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Evaluation of the Pharmacodynamic Effects of the Potassium Binder RDX7675 in Mice

James P. Davidson, PhD[1], Andrew J. King, PhD[1], Padmapriya Kumaraswamy, MPharm[1], Jeremy S. Caldwell, PhD[1], Paul Korner, MD[1], Robert C. Blanks, MS[1], and Jeffrey W. Jacobs, PhD[1]

Abstract

Introduction: Hyperkalemia is a common complication in patients with heart failure or chronic kidney disease, particularly those who are taking inhibitors of the renin–angiotensin–aldosterone system. RDX7675, the calcium salt of a reengineered polystyrene sulfonate-based resin, is a potassium binder that is being investigated as a novel treatment for hyperkalemia. This study evaluated the pharmacodynamic effects of RDX7675 in mice, compared to 2 current treatments, sodium polystyrene sulfonate (SPS) and patiromer. **Methods:** Seven groups of 8 male CD-1 mice were given either standard chow (controls) or standard chow containing 4.0% or 6.6% active moiety of RDX7675, patiromer, or SPS for 72 hours. Stool and urine were collected over the final 24 hours of treatment for ion excretion analyses. **Results:** RDX7675 increased stool potassium (mean 24-hour excretion: 4.0%, 9.19 mg; 6.6%, 18.11 mg; both $P < .0001$) compared with controls (4.47 mg) and decreased urinary potassium (mean 24-hour excretion: 4.0%, 12.05 mg, $P < .001$; 6.6%, 6.68 mg, $P < .0001$; vs controls, 20.38 mg). The potassium-binding capacity of RDX7675 (stool potassium/gram of resin: 4.0%, 1.14 mEq/g; 6.6%, 1.32 mEq/g) was greater (all $P < .0001$) than for patiromer (4.0%, 0.63 mEq/g; 6.6%, 0.48 mEq/g) or SPS (4.0%, 0.73 mEq/g; 6.6% 0.55 mEq/g). RDX7675 and patiromer decreased urinary sodium (mean 24-hour excretion: 0.07-1.38 mg; all $P < .001$) compared to controls (5.01 mg). In contrast, SPS increased urinary sodium excretion (4.0%, 13.31 mg; 6.6%, 17.60 mg; both $P < .0001$) compared to controls. **Conclusions:** RDX7675 reduced intestinal potassium absorption and had a greater potassium-binding capacity than patiromer or SPS in mice. The calcium-based resins RDX7675 and patiromer reduced intestinal sodium absorption, unlike sodium-based SPS. These results support further studies in humans to confirm the potential of RDX7675 for the treatment of patients with hyperkalemia.

Keywords
hyperkalemia, patiromer, potassium, RDX7675, sodium polystyrene sulfonate

Introduction

Hyperkalemia is an electrolyte imbalance in which extracellular levels of potassium become elevated (typically defined as a serum potassium concentration of $\geq$5.0 or $\geq$5.5 mEq/L).[1] The condition is usually caused by insufficient or impaired excretion of potassium via the kidneys, and patients with chronic kidney disease (CKD), diabetes, or heart failure are particularly at risk.[2-4] Hyperkalemia is often asymptomatic but can have serious consequences for the patient, including arrhythmia and sudden cardiac death, and it has been suggested that the incidence of hyperkalemia in the general population is underestimated.[1] Patients with heart failure, CKD, hypertension, or diabetes are often prescribed inhibitors of the renin–angiotensin–aldosterone system (RAAS), which have key cardiovascular benefits, delay CKD progression, and reduce morbidity and mortality[5-7] but can decrease potassium excretion and exacerbate hyperkalemia risk.[2,4] Following the Randomized Aldactone Evaluation Study, which showed that the aldosterone receptor blocker spironolactone reduced morbidity and mortality in patients with severe heart failure,[7] the frequency of spironolactone use increased as did the incidence of hospitalization for hyperkalemia and subsequent death.[8] Current treatment guidelines recommend dose reduction or discontinuation of RAAS inhibitors for patients who develop hyperkalemia, which can be detrimental to their overall treatment outcomes.[9-12] Discontinuation of RAAS inhibitors may not always be appropriate; for example, in a study of the mineralocorticoid receptor antagonist eplerenone in patients with heart failure receiving optimal therapy, treatment with eplerenone was associated with an increased risk

[1] Ardelyx, Inc, Fremont, CA, USA

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Corresponding Author:
Jeffrey W. Jacobs, Ardelyx, Inc, 34175 Ardenwood Blvd, Fremont, CA 94555, USA.
Email: jjacobs@ardelyx.com

of mild hyperkalemia, but this did not offset the survival benefit of eplerenone.[13,14] The patients included in the study were, however, highly selected, and their serum potassium concentrations were closely monitored therefore they may not be generally representative of patients at risk of developing hyperkalemia. In clinical practice, RAAS inhibitor use is routinely discontinued or reduced following the development of hyperkalemia, which is associated with worse outcomes compared to patients receiving optimal RAAS inhibitor treatment.[12] This undesirable clinical compromise highlights the need for long-term treatments that can effectively maintain serum potassium levels and facilitate the optimal use of therapeutic agents known to improve long-term health outcomes in patients with heart failure or CKD.

