranolol were defined as low dialyzable β-blockers.

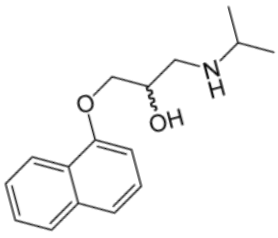
The primary outcome was mortality; secondary outcomes included cardiovascular disease (composite of death, MI, CHF), and other various analyses (dose stability, indications, bowel obstruction, ventricular arrhythmias).

From 339 519 patients in the ODB database of hemodialysis patients, based upon inclusion and exclusion criteria, the authors were able to identify 7205 patients prescribed a high dialyzable β-blocker and 3350 patients prescribed a low dialyzable β-blocker. After using propensity matching to remove potential confounding, each group had 3294 patients. Using the conditional logistic regression model to analyze the data, the authors found that there was a significant risk of death within the first 180 days of starting a high dialyzable β-blocker, compared to a low dialyzable β-blocker [RR 1.4, (95% CI 1.1-1.8), $p < 0.01$]. A subsequent Cox proportional hazards model analysis (i.e. to test the validity of the propensity matching) found similar significant increase in mortality [RR 1.3, (95% CI 1.1-1.7), $p < 0.02$].

As for secondary endpoints, there was no significant difference in dose, indication, bowel obstruction or ventricular arrhythmias between β-blocker groups. However, the composite of death, MI, CHF found a significant difference [RR 1.2, 95% CI 1.0-1.5, $p < 0.03$]. Interestingly, looking at MI and CHF as individual secondary analyses, there was no significant difference between high dialyzable and low dialyzable β-blocker, which would imply that the driving force for the significant secondary composite endpoint was death.

The authors concluded among elderly chronic hemodialysis patients, there was a significantly higher risk of death in the first 180 days of starting a high dialyzable β-blocker. Further studies are required into the pharmacokinetics and pharmacodynamics in this population.

To critique this study, the methodology was robust – the statistical methods and various analyses attempted to minimize any confounding from a retrospective study. Also, the study included a large database involving Ontario patients, making this data generalizable for Canadian patients. However, some of the weaknesses include the study's retrospective nature, categorization of β-blockers (i.e. metoprolol classified as high dialyzable?), probable inclusion bias (i.e. majority of high dialyzable β-blockers was driven by metoprolol use and low dialyzable β-blockers was driven by bisoprolol use) and most importantly, not all β-blockers were included (noticeably, carvedilol was missing). There is a prospective, randomized study looking if carvedilol will lower cardiovascular events in hemodialysis patients (re: BLOCADE study) but its results won't be evaluated for quite some time. But more importantly, a well-designed, randomized prospective study to include the most commonly used β-blockers would be the ideal trial design to answer the original question. In the interim, it might be prudent to review each patient in your hemodialysis population and ask if using high dialyzable β-blockers is the best choice and possibly consider alternatives.



ANCA Vasculitis – An Update

Submitted by Carlee Balint, BSP, ACPR, Foothills Medical Center, Alberta

Recent publication of MAINRITSAN in November of 2014 in the NEJM highlighted emerging information on the treatment of ANCA Vasculitis. The goal of this presentation was to review the options and the literature associated with induction and maintenance treatments for ANCA vasculitis.

ANCA (Anti Neutrophil Cytoplasmic Autoantibody) vasculitis is an auto immune mediated inflammation of the small blood vessels caused by auto antibodies. ANCA binds neutrophils to cause the white blood cells to attack the walls of small blood vessels. ANCA is identified by immunofluorescence/ELISA as C-ANCA, which is directed against PR3, and P –ANCA which is directed against MPO. The two main diseases reviewed include Granulomatous Polyangitis (GPA) and Microscopic Polyangitis (MPA). Clinical features of these diseases include upper and lower respiratory tract symptoms such as cough, hemoptysis, dyspnea, rhinorrhea and epistaxis. Renal involvement consists of glomerulonephritis (GN), which manifests as hematuria, proteinuria, and elevated serum creatinine. Other systems such as skin, joints, cardiac, GI and neuro can also be affected.

