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Preclinical and Healthy Volunteer Studies of Potential Drug–Drug Interactions Between Tenapanor and Phosphate Binders

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Abstract

Tenapanor (RDX5791, AZD1722), a first-in-class small molecule with minimal systemic availability, is an inhibitor of the sodium/hydrogen exchanger isoform 3. Tenapanor acts locally in the gut, where it reduces absorption of sodium and phosphate. It is being studied in patients with chronic kidney disease requiring dialysis, who are often administered phosphate binders such as sevelamer to help control hyperphosphatemia. We investigated whether coadministration of tenapanor with phosphate binders (sevelamer or calcium-based binders) impacts the pharmacodynamic effects of tenapanor. In vitro studies suggested a binding interaction between tenapanor and sevelamer, but this did not translate into altered pharmacodynamic effects in rats. An open-label, 2-way crossover study was then conducted in healthy volunteers (NCT02346890). This showed that 4 days' treatment with tenapanor hydrochloride (15 mg twice daily) with or without sevelamer carbonate (800 mg 3 times daily) resulted in comparable 24-hour stool and urinary sodium and phosphorus levels. Stool frequency, consistency, and weight were also comparable between the treatments. These results suggest that the binding between sevelamer and tenapanor observed in vitro does not translate into altered pharmacodynamic effects in humans.

Keywords

tenapanor, drug–drug interactions, sodium absorption, chronic kidney disease, hyperphosphatemia

A major function of the gastrointestinal tract is to maintain intestinal water/sodium homeostasis through a delicate balance of secretory and absorption mechanisms. This balance is clinically important in many disease states such as hypertension, heart failure, and chronic kidney disease (CKD).[1] Tenapanor (AZD1722, RDX5791) is a first-in-class small-molecule inhibitor of the sodium/hydrogen exchanger isoform 3 (NHE3), a transporter expressed in the apical membrane of enterocytes. NHE3 plays an important role in sodium absorption from the gastrointestinal tract.[2–4] Following oral administration, tenapanor acts locally in the gastrointestinal tract, with minimal systemic availability, to inhibit NHE3, thereby reducing intestinal sodium uptake in both rats and healthy humans.[5] Furthermore, preclinical and early clinical studies have shown that tenapanor reduces dietary phosphate uptake.[6–8]

Tenapanor is being investigated for the treatment of patients with CKD requiring dialysis because reduced sodium and phosphate uptake is expected to be beneficial for control of hyperphosphatemia, volume retention/blood pressure, and CKD progression.[9–11] For treatment of hyperphosphatemia, the vast majority of patients with CKD requiring maintenance hemodialysis are prescribed phosphate binders,[12] as are a proportion of patients with CKD not yet on dialysis.[13] Calcium-based binders and the non-calcium-based binder sevelamer are the most commonly used agents[14] and are recommended in treatment guidelines.[15,16]

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In the development of new drugs, it is necessary to investigate any potential, clinically relevant drug–drug interactions (DDIs), typically assessed by examining changes in systemic exposure of one drug when coadministered with another. In the case of non-absorbed drugs, the potential for intestinal binding between drugs is also of key importance. Such interactions may alter the drugs' behavior within the gastrointestinal tract as well as their resulting pharmacodynamic activities. For instance, a drug may not be available to the apical surface beyond the mucus layer because it is kept in the lumen by being bound tightly to another agent within the chyme.

We investigated whether combining tenapanor with commonly used phosphate binders could result in binding interactions that impact the pharmacodynamic activity of tenapanor. We report translational data, ranging from in vitro binding to in vivo DDIs in rats and in humans, from studies conducted with tenapanor and phosphate binders (sevelamer and calcium-based binders) to identify any clinically relevant interactions.