Potassium binders are ion exchangers that reduce potassium absorption by binding gastrointestinal potassium in exchange for a counterion, resulting in increased excretion of potassium in stool. The first US Food and Drug Administration (FDA)-approved potassium binder for the treatment of hyperkalemia was sodium polystyrene sulfonate (SPS), which has been available in the United States for more than 60 years.[15,16] Owing to issues with palatability and safety concerns associated with increased sodium intake and the coadministration of sorbitol, SPS is infrequently used for the long-term management of hyperkalemia[17,18]; research has, therefore, been directed toward novel therapies.[4] Calcium polystyrene sulfonate is approved for the treatment of hyperkalemia in some countries outside the United States.[19] Patiromer, a potassium binder that uses calcium-sorbitol as the counterion,[20] has been shown to reduce serum potassium levels in patients with CKD, heart failure, or diabetes who are receiving RAAS inhibitors[21-23] and was approved by the FDA in 2015.[24] Sodium zirconium cyclosilicate (ZS-9) is another agent being developed as a treatment for hyperkalemia.[25]

RDX7675 is a novel calcium polystyrene sulfonate-based, potassium-binding resin in development for the treatment of patients with hyperkalemia. RDX7675 has been designed to be orally administered, not to be absorbed, and to bind potassium locally in the gastrointestinal tract. Particle size, particle morphology, and cross-linking have been reengineered beyond SPS to improve binding efficiency, flow properties, and palatability.[26] Unlike SPS, which consists of large, solid, irregular shard-like particles that impart a gritty feeling in the mouth, RDX7675 has been designed using polymeric processing principles to obtain particles that are small, round, and soft.[20,26] The RDX7675 formulation does not include sorbitol, which has been linked to adverse events and is therefore aligned with best clinical practice.[16] The use of calcium rather than sodium as the counterion also provides a key benefit for patients whose sodium intake and blood volume need to be carefully controlled, such as those with heart failure, hypertension, or CKD, who are also the patients most susceptible to developing hyperkalemia.[1,27] This study evaluated the pharmacodynamic effects of RDX7675 in mice compared to the potassium binders currently available in the United States, SPS and patiromer.

Methods and Materials

Animals

All experiments and analyses were performed at Ardelyx, Inc (Fremont, California) with protocols approved by the Ardelyx Institutional Animal Care and Use Committee. All experiments were performed in accordance with the Guide for the Care and Use of Laboratory Animals from the Institute for Laboratory Animal Research, National Research Council, Washington, DC, National Academy Press, 2011. Eight-week-old male CD-1 mice (30-40 g; Charles River Laboratories, Wilmington, Massachusetts) were housed in micro-insulator cages for at least 48 hours before being assigned to study groups. They were then housed individually in metabolic cages for the duration of the study. All mice were provided with food (standard rodent chow; 2018C, Harlan Teklad, Madison, Wisconsin) and water ad libitum throughout the study.

Study Design

Seven groups of mice (all $n = 8$) were assigned to 72 hours of treatment with either chow with no addition (controls) or chow to which potassium binder had been added (potassium binders: RDX7675 [Ardelyx, Inc], patiromer [Veltassa®; Relypsa, Inc, Redwood City, California], and SPS [Purolite, Bala Cynwyd, Pennsylvania]). The potassium-binder groups were RDX7675 4.0%, RDX7675 6.6%, patiromer 4.0%, patiromer 6.6%, SPS 4.0%, and SPS 6.6%. All dosage levels were wt/wt active moiety (corrected for excipients, water, and counterions). Body weights, along with food and water consumption, were recorded every 24 hours until study completion. After a 48-hour acclimation period, stool and urine were collected over the final 24 hours of treatment for ion excretion analyses. Ion excretion is reported as the mass of the ion excreted for the final 24-hour period (mg/24 h) and as the mass of the ion excreted for the 24-hour period normalized to 24-hour dietary intake of the ion (mg/mg).

Stool and Urine Analyses

Stool samples were dried using a lyophilizer for at least 3 days. Dry weight was recorded, and stool fluid content was calculated based on the difference between the initial wet sample and final dry stool weights. Stool samples were analyzed by microwave plasma-atomic emission spectrometry (MP-AES) using a 4100 MP-AES System (Agilent Technologies, Inc, Santa Clara, California). The lyophilized samples were ground into a fine powder, and 400 to 600 mg aliquots were digested with nitric acid using a MARS 6 microwave digestion system (CEM Corporation, Matthews, North Carolina) before being diluted with 1% nitric acid for analysis. Concentrations were calculated using a standard curve (prepared in 1% nitric acid) for each analyte ion based on the signal intensity. Phosphorus, sodium, potassium, and calcium were monitored at wavelengths of 213.6, 589.0, 766.5, and 612.2 nm, respectively. For each agent, the in vivo potassium-binding capacity was

calculated as the amount of stool potassium excreted (mEq) per gram of resin administered.

