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Patiromer for Hyperkalemia Secondary to Missed Haemodialysis - A Cost and Benefit Analysis in an Australian Setting

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Abstract

Haemodialysis units in Australia and the Pacific are increasingly affected by extreme weather events. Disaster packs containing sodium polystyrene sulfonate (SPS) for prevention of hyperkalemia are commonly utilised when patients are temporarily unable to attend dialysis.

Patiromer offers a newer alternative to SPS, with better oral tolerability, and its use is becoming widespread in Queensland public health haemodialysis units. We aimed to assess the possible financial benefit of replacing SPS with patiromer in haemodialysis disaster packs.

We conducted a literature review on the use of patiromer and SPS in end-stage kidney disease and the Queensland Health List of Approved Medicines (LAM) submissions for patiromer in Queensland. A cost-benefit analysis for our own health service was conducted.

Obtaining pre-packed SPS from Central Pharmacy would cost AU$20.65 per patient, followed by current practice at $22.32. Switching to a single or double sachet of patiromer would increase costs to $22.82 or $33.68 respectively, with anticipated further cost related to refrigerated storage requirements.

There is a paucity of high-quality evidence for efficacy of both patiromer and SPS in the treatment of hyperkalemia in haemodialysis. Patiromer's risk profile for chronic use appears more acceptable, however, severe adverse events associated with SPS are rare, and their relevance to single use packs is unclear.

We conclude that the improved tolerability and potential reduction in adverse events does not currently justify the increased cost of patiromer. However, accessing pre-packed SPS from Central Pharmacy would allow for cost saving and reduce handling risks for pharmacy staff. We expect this finding to be applicable to the broader Queensland context.

Introduction

Queensland is Australia's most disaster-prone state, with 70% of its inhabitants having experienced floods and 57% cyclones and destructive storms in the last 5 years, resulting in significant displacement.[1]

These events pose particular challenges to those with end stage kidney disease (ESKD) dependent upon kidney replacement therapies, particularly those utilising haemodialysis (HD) given their requirement for reliable supply of power, suitably treated water and, for the majority, access to a facility for in-centre dialysis. The complexity of such a situation and the importance of effective forward planning is seen in the response to Cyclone Yasi which ravaged Cairns, North Queensland, in 2011. Effective disaster planning and multicentre collaboration allowed 76 HD patients to have dialysis facilitated in Brisbane within 48 hours, avoiding any excess morbidity or mortality as a result of the disaster.[2] Less favorable outcomes can be seen from the aftermath of Hurricane Katrina in New Orleans in 2005. Retrospective analysis showed that of almost 6000 patients affected, 44% of patients missed at least one dialysis session.[3] Of these patients, 148 died in the month following the event.[3]

Hyperkalaemia Management - Sodium Polystyrene Sulfonate

Despite the increasing incidence of such events, there are limited international guidelines to guide the management of patients unable to attend dialysis. Management of hyperkalaemia, an inevitable result of inability to attend dialysis, is a *sine qua non* of such disaster planning. As a result, providing "disaster packs" containing medications for the management of hyperkalaemia to all HD patients is standard practice across many dialysis units. SPS, a cation-exchange resin which exchanges sodium for potassium in the colon facilitating its excretion, has long been the most commonly utilised medication in such packs in Australia.

SPS was first approved for use for the management of hyperkalaemia in June 1958.[4] Despite extensive and widespread use of SPS, data on its efficacy are sparse, based for most of its history on small, open label trials from the 1960s.[5] Randomised, prospective data is particularly lacking, though a 2013 randomised trial of 33 patients with chronic kidney disease (CKD) did show significant potassium lowering with the use of SPS as compared to placebo.[6]

There have long been concerns about the safety profile of SPS. Notable adverse events associated with its use include GI upset, fluid retention and rare, though potentially fatal, bowel ischaemia and necrosis.[7] The existence of this last complication has been the subject of controversy, though there is a history of convincing case series with histological evidence of extensive bowel necrosis with deposition of SPS in the bowel lumen.[7, 8, 9] This association was thought to be due to co-administration with sorbitol, hence a 2009 FDA warning that the two drugs not be used concurrently. However, case reports of bowel necrosis seen with SPS monotherapy have also been published[10,11], with a systematic review finding that 17 of 58 identified cases were not associated with sorbitol co-administration.[12]

A retrospective cohort study by Watson *et al.* in 2021, reported a cumulative incidence of colonic necrosis with SPS use of 0.14%, with a relative risk of 2.1 as compared to non-use, though this did not meet significance.[13] A more recent propensity matched case control study of over 40,000 subjects comparing inpatient use against non-use of SPS in older patients, reported a statistically significant increased incidence of serious adverse gastrointestinal events with SPS use, with a hazard ratio for bowel necrosis of 4.92 (1.09–22.25).[14] Similarly, a Swedish study of 19,530 patients with CKD4-5, found a higher incidence of severe adverse gastrointestinal events with SPS use (adjusted HR 1.25, 95% CI 1.05–1.49).[15] Though in all studies, event rates were very low even with extended regular use.