Methods

In Vitro Drug–Drug Binding Study

Sevelamer carbonate (Renvela; Genzyme Corporation, Cambridge, Massachusetts; 1.6 mg/mL, to approximate the concentration of polymer in the gut after a dose of 2.4 g, or 3.2 mg/mL, to approximate a higher dose), calcium acetate (PhosLo; Fresenius Medical Care North America, Waltham, Massachusetts; 1 mg/mL based on a dose of 2 × 667 mg), and calcium carbonate (Caltrate; Pfizer Inc., Kings Mount, North Carolina; 2.4 mg/mL based on a dose of 2 × 600 mg) were each dissolved in a buffer designed to simulate the intestinal environment (8 mM NaH_2PO_4/K_2HPO_4 [pH 6.5], 150 mM NaCl, 5 mg/mL pancreatin, 5 mg/mL bovine serum albumin, 3 mM sodium taurocholate, 0.75 mM lecithin, and 9 mM free fatty acid [1.5 mM each of lauric, palmitic, stearic, oleic, linoleic, and arachidonic acid]). Tenapanor hydrochloride at a selection of final concentrations of 1, 10, 50, 100, and 200 μM, prepared from 1 and 10 mM stock solutions in dimethyl sulfoxide, was added to each phosphate binder solution.

The mixtures of phosphate binders and tenapanor were incubated with gentle agitation for 2 hours at 37°C. This length of time was chosen as an intermediate time between gastric emptying time and total gastrointestinal transit time that was relevant to postprandial conditions. The mixtures were then centrifuged at 1200*g* for 15 minutes, and samples taken in duplicate from the middle of the upper phase. Concentrations of tenapanor were measured by Ardelyx, Inc. (Fremont, California). Proteins were precipitated using a solution of acetonitrile containing a deuterium-labeled analogue of tenapanor (d_8-tenapanor) as the internal standard. The deproteinized samples were injected and analyzed on a liquid chromatography–tandem mass spectrometry (LC-MS/MS) system (Agilent 1260 HPLC/6410 triple quadrupole mass spectrometer). Chromatography was performed using a Synergi Hydro-RP 30 × 2.0 mm (particle size, 4 μm) C18 column (Phenomenex, Torrance, California) maintained at 40°C using a gradient of 10%–95% acetonitrile in water (0.1% formic acid) as the mobile phase. The eluent was nebulized using heated nitrogen and ionized in an electrospray ionization source set to positive mode. Two multiple reaction monitoring (MRM) transitions were used to detect tenapanor: *m/z* 573.3 > 502.1 (quantifier) and *m/z* 573.3 > 459.1 (qualifier). The d_8-tenapanor MRM transition monitored was *m/z* 577.3 > 502.1. All ions detected were doubly charged ($[M + 2H]^{2+}$). A calibration curve of the peak area ratio of tenapanor to d_8-tenapanor versus tenapanor concentration was plotted and fitted by linear regression using MassHunter software (Agilent, Santa Clara, California).

For each concentration of tenapanor, the percentage bound was determined using the following equation:

$$\%\ \text{bound} = \left(\frac{[\text{tenapanor}]_{\text{control}} - [\text{tenapanor}]_{\text{test}}}{[\text{tenapanor}]_{\text{control}}}\right) \times 100$$

where $[\text{tenapanor}]_{\text{control}}$ is the concentration of tenapanor in the control sample (a reference sample in which no potential binder is added), and $[\text{tenapanor}]_{\text{test}}$ is the concentration of tenapanor in the test sample. The observed recovery of tenapanor in quality-control samples across all experiments ranged from 84% to 124%, demonstrating that the analytical method was suitable to determine tenapanor concentrations in the binding buffer over the relevant concentration range.