Induction treatment is generally with either Cyclophosphamide or Rituximab in various combinations with or without glucocorticoids, and with or without plasmapheresis. Cyclophosphamide has been used as gold standard treatment for years as either an IV pulse or an oral daily treatment. CYCLOPS (Ann Inter Med 2009;150:670-680) first compared the two regimens finding that both were effective in remission of disease. Fewer episodes of leukopenia were seen in the pulse group (HR 0.41 in favor of pulse) and more relapses were seen in the pulse group (13 pulse vs 6 oral), but the pulse group used only approximately half the dose of the oral group. A follow up to this study 4 years later (Ann Rheum Dis 2012;71:955-960) showed this trend continued, but no difference was seen in renal outcomes, survival, or serious adverse effects. It did highlight that the PR3 subtype was at a higher risk of relapse.

Rituximab is an anti CD 20 monoclonal antibody that can deplete the B –cells which are implicated in the pathogenesis of vasculitis, and may offer benefit in treatment of refractory ANCA, without risks of infertility and overall could reduce the exposure of patients to cyclophosphamide and its side effects. RITUXVAS (Jones et al. NEJM 2010) one of the original papers published showing its efficacy in ANCA compared Rituximab plus Cyclophosphamide to Cyclophosphamide alone, because at this point Rituximab had not been proven as a sufficient treatment on its own. It proved that Rituximab was effective, but not superior and at this point no difference in safety (although was given in combo with cyclophosphamide so this may be difficult to tease out). RAVE (Stone et al. – NEJM 2010) was also published in 2010 and randomized patients to Rituximab alone to oral Cyclophosphamide plus glucocorticoids then Azathioprine for maintenance. Rituximab met the criteria for non-inferiority, and it was shown to possibly be superior to Cyclophosphamide in inducing remission in relapsing disease (PR3 subtype). Overall adverse events were higher in the cyclophosphamide group, leukopenias were mostly what accounted for the difference.

Maintenance therapy for ANCA vasculitis used to consist of the gold standard, Azathioprine. Relapse rates were approximately 30% after 18 months of therapy. MAINRITSAN (NEJM 2014 v371;19:1771-1780) was published in the NEJM in November of 2014 and showed the promise of Rituximab as a maintenance therapy. The randomized controlled un-blinded superiority trial involved patients that had been induced with a cyclophosphamide, glucocorticoid regimen and compared maintenance therapy with oral Azathioprine vs. Rituximab (500 mg IV at day 0, 14 and at months 6, 12 & 18). Primary endpoint was major relapse. Relapse rates were significantly different with 29% in the Azathioprine group and 5% in the Rituximab group (HR 6.61, and NNT 4). Serious adverse events were similar in each group, and Rituximab was shown to be superior to Azathioprine at 28 months for ANCA associated vasculitis. The results were particularly convincing in those with PR3 disease as the majority of patients were the PR3 subtype, while numbers were too small to show definite results in MPO associated disease, but further study is definitely warranted. RITAZREM is another study that we await results from as it compares AZA to Rituximab for remission after Rituximab induction. It is currently enrolling patients.

Plasmapheresis has long been contemplated in these patients as plasma removal can remove the circulating antibodies, immune complexes and cytokines including ANCA. PEXIVAS is a study that is currently underway and randomizes patients with Cyclophosphamide or Rituximab induction to plasma exchange vs no plasma exchange, as well as a randomization to standard or reduced dose steroid regimens. Enrollment in this study is continuing and will enroll 700 patients globally and follow for 2-7 years.

