Volume 16 Issue 1 / Spring– Summer 2013

The Renal Pharmacist

Vol 16

Spring - Summer 2013

Issue 1

In this issue ...

A biannual Insight into the Renal Pharmacist Network

View from the Chair

My roses are blooming so summer must be just around the corner! I live in Kelowna, British Columbia and am the renal pharmacist for the Okanagan and Thompson-Cariboo area so being part of the Renal Pharmacists Network helps me keep in touch with my colleagues across Canada. This was proven when I attended the Renal Pharmacists Network Nephrology (RPN) Education Day on April 25th in Montreal, Quebec. Renal pharmacists from coast to coast attended the education day where we had an opportunity to learn from experts in renal pharmacy and share our experiences caring for dialysis and chronic kidney disease patients. For those of you who could not attend the RPN Education Day, we have uploaded the speaker's slides onto the website.

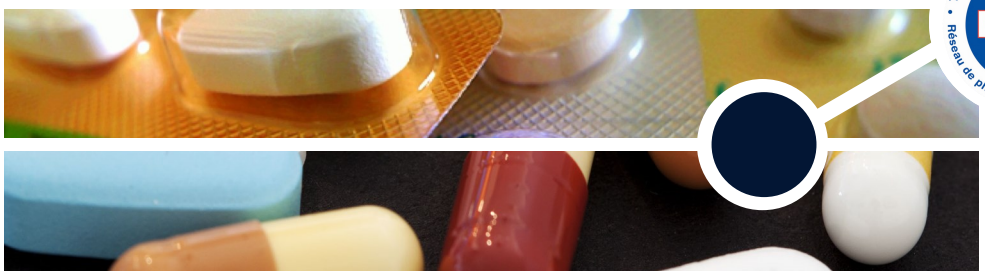
"highly motivated, imaginative and dedicated"

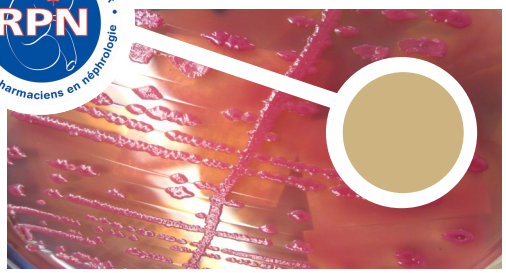
The RPN Education Day was held in partnership with the Canadian Society of Nephrology (CSN) and Societe Quebecoise de Nephrologie (SQN). Again this year, we were invited to present in a joint session at the CSN. Marisa Battistella moderated the session where Dan Martinusen presented on the "Dilemma of Biosimilars" and Marianna Leung and Karen Shalansky discussed selected topics on "Renal Dosing of New Drugs". Make sure and mark your calendar to attend the RPN Educational Day and CSN AGM May 2014 in Whistler, BC! Consider exhibiting a poster at the CSN-it's a great way to showcase the work you have done in your renal program and share your ideas with your renal colleagues!

Looking forward to Fall 2013, the RPN is planning local Renal Education events in Vancouver, Winnipeg and Toronto. The RPN executives, Elaine Cheung, Judith Marin, Amy Sood and Jenny Ng are planning the events and will be making an announcement as soon as dates, locales and speakers are confirmed. We have been fortunate to have highly motivated, imaginative and dedicated individuals on the Executive Committee acting as the renal pharmacist community representatives. I want to especially thank Derrick Soong who has agreed to join the Executive Committee as Chair-Elect. If you are interested in volunteering to serve on the Executive Council or volunteering at an educational event, contact us through the RPN website. We look forward to seeing you at a future RPN event!

Piera Calissi

RPN Chair 2013





Biography: Derrick Soong

Derrick Soong is a renal pharmacist working at Hotel-Dieu Grace Hospital in Windsor, Ontario where he is responsible for the development and implementation of pharmaceutical care for hemodialysis and peritoneal dialysis inpatients and outpatients.

Derrick first obtained a Bachelor's Degree in Science at the University of Windsor before completing his Bachelor of Pharmacy degree at the University of Toronto. He returned to his hometown of Windsor, ON to pursue a career in both hospital and community pharmacy. After working for 5 years in general medicine, cardiology, surgery, and emergency medicine, he sensed the need for further education, returning back to the University of Toronto to complete his Doctorate of Pharmacy.

After completing his PharmD, he accepted a full-time position in the renal dialysis unit where he helped develop and implement several clinical services including pharmacist-led anticoagulation, anemia management, and antimicrobial stewardship. His particular areas of interest in clinical research include anemia management and anticoagulation.