Patiromer - a Novel Agent for Hyperkalaemia Management

Patiromer, a non-absorbable polymer that contains a calcium-sorbitol complex that reduces serum potassium levels through the exchange of calcium for potassium in the distal colon,[16] offers an alternative to SPS in the management of hyperkalaemia in ESKD. Its efficacy in CKD for the chronic management of hyperkalaemia, particularly in affording continued use of medications for renin-angiotensin-aldosterone system blockade, is well established.[17, 18] Its efficacy in potassium lowering is also supported in HD patients, albeit in smaller randomised and observational studies.[19, 20]

There has been considerable interest in the feasibility and possible benefit of utilisation of patiromer in place of SPS, given a predicted greater tolerability and lower burden of severe adverse events. This is attested to by the findings of a 4-year global pharmacovigilance database study with an estimated 45,000 patient-years of exposure. The major adverse events reported were constipation, hypomagnesemia and diarrhoea, with no evidence of severe gastrointestinal adverse events such as bowel ischaemia/necrosis attributable to patiromer use.[21]

There exist scant data directly comparing the efficacy of patiromer and SPS. A 2022 unblinded two arm crossover trial of 51 HD patients across three American centres showed significant decrease in serum potassium with the use of both medications.[21] There was a higher degree of potassium lowering in the SPS treatment arms, however it was noted to be less tolerable and associated with reduced compliance. Furthermore, it appears that as compared to SPS, patiromer may offer a more rapid reduction in serum potassium levels, with cohort evidence suggesting a significant reduction in potassium in patients with advanced CKD within 2–6 hours of patiromer ingestion.[22, 23]

Other indirect comparisons suggest equipoise in potassium lowering. The Pharmaceutical Benefits Advisory Committee (PBAC) of Australia in their 2022 public summary document on the acceptance of patiromer to the pharmaceutical benefits scheme (PBS), which provides universal funding for medications, found no significant difference in regards efficacy between four weeks of therapy between SPS and patiromer in an unanchored, indirect comparison,[24] however, noted that the results of these comparisons were “highly uncertain”.

Real World Utilisation of Potassium Lowering Therapies

Bayside Health Service provides HD across two centres to 96 patients from the Greater Brisbane area of Redland City. Many inhabit the nearby Bay Islands, and their transport relies upon regular ferry services to access the HD centres on the mainland, placing them at significant risk of compromised access to therapy in the event of adverse weather events.

Each November, prior to the summer storm and cyclone season, as part of the service’s disaster management plan, each dialysis patient receives a disaster pack containing two 15g bottles of SPS, alongside an information brochure and disaster preparedness checklist. In the event of delayed or missed dialysis, patients are advised by their nephrologist to take one or two bottles of SPS.

Given the possible benefits of newer potassium lowering therapies, we aimed to assess the viability of replacement of SPS by patiromer in HD disaster packs for our patients, a practice which has already been adopted by multiple health care services in Queensland. To do so, we conducted a review of the existing literature behind the use of patiromer and SPS in disaster packs (none extant), the evidence for patiromer and SPS in the treatment of hyperkalaemia in CKD and ESKD (outlined above) and submissions to the List of Approved Medicines (LAM) (the official statewide formulary for approval of medicines for use in all Queensland Health institutions) of other Queensland Health services for the use of patiromer for this indication and finally a cost-benefit analysis for its use in our own health service.

A review of the LAM submission from the Cairns and Hinterland Health Service on the use of patiromer in dialysis disaster packs reinforces the paucity of evidence in this area. The most compelling factor offered favoring such a transition is a predicted cost benefit of prepackaged patiromer 8.4g sachets ($11.56) as compared to externally compounded SPS 30g + lactulose 15ml packs ($30.14). There was further predicted saving with patiromer given it abrogates the need to co-supply lactulose, given with SPS to prevent higher rates of GI side effects in the event of constipation. Further, a “more predictable potassium lowering effect”[25] was predicted with patiromer than SPS, however, the rationale and evidence behind this supposition is unstated.

It is notable that there has been a subsequent LAM submission to request the addition of a 16.8g dosing to be approved for disaster packs, given the opinion that this increased dosing would be required to have a significant enough potassium lowering effect to prevent cardiovascular mishap in the event of missed dialysis.

Results: Cost Analysis

A cost breakdown was obtained from our pharmacy for the current method of manually packaging two 15g SPS packs in-house, accounting for labour costs of pharmacy staff and compared to the cost of purchasing and stocking pre-packed SPS and patiromer sachets from Central Pharmacy (CP). CP is a commercialised business unit, warehouse and distribution service for pharmaceuticals inside Queensland Health, which provides small-scale manufacturing and repackaging of specific products that may not be commercially available. These services are accessible by hospital and health services, dental services and ambulance services across Queensland.

Per-Patient Breakdown

The comparative costs of the 2 products are detailed in Table 1 and consist of the fixed costs of the products as well as the costs associated with dispensing by the hospital pharmacists.