In Vivo Drug–Drug Interaction Study in Rats

Study design. Experiments were conducted in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals and were approved by the Institutional Animal Care and Use Committee of Ardelyx Inc. Seven-week-old male Sprague-Dawley rats in individual metabolic cages were fed 2018 Teklad global powdered rodent chow containing 0.23% sodium (Harlan Laboratories, Indianapolis, Indiana) and given water ad libitum. Rats first received oral tenapanor hydrochloride dissolved in water at doses of 0.1, 0.3, 1, or 3 mg/kg or water (as the control). After 10 minutes, rats at each dose level were subsequently orally administered either sevelamer carbonate (dissolved in water at a dose of 48 mg/kg) or water, resulting in 10 different treatment groups

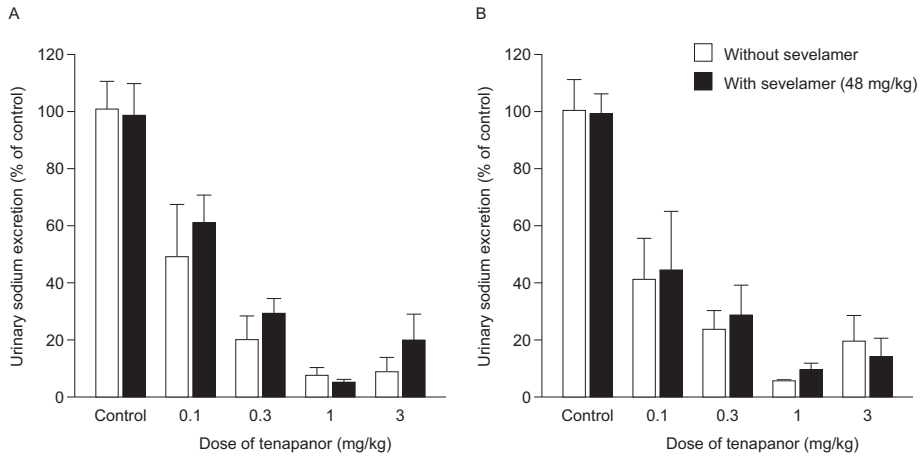

Figure 1. Sodium content of urine from rats dosed with (A) tenapanor hydrochloride (including a water control group as part of the tenapanor dosing), then sevelamer carbonate or water; or (B) sevelamer carbonate or water, then tenapanor hydrochloride (including a water control group as part of the tenapanor dosing). Data are presented as mean + standard error.

(n = 6 in each group; Figure 1A). A reversed dosing scheme was applied to another group of rats (ie, sevelamer was administered first, followed by tenapanor) to provide a second set of 10 treatment groups (n = 6 in each group; Figure 1B). Urine samples were collected 16 hours postdose, and volume was determined gravimetrically using previously determined Sprague-Dawley rat urine specific gravity.

Determination of sodium content in rat urine. Urine samples were centrifuged at 4000 rpm, and the resulting supernatants were diluted 100-fold in deionized water. The diluted urine was filtered through a 0.2-μm hydrophilic polypropylene filter plate before analysis by ion chromatography (ICS-3000 System; Dionex, Sunnyvale, California). Cations were separated by an isocratic method using 25 mM methanesulfonic acid as the eluent on a 2 × 250 mm (particle size, 8 μm) cation exchange column (Dionex CS12A). Sodium was quantified using standards prepared from a cation standard mix containing sodium and potassium (Dionex).

The total mass of sodium excreted in urine during the 16-hour collection period was calculated for each rat. Urinary sodium for each dosing group was expressed as a percentage of the mean of the water-dosed group, which was approximately 20 mg of sodium over the 16-hour collection period. The means of the various dosing groups were compared statistically by 2-way analysis of variance (ANOVA) followed by Sidak's multiple-group comparisons test.

Healthy Volunteer Study

Study participants. The protocol, amendments, and informed consent forms for this study were approved by IntegReview (Austin, Texas). Individuals provided written informed consent prior to eligibility screening and study participation. The study was conducted in accordance with the Declaration of Helsinki and International Conference on Harmonisation Good Clinical Practice guidelines. The study was conducted at ICON Development Solutions (San Antonio, Texas).