Urine samples were acidified and analyzed on an ion chromatography system (ICS-3000 or ICS-5000+; Thermo Fisher Scientific, Inc, Waltham, Massachusetts) coupled with conductivity detectors. Chromatographic separation of cations was performed using a Dionex IonPac CS12A (Thermo Fisher Scientific, Inc) 2 × 250 mm analytical column with an isocratic elution using 25 mM methanesulfonic acid. Chromatographic separation of anions was performed using a Dionex IonPac AS18 (Thermo Fisher Scientific, Inc) 2 × 250 mm analytical column with an isocratic elution using 35 mM potassium hydroxide. Concentrations were calculated relative to a standard curve (prepared in 10 mM hydrochloric acid) for each analyte ion based on retention time and peak area.

Statistical Analyses

Statistical analyses were performed using 1-way analysis of variance followed by Tukey post hoc test to correct for multiple comparisons and enable individual group comparisons. A P value <.05 was considered statistically significant.

Results

Effects of Potassium-Binder Treatment on Potassium Excretion in Mice

Mean 24-hour stool potassium excretion was significantly higher (8.00-18.11 mg; $P < .01$) in all potassium-binder-treated groups except for SPS 4.0% (6.78 mg) than in controls (4.47 mg; Figure 1A). These effects were similar when excretion was normalized to potassium intake (Figure 1B). Mean 24-hour urinary potassium excretion was significantly lower in mice treated with RDX7675 or patiromer (6.68-13.81 mg; $P < .001$) than in controls (20.38 mg; Figure 1C), and this effect was retained when normalized to potassium intake (Figure 1D). Sodium polystyrene sulfonate did not significantly affect urinary potassium excretion compared with controls at either dose. Compared with all other active and control groups, the RDX7675 6.6% group had the highest normalized 24-hour stool potassium excretion (0.65 mg/mg; $P < .0001$) and the lowest normalized 24-hour urinary potassium excretion (0.24 mg/mg; $P < .01$). There was a strong positive correlation between urinary potassium excretion and stool potassium excretion ($R^2 = 0.95$; Figure S1A), and no treatment was associated with significant changes in potassium balance (intake–excretion) compared to controls (Figure S1B).

The potassium-binding capacity of RDX7675 was slightly greater at the higher dose (4.0%, 1.14 mEq/g; 6.6%, 1.32 mEq/g; $P = .0496$) and was significantly ($P < .0001$) higher than that of both patiromer (4.0%, 0.63 mEq/g; 6.6%, 0.48 mEq/g) and SPS (4.0%, 0.73 mEq/g; 6.6%, 0.55 mEq/g; Figure 1E). The potassium-binding capacity of RDX7675 6.6% remained significantly higher than that of both patiromer ($P < .01$) and SPS ($P < .0001$) when all agents were corrected for active moiety, while the potassium-binding capacity of RDX7675 4.0% remained significantly higher than that of patiromer 6.6% ($P < .0001$) and both doses of SPS ($P < .0001$; Figure 1F).

Excretion of Other Ions

The RDX7675 and patiromer groups had higher mean 24-hour stool sodium excretion (5.98–7.33 mg) than controls (3.02 mg; $P < .05$) and lower mean 24-hour urinary sodium excretion (0.07-1.38 mg; controls, 5.01 mg; $P < .001$; Figure 2A and B). These effects remained significant when normalized to sodium intake ($P < .0001$; Figure 3A and B). The SPS groups, with sodium as the counterion, had higher mean 24-hour stool and urinary sodium levels (stool: SPS 4.0%, 15.85 mg; 6.6%, 22.95 mg; urinary: SPS 4.0%, 13.31 mg; 6.6%, 17.60 mg) than all other groups ($P < .0001$). The effects of SPS on stool and urinary sodium excretion were largely accounted for by the levels of sodium contained in SPS as indicated by normalization to sodium intake.

The RDX7675 and patiromer groups, with calcium as the counterion, had dose dependently higher mean 24-hour stool calcium excretion levels (49.45-83.97 mg) than controls (34.07 mg; $P < .01$; Figure 2C). When normalized to calcium intake, stool calcium excretion with RDX7675 was similar to controls and higher than with patiromer ($P < .0001$; Figure 3C). Normalized stool calcium excretion was lower with patiromer than in controls ($P < .01$). The higher dose of RDX7675 resulted in higher mean 24-hour urinary calcium excretion (0.55 mg; $P < .05$) than in controls (0.22 mg; Figure 2D), but this was not significantly different from that in the group treated with the higher dose of patiromer (0.49 mg). When normalized to calcium intake, urinary calcium excretion was not significantly different from that in controls for any of the treatment groups (Figure 3D). SPS had minimal effects on stool and urinary calcium excretion, although when excretion was normalized to calcium intake both SPS groups had higher stool calcium levels than controls ($P < .01$; Figure 3C).