Education is a large part of Derrick's job description where he precepts pharmacy students from the University of Toronto, University of Waterloo, and Wayne State University (Detroit, MI) as well as medical students from Western University. Derrick also plays an integral role in clinical teaching for the accredited pharmacy residency program at the Windsor hospitals. Outside of the hospital, he is a PEBC assessor and an interviewer for University of Toronto pharmacy school admissions. Derrick will be the RPN Chair for 2014.

Derrick Soong, PharmD
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Highlights: The Renal Pharmacists Network Nephrology Education Day 2013, Montreal, Quebec

Submitted by Amy Sood BScPhm, PharmD, St Boniface Hospital, Winnipeg, Manitoba

From left to right: Marisa Battistella, Grace Leung, Elaine Cheng, Judith Marin, Piera Calissi, Amy Sood, Jenny Ng, Derrick Soong

This year, the Annual Renal Pharmacists Network Nephrology Education Day was held in conjunction with the Canadian Society of Nephrology Annual General Meeting in Montreal, Quebec. We had a fantastic turn out of renal pharmacists across Canada with pharmacists in attendance from British Columbia, Alberta, Saskatchewan, Manitoba, Ontario, Quebec, New Brunswick, Nova Scotia and New Foundland.

Our Key Note Speaker was Dr. Marcello Tonelli, Professor in the Department of Medicine, Division of Nephrology and Immunology, at the University of Alberta. He gave us a sneak peak of the upcoming KDIGO Guideline on Dyslipidemia in CKD. There were many 'practice-changing' recommendations which were explained to us with the best available evidence in the CKD population. The talk sparked lots of discussion among the attendees. Please note that his slides will be available on the website once the guideline has been published.

We had several pharmacist speakers on various topics of interest. Lisa Zhu, PharmD based at Sunnybrook Health Sciences, Toronto, Ontario, gave us an in depth "Update on Blood Pressure Management Goals in CKD". She focused on non-diabetic CKD patients, diabetic patients and very elderly patients (≥80 yrs). Please read further about this in the newsletter article "Update on Blood Pressure Management Goals in CKD: A Moving Target?".

Next, we had the opportunity to learn about "Drug Dosing in Renal Failure", presented by Dan Martinusen, a PharmD practicing at the Royal Jubillee Hospital in Victoria, BC. Dan presented an approach to determine when to use the Cockroft-Gault equation and/or the MDRD eGFR for drug dosing in CKD.

Marianna Leung, a PharmD practicing at St. Paul's Hospital in Vancouver reviewed the pharmacological treatment and management for insomnia, pruritis and pain. She has shared these algorithms in the previous RPN newsletter issue.

We continued on with "Short and Snappy" Journal reviews where 3 of our executive RPN members presented on the recent studies: Evolve (Piera Calissi), MP3 (Elaine Cheng) and FISH study (Marisa Battistella).

Finally we heard a comprehensive presentation by Jennifer Harrison who has had extensive experience in Transplant at University Health Network. She gave us "Pearls for managing the transplant recipient with chronic kidney disease."

The successful day ended with a big Round Table Discussion on various topics, especially focusing on IV iron practices at various sites. It was a great day to network with colleagues across Canada and discuss common practice issues.

Do you want to get involved with the **Renal Pharmacists Network**?

We are currently taking nominations for the **2014 Chair Elect**. Find out more by contacting one of our **executive members**!

Highlights: Canadian Society of Nephrology 2013, Montreal Quebec

Submitted by Amy Sood BScPhm, PharmD, St Boniface Hospital, Winnipeg, Manitoba

The Canadian Society of Nephrology Annual General Meeting was held on April 24-30th, 2013 in Montreal Quebec. On Friday April 26th, there was a joint session with the RPN and CSN which was very well attended. We had several pharmacist speakers at this session.

First, Dan Martinusen presented on "The Dilemma of Bio-similar Agents". He discussed the subsequent entry biologics (e.g. generic ESAs) from a manufacturing, regulatory and payer perspective. Key challenges that clinicians may face as decision makers for bio-similars were identified. This was a very interesting topic and very timely as we enter a new era of generic bio-similar molecules.

Next we had 3 speakers discussing renal dosing of new drugs. Marianna Leung compared and contrasted the new oral anticoagulants, dabigatran, rivaroxaban and apixaban and reviewed their dosing recommendations in patients with CKD. Dr Varun Dev, a second year internal medicine resident at University of Western Ontario, discussed renal dosing recommendations for newer antidepressants. Finally, Karen Shalansky, a PharmD practicing at Vancouver General Hospital, discussed the use of LMWHs for prophylaxis and treatment in CKD.

The last speaker for this RPN-CSN joint session was Dr Jean-Francois Yale, an endocrinologist and Professor of Medicine at McGill University. He was Clinical and Scientific Chair of the Canadian Diabetes Association (1992-4) and Chair of the Expert Committee (2001) and a member of the Steering Committee (1998, 2003, 2008) of the CDA Clinical Practice Guidelines. He gave us an "Update on hypoglycemic agents and new insulin regimens for the Nephrologist". He discussed the antihyperglycemic therapies available for patients with CKD stage 4/5, as well as introduced us to a new class of antihyperglycemic agents, the SGLT2 inhibitors and their potential use in CKD.