Healthy volunteers aged 19−65 years with a body mass index of at least 18 kg/m^2, but less than 30 kg/m^2 were eligible for this study (ClinicalTrials.gov identifier: NCT02346890). Exclusion criteria included structural abnormality of the gastrointestinal tract; any surgery on the small intestine or colon, excluding appendectomy or cholecystectomy, or any other condition known to interfere with absorption, distribution, metabolism, or excretion of drugs; loose stools (Bristol Stool Form Scale [BSFS][17] score of 6 or 7) on 2 or more days in the 7 days before screening; use of diuretics, medications known to affect stool consistency and/or gastrointestinal motility, or salt or electrolyte supplements containing sodium, potassium, chloride, or bicarbonate formulations.

Study design. In this phase 1 single-center, open-label, 2-way crossover study, 16 volunteers (11 men; 12 white) mean age ± standard deviation (SD) of 45.3 ± 9.0 years were randomly assigned to begin study treatment with either tenapanor hydrochloride 15 mg orally twice daily alone for 4 days (hereafter referred to as tenapanor) or tenapanor hydrochloride 15 mg orally twice daily and sevelamer carbonate 800 mg orally 3 times daily for 4 days (hereafter referred to as tenapanor + sevelamer) before crossover to the other treatment, with a 2-day washout between treatments. All participants completed the study and undertook all the pharmacodynamic, pharmacokinetic, and safety evaluations described below.

The dose of tenapanor used was based on the results of a previous dose regimen evaluation study, in which treatment with tenapanor 15 mg twice daily for 1 week was well tolerated and showed evidence of an effect on stool sodium.[5] This regimen is also in the midrange of doses being evaluated in phase 2 trials and so is expected to be clinically relevant. The dose of sevelamer carbonate (a polymer-based agent) used is an approved dose for the control of serum phosphate in patients with CKD on dialysis.[18,19]

Each participant checked into the clinical pharmacology unit (CPU) on day -2 (ie, 2 days before the first treatment period) before dinner. Participants were discharged from the CPU on day 11 after all the safety assessments and sample collections were complete. All participants received a diet standardized for sodium content (~1.5 g [65 mmol] per meal), which included the same food on respective treatment days of each study period (ie, the same breakfast, lunch, and dinner on the first day of both periods, etc.). Tenapanor was taken approximately 5 minutes before breakfast and dinner. In the tenapanor + sevelamer treatment period, sevelamer was taken with each meal (breakfast, lunch, and dinner).

Pharmacodynamic assessments included stool and urinary excretion of sodium and phosphorus, and stool frequency, consistency (as measured by the BSFS), and weight. Stool and urine were collected over 24-hour intervals throughout the study, from day -2 to day 11. Blood sampling for measurement of plasma tenapanor concentrations was performed on the last day of both of the 2 treatment periods — sampling occurred predose and 1, 2, and 4 hours after the morning dose of tenapanor. Safety assessments included monitoring of adverse events (AEs), vital signs, clinical laboratory evaluations, electrocardiograms (ECGs), and physical examinations.

Determination of sodium and phosphorus content in stool and urine. Sodium and phosphorus content in stool was determined by RTI International (Research Triangle Park, North Carolina). Stool samples were transferred to the laboratory in a frozen state and stored at -20°C. Samples were partially digested in approximately twice their weight of concentrated nitric acid and then heated at 60°C for 3 hours; 5 mL of the resulting partially digested samples was further digested with nitric and hydrochloric acids and diluted to 50 mL with deionized water before centrifugation to precipitate insoluble matter. The sodium and phosphorus content of the supernatant liquid was measured using inductively coupled plasma-optical emission spectrometry (Optima 4300DV ICP-OES, Perkin-Elmer, Waltham, Massachusetts). A calibration curve of intensity versus each electrolyte concentration was plotted and fitted by linear regression through the instrument software. The validated lower limit of quantification was defined by the lowest replicate electrolyte concentration that was measured with acceptable accuracy (± 20% of the nominal back-calculated concentration from the calibration curve). At least 4 of 6 quality-control samples had to be quantified as within 20% of their theoretical value for an analysis run to be acceptable. The overall precision and overall bias (a measure of accuracy) of the assay were determined by analysis of quality-control samples as follows: for sodium, these were 3.2%–5.8% and 2.9%–14.5%, respectively; for phosphorus, these were 1.9%–3.3% and 0.4%–3.8%, respectively. Sodium and phosphorus content of urine samples was determined from ion-selective electrode measurements by Quest Diagnostics (San Antonio, Texas) using standard clinical laboratory techniques.