Stool phosphorus excretion was not significantly different from that in controls for any of the treatment groups (Figure 2E); however, both the RDX7675 and patiromer groups had lower mean 24-hour urinary phosphorus excretion (0.99-2.17 mg; $P < .05$; Figure 2F) than controls (4.04 mg). The SPS groups had higher mean 24-hour urinary phosphorus excretion (SPS 4.0%, 6.86 mg; 6.6%, 9.35 mg) than controls ($P < .001$). Effects on stool and urinary phosphorus were similar when excretion was normalized to phosphorus intake (Figure 3E and F).

Effects of Potassium-Binder Treatment on Stool Mass and Fluid Content

None of the potassium-binder treatments was associated with changes in food intake or body weight compared to controls.

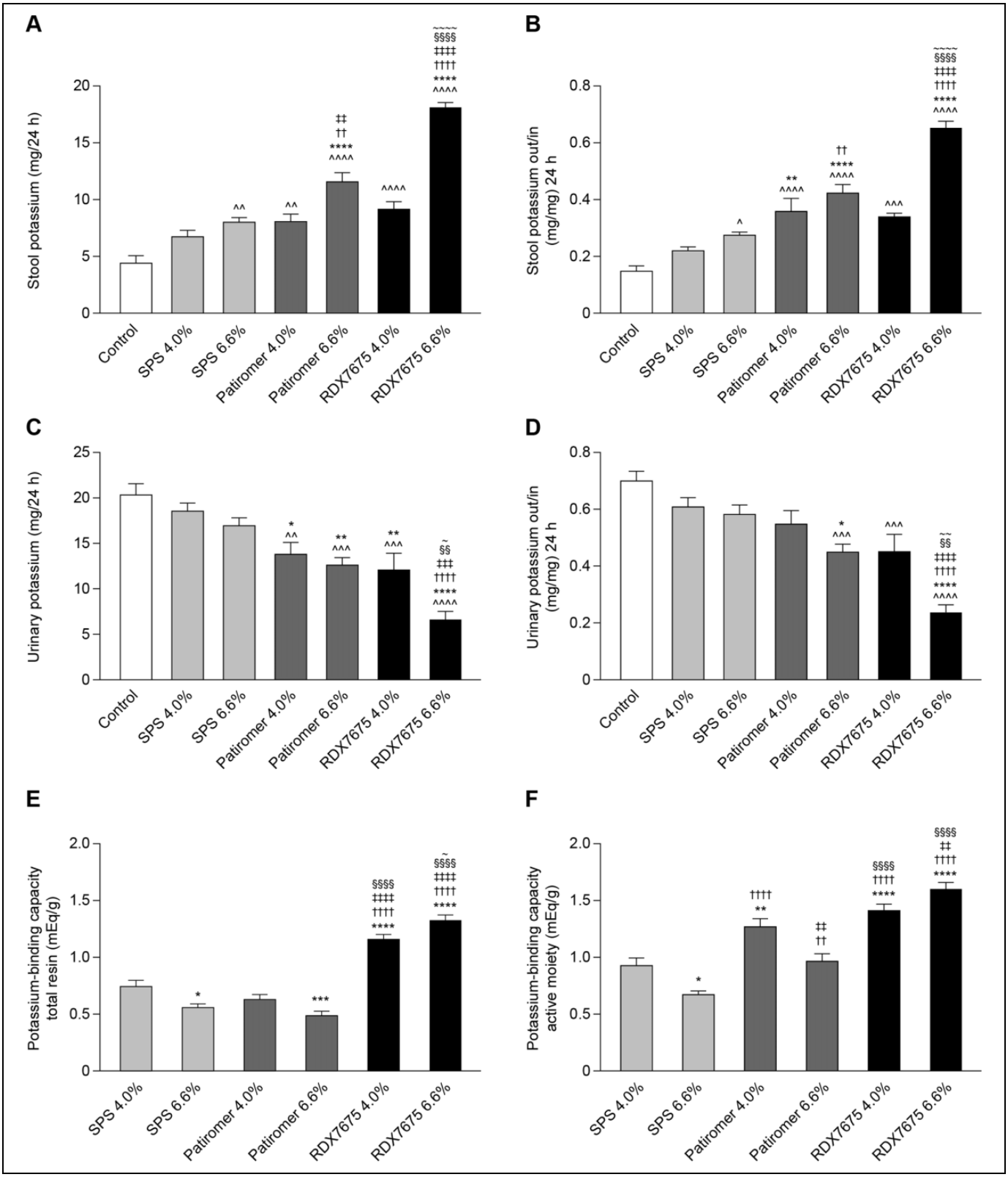

Figure 1. Effects of potassium-binder treatment on mean 24-hour potassium excretion in mice. Total stool and urinary excretion (A, C). Stool and urinary excretion normalized to intake (out/in; B, D). Potassium-binding capacity calculated for total resin and active moiety, respectively (E, F). Data shown are mean + standard error of mean. All n = 8. Symbols denote significance versus corresponding comparator (1-way ANOVA followed by Tukey test): 1 symbol, $P < .05$; 2 symbols, $P < .01$; 3 symbols, $P < .001$; 4 symbols, $P < .0001$. ^control, *SPS 4.0%, †SPS 6.6%, ‡patiromer 4.0%, §patiromer 6.6%, and ~RDX7675 4.0%. ANOVA indicates analysis of variance; SPS, sodium polystyrene sulfonate.