Overall, the RPN-CSN joint session was very well attended by pharmacists and nephrologists across Canada. The RPN executive received great feedback of this successful session. We hope to continue this collaboration with CSN in future years.

NEW SECTION

Showcasing Research by Renal Pharmacists!

Comparison of alteplase (tissue plasminogen activator) high-dose vs. low-dose protocol in restoring hemodialysis catheter function: The ALTE-DOSE study.

Submitted by Derrick Soong, BScPhm, PharmD, Hotel-Dieu Grace Hospital, Windsor, Ontario

There are no guidelines to recommend the optimal dose of alteplase to treat central venous catheter (CVC) malfunctioning due to thrombosis in patients receiving hemodialysis. While there is controversial literature to suggest equivalence between alteplase 1mg and 2mg dose, these initial studies had short observation periods and small sample sizes. The ALTE-DOSE study was conducted to clarify if there is equivalence between the 2 doses.

The ALTE-DOSE study was a retrospective cohort study that included patients from a single community-based Ontario hemodialysis centre treated between May 2005 and May 2011 and had a CVC. On May 2008, there was a switch in protocol from 2mg of alteplase down to 1 mg. The investigators compared those who received 1mg of alteplase in each catheter dwelling post-dialysis with patients receiving 2mg of alteplase. The authors used a 'convenience sample' with the following exclusion criteria: less than 18 years of age, pregnant women, patient receiving less than 8 dialysis sessions or been on dialysis for less than 15 eays, patient with any allergy or contraindication to alteplase, patients receiving both 2mg and 1mg doses of alteplase on different occasions, or patients who were catheterized after removal of their initial catheter outside of the observation period.

A total of 244 hemodialysis patients were included in this study. After Cox regression analysis to minimize any potential confounding, the authors concluded that the 2mg alteplase dose was significantly better than the 1mg dose in terms of CVC overall function, lifespan of CVC, and need for radiologic-guided repair / replacement. The adjusted hazard ratio (HR) of catheter removal due to unresolved occlusion for using the 1mg compared to 2mg dose was 2.75 (95% confidence

interval 1.25-6.04). On an absolute basis, a 2mg alteplase dose had a 89.8% success rate in clearing catheter occlusion whereas a 1mg alteplase dose had a 80.6% success rate (p = 0.036). Some other remarkable results: female gender was associated with higher risk of cathether replacement (HR 2.51, 95% confidence interval 1.20-5.27), whereas age having a slightly protective effect (HR 0.96, 95% confidence interval 0.94-0.98). Ironically, anticoagulant use did not impact CVC survival regardless of alteplase dose used (p = NS). Although these results are compelling to favour 2mg dose, a prospective, randomized study should be completed before any definitive conclusions can be made.

Yaseen O, El-Masri MM, El Nekidy WS, **Soong D** et al.
Hemodialysis International. 2012 Nov 26. doi: 10.1111/hdi.12004. [Epub ahead of print])

Update on Blood Pressure Management Goals in CKD: A Moving Target?

Submitted by Lisa Zhu, BScPhm, ACPR, PharmD, Clinical Pharmacist, Sunnybrook Health Sciences Centre, Toronto, ON

Blood pressure control is a key component of managing chronic kidney disease (CKD) patients. Recently there have been important changes to the recommended blood pressure targets which are relevant for non-dialysis dependent CKD patients. This article will discuss blood pressure targets for the following groups of patients:

- Non-diabetic CKD patients
- Diabetic patients
- Very elderly patients (≥80 yrs)

BP Targets for Non-diabetic CKD Patients

Blood pressure targets for non-diabetic CKD patients have evolved over time. Looking from past to present the recommended targets have shifted from being more aggressive to less intensive. Formerly the 1999 Canadian guidelines and the 2004 National Kidney Foundation Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines both recommended targeting <130/80 mmHg and an even tighter target of <125/75 mmHg for patients with proteinuria.[1,2] The move toward less aggressive targets began in 2006 when the Canadian Hypertension Education Program (CHEP) removed the lower target for proteinuric patients.[3] Continuing with this trend in 2012 the next significant change was made when CHEP increased the target to <140/90 mmHg.[4] The same target was recommended in the 2012 Kidney Disease Improving Global Outcomes (KDIGO) guidelines.[5]

Evidence for Changes and Current Recommendations

The shift from more to less stringent blood pressure targets is the result of a reappraisal of the literature using a more critical evidence-based approach.[6] Previous guidelines had based recommendations on the collective body of evidence including lower quality observational trials and post-hoc analyses. When restricting the evidence to only high quality randomized controlled trials (RCT) which specifically randomized CKD patients to different blood pressure targets there are essentially 3 key studies.