The mean levels of sodium and phosphorus in stool and urine during the 4 days of treatment were analyzed using a mixed-model ANOVA with fixed effects for sequence, period, and treatment and a random effect for participants within sequence. The least-squares mean (LSM) for each treatment group, and the LSM treatment difference were calculated using point estimates and 2-sided 90% confidence intervals (CIs). In the treatment comparison, tenapanor alone served as the reference treatment, and tenapanor + sevelamer served as the test treatment.

Determination of plasma concentrations of tenapanor. Plasma concentrations of tenapanor were measured by MicroConstants, Inc. (San Diego, California). Human plasma samples containing tenapanor, d_8-tenapanor as the internal standard, and dipotassium ethylenediaminetetraacetic acid as the anticoagulant were processed first by protein precipitation with acetonitrile, followed by back-extraction into an acidic aqueous solution. The extracts were injected and analyzed by reversed-phase high-performance liquid chromatography using a Phenomenex Synergi Hydro-RP 100 × 2.0 mm (particle size, 4 μm) column (Phenomenex, Torrance, California) maintained at 35°C using a gradient of 35%–95% acetonitrile in water (2.7 ppm citric acid, 0.025% trifluoroacetic acid, 0.025% ammonium trifluoroacetate) as the mobile phase. The eluent was nebulized using heated nitrogen in a Z-spray source/interface set to electrospray positive ionization mode. The ionized compounds were detected using LC-MS/MS (MRM transitions: tenapanor, m/z 573.4 > 502.0 $[M + 2H]^{2+}$; d_8-tenapanor, m/z 577.4 > 502.0 $[M + 2H]^{2+}$). The lower and upper limits of quantification were 0.5 and 500 ng/mL, respectively. The accuracy (variation in measured concentration compared with theoretical concentration) and precision (coefficient of variation [SD/mean] within replicates) of quality-control standards of tenapanor were determined at concentrations of 0.5, 1.5,

Table 1. In Vitro Binding Study of Tenapanor With Phosphate Binders

	% Tenapanor Bound[a]						
	Experiment 1 (n = 2)[b]		Experiment 2 (n = 4)[c]		Experiment 3 (n = 2)[c]		
Binder	Tenapanor[d] 1 μM	Tenapanor[d] 10 μM	Tenapanor[d] 1 μM	Tenapanor[d] 10 μM	Tenapanor[d] 50 μM	Tenapanor[d] 100 μM	Tenapanor[d] 200 μM
Sevelamer carbonate (1.6 mg/mL)	74 (1)	79 (0)	80 (4)	87 (1)	73 (1)	72 (1)	86 (0)
Sevelamer carbonate (3.2 mg/mL)	—	—	—	—	79 (0)	75 (0)	86 (0)
Calcium carbonate (2.4 mg/mL)	≤ 5	≤ 5	≤ 5	≤ 5	—	—	—
Calcium acetate (1 mg/mL)	≤ 5	≤ 5	≤ 5	≤ 10	—	—	—

[a]Data are presented as mean (standard deviation). Assay error was estimated at 5%.
[b]Fatty acid concentrations were 24 mM and contained only saturated fatty acids.
[c]Fatty acid concentrations were 9 mM and contained a mixture of saturated and unsaturated fatty acids.
[d]As tenapanor hydrochloride.

