IRAN UNIVERSITY OF MEDICAL SCIENCES

Hyperkalemia in Diabetic Patients

A. Amouzegar MD, Nephrologist

Hyperkalemia

Definition

Hyperkalemia, usually defined as serum potassium concentrations greater than **5.0 to 5.5 mmol/l**, is widely recognized as a direct and life-threatening complication.

Clinical Presentation

Hyperkalaemia is often asymptomatic and is discovered on routine laboratory tests.

Patients with **severe** hyperkalaemia (**potassium >6.5 mmol/l**) may, however, present with **generalized weakness**, **paralysis**, and **cardiac arrhythmia**, including **cardiac stand still** and **sudden death**.

In general, the severity of clinical presentation does correlate with the severity of hyperkalaemia.

Etiologies of Hyperkalemia

Spurious hyperkalemia

- Due to high platelet and/or leucocyte count
- Due to muscular activity during venipuncture

Increase intake

- Infusion of potassium containing solutions
- Increase potassium intake in patients with defect in potassium excretion

Table 1 | Effect of prolonged K^+ intake in healthy humans

Reference	Number of subjects	Method of increasing K^+ intake	Baseline K^+ intake (mEq/d)	Final K^+ intake (mEq/d)	Duration of intervention (days)	Baseline serum K^+ (mmol/l)	Final serum K^+ (mmol/l)
Rabelink 1990[20]	6	KCL supplement 300 mEq/d	100	400	20	3.75	4.22
Witzgall 1986[22]	16	K citrate + $KHCO_3$ 2000 mEq/d	60	260	6	4.2	4.6
Sebastian 1994[21]	6	$KHCO_3$ 120 mEq/d	59	179	18	3.92	4.15
Jenkins 2001[19]	10	Grain-free vegetarian diet	98	341	14	4.26	4.03
Hene 1986[18]	6	K citrate 220 mEq/d	80	300	14	4.07	4.48

Kidney International Supplements (2017) 7, 164–170

Etiologies of Hyperkalemia

Transcellular shift of potassium

- Acidaemia (for example, acute renal failure).
- Hyperosmolality (for example, severe hyperglycaemia).
- β2-blockers (for example, propranolol).
- Insulin deficiency (for example, type I diabetes mellitus).

Etiologies of Hyperkalemia

Decrease renal excretion

- **Mineralocorticoid deficiency**: (a) Addison's disease, (b) isolated aldosterone deficiency, (c) renin deficiency (for example, diabetic nephropathy), (d) angiotensin II receptor blockers, (e) angiotensin converting enzyme inhibitors, (f) use of non-steroidal anti-inflammatory drugs
- **Resistance to mineralocorticoids effect**: (a) tubulointerstitial disease, (b) high dose mineralocorticoids antagonists (for example, spironolactone, trimethoprim)
- **Severe renal failure**

Hyperkalemia and Diabetes Mellitus

Hyperkalemia and Diabetes Mellitus

- Hyperkalemia occurs more frequently in patients with diabetes mellitus than in the general population.

- The most common causal factor of chronic hyperkalemia in diabetics is the reduced tubular secretion of K+ due to the syndrome of hyporeninemic hypoaldosteronism

Hyperkalemia and Diabetes Mellitus

Hyperkalemia due to hyperglycemia:

- Response to rising osmolality of the extracellular fluid.
- May not be clinically important in the diabetic with normal baseline potassium levels, because the elevation of plasma potassium is usually modest in degree.
- Those with renal impairment and/or hypoaldosteronism, may manifest more severe elevations in plasma potassium.

Be aware of the possible consequences of glucose loads in such patients

Syndrome of hyporeninemic hypoaldosteronism (SHH)

This syndrome is characterized by mild to moderate renal insufficiency and patients typically present with asymptomatic hyperkalemia.

The development of overt hyperkalemia is most common in patients with renal insufficiency, volume depletion, or the use of medications that interfere with potassium handling.