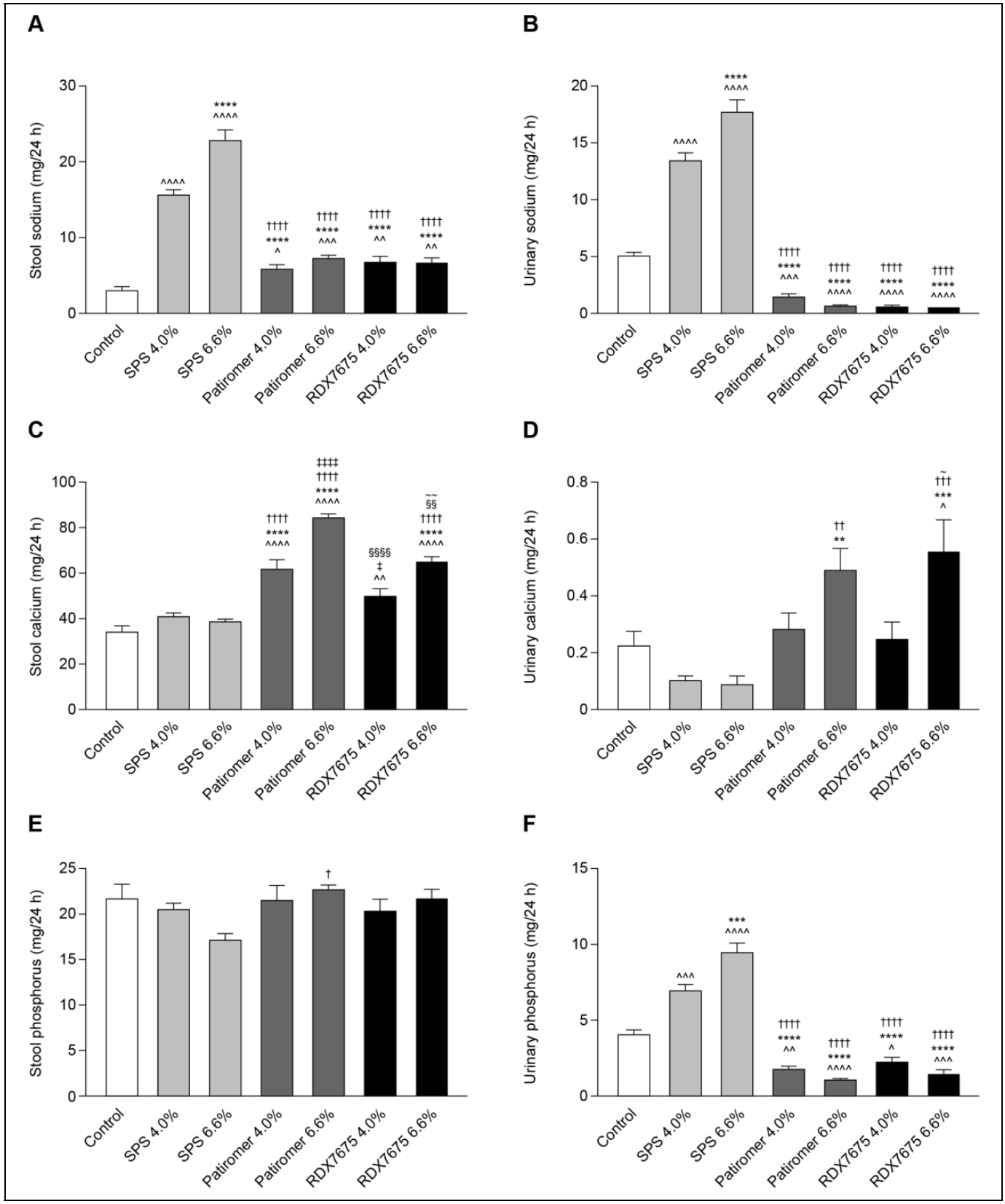

Figure 2. Effects of potassium-binder treatment on mean 24-hour excretion of sodium (A, B), calcium (C, D), and phosphorus (E, F) in mice. Data shown are mean + standard error of mean. All n = 8. Symbols denote significance versus corresponding comparator (1-way ANOVA followed by Tukey test): 1 symbol, $P < .05$; 2 symbols, $P < .01$; 3 symbols, $P < .001$; 4 symbols, $P < .0001$. ^control, *SPS 4.0%, †SPS 6.6%, ‡patiromer 4.0%, §patiromer 6.6%, and ~RDX7675 4.0%. ANOVA indicates analysis of variance; SPS, sodium polystyrene sulfonate.