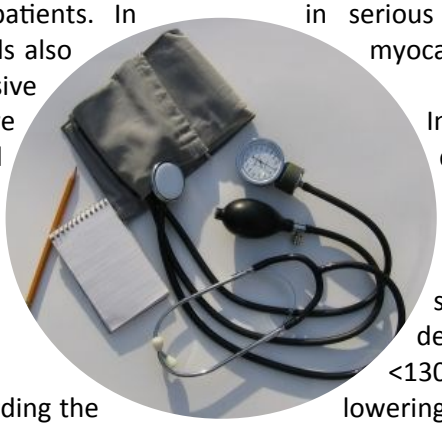
The first is the Modification of Diet in Renal Disease (MDRD) trial, which examined the effects of more intensive blood pressure lowering on progression of renal disease.[7] This study randomized 840 patients with stage 3-5 CKD to either usual BP target (mean arterial pressure [MAP] 107mmHg; approximately 140/90mmHg) or low BP target (MAP 92mmHg; approximately 125/75). Despite more intensive blood pressure lowering there was no significant difference in the decline in glomerular filtration rate (GFR). In addition, there was no significant difference in the proportion of patients progressing to end-stage renal disease (ESRD) or death. A subsequent post-hoc analysis was performed which suggested a significant interaction between baseline proteinuria and achieved BP level. A reanalysis of the study data found that the rate of decline in GFR appeared to increase above a MAP of 98mmHg (approximately 130/80mmHg) in patients with 0.25-3 grams of proteinuria per day. In patients with 3g/day of proteinuria the rate of decline in GFR increased above a MAP of 92mmHg. This along with other observational data formed the basis for the prior target of <130/80mmHg in non-diabetic CKD patients and the more intensive <125/75mmHg in patients with ≥1g/day of proteinuria. Given that this was a post-hoc analysis there are a number of important limitations. The proteinuria categories were not pre-specified, randomization was not stratified by proteinuria levels and there were no statistical adjustments made to account for multiple testing. Thus this evidence should really only be considered hypothesis generating.[8]

The second RCT is the African American Study of Kidney Disease (AASK) trial which also examined the effect of intensive blood pressure lowering on progression of renal

disease.[9] The study randomized 1094 African American patients with stage 3-4 CKD to either usual (MAP 102-107mmHg) or lower (MAP 92mmHg/ approximately 125/75) BP targets. Similar to the MDRD, the study failed to demonstrate a significant difference in the decline in GFR between the two groups.

The final RCT is the Blood Pressure Control for Renoprotection in Patients with Chronic Renal Disease (REIN-2).[10] This study is unique in that it is the only trial to specifically examine the impact of BP targets in proteinuric (>1g/day), non-diabetic CKD patients. Patients were randomly assigned to either a conventional target (DBP <90) or intensive target (<130/80). The study was terminated early due to futility and failed to demonstrate a reduction in progression to ESRD in proteinuric patients despite intensive BP lowering.

In summary, based on the evidence from these 3 trials lower blood pressure targets (<130/80mmHg) do not provide greater benefits compared to targeting <140/90mmHg among non-diabetic CKD patients. In addition a systematic review of these trials also found that participants in the more intensive BP lowering arms required more antihypertensive medication and experienced slightly higher rates of adverse events.[11] Thus the risks outweigh the benefits and the evidence supports the less intensive target of <140/90mmHg.



BP Targets for Patients with Diabetes

Recently there has been controversy regarding the blood pressure targets for patients with diabetes. This year the American Diabetes Association guidelines raised the systolic blood pressure target from the traditional <130 mmHg to <140 mmHg.[12] In contrast, the current CHEP guidelines continue to recommend the traditional target of <130/80mmHg.[13]

Evidence for Changes and Current Recommendations

In terms of BP targets for patients with diabetes the most robust evidence is for diastolic blood pressure (DBP). The Hypertension Optimal Treatment (HOT) trial randomized 18,790 hypertensive patients to 3 different diastolic BP targets: <90mmHg, <85mmHg or <80mmHg.[14] Focusing on the diabetes subgroup (N=1501), after nearly 4 years of follow-up there was a 2-fold lower risk of major cardiovascular disease (CVD) events and a 3-fold lower risk of CVD mortality for patients randomized to a DBP <80mmHg versus DBP <90mmHg.