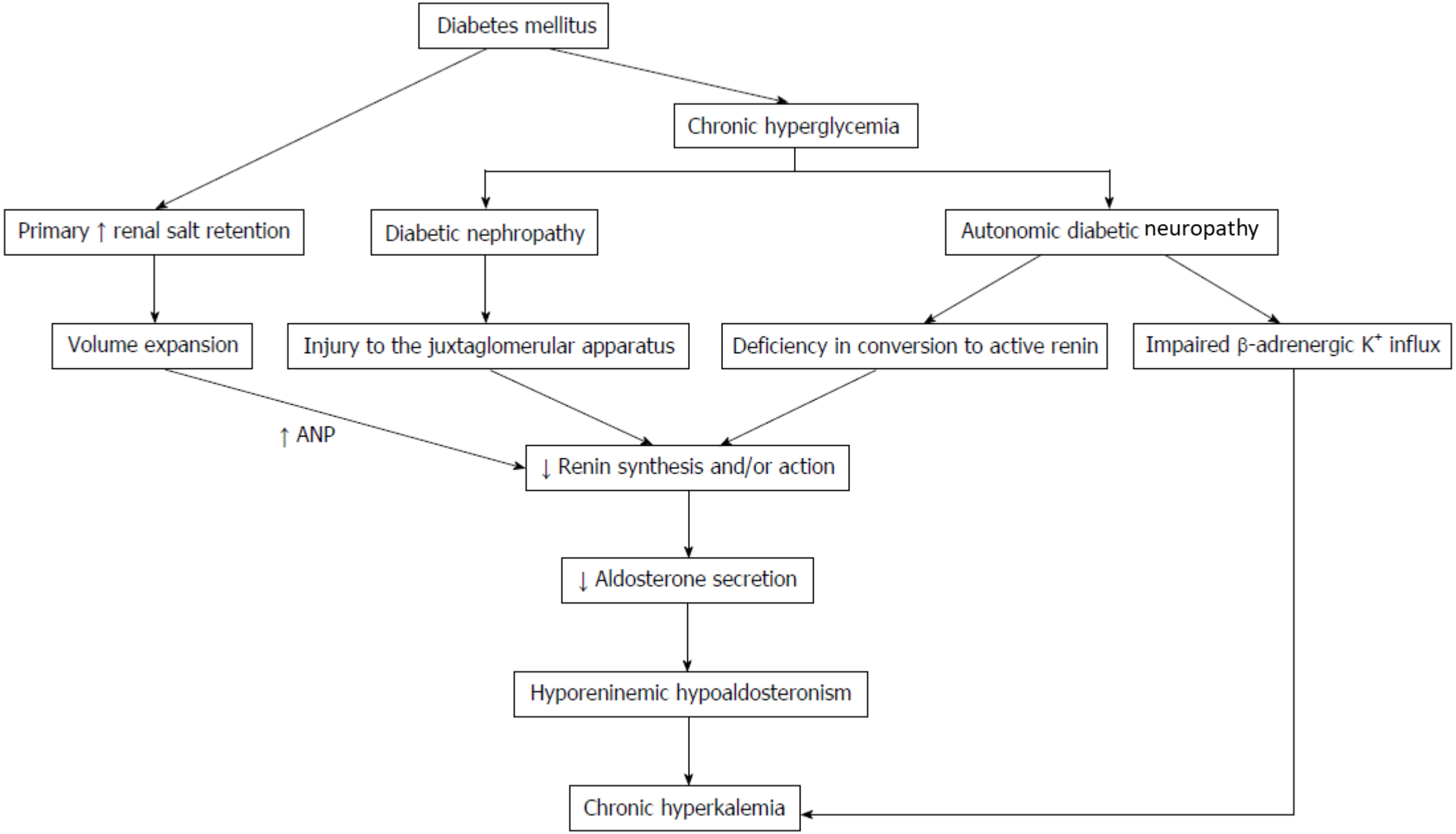
In most series, about half the subjects with the syndrome of SHH are diabetics. Diabetic nephropathy accounts for 43%-63% of cases comprising the most common cause of hyporeninemic hypoaldosteronism.

