Northern Treatment Advisory Group

Patiromer cation exchange resin for hyperkalaemia

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Introduction and background

Hyperkalaemia can be defined as[1]:

- Mild (serum potassium (K^+ 5.5 – 5.9 mmol/L)
- moderate (K^+ 6.0 - 6.4 mmol/L)
- severe (K^+≥ 6.5 mmol/L)

Hyperkalaemia is regarded as a medical emergency due to potential for life-threatening consequences. For treatment of hyperkalaemia, a stepwise approach for treatment is recommended.[1]

Step 1: ***Remove K^+ from body*** – Cation-exchange resins may be considered in mild to moderate hyperkalaemia, but should not be routinely used for emergency treatment of severe hyperkalaemia due to slow onset of action (varies between 2-48 hours).

Step 2: ***Protect the heart*** – Use calcium gluconate or calcium chloride. 10ml of 10% calcium chloride = 6.8mmol Ca^{2+} & 10ml of 10% calcium gluconate = 2.26 mmol Ca^{2+}

Step 3: ***Shift K^+ into cells*** – For severe & moderate hyperkalaemia, use insulin glucose intravenous infusion (10 units' soluble insulin in 25g glucose) with nebulised salbutamol (10-20mg) as an adjuvant therapy. **Sodium bicarbonate infusion should not be routinely used for acute treatment of hyperkalaemia.**

Step 4: ***Monitor K^+ and glucose***

- Serum potassium should be assessed at 1,2,4,6 and 24 hours after identification and treatment of hyperkalaemia
- Blood glucose concentrations should be monitored at regular intervals (30, 60, 90, 120, 180, 240, 300, 360 minutes) for a minimum of 6 hours after administration of insulin-glucose infusion in all patients with hyperkalaemia.

There is no information available on duration of therapy, which should be individualised based on severity of hyperkalaemia and response based on treatment option prescribed / administered.[1]

Table 1: Cost comparison of cation exchange resins for hyperkalaemia

Treatment option	Available Pack Size / Cost	Duration of onset	Duration of effect	Cost per day	Cost per 7 days
Sodium polystyrene sulfonate (Resonium A®)	454g tub = £81.11[2]	2-6 hours[3]	6-24 hours[3]	Usual dose is 45g to 60g in divided doses. Treatment duration varies but is likely to around 5 days. A 454g tub would last over 7 days. Cost per day - £10.71	May not be needed for 7 days depending on response but could be continued until K^+ at or below 5 mmol/L. Total cost over 7 days - £74.97
Calcium polystyrene sulfonate (Resonium 99.934% w/w Powder for Oral/Rectal Suspension)	300g tub= £82.16	2-6 hours	6-24 hours	Usual dose is 45g to 60g in divided doses. Treatment duration varies but is likely to around 5 days. A 300g tub would last 5 days. Cost per day - £16.43	May not be needed for 7 days depending on response but could be continued until K^+ at or below 5 mmol/L. Total cost over 7 days - £115.01
Sodium zirconium cyclosilicate	30x5g sachets = £213.60[4] or 30x10g sachets = £427.20[5]	1-6 hours[3]	Appears to 4-12 hours based on trial data[3]	Maximum treatment duration is 3 days for correction phase which costs £128.19 based on 10g three times a day dosage. This equates to £42.73 per day.	Correction phase: 3 days = £42.73 Maintenance dose is 10g daily or 5g every other week. For an additional 4 days, a dose of 10g daily would equate to £56.96. Total cost over 7 days = £99.69
Patiromer Calcium	30x8.4g & 30x16.8g sachets = £300 each[6,7]	7-48 hours[3]	12-24 hours[3]	Starting dose is 8.4g daily and should be adjusted over a minimum period of 7 days. Cost per day - £10	£70