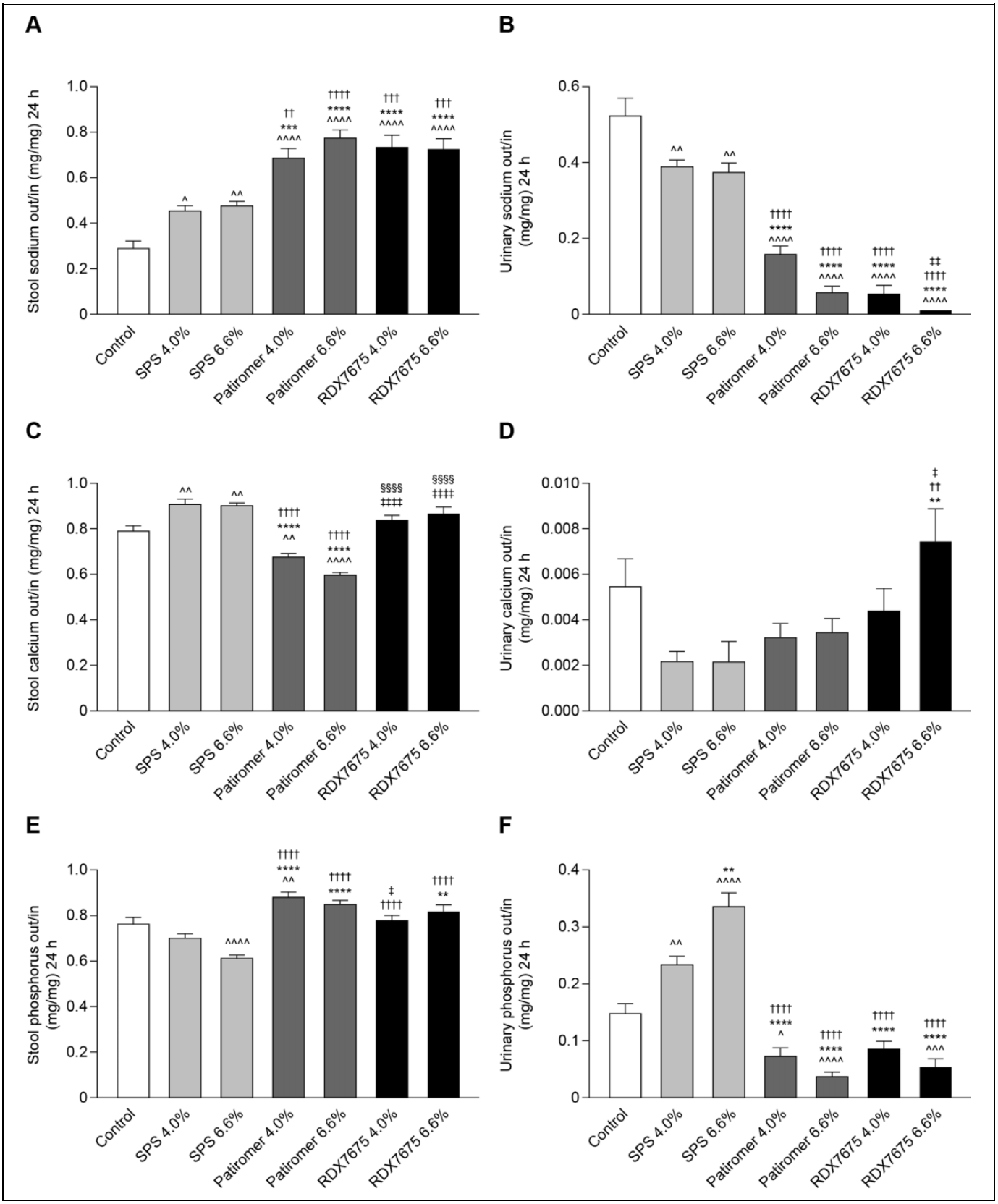

Figure 3. Effects of potassium-binder treatment on mean 24-hour excretion of sodium (A, B), calcium (C, D), and phosphorus (E, F) in mice, normalized to intake (out/in). Data shown are mean + standard error of mean. All n = 8. Symbols denote significance versus corresponding comparator (1-way ANOVA followed by Tukey test): 1 symbol, $P < .05$; 2 symbols, $P < .01$; 3 symbols, $P < .001$; 4 symbols, $P < .0001$. ^control, *SPS 4.0%, †SPS 6.6%, ‡patiromer 4.0%, §patiromer 6.6%, and ~RDX7675 4.0%. ANOVA indicates analysis of variance; SPS, sodium polystyrene sulfonate.