In comparison, evidence for systolic blood pressure (SBP) targets is less robust. The traditional target of <130mmHg is not based on data from RCTs but rather observational studies. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) Blood Pressure trial randomized 4733 type II diabetes patients to intensive SBP <120mmHg or control SBP <140mmHg.[15] After nearly 5 years of follow-up there was no significant difference in the primary composite of non-fatal myocardial infarction, non-fatal stroke or death from CVD. There was, however, a significant reduction in the individual endpoint of fatal and non-fatal stroke, translating to a number needed to treat (NNT) of approximately 89. Of note, intensive blood pressure lower did come at a cost of significantly higher rates of serious adverse events such as hyperkalemia and syncope (3.3% vs. 1.3%; p=0.001). Similar results were reported by two subsequent meta-analyses. Reboldi et al. analyzed 31 prospective trials of antihypertensive therapy in patients with diabetes and found that tight SBP control reduced the risk of stroke but did not reduce the risk of myocardial infarction.[16] Bangalore et al. analyzed 13 RCTs and found that intensive BP control was associated with a 17% relative reduction in stroke but a 20% relative increase in serious adverse effects and no difference in myocardial infarction or CVD mortality.[17]

In summary, the current evidence demonstrates significant reductions in major CVD events and CVD mortality with a DBP target of <80mmHg. Intensive SBP lowering, on the other hand, has not been shown to reduce major CVD events or CVD death. Intensively lowering SBP to <130mmHg results in a trade-off between lowering the risk of stroke and increasing the risk of serious adverse events. Despite the low absolute risk reduction, the CHEP guidelines consider the potential catastrophic consequences of a stroke to outweigh the risk of adverse events and continue to recommend the targeting SBP <130mmHg.

BP Targets for the Very Elderly (≥80 years)

This year the CHEP guidelines added a new recommendation for blood pressure targets in very elderly patients (≥80 years).[13] For very elderly patients with isolated systolic hypertension the guidelines now recommend targeting a SBP <150mmHg. In 2011 the American College of Cardiology Foundation (ACCF) and the American Heart Association (AHA) published a joint consensus document on the management of hypertension in the elderly.[18] The document acknowledges that the ideal BP for patients ≥80 years with or without comorbidities has not been established. The expert committee suggests that a SBP of 140-145mmHg is acceptable if tolerated for those ≥80 years regardless of comorbidities. They further suggest that treatment may be withheld in frail patients, those medically

unstable or who are approaching ≥90 years.

Evidence for Changes and Current Recommendations

Evidence from more than a decade ago began to suggest that the effects of blood pressure lowering may be different in elderly patients. A 1999 meta-analysis of antihypertensive drugs in the elderly found conflicting results with reductions in non-fatal CVD events but an unexpected trend toward increased fatal events.[19] A subsequent observational study by Oates et al. in patients ≥80 years found a U-shaped relationship between blood pressure and mortality.[20] Patients with lower blood pressures had lower rates of survival. The authors postulated that the shortened survival may be due to orthostasis, falls or other medication side effects which are offsetting the cardiovascular benefits of lowering blood pressure. The highest survival was seen at SBP levels between 130-149mmHg and DBP levels between 70-89mmHg. In 2008 the Treatment of Hypertension in Patients 80 Years of Age and Older (HYVET) study randomized 3845 relatively healthy, very elderly patients to sustained-release indapamide versus placebo with a BP goal of <150/80.[21] After nearly 2 years of follow-up there were significant reductions in death from stroke, all cause mortality, heart failure and any CVD event.

In summary, the evidence for blood pressure targets in the very elderly is limited. Previous data found conflicting results with reductions in non-fatal events but potential increases in fatal events. Epidemiologic evidence points to a U-shaped curve with lower BP targets associated with lower survival. The HYVET trial does demonstrate reductions in all cause mortality and CVD events with lowering of SBP to <150mmHg in relatively healthy very elderly patients and provides the basis for the new CHEP guideline recommendation. Ultimately the precise BP target for very elderly patients, especially for those with comorbidities such as diabetes or CKD, remains uncertain and is based on expert opinion.

Summary of Canadian BP Targets

Patient Population	BP Target
Non-diabetic CKD	<140/90 mmHg
Diabetes	<130/80 mmHg
Very elderly (≥80)	SBP <150 mmHg

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Ferumoxytol for all? IV iron for the treatment of Anemia in Chronic Kidney Disease Patients

Submitted by Matt Swankhuizen BSc. (Pharm), CDE, PharmD Student, University of Toronto

Anemia is a common consequence of chronic kidney disease (CKD) with up to 70% of stage 5 CKD patients exhibiting signs or symptoms (1,2). While appropriate management of anemia in CKD often requires both iron and erythropoietin-simulating agents (ESA), recent studies caution against the liberal use of ESA therapy(3,4). This is as a result of literature suggesting a link between targeting higher hemoglobin levels using ESA therapy with stroke and venous thromboembolism (3,4). As a result of this link there has been increased interest in the management of anemia with an emphasis on iron therapy to reduce ESA requirements. This is reflected in the 2012 international guidelines (KDIGO-Kidney Disease: Improving global outcomes) for the management of anemia in chronic kidney disease. The guidelines suggest that intravenous (IV) iron therapy (or alternatively a 3 month trial of oral iron therapy in non-dialysis patients) should be considered in both those who are and those who are not on ESA therapy to increase hemoglobin levels or to decrease the dose of ESA therapy when transferrin saturation (TSAT) ≤ 30 % and ferritin of ≤ 500 ng/ml (4).

