New Therapies in Management of Hyperkalemia

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Sunnybrook
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Background

- Hyperkalemia is a common and potentially life-threatening electrolyte abnormality in patients with CKD
- May be related to use of medications such as ACEi/ARBs and mineralocorticoid receptor antagonists (MRAs)
- Limited outpatient treatments available for treatment of hyperkalemia

Sodium Polystyrene Sulfonate (SPS)

- Approved by FDA in 1958 before safety/efficacy testing was mandated
- 2009 FDA released a black box warning about increased intestinal necrosis with use + sorbitol
- Nov 2018 - Health Canada warning to that SPS can decrease efficacy of other oral medications and to separate administration

Potassium Lowering Agents Coming to Canadian Market

- Patiromer (Veltassa)
  - Fresenius
  - Estimated availability early 2020
- Sodium zirconium cyclosilicate ZS-9 (Lokelma)
  - Astra Zeneca
  - Estimated availability early 2020

Comparison of Agents

Pharmacologic Property	Sodium polystyrene sulfonate (SPS)	Patiromer calcium sorbitex	Sodium zirconium cyclosilicate (SZC)
Brand Name	Kayexalate	Veltassa	Lokelma
Mechanism of action	Binds potassium in GI tract and facilitates excretion in the feces		
Selectivity for potassium ion	Non-selective; also binds calcium and magnesium	Selective; also binds magnesium	Highly selective: 9x the K binding capacity compared to SPS; also binds ammonium
Sodium content	1500 mg sodium per 15 g dose	None	1000 mg sodium per 10 g dose
Sorbitol content	20 g sorbitol per 15 g dose (in oral suspension formulation)	4 g sorbitol per 8.4 g dose	No sorbitol
Onset of effect	Variable: 2-6 hours	7-48 hours	1-6 hours
Duration of effect	Variable: 6-24 hours	12-24 hours	Unclear; appears to be 4-12 hours based on trial data

Adapted from Beccari. Core Evidence 2017

Comparison of Agents

Pharmacologic Property	Sodium polystyrene sulfonate (SPS)	Patiromer calcium sorbitex	Sodium zirconium cyclosilicate (SZC)
Dosing	15 g PO 1-4 times daily	8.4 g PO once daily may be titrated to 25.2 g/day	Correction: 10 g TID for up to 48 hours Maintenance: 5 g daily; titrated to 10 g daily
Administration	Powder for suspension, mix with water (3-4 mL per gram of SPS)	Powder for suspension, mix with water (90 mL), administer within an hour of suspending	Powder for suspension, mix with water (45 mL), administer immediately
Availability	454 g container	8.4/16.8/23.2 gram sachets	5/10 gram sachets
Cost	$42 per 454 grams	?	? (CADTH review)

Adapted from Beccari. Core Evidence 2017

Comparison of Agents

Pharmacologic Property	Sodium polystyrene sulfonate (SPS)	Patiromer calcium sorbitex	Sodium zirconium cyclosilicate (SZC)
Safety	Risk of intestinal necrosis, hypernatremia, diarrhea, GI intolerance	Mild-moderate constipation, hypokalemia, hypomagnesemia	Edema, hypokalemia GI effects similar to placebo however patients with previous GI history excluded from studies
Drug Interactions	≥ 3 hours before or 3 hours after other oral medications If gastroparesis, a 6-hour separation should be considered	≥ 3 hours before or 3 hours after other oral medications	≥ 2 hours before or 2 hours after other oral medications

All 3 options may interfere with absorption other medications and would need to separate out timing of medications

Table 1 Summary of Patiromer clinical trial data

Study	Trial population	Comparator groups	*N*	Study design	Follow-up (weeks)	Major finding
PEARL-HF	Chronic HF, CKD, or prior history of HK that led to stopping RAASi and indication to start spironolactone	Patiromer 15 g b.i.d. or placebo	105	Randomized and double blind. Patients started on 25 mg of spironolactone and titrated	4	Patiromer lowered serum K^+ levels −0.45 mmol/L vs. placebo ($P < 0.001$)
OPAL-HK	eGFR (15-59 mL/min/1.73 m^2 and K^+ 5.1-6.4 mmol/L)	Initial phase: cohort with mild HK (5.1-5.5 mmol/L) 4.2 BID i.e. 8.4 g per day. Cohort with moderate HK (5.6-5.9 mmol/L) 8.4 BID i.e. 16.8 g per day	243	Initial phase: single cohort and single blind	4	Mean K^+ reduction −1.01 mmol/L
		Maintenance phase: continued on same dose of patiromer or switched to placebo		Maintenance: randomized, single-blind, and placebo-controlled withdrawal	8	Mean increase in K^+ 0.72 mmol/L for placebo and 0 mmol/L for patiromer ($P < 0.001$)
AMETHYST-DN	Type 2 DM, and eGFR (15-59 mL/min/1.73 m^2) receiving RASSi. During run in period those that developed, mild or moderate HK enrolled. Patients with known HK allowed to skip run-in and proceed directly to randomized phase	Cohort with mild HK (5.1-5.5 mmol/L) 4.2 g, 8.4 g, or 12.6 g PO b.i.d. Cohort with moderate HK (5.6-5.9 mmol/L) 8.4 g, 12.6 g, or 16.8 g PO b.i.d.	306	Randomized and open label trial. Patients on baseline ACE-I or ARB, and started on spironolactone	52	Mild HK cohort: mean K^+ reduction −0.35 mmol/L for 4.2 g, −0.51 mmol/L for 8.4 g, and −0.55 mmol/L for 12.6 g. Moderate HK cohort: mean K^+ reduction −0.87 mmol/L for 8.4 g, −0.97 mmol/L for 12.6 g, and −0.92 mmol/L for 16.8 g.

ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CKD, chronic kidney disease; HF, heart failure; HK, hyperkalaemia; K^+, potassium; RAASi, renin-angiotensin-aldosterone system inhibitors.

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Table 2 Summary of SZC clinical trial data

Study	Trial population	Comparator groups	N	Study design	Follow-up	Major finding
ZS-002	Stable CKD (eGFR 30-60 mL/min/1.73 m^2) and mild to moderate HK (5.1-5.9 mmol/L)	SZC 0.3 g, 3 g, or 10 g vs. placebo	90	Randomized, double blind, and placebo-controlled	48 h	SZC had a 0.92 mmol/L mean reduction of serum K^+ at 38 h in the 10 g dose group, comparing 0.26 mmol/L with placebo ($P < 0.001$).
ZS-003	Initial phase serum K^+ 5.0-6.5 mmol/L	SZC 1.25 g, 2.5 g, 5 g, or 10 g or placebo three times daily	753	Initial phase: double blind and placebo controlled	48 h	SZC had a mean serum K^+ reduction of −0.3 mmol/L, −0.5 mmol/L, −0.5 mmol/L, and −0.7 mmol/L for the 1.25 g, 2.5 g, 5 g, and 10 g groups, respectively (vs. −0.3 mmol/L with placebo)
	Maintenance phase: those who achieved serum K^+ 3.5-4.9 mmol/L at 48 h	Maintenance phase: continued on same dose of SZC or switched to placebo	542	Maintenance: randomized, double-blind, and placebo controlled	12 days	5 g and 10 g of SZC maintained serum K^+ at 4.7 mmol/L and 4.5 mmol/L, respectively, when compared with a level of more than 5.0 mmol/L in the placebo group ($P < 0.01$ for all)
HARMONIZE	Initial phase serum K^+ >5.1 mmol/L	SZC 10 g three times daily	253	Initial phase: double-blind and placebo controlled	48 h	Normokalaemia (3.5-4.9 mmol/L) was achieved in 84% at 24 h and 98% at 48 h.
	Maintenance phase: those who achieved serum K^+ 3.5-5.0 mmol/L at 48 h	Maintenance phase: randomized to 5 g, 10 g, or 15 g of SZC or placebo	237	Maintenance: randomized, double-blind, and placebo controlled	28 days	Normokalaemia (3.5-5.0 mmol/L) was maintained in 80%, 90%, 94%, and 46% of patients in the 5 g, 10 g, 15 g, and placebo groups, respectively vs. placebo ($P < 0.001$).

eGFR, estimated glomerular filtration rate; HK, hyperkalaemia; K^+, potassium; RAASi, renin-angiotensin-aldosterone system inhibitors.

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Where will these new therapies fit into practice?

- Offers alternative to SPS to assist with hyperkalemia management
- Potentially adjunct therapy in order to optimize ACEi/ARB/MRA therapies
- No head to head studies to compare these therapies
- Cost/coverage of newer therapies will need to be considered

References

- Leon, SJ., Haraswmiw, O., Tangri, N. 2019. New therapies for hyperkalemia. Curr Opin Nephrol Hypertens 28:238-244
- Meaney, C., Beccari, M., Yang, Y., Zhao, J. 2017. Systematic Review and Meta-Analysis of Patiromer and Sodium Zirconium Cyclosilicate: A New Armamentarium for the Treatment of Hyperkalemia. Pharmacotherapy 37(4): 401-411.
- Nassif, ME., Kosiborod, M. 2019. New frontiers for management of hyperkalemia: for emergence of novel agents. European Heart Journal Supplements 21 (Supplement A), A34-A40.
- Pakham, D., Rasmussen, H., Lavin, P. et al. Sodium Zirconium Cycosilicate in Hyperkalemia. 2015, NEJM 372: 222-231
- Pitt, B., Bakris, G. New Potassium Binders for the Treatment of Hyperkalemia. Current Data and Opportunities for the Future. 2015 Hypertension 66: 731-738.
- Rossignol, P. 2019. A new area for the management of hyperkalemia with potassium binders: clinical use in nephrology. European Heart Journal Supplements 21 (Supplement A), A48-A54.
- Schaefer, JA., Gales, MA. 2016. Potassium-Binding Agents to Facilitate Renin-Angiotensin-Aldosterone System inhibitor therapy. 2016. Annals of Pharmacotherapy 50(6) 502-510
- Weir, M., Bakris, G., Bushinsky, D. et al. Patiromer in Patients with Kidney Disease and Hyperkalemia Receiving RAAS Inhibitors. 2015. NEJM 372 (3) 211-221.