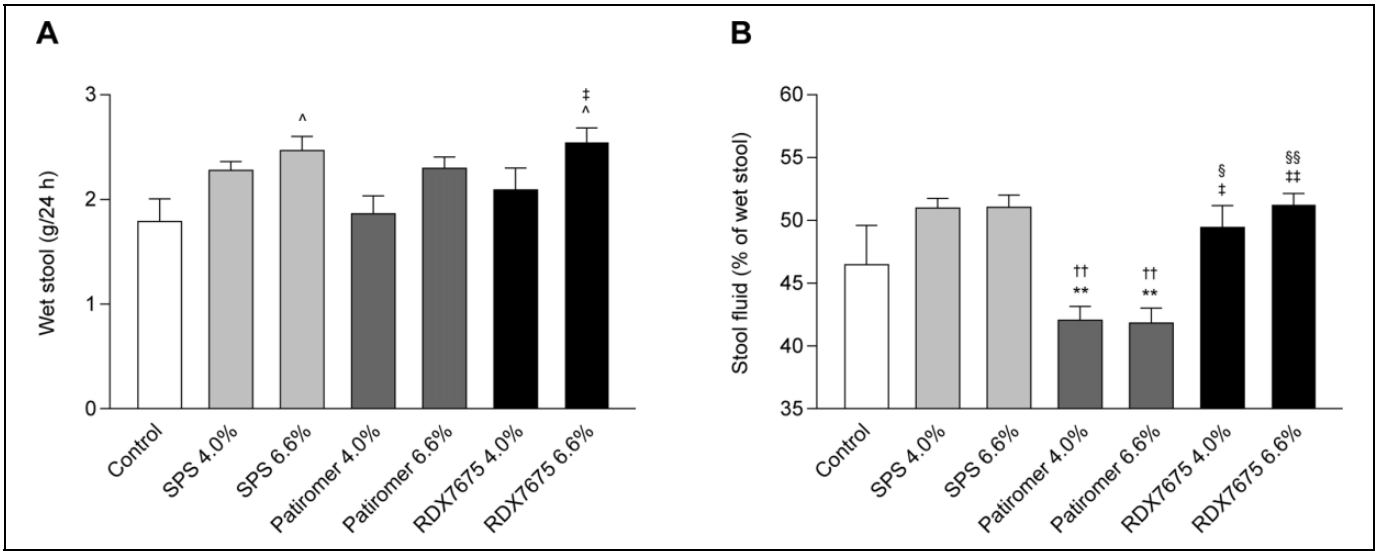

Figure 4. Effects of potassium-binder treatment on mean 24-hour stool wet weight (A) and fluid content (B) in mice. Data shown are mean + standard error of mean. All n = 8. Symbols denote significance versus corresponding comparator (1-way ANOVA followed by Tukey test): 1 symbol, $P < .05$; 2 symbols, $P < .01$. ^control, *SPS 4.0%, †SPS 6.6%, ‡patiromer 4.0%, and §patiromer 6.6%. ANOVA indicates analysis of variance; SPS, sodium polystyrene sulfonate.

Over the 24-hour sample collection period, mean wet stool weight was greater in the groups treated with RDX7675 6.6% and SPS 6.6% than in controls ($P < .05$; Figure 4A). Stool fluid content was not significantly different between the control group and any of the potassium binder-treated groups but was generally higher in the RDX7675 and SPS groups than in the patiromer groups ($P < .05$; Figure 4B). There was a weak correlation between stool fluid content and stool potassium excretion ($R^2 = .20$; Figure S2), but this effect was not a significant contributor to binder activity. For example, SPS and RDX7675 had equivalent effects on stool fluid content (Figure 4B), yet RDX7675 diverted significantly more potassium to the stool (Figure 1A, B).

Discussion

Hyperkalemia is a common complication in patients with CKD, diabetes, and heart failure, disease states that have high unmet medical needs.[1-4] Chronic or recurrent hyperkalemia is typically addressed with dietary potassium restriction and the dose reduction or discontinuation of medications known to impair renal potassium excretion, such as RAAS inhibitors.[9-12] The use of RAAS inhibitors is associated with renal protection and decreased morbidity and mortality in patients with heart failure, CKD, or diabetes.[5-7] Discontinuation of RAAS inhibitors in these patients is therefore clinically undesirable because it can negatively affect long-term health outcomes.[4,12] There is a need for efficacious novel therapies for the treatment of patients with hyperkalemia that have improved palatability and tolerability over current treatment options to facilitate long-term use. RDX7675 is a novel calcium polystyrene sulfonate-based potassium binder that is in clinical development for the treatment of patients with hyperkalemia. In this study, the pharmacodynamic effects of RDX7675 were investigated in mice alongside those of 2 potassium binders currently approved for the treatment of hyperkalemia in the United States, SPS and patiromer. RDX7675 significantly reduced intestinal potassium absorption in mice as demonstrated by increased stool potassium excretion and reduced urinary potassium excretion compared with controls. In addition, RDX7675 had a significantly higher in vivo potassium-binding capacity than patiromer or SPS.

Sodium polystyrene sulfonate has been used as a treatment for hyperkalemia for over 60 years and, for a long time, was the only potassium binder available in the United States.[16] Limited data on the efficacy of SPS treatment were available at the time of its FDA approval and concerns have since been raised regarding its ability to reduce potassium absorption.[15,18,28] In addition, the concomitant use of SPS with sorbitol to reduce constipation and achieve optimal effect was found to be associated with gastrointestinal adverse events, including colonic necrosis.[16,17] Together, these efficacy and safety concerns, as well as its unpalatable formulation, make SPS unsuitable for the long-term management of hyperkalemia. Patiromer received FDA approval for the treatment of patients with chronic hyperkalemia in 2015.[24] Clinical trials have demonstrated the efficacy of patiromer in reducing serum potassium levels in patients receiving RAAS inhibitors who have CKD,[21] chronic heart failure,[22] or diabetic kidney disease.[23] In these studies, patiromer was well tolerated, although its use was associated with gastrointestinal side effects. In our study described here, patiromer had greater in vivo potassium-binding capacity than SPS when calculated by active moiety. Treatment of patients with either SPS or patiromer involves doses of large quantities of potassium-binding agent (for SPS, a suspension of 15 g in

100 mL water up to 4 times daily; for patiromer, a suspension of 8.4-25.2 g in ~80 mL water once daily).[16,24] This can have low acceptability to patients and reduce treatment compliance, particularly because patients with CKD or heart failure often have several comorbid conditions and are prescribed multiple medications that can result in a high pill burden.[29] A novel agent with improved in vivo potassium-binding capacity, such as RDX7675, has the potential to effectively control serum potassium levels at lower doses of administered drug, which could improve acceptability to patients.