World Journal of Diabetes

Hyporeninemic hypoaldosteronism and diabetes mellitus: Pathophysiology assumptions, clinical aspects and implications for management

The most important causal factor of chronic hyperkalemia in patients with diabetes is the syndrome of hyporeninemic hypoaldosteronism (HH) hyperkalemia is related to the blockage of the renin-angiotensin-aldosterone system (RAAS) and HH is most common among patients with mild to moderate renal insufficiency due to diabetic nephropathy (DN). Conclusion:ACEIs and ARBs may precipitate hyperkalemia in a patient whose disease has not been recognized and increase the risk of severe hyperkalemia in patients with previously mild hyperkalemia

World J Diabetes 2016 March 10; 7(5): 101-111

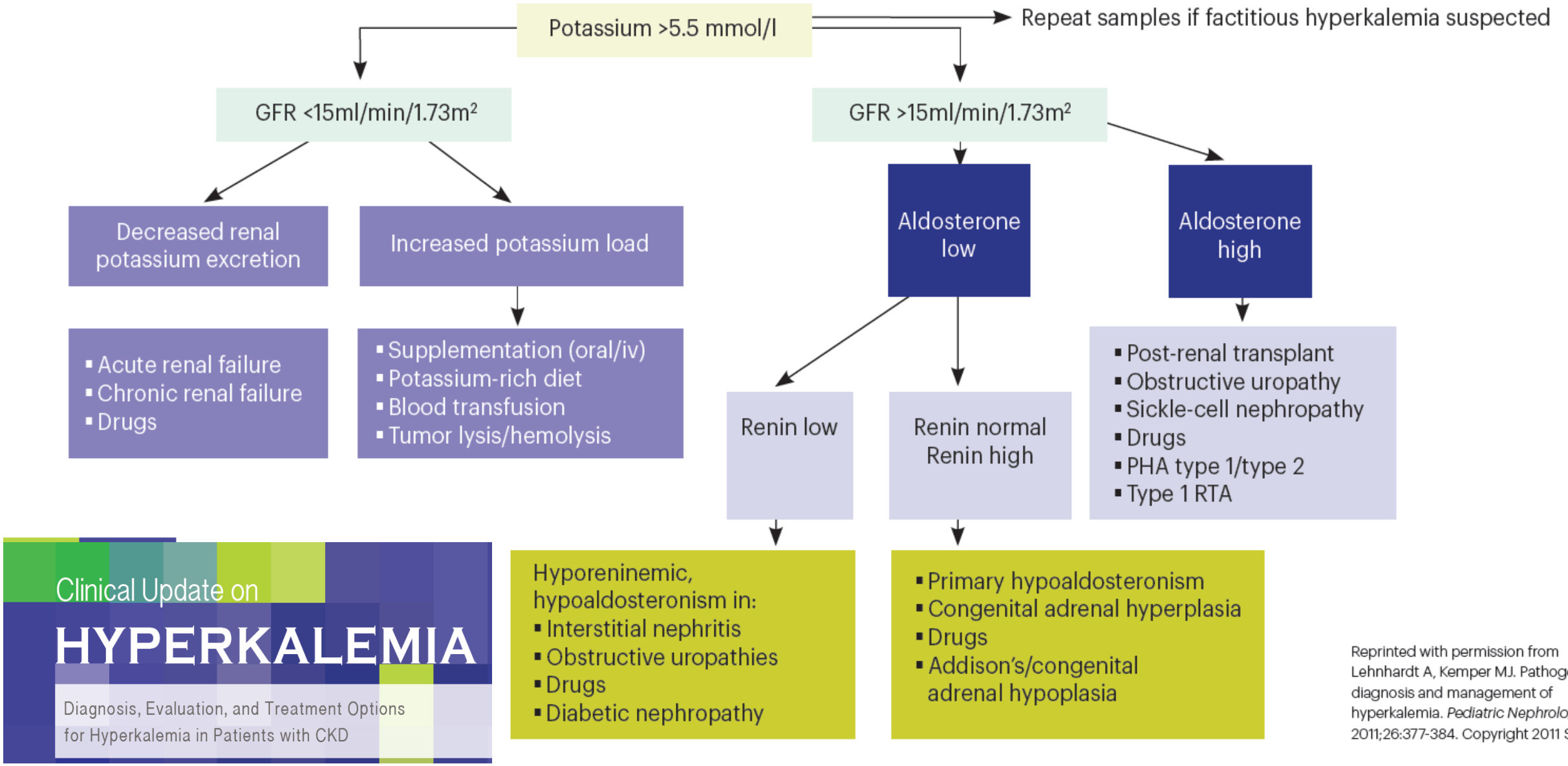


Pathophysiology of hyporeninemic hypoaldosteronism related to diabetes mellitus

Drug-induced Hyperkalemia:

- ACE inhibitor
- Angiotensin receptor blocker
- Nonsteroidal anti-inflammatory agents
- Calcineurin inhibitors (tacrolimus,cyclosporine)
- Heparin
- Lithium
- Aldosterone antagonist (spironolactone, eplerenone)
- Antibiotics (Potassium penicillin G contains 1.7 mEq of potassium per million units)
- Beta-blockers
- Digitalis
- Succinylcholine

- Dapagliflozin (a SGLT2 inhibitor) may be protective from the development of hyperkalemia inpatients with moderate renal impairment due to osmotic diuresis.
- However, the administration of SGLT2 inhibitors in hypovolemic patients may cause elevated serum creatinine levels and decreases in glomerular filtration rate due to deterioration of intravascular volume contraction.



Clinical Update on

HYPERKALEMIA

Diagnosis, Evaluation, and Treatment Options for Hyperkalemia in Patients with CKD

TREATMENT

Table 2. Treatment of severe hyperkalemia

Mechanism	Treatment (initial dose)	Onset (duration) of action	Redosing