Efficacy & Safety Evidence for Patiromer

The pivotal multicentre Phase 3 study, OPAL-HK which assessed the efficacy and safety of patiromer recruited hyperkalaemic (serum K^+ 5.1 to <6.5mmol/L) adult patients up to age of 80 years with chronic kidney disease (eGFR of 15 to <60ml/min/1.73m^2), who were on stable doses (for at least 4 weeks) of angiotensin converting enzyme inhibitor, angiotensin II receptor blocker or aldosterone antagonist (known as RAAS inhibitor therapy - RAASi).[8] 98% of patients were Caucasian with a mean age of 64 years (54% were over 65 years and 17% were over 75 years). Patients had previous history of hypertension (97%), type 2 diabetes (57%) and heart failure (42%).[8]

The study comprised of 2 parts – Part A and Part B. Part A is also known as the treatment phase as the efficacy of lowering K^+ was the main aim. Part B is known as the withdrawal phase as it demonstrated if the effects seen in Part A are maintained once patiromer therapy is discontinued. RAASi therapy was discontinued if serum K^+ exceeded 6.5mmol/L.[8]

In Part A, 243 patients were treated with patiromer for 4 weeks. Initial dosage was dependent on serum K^+ level at baseline. Those with a K^+ level of 5.1 to <5.5mmol/L (subgroup 1) received 4.2g twice daily patiromer whilst individuals with a K^+ level of 5.5 to <6.5 mmol/L (subgroup 2) received 8.4g twice daily. The dose was titrated according to response assessed at Day 3 then at weekly intervals until Week 4 with up to 50.4g daily (in divided doses), if needed as specified within the study protocol. The aim was to maintain serum K^+ between 3.8 and <5.1 mmol/L. The mean daily doses used were 12.8g (subgroup 1) and 21.4g (subgroup 2). The primary outcome in Part A, was the mean change in serum K^+ levels from baseline to Week 4. Of the 243 initially recruited, 237 (97.5%) completed Part A. Of these 76% of patients achieved serum K^+ levels between 3.8 and 5.1mmol/L across both subgroups. The primary outcome result is stated in the table below.[8]

Table 2: OPAL-HK Part A Primary Outcome Results

	Baseline Population		Overall population (n=237)
K^+ level	5.1 to <5.5 mmol/L (n=90)	5.5 to <6.5mmol/L (n=147)	
Baseline mean (SD)	5.31 (0.57)	5.74 (0.40)	5.58 (0.51)
Week 4 change from baseline Mean ± SE (95% CI)	-0.65 ± 0.05 (-0.74, -0.55)	-1.23 ± 0.04 (-1.31, -1.16)	-1.01 ± 0.03 (-1.07, -0.95)
p-value			<0.001

Patients were eligible to enter Part B only if they met the conditions stated below:

- Baseline serum K^+ 5.5 to <6.5mmol/L
- Serum K^+ level between 3.8 and <5.1mmol/L at the end of Week 4 of Part A
- Ongoing RAASi treatment

107 patients entered part B and were allocated 1:1 to receive patiromer at the dose stated in Part A (n=55) or placebo (n=52) at equivalent dose for 8 weeks. Randomisation was based on baseline serum K^+ level (5.5 to 5.8mmol/L or ≥5.8mmol/L) and presence or absence of diabetes. Monitoring schedule was same as Part A. The primary outcome of Part B was the between-treatment-group difference in median change in serum K^+ concentrations

from the start of Part B to Week 4 or to the earliest visit when the patient's serum K^+ level was <3.8mmol/L to ≥5.5mmol/L. The Part B primary outcome result is stated in the table below[8]

Table 3: OPAL-HK Part B Primary Outcome Results

	Patiromer (n=55)	Placebo (n=52)
Mean serum K+ level at start of Part B (baseline)	4.49 mmol/L	4.45 mmol/L
Median change in serum K+. level from baseline to Week 4*	0 mmol/L	0.72 mmol/L
Between-group difference	0.72 mmol/L (95% CI: 0.46 to 0.99) p<0.001	

*or to earliest visit at which the serum K+ was <3.8 to ≥5.5mmol/L

The secondary outcomes in Part B also assessed the following:

- proportion of patients who had at least one serum K^+ level ≥ 5.1mmol/L in both groups over 8 weeks (43% in patiromer vs 91% in placebo; p-value for difference <0.001)
- proportion of patients who had at least one serum K^+ level ≥ 5.5mmol/L in both groups over 8 weeks (15% in patiromer vs 60% in placebo; p-value for difference <0.001)