As initial therapy in the CKD non-dialysis population, the KDIGO guidelines suggest a trial of oral iron(4). While oral iron is inexpensive, readily available and less invasive than its IV counterpart, it is not without limitations. Oral iron is associated with significant gastrointestinal side effects that often limit patients' adherence to therapy (1,2,3,4,5). Oral iron also interacts with medications such as calcium-based phosphate binders which are commonly used in the CKD population (1). It is for these reasons that IV iron offers an attractive option as it is considered to have fewer gastrointestinal adverse reactions, and superior efficacy (4,5,6).

In late 2011 Health Canada approved a novel IV iron for use. Ferumoxytol (Feraheme®) is an iron oxide nanoparticle surrounded by a poly glucose sorbitol carboxymethyl ether coating that was designed to minimize immunological sensitivity and release less free iron(1,2,3). Ferumoxytol is an attractive option for patients with anemia of CKD because it can be given as a dose of 510 mg over 17 seconds then repeated in 2-8 days(1,2,3). Compared with other available agents that can take up to 4 hours for an infusion to complete, ferumoxytol may offer a convenience advantage for non-dialysis CKD, peritoneal dialysis and home hemodialysis patients. Moreover, it may be an attractive option for hospitals due to reduced nursing workload and improved patient flow that may well translate into significant cost savings and/or reduced wait-lists.

Efficacy:

The efficacy of this new agent was investigated in three open-label, randomized, controlled trials(1,2,3). Results from these phase 3 studies suggest that IV ferumoxytol is superior to oral iron in raising hemoglobin, ferritin and TSAT levels in CKD 1-5 and hemodialysis patients(1,2,3). However, this finding is not surprising as a number of randomized controlled trials and meta-analyses have suggested these same results with all IV irons, especially in the hemodialysis population (4,5,6). Unfortunately there is a paucity of well conducted evidence that directly compares ferumoxytol to one of the other currently available IV iron preparations. In 2011, at the American Society of Nephrology's kidney week conference, a poster describing the results of the FIRST trial was presented that compared ferumoxytol to iron sucrose(7). To date this new evidence has not yet been published, however from this preliminary data it seems that ferumoxytol is as effective at raising hemoglobin(Hgb) levels as iron sucrose(7).

Safety:

A growing concern about IV iron use is the potential to release free iron into the blood stream resulting in oxidative stress (8,9). It is hypothesized that the release of oxygen free radicals results in atherosclerosis, proteinuria and renal tubular damage in IV iron users (8,9). Preliminary in vitro and in vivo rat model studies have contradictory findings (8). On one hand it seems that ferumoxytol may result in no increase in surrogate markers of oxidative stress in the kidney while ferrous gluconate, and iron sucrose are associated with an increase(8).However, other evidence suggests that ferumoxytol is associated with increases in urinary protein excretion in rat models(8). Although this data is preliminary, it suggests that we need long term prospective studies to determine if IV iron in the CKD population is doing more harm than good.

Severe infusion related reactions are another concerning side effect of IV iron. These include anaphylaxis, anaphylactoid type reaction, hypotension, and severe flushing (4,8). It is hypothesized that these reactions are related to the speed that the infusion is given, which is why traditionally agents are given slowly over many hours (4,8). As a result of its propensity to cause severe anaphylactic reactions iron dextran requires a test dose to be given before each iron infusion. In addition, in January 2013, Health Canada mandated a class labelling update for all intravenous iron product monographs which includes a