Antagonize ECG changes	CaCl or Ca gluconate (1 g i.v. over 2–3 min)	1 min (30–60 min)	If ECG changes do not resolve or recur
Redistribute K into cells	$NaHCO_3$ (150 mEq i.v. over 3–4 h)	2–3 h (permanent)	Not necessary if HCO_3 normalized
	Insulin (10 U i.v.)	10–20 min (4–6 h)	If K rises >6 mEq/l
	Albuterol (10–20 mg in 4 ml saline over 10 min by nebulizer)	30 min (2–6 h)	If K rises >6 mEq/l
Remove K from the body	Na polystyrene sulfonate (30–60 g in 33% sorbitol)	1–2 h (permanent)	Every 2 h to achieve K<6
	Hemodialysis	Minutes (permanent)	If K rises >6 mEq/l

Kidney International Reports (2018) 3, 47–55

Sodium Polystyrene Sulfonate (SPS)

- First introduced in the 1950s before the FDA was required to establish drugs as both safe and effective
- A cation-exchange polymer that exchanges sodium for potassium, in addition to other cations such as calcium, ammonium, and magnesium
- contains a considerable amount of sodium content and should be used cautiously in patients with concomitant conditions such as congestive heart failure, edema, and severe hypertension.

Sodium Polystyrene Sulfonate (SPS)

- Most effective when it is in the colon, where the pH level is higher than in the upper GI tract.
- The rectal dose is 30 to 50 g but has been found to be less effective compared to an equivalent dose administered orally.
- SPS does not work as quickly as alternative treatment options; onset of action is >2 hours.
- The degree to which potassium is reduced and its onset of action are also variable.

Sodium Polystyrene Sulfonate (SPS)

- SPS may rarely be associated with fatal colonic necrosis and other serious GI adverse events, which are believed to be related to administration with sorbitol. Therefore, it is not recommended to be given with sorbitol.
- If patients develop constipation, use of SPS should be discontinued, and repeated doses should not be given to those who have not passed a bowel movement.