During Part A, adverse effects were reported in 47% of patients with constipation being the most common (11%). Adverse effects led to discontinuation of patiromer in 6 patients. During Part B, the adverse effects reported across both groups were similar (47% in patiromer group and 50% in placebo group). Mild to moderate constipation, diarrhoea and nausea (each with an incidence of 4%) were reported in the patiromer group. Hypokalaemia was seen in 3% of patients throughout Part A & Part B. During Part B withdrawal of therapy for hyperkalaemia was needed as per study protocol if serum K^+ dropped to <3.8mmol/L. This occurred in 5% of patiromer and 2% of placebo patients.[8]

Population eligible for treatment

The estimated incidence of hyperkalaemia is 1% to 10% of hospitalised patients, with renal impairment listed as the most common risk factor.[9] In 2017-18, there were 1,235,580 admissions in the North East England & North Cumbria CCGs with a mean patient age of 55 years.[10] For a list of included CCGs please see Appendix 1

Using a maximum incidence rate of 10%, the population who may experience hyperkalaemia and would consequently require treatment during inpatient stay would be 123,558.

Data is also available for number of patients who were admitted to individual hospitals within North East England and North Cumbria in 2017-18.[11] For a list of included hospitals please see Appendix 2. There were a total of 1,242,265 admissions in 2017-18; 10% of which equates to 124,226 patients who may have suffered from hyperkalaemia and would require

the treatments mentioned above. The individual hospital admission values are slightly greater than the CCG values by 668. This may be due to the inclusion of mental health NHS trusts and private hospitals within the region.

UK guidance for use of patiromer

NICE: The NICE guidance for patiromer is expected in February 2020. The draft document states that patiromer is not recommended for treating hyperkalaemia in adults. NICE notes the following points in the draft guidance[12]:

- Clinical trial results of patiromer may not be relevant to the NHS clinical practice because in the trial most people had a lower level of potassium than would be treated in the NHS.
- There is also no evidence to show that patiromer extends life or improves quality of life compared with standard care in people who would have treatment for hyperkalaemia in the NHS.
- During Part A of the study, serum K+ decreased for the total population by 1.01 mmol/litre. In part B, serum K+ levels were 0.72 mmol/litre higher than for patients randomised to remain on patiromer. However, the serum K+ level in both arms were within the range that would not be treated in the NHS and therefore the difference was not clinically meaningful.

SMC: Patiromer is not recommended for management of hyperkalaemia in adults in NHS Scotland as the manufacturer did not present a sufficiently robust economic analysis.[13]

AWMSG: The product is excluded for review by AWMSG due to NICE appraisal.[14]