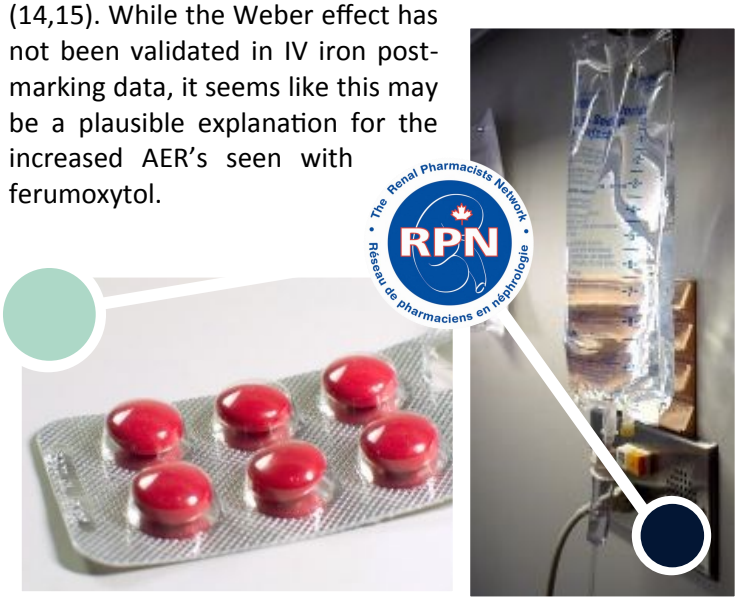
Black Box Warning to monitor patients for signs and symptoms of hypersensitivity reactions during and for at least 30 minutes after administration.

Initial data published for the safety of ferumoxytol seemed to be promising. Phase 3 studies that compared ferumoxytol to oral iron suggest that it was associated with less nausea (3.1 % vs 7.5%) and vomiting (1.5% vs 5.0%), with only a slight increase in hypotension (2.5 % vs 0.4 %) (1,3).However, there are several limitations to the reliability of the data. First, patients were excluded if they had allergies to iron products or if they had ≥ 2 allergies to any drug(1,3). Excluding patients who have hypersensitivities to IV iron and other drug products may decrease the likelihood that the study would be able to capture anaphylactic and anaphylactoid type reactions. Furthermore, the studies were small and adverse events were a secondary outcome (1,3). These studies were not designed to capture safety endpoints, and were significantly underpowered to capture the more rare events like anaphylaxis.

A 2008 randomized, double-blind, placebo controlled, crossover trial (n=713) by Singh and colleagues attempted to overcome some of these limitations (10). The phase 3 study specifically examined safety endpoints of IV ferumoxytol 510 mg x 1 dose versus IV normal saline (10). Serious adverse events(SAE) were reported in 2.9 % of individuals in the ferumoxytol group and 1.8 % of patients in the placebo group(no p-values reported); however, a blinded clinician evaluated relation of SAE to the study drug which resulted in rates of 0.1 % in both groups(10).As we have seen with the other studies involving ferumoxytol, patients with allergies to iron products or allergies ≥2 drugs were excluded from the trial(10).Again this limits the patient population that we can apply these results to. Interestingly, patients in this study only received 1 dose of ferumoxytol(10). Although the anaphylactic reaction that is seen with IV iron is not IgE mediated, there is some data suggesting that adverse events and serious adverse events are still exhibited after subsequent doses of ferumoxytol, therefore, giving one dose may deflate actual adverse event rates (11).

Ferumoxytol was compared to iron sucrose in the FIRST trial that was briefly discussed in the efficacy section above (7). Adverse events were a secondary outcome in this small study (n=162)(7). SAE's were reported in 9% of patients in the ferumoxytol arm and 7% of patients in the iron sucrose arm(no p-values reported); yet, after the site investigator subjectively determined if effects were related to the study drug, 1% of patients in each group had a related SAEs. The use of a non-blinded investigator affects our ability to interpret the data from the trial. Furthermore, the infusion rate for iron sucrose was absent from the poster. Because high infusion rates are associated with adverse reactions, the side effect profiles are difficult to compare without this data. As with the other trials comparing ferumoxytol to other agents, patients were excluded if they had allergies to iron products and/or ≥ 2 allergies to any drug, adverse reactions were a secondary outcome, and the trial was underpowered for safety outcomes.

Based on the results of the available trials described above it seems that ferumoxytol exhibits fewer gastrointestinal side effects than oral iron, and potentially equal side effects to placebo and iron sucrose(1,2,3,7,10). However, in 2012 a retrospective analysis of adverse event rates(AER) data from the FDA database was published(12). In this analysis, where ferumoxytol was used in the general population, it was associated with a higher risk of all adverse events (745.76/million units sold(MUS)), death (50/(MUS) and serious adverse events (583.3/MUS) when compared to other available iron agents. The agent with the next closest adverse drug reaction rate was high molecular weight iron dextran (All A/E's=66.47/MUS, SAE=18.13/MUS, Death=6.04/MUS)(12) . While this data signals that there may be issues with using ferumoxytol in the general population, it must be interpreted with caution. The academic community and FDA reviewers both note that it is not possible to draw conclusions about comparative risk from AER data (13). This is because AER data is subject to significant bias because it is voluntary, passive and spontaneous which may result in under reporting (13). Additionally,FDA AER data may be subject to the Weber effect, a phenomenon that includes increased awareness, interest and vigilance during the period after the release of a new agent (12,14). Weber observed this occurrence while interpreting FDA AER data for NSAIDs that were recently introduced to market (14,15). He noticed that AER reporting to the FDA rises until the middle to end of the second year after introduction, peaks and then declines (14,15). While the Weber effect has not been validated in IV iron post-marking data, it seems like this may be a plausible explanation for the increased AER's seen with ferumoxytol.