Gastrointestinal Adverse Events with Sodium Polystyrene Sulfonate (Kayexalate) Use: A Systematic Review

METHODS: MEDLINE (1948 to July 2011), EMBASE (1980 to July 2011), Cochrane Central Register of Controlled Trials (CENTRAL) (1993 to July 27, 2011), bibliographies of identified articles, and websites of relevant drug agencies and professional associations in the United States and Canada were reviewed to identify eligible reports of adverse gastrointestinal events associated with sodium polystyrene sulfonate use.
CONCLUSIONS: Sodium polystyrene sulfonate use, both with and without sorbitol, may be associated with fatal gastrointestinal injury.

The American Journal of Medicine (2013)

Sodium Polystyrene Sulfonate (SPS)

SPS should not be used in following patients:

- patients who do not have normal bowel function
- postoperative patients who have not had a bowel movement after surgery
- patients at risk for developing constipation or impaction

NEW TREATMENT OPTIONS

U.S. Food and Drug Administration
Protecting and Promoting *Your* Health

FDA News Release

FDA approves new drug to treat hyperkalemia

For Immediate Release

October 21, 2015

Release

The U.S. Food and Drug Administration today approved Veltassa (patiromer for oral suspension) to treat hyperkalemia, a serious condition in which the amount of potassium in the blood is too high.

Patiromer Sorbitex Calcium (Veltassa)

Patiromer is a nonabsorbed **polymer** synthesized as a 100 μm bead.

It is designed to bind potassium in exchange for **calcium** in the gastrointestinal tract.

It can also bind Na, Ca and Mg, but preferentially binds potassium in the colon where potassium concentration is higher.

Each pack contains 2 g of sorbitol + 0.8 g of calcium for every 4.2 g of Patiromer.

- ***Patiromer can not be used for emergency treatment in life-threatening hyperkalemia because of its delayed onset of action.***
- It is considered an option for patients with CKD and diabetic patients with a serum potassium >5 mEq/L who would benefit from treatment with an ACE inhibitor, angiotensin receptor blocker (ARB), or aldosterone inhibitor.
- Separate the administration of patiromer and other drugs by at least **6h** as it can bind other drugs and alter their absorption.

The most common adverse reactions that occur in ~ 2% of patients include:

- constipation that generally resolved during the course of treatment,
- hypomagnesemia, ability to bind to magnesium in the colon
- hypokalemia
- diarrhea
- nausea
- abdominal discomfort
- flatulence
- Mild-to-moderate hypersensitivity reactions including edema of the lips occurred in 0.3% of patients treated

Evaluation of the efficacy and safety of RLY5016, a polymeric potassium binder, in a double-blind, placebo-controlled study in patients with chronic heart failure (the PEARL-HF) trial

Bertram Pitt ✉, Stefan D. Anker, David A. Bushinsky, Dalane W. Kitzman, Faiez Zannad, I-Zu Huang on behalf of the PEARL-HF Investigators

European Heart Journal, Volume 32, Issue 7, 1 April 2011, Pages 820–828,
https://doi.org/10.1093/eurheartj/ehq502

Published: 05 January 2011 **Article history** ▾

Conclusion

RLY5016 prevented hyperkalaemia and was relatively well tolerated in patients with HF receiving standard therapy and spironolactone (25–50 mg/day) (ClinicalTrials.gov registry identifier: NCT00868439).

Patiromer in Patients with Kidney Disease and Hyperkalemia Receiving RAAS Inhibitors

Matthew R. Weir, M.D., George L. Bakris, M.D., David A. Bushinsky, M.D., Martha R. Mayo, Pharm.D., Dahlia Garza, M.D., Yuri Stasiv, Ph.D., Janet Wittes, Ph.D., Heidi Christ-Schmidt, M.S.E., Lance Berman, M.D., and Bertram Pitt, M.D., for the OPAL-HK Investigators*

CONCLUSIONS

In patients with chronic kidney disease who were receiving RAAS inhibitors and who had hyperkalemia, patiromer treatment was associated with a decrease in serum potassium levels and, as compared with placebo, a reduction in the recurrence of hyperkalemia. (Funded by Relypsa; OPAL-HK ClinicalTrials.gov number, NCT01810939).