20, and 400 ng/mL. Accuracy and precision were in the ranges of -1.5% to 8.0% and 2.8%–9.1%, respectively. Precision and accuracy no greater than 20% were required for quality-control standards at the lower limit of quantification.

Results

In Vitro Drug–Drug Binding Study

Under the experimental conditions evaluated, there appeared to be an interaction between tenapanor and sevelamer carbonate in vitro, as demonstrated by 72%–87% of tenapanor being bound (Table 1); the level of binding was not dependent on tenapanor concentration (or sevelamer concentration). No binding was observed between tenapanor and calcium carbonate or calcium acetate.

In Vivo Drug–Drug Interaction Study in Rats

In the rat study, there was no detectable change in the pharmacodynamic effect of tenapanor as a result of treatment with sevelamer carbonate ($P = .38$); there was a dose-dependent reduction in urinary sodium in rats treated with tenapanor alone ($P < .0001$), which was unaffected by coadministration of sevelamer 10 minutes later (Figure 1A). Some contamination of urine samples with stool was evident in the rats given the higher doses of tenapanor, contributing to a small apparent increase in urinary sodium in the group that received the 3 mg/kg dose compared with those receiving the 1 mg/kg dose. This was because the rats given the highest dose of tenapanor passed stool that was of a more liquid form.

Reversing the dose order of the 2 coadministered drugs (ie, administration of sevelamer carbonate, then administration of tenapanor 10 minutes later) also had no detectable effects on the dose-dependent reduction in urinary sodium associated with tenapanor treatment (Figure 1B).

Healthy Volunteer Study

Following the suggestion of binding between tenapanor and sevelamer carbonate in vitro, a study was performed in healthy volunteers to investigate the clinical effects of any binding in vivo.

Pharmacodynamic evaluations. Comparable stool sodium levels were measured over the treatment periods, regardless of whether tenapanor was administered alone or in combination with sevelamer, with an LSM (90%CI) difference of -3.4 mmol/day (-8.7 to 1.8 mmol/day) between treatments (Figure 2). Similar results were found for urinary sodium levels, with an LSM difference of 3.8 mmol/day (-5.4 to 13.1 mmol/day) between treatments (Figure 2). Likewise, stool and urinary phosphorus levels were each comparable between treatments, with LSM differences of 0.3 mmol/day (-4.4 to 5.0 mmol/day) for stool and -0.9 mmol/day (-2.1 to 0.3 mmol/day) for urine (Figure 3).

On day -1, only 2 of the 16 participants had a stool frequency of 3 or more bowel movements per day. Stool frequency during treatment was comparable when tenapanor was coadministered with sevelamer and when tenapanor was administered alone, with 8 and 10 of the 16 participants having a stool frequency of 3 or more bowel movements per day (mean of 4 days), respectively. Stool consistency was looser during tenapanor treatment, compared with before dosing; the BSFS score (mean ± SD) on day -1 was 3.5 ± 1.2, compared with 4.6 ± 1.0 and 4.8 ± 0.9 during