Although the academic community and FDA reviewers caution against use of AER data to make sweeping judgements on comparative side effects of IV irons, this does not necessarily mean that we should disregard the results of post marketing data(13). There is a signal that ferumoxytol may have increased rates of adverse events in the general population. Based on these results further large observational trials in the general population need to be conducted to determine if ferumoxytol actually is associated with significantly more side effects than the other available agents.

In addition to the concerns on a population level, ferumoxytol displays an interaction with magnetic resonance imaging (MRI) which is unique to this IV iron supplementation. The reason for this interaction is that ferumoxytol is a superparamagnetic iron oxide particle that interferes with the MRI's ability to enhance tissues, rendering imaging non-diagnostic. Because of the long half-life of ferumoxytol this affect can last up to 3 months after administration; therefore, clinicians must be mindful of this each time ferumoxytol is scheduled. If possible, the ferumoxytol should be delayed until after the scheduled MRI or an alternative IV iron should be used.

Conclusion:

The sole advantage of ferumoxytol over other intravenous iron products is its ability to be infused undiluted over 17 seconds. As such, it may have a role in outpatient CKD nondialysis, peritoneal dialysis and home hemodialysis patients due to faster patient turnover and reduced nursing workload. However, as there is limited comparative safety data, use of ferumoxytol should be carefully monitored and all adverse reactions should be recorded. It should also be kept in mind that all previous prospective studies with ferumoxytol excluded patients with allergies to iron products or ≥ 2 allergies to any drug so these patients should be monitored more vigilantly. Additional comparative safety data is needed to further define ferumoxtyol's place in therapy .

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Use of high potency statins and rates of admission for acute kidney injury: multicenter, retrospective observational analysis of administrative databases.

*Dormuth CR, Hemmelgarn BR, Paterson JM, James MT, Teare GF, **Raymond CB** et al. BMJ 2013;346:f880 doi: 10.1136/bmj.f880 [Epub ahead of print]*

In this retrospective observational analysis of administrative data bases including over 2 million patients aged 40 years or older, high potency statins use among patients without CKD were 34% more likely to be hospitalized with acute kidney injury than those on low potency statins. High potency statin was defined as equal to or greater than 10 mg rosuvastatin, 20 mg atorvastatin, or 40 mg simvastatin.

How can erythropoietin-stimulating agent use be reduced in chronic dialysis patients? The "Forgotten Adjunct Therapy": The link between ESA use and control of hyperparathyroidism in chronic kidneay disease.

***Battistella M**, Chan CT. Semin Dial 2013;Jun 5 doi 10.1111/sdi.12106 [Epub ahead of print]*

This review article discusses the beneficial effect of correcting PTH on ESA responsiveness. The mechanism and clinical evidence to date is summarized. The author explains that treating hyperparathyroidism is one way to minimize ESA use.

Using an electronic self-management tool to support patients with chronic kidney disease (CKD): A CKD clinic self-care model.

***Ong SW,** Jassal SV, Porter E et al. Seminars in Dialysis 2013 doi:10.1111/sdi.12054 [Epub ahead of print]*

This paper describes a great new initiative called "My KidneyCare Centre", at University Health Network, Toronto, ON. This information technology solution was developed to support self-management strategies for patients with CKD. The tool focuses on educating patients about CKD, helps monitor their progress and encourages them to set learning goals.

Understanding pruritis in dialysis patients.

*Makari J, Cameron K, **Battistella M**. CANNT J 2013;23:19-23; quiz 24-5.*

This is a great review article on the epidemiology, diagnosis, clinical presentation, pathophysiology and evidence-based treatment of pruritis in dialysis patients.

Motivational interviewing for patients with chronic kidney disease.

Sanders KA, Whited A, Martino S. Seminars in Dialysis 2013 doi:10.1111/sdi.12052 [Epub ahead of print]

This article discusses the details of motivational interviewing and its important role and application in the care of CKD patients.

Medication nonadherence. A diagnosable and treatable medical condition.

Marcum ZA, Sevick MA, Handler SM. JAMA 2013;309:2105-6.

This recent publication in JAMA encourages us to think about medication nonadherence as medical condition that can be diagnosed and treated. The authors highlight 6 types of nonadherence that require different approaches from a diagnostic and treatment perspective.

Antiplatelet therapy in the management of cardiovascular disease in patients with CKD; what is the evidence.

Jain N, Hedayati SS, Sarode R, et al. Clin J Am Soc Nephrol 2013;8:665-74.

In this recent review article, the controversial topic of antiplatelet use in CKD is discussed.

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