The NEW ENGLAND JOURNAL *of* MEDICINE

November 23, 2014

Sodium Zirconium Cyclosilicate 9

Sodium ZS-9 is an inorganic cation-exchange crystal that is highly selective for potassium and ammonium (NH_4^+) ions, which are nearly identical in size

Because of its high selectivity, ZS-9 may bind potassium in the upper gastrointestinal tract where the amount of potassium is high but the concentration is low. Therefore, the drug does not need to reach the colon to be effective, which may lead to a rapid effect.

As ZS-9 can bind ammonium, it can result in an increase in serum bicarbonate.

ZS-9

Unlike SPS, divalent cations (Ca and Mg) do not form stable bond with ZS-9.

The only significant drug interaction is with lithium carbonate.

ZS-9 will be available as a tasteless, odorless, insoluble, and nonabsorbed powder (given with 40-120 mL of water per dose), and potentially a tablet.

It does not have to be given in solution or with cathartics such as Sorbitol.

		Sodium Zirconium Cyclosilicate	Patiromer Sorbitex Calcium
Mechanism and Administration	Mechanism of action	Inorganic crystal → selective potassium trap	Organic polymer → nonspecific binding of cations
	Site potassium binding	Entire GI tract	Colon
	Administration	Once daily	Twice daily
	Daily drug total (g)	5-10	21-35
	Volume expansion	None	Swelling (H_2O absorbed)
	Storage	Room temperature	2-8°C

		Sodium Zirconium Cyclosilicate	Patiromer Sorbitex Calcium
Efficacy	Time of Onset (h)	1	7
	@ 4 h [baseline potassium > 5.5 (mEq/L)]	−0.51	−0.14
	Median time to normalization (h)	2.2	> 48 (estimated 1 wk)
	Response rate	98% at 24 h	76% at 1 mo
	Potassium level maintained (mEq/L)	4.5 (5-10 g QD)	4.6 (17.5 g BID)

		Sodium Zirconium Cyclosilicate	Patiromer Sorbitex Calcium
Safety	Gastrointestinal adverse event rate		
	Open-label phase	3.5%	19%
	Randomized phase	6% vs 14% for placebo	13% vs 6% for placebo
	Sorbitol	None	10 g for every 21 g of polymer
	Calcium	No impact	~ 4 g calcium load but small amounts absorbed, may bind PO_4
	Magnesium	No hypomagnesia	24% with $Mg^{2+} < 1.8$ mg/dL
	Fluoride	No impact	Increased serum fluoride
	Bicarbonate	↑ 2.3 mEq/L in 15 d	No significant changes
	Blood urea nitrogen	↓ Potentially due to binding of ammonium	No significant changes
	Drug-drug interaction	None	Valsartan and rosiglitazone
	Sodium absorption	None	None

BID, twice daily; GI, gastrointestinal; OD, daily; TID, three times per day

Limitations

First, there are no head-to-head randomized, controlled trials of two or more agents (novel agent vs novel agent or versus sodium polystyrene sulfate).

Second, in the setting of AKI, in which a progressive rise in serum potassium is present, the effects of patiromer and ZS-9 are unknown

Third, various routes of administration, such as nasogastric tube or rectal administration for patiromer sorbitex calcium and ZS-9, have not been tested to date.

Key Points

- Hyperkalemia is a frequent cause of discontinuation or omission of renin–angiotensin–aldosterone system inhibitors in chronic kidney disease patients.
- Without much evidence in the literature on its efficacy, sodium polystyrene sulfonate is being used frequently in the clinical setting to treat hyperkalemia.

Key Points

- Both patiromer and ZS-9 have shown promising results for the treatment of hyperkalemia in recent studies regarding their efficacy and their safety in chronic kidney disease, heart failure and diabetic populations.
- However, many questions remain about patiromer and ZS-9, such as their use in dialysis patients, their long term efficacy and safety, and their costs.