In this study, significantly higher levels of urinary sodium excretion were observed in the mice treated with SPS than in all other groups, indicating increased sodium absorption. The effects of SPS on stool and urinary sodium excretion were less apparent when excretion was normalized to sodium intake, suggesting that the disturbances in sodium balance caused by SPS are largely due to the delivery of excess sodium as the counterion. Sodium intake is particularly deleterious for the patients who are most susceptible to developing hyperkalemia—those with heart failure, hypertension, or CKD—and can reduce the effectiveness of therapy with RAAS inhibitors.[30] In contrast, treatment with RDX7675 or patiromer was associated with significantly reduced intestinal absorption of sodium. The higher dose of RDX7675 did increase urinary calcium in this study compared with controls, likely owing to the presence of the calcium counterion; however, the resultant urinary calcium level was not significantly different from that in the group treated with the equivalent dose of patiromer. The lower dose of RDX7675 did not have this effect on urinary calcium, despite having an effect on urinary potassium comparable to that of the higher dose of patiromer.

Both RDX7675 and patiromer significantly lowered urinary phosphorus compared to controls, indicating reduced gastrointestinal phosphate absorption, perhaps owing to the formation of calcium × phosphate product in the intestine, thereby reducing the amount of dietary phosphate available for absorption. In contrast, SPS significantly increased urinary phosphorus. RDX7675 may therefore provide a new treatment option for patients with hyperkalemia with the added benefit of reducing phosphate load, important in patients with CKD who often also have hyperphosphatemia and/or elevated serum fibroblast growth factor 23 levels.[29,31] The mice in the RDX7675 groups also had significantly higher stool fluid content than those in the patiromer groups, although neither RDX7675 group had stool fluid content significantly different from that of control mice. The relationship between stool fluid content and stool potassium excretion was weak, indicating that increased fluid volume was not the primary driver behind increased stool potassium excretion. Patients with CKD or heart failure are often constipated, and this is one of the most common adverse events associated with SPS and patiromer use[16,24]; therefore, the effect of RDX7675 on stool fluid content could be beneficial to some patients if it is reproduced in clinical trials.

This study has several limitations. First, the experiments were conducted in healthy mice. Thus, clinical studies will be required to evaluate the pharmacodynamics effects of RDX7675 in humans, including effects on serum potassium concentrations in patients with hyperkalemia. Second, this study evaluated only the pharmacodynamic effects of RDX7675 and was not designed to provide any information about palatability, safety, or tolerability.

Conclusion

This study found that RDX7675 reduced intestinal potassium absorption in mice and had higher potassium-binding capacity than SPS or patiromer. The calcium-based resins RDX7675 and patiromer reduced sodium absorption, unlike sodium-based SPS, which increased sodium absorption. This study was conducted in healthy animals, and clinical studies will be needed to determine how well the results translate to humans. These results, however, support the potential for RDX7675 as a novel treatment for hyperkalemia and justify its further development through human studies.

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Author Contributions

JP Davidson contributed to conception and design, contributed to acquisition and interpretation, critically revised manuscript, gave final approval, and agrees to be accountable for all aspects of work ensuring integrity and accuracy. AJ King contributed to conception and design, contributed to acquisition and interpretation, critically revised manuscript, gave final approval, and agrees to be accountable for all aspects of work ensuring integrity and accuracy. P. Kumaraswamy contributed to analysis and interpretation, drafted manuscript, critically revised manuscript, gave final approval, and agrees to be accountable for all aspects of work ensuring integrity and accuracy. JS Caldwell contributed to interpretation, critically revised manuscript, gave final approval, and agrees to be accountable for all aspects of work ensuring integrity and accuracy. P. Korner contributed to interpretation, drafted manuscript, critically revised manuscript, gave final approval, and agrees to be accountable for all aspects of work ensuring integrity and accuracy. RC Blanks contributed to conception and design, contributed to interpretation, critically revised manuscript, gave final approval, and agrees to be accountable for all aspects of work ensuring integrity and accuracy. JW Jacobs contributed to conception and design, contributed to analysis and interpretation, critically revised manuscript, gave final approval, and agrees to be accountable for all aspects of work ensuring integrity and accuracy.

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: All authors are employed by, and have ownership interest in, Ardelyx, Inc, Fremont, CA, USA.

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Supplemental material

Supplementary material for this article is available online.

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