Overall, ANCA vasculitis is a complicated disease with no definitive number one choice for therapy, but Rituximab is gaining acceptance as first line particularly in PR3 disease and in fertile patients. There is continued debate on using Cyclophosphamide as a primary therapy, as we continue to try and reduce exposure to Cyclophospamide and its adverse effects. Overall our goal is induce remission and prevent relapse while minimizing side effects of therapy. There is a definitive rise in treatment with Rituximab and Plasmapheresis, and we are hopeful the at PEXIVAS and RITUXVAS will answer some of our unanswered questions in this disease.

What's New in the Nephrology Literature?

A Focus on Renal Pharmacotherapeutics...

Click on the title to go to the PubMed link

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

Canadian chronic kidney disease clinics: a national survey of structure, function and models of care.

Levin A, Steven S, Selina A et al.

Can J Kidney Health Dis. 2014 Nov 18;1:29.

This prospective, cross-sectional, observational study describes the structure and function of multidisciplinary clinics across Canada. Seventy one clinics were surveyed. There was a large variation in staffing ratios. Fifty clinics (70%) employed pharmacists. Suggestions for improvement and identification of aspects that worked well were compiled.

Metformin use and mortality in patients with advanced chronic kidney disease: national, retrospective, observational, cohort study.

Hung SC, Chang YK, Liu JS, et al.

Lancet Diabetes Endocrinol. 2015 Jun 17. pii: S2213-8587(15) 00123-0. doi: 10.1016/S2213-8587(15)00123-0. [Epub ahead of print]

In this retrospective, observational, cohort study of patients with type 2 diabetes and serum creatinine greater than 530 umol/L (stage 5 CKD), use of metformin is associated with a significantly increased risk of all-cuase mortality compared with non-users. The authors emphasize that metformin should not be used in this group.

A Survey of Pharmacists in Academia on the Current Practice of Estimation of Kidney Function for Antimicrobial Dosing in Adults.

Jodlowski TZ, Sym D, Marziliano A, et al.

J Pharm Pract. 2015 Jan 22. pii: 0897190014566310. [Epub ahead of print]

Among 40 Colleges of Pharmacy, academic faculty were randomly chosen to participate in a survey to determine the methods used to estimate kidney function for antimicrobial dosing. Most respondents reported using Cockcrof-Gault (CG) equation (31/36). Discrepancies were found, particularly with elderly and obese patients.

Phenotype standardization for drug-induced kidney disease.

Mehta RL, Awdishu L, Davenport A et al.

Kidney Int. 2015 Apr 8. doi: 10.1038/ki.2015.115. [Epub ahead of print]

The International Serious Adverse Events Consortium initiated a project to develop standardized phenotypes for drug-induced kidney disease. Among a panel of international nephrologists and pharmacists, four phenotypes were proposed along with primary and secondary clinical criteria to define each phenotype.

A pharmacist based intervention to improve the care of patients with CKD: a pragmatic, randomized, controlled trial.

Cooney D, Moon H, Liu Y et al.

BMC Nephrol. 2015 Apr 16;16:56.

A multifactorial intervention that included pharmacist-based interventions were compared to usual care in this randomized controlled trial of patients with moderate to severe chronic kidney disease receiving primary care at community-based Veterans Affairs outpatient clinics. Though there was no difference in the primary outcome of blood pressure control, there was an increase in the number of antihypertensive medications prescribed.

A formal medication reconciliation programme in a haemodialysis unit can identify medication discrepancies and potentially prevent adverse drug events.

Chan WW, Mahalingam G, Richardson RM, Fernandes OA, ***Battistella M.***

J Ren Care. 2015 Jun;41(2):104-9.

Among 228 hemodialysis patients interviewed to obtain a best possible medication history, 3.4 medication discrepancies per patient were identified with 66% classified as unintentional discrepancies. Six percent of discrepancies were deemed to be clinically significant potential adverse drug events by an interprofessional panel.

The Renal Pharmacists Network would like to thank the following sponsors for their continued support and generous contributions.

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