Table 1
Comparative costs of patiromer and sodium polystyrene sulfonate ($AUD)

Medication	Prepack	Dispensing	Checking	Stock	Cost per Pack	Total Cost per Year
SPS manufactured in-house (2 x 15g bottles)	$6.05	$3.03	$8.92	$4.32	$22.32	$2,142.72
SPS ordered via CP (2 x 15g bottles)	—	$3.03	$8.92	$8.70	$20.65	$1,982.40
Patiromer ordered via CP (1 x 8.4g sachet)	—	$3.03	$8.92	$10.87	$22.82	$2,190.72
Patiromer ordered via CP (2 x 8.4g sachets)	—	$3.03	$8.92	$21.73	$33.68	$3,233.28
SPS = Sodium Polystyrene Sulfonate, CP = Central Pharmacy, costs expressed in Australian dollar						

This analysis revealed that obtaining SPS from CP would be the cheapest option with a cumulative yearly cost of $1,982.40, followed by current practice ($2,142.72), with a switch to patiromer being roughly equivalent if a single 8.4g sachet was used ($2,190.72), though significantly more expensive for packs containing two sachets ($3,233.28).

However, given the limited shelf life of patiromer when not refrigerated (6 months), it is likely that a significant proportion of patiromer containing packs would need to be provided on a twice-yearly basis, again increasing costs.

Discussion

There has been significant discourse about the appropriate utilisation of oral potassium binders in view of availability of newer agents and concerns for safety with SPS use. Indeed, this has led to conditional recommendations in some expert guidelines against the use of SPS in CKD,[26] especially in patients with risk factors that may potentiate its more severe GI side effects. However, given the rarity of such events, even with chronic use, and the lack of high-quality data comparing SPS and newer agents such as patiromer, particularly in the ESKD context, it is difficult to draw conclusions with much confidence as to their optimal use in single use disaster packs. We do not feel there is sufficient evidence to support a clear safety benefit in this context for patiromer over SPS.

As well as those points discussed, there are also further considerations about either drugs utilisation for disaster packs and the current standard used by our health system.

There are theoretical risks about the safety of staff involved in the packaging of SPS. SPS itself and one of its excipients, vanillin, are considered hazardous to the lungs and eyes, with reported cases of acute bronchitis and bronchopneumonia associated with inhalation of SPS particles.[27] CP utilises a dedicated Grade C room for SPS packaging, to minimise this aerosolisation risk, which is not feasible with in-house packaging of SPS in many facilities, including our own.

Further, in-house preparation of SPS is complex from a regulatory standpoint as it might not technically meet the definition of re-packaging given it is a powder formulation. As a result, expiry dating would need to be applied to the products which would not allow them to practically be kept on hand by patients for a prolonged period of time and replacement costs would outweigh any of the costs saved from preparing in-house.

There also exists the issue of storage. According to the product information, patiromer should be stored at 2 to 8°C.[16] When in-use, it may be stored below 25°C for up to 6 months (not exceeding the expiry date printed on the sachet). If necessary, the product can be returned to refrigerated temperatures for continued use, as long as it is not exposed to room temperature for more than a cumulative total of 6 months. Anecdotal experience from those health services already utilising patiromer in disaster packs, suggests that a large proportion of patients either do not store these packs appropriately or have misplaced these packs when the need for their use arises.

Our cost analysis does not suggest a compelling reason for a switch to the use of patiromer based disaster packs. The minimum possible cost for a patiromer based approach assumes the use of a single sachet per pack and assiduous attention to its proper storage, such that once yearly provision would be sufficient. Even under these unlikely conditions, this would still incur a higher yearly cost than centrally packed SPS. We expect these findings would likely be applicable to the broader Queensland context, given widespread access to CP.

Finally, there is a complete absence in the literature as to formulation or utilisation of disaster management plans and packs for dialysis patients. Given the spectre of further climate-related missed dialysis, these areas will hopefully receive more attention in the future.

Conclusion

Overall, there exists a paucity of high-quality data to allow a confident comparison of the efficacy patiromer and SPS in the treatment of hyperkalaemia in CKD or ESKD. The risk profile for chronic use appears to be more acceptable with patiromer as compared to SPS, however the most severe adverse events associated with SPS use are extremely rare, and its relevance to single use disaster packs is unclear. Further, there is a far greater cumulative clinical experience with SPS as compared to patiromer. Our cost analysis suggests a higher cost incurred with the use of patiromer, given its higher cost per pack, shorter shelf life and the anticipated need for provision of multiple packs.

We conclude that existing evidence for potential clinical benefit so far as tolerance or possible obviation of clinically significant adverse events does not justify this added expense. We have, however, identified that accessing SPS packs from CP would allow for minor cost savings, as well as minimalisation of

exposure risk to pharmacy staff. This analysis may also offer a more cost-effective option for other Queensland and wider Australian health services for the provision of disaster packs to their HD populations and prove helpful to any other services considering a switch to patiromer.

Declarations

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The authors declare that they do not have any financial conflict of interest

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S.R. and V.C. wrote the main manuscript text and prepared the figures. D.M. provided editorial input and revisions to the manuscript. All authors reviewed and approved the final version of the manuscript

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