Author's declaration: The author has no competing interests to declare

References

1. Clinical Practice Guidelines – Treatment of Acute Hyperkalaemia in Adults. UK Renal Association. Published March 2014. Available at: https://renal.org/wp-content/uploads/2017/06/hyperkalaemia-guideline-1.pdf (Accessed 01 July 2019).
2. NHSBSA – Dictionary of Medicines and Devices (dm+d). Resonium A powder (Sanofi) 454g. Available at: https://apps.nhsbsa.nhs.uk/DMDBrowser/DMDBrowser.do#product (Accessed 04 July 2019)
3. Di Lullo L, Ronco C, Granata A, Paoletti E, Barbera V, Cozzolino M, Ravera M, Fusaro M & Bellasi A. Chronic Hyperkalaemia in Cardiorenal Pateints: Risk Factors, Diagnosis and New Treatment Options. Cardiorenal Med 2018;9:8-21.
4. NHSBSA – Dictionary of Medicines and Devices (dm+d). Lokelma 5g oral powder sachets (AstraZeneca UK Ltd) 30 sachet. Available at: https://apps.nhsbsa.nhs.uk/DMDBrowser/DMDBrowser.do#product (Accessed 05 July 2019).
5. NHSBSA – Dictionary of Medicines and Devices (dm+d). Lokelma 10g oral powder sachets (AstraZeneca UK Ltd) 30 sachet. Available at: https://apps.nhsbsa.nhs.uk/DMDBrowser/DMDBrowser.do#product (Accessed 05 July 2019).
6. NHSBSA – Dictionary of Medicines and Devices (dm+d). Veltassa 8.4g oral powder sachets (Vifor Fresenius Medical Care Renal Pharma UK Ltd) 30 sachet. Available at: https://apps.nhsbsa.nhs.uk/DMDBrowser/DMDBrowser.do#product (Accessed 05 July 2019).
7. NHSBSA – Dictionary of Medicines and Devices (dm+d). Veltassa 16.8g oral powder sachets (Vifor Fresenius Medical Care Renal Pharma UK Ltd) 30 sachet. Available at: https://apps.nhsbsa.nhs.uk/DMDBrowser/DMDBrowser.do#product (Accessed 05 July 2019).
8. Weir MR BG, Bushinsky DA, Mayo MR, Garza D, Stasiv Y, Wittles J, et al.,. Patiromer in patients with kidney disease and hyperkalemia receiving RAAS inhibitors. New Eng. J. Med. 2015;372:doi: 10.1056/NEJMoa1410853.
9. Prescribing Outlook – New Medicines and National Developments 2018-19. Published September 2018. Available at: https://www.sps.nhs.uk/articles/prescribing-outlook-2018/ (Accessed 29 July 2019).
10. Hospital Admitted Patient Care Activity 2017-18: CCG of responsibility. NHS Digital. Published 20 Sep. 2018. Available at: https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/2017-18 (Accessed 29 July 2019).
11. Hospital Admitted Patient Care Activity 2017-18. Provider Level Analysis 2016-17 to 2017-18. Published 20 Sep. 2018. Available at: https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/2017-18 (Accessed 29 July 2019).
12. NICE - Patiromer Appraisal Consultation Document. Published Oct. 2018. Available at: https://www.nice.org.uk/guidance/gid-ta10273/documents/appraisal-consultation-document (Accessed 12 August 2019).
13. SMC & Health Improvement Scotland - Medicines Advice: Patiromer Published Aug. 2018. Available at: https://www.scottishmedicines.org.uk/medicines-advice/patiromer-sorbitex-calcium-veltassa-fullsubmission-smc2084/ (Accessed 13 August 2019).
14. AWMSG - Patiromer Appraisal Published May 2018. Available at: http://www.awmsg.org/awmsgonline/app/appraisalinfo/1991 (Accessed 13 Aug. 2019).

Appendix 1 – CCG list for hospital admissions

- Cumbria and North East Commissioning Hub
- NHS Darlington
- NHS Durham Dales, Easington and Sedgefield CCG
- NHS Hambleton, Richmondshire and Whitby CCG
- NHS Harrogate and Rural District CCG
- NHS Hartlepool and Stockton-on-Tees CCG
- NHS Newcastle Gateshead CCG
- NHS North Cumbria CCG
- NHS North Durham CCG
- NHS North Tyneside CCG
- NHS Northumberland CCG
- NHS Scarborough and Ryedale CCG
- NHS South Tees CCG
- NHS South Tyneside CCG
- NHS Sunderland CCG
- NHS Vale of York CCG

Appendix 2 – Hospital List for admissions

- City Hospitals Sunderland NHS Foundation Trust
- County Durham & Darlington NHS Foundation Trust
- Cumbria Partnership NHS Foundation Trust
- Gateshead Health NHS Foundation Trust
- Harrogate and District NHS Foundation Trust
- North Cumbria University Hospitals NHS Trust
- North Tees and Hartlepool NHS Foundation Trust
- Northumberland Tyne and Wear NHS Foundation Trust
- Northumbria Healthcare NHS Foundation Trust
- Nuffield Health, Newcastle upon Tyne Hospital
- Nuffield Health, Tees Hospital
- South Tees Hospitals NHS Foundation Trust
- South Tyneside NHS Foundation Trust
- Spire Washington Hospital
- Tees Valley Hospital
- Tees Valley Treatment Centre
- Tees Esk and Wear Valleys NHS Foundation Trust
- The Newcastle upon Tyne Hospitals NHS Foundation Trust
- York Teaching Hospitals NHS Foundation Trust.