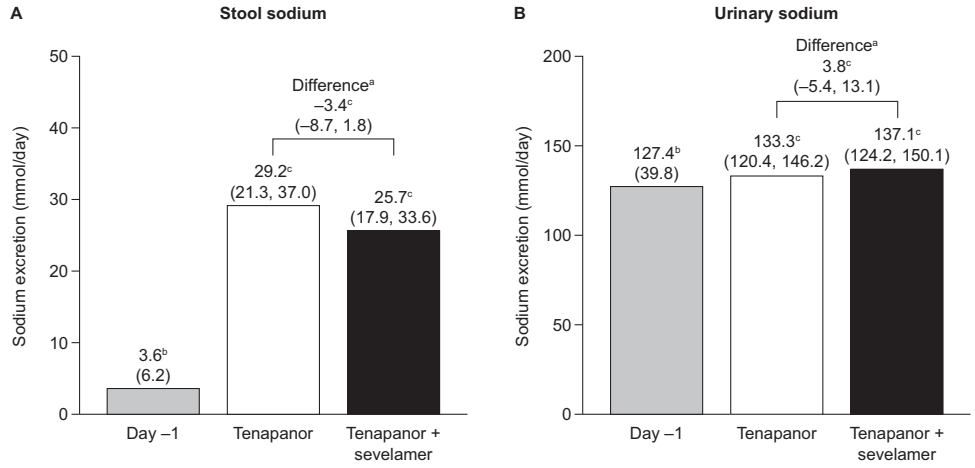

Figure 2. Sodium content of (A) stool and (B) urine in healthy volunteers before and after 4 days' treatment with tenapanor hydrochloride (15 mg orally twice daily) or tenapanor hydrochloride (15 mg orally twice daily) plus sevelamer carbonate (800 mg orally 3 times daily). [a]Difference = ([tenapanor + sevelamer] - tenapanor alone) and is presented as least-squares mean (90% confidence interval). [b]Data for day -1 (the day before the first treatment period) are presented as arithmetic mean (standard deviation). [c]Treatment period data are presented as least-squares mean (90% confidence interval) over 4 days' treatment.

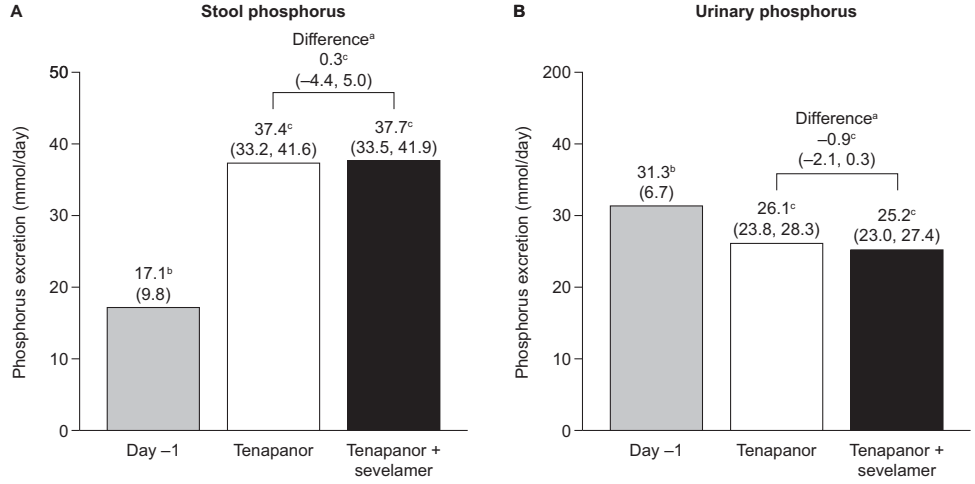

Figure 3. Phosphorus content of (A) stool and (B) urine in healthy volunteers before and after 4 days' treatment with tenapanor hydrochloride (15 mg orally twice daily) or tenapanor hydrochloride (15 mg orally twice daily) plus sevelamer carbonate (800 mg orally 3 times daily). [a]Difference = ([tenapanor + sevelamer] - tenapanor alone) and is presented as least-squares mean (90% confidence interval). [b]Data for day -1 (the day before the first treatment period) are presented as arithmetic mean (standard deviation). [c]Treatment period data are presented as least-squares mean (90% confidence interval) over 4 days' treatment.

treatment with tenapanor + sevelamer and tenapanor alone, respectively (n = 16 for both groups). Stool weight was similar in the 2 treatment periods, with weights (mean ± SD) of 265.6 ± 121.1 and 292.3 ± 151.0 g/day for tenapanor + sevelamer and tenapanor alone, respectively (n = 16 for both groups).

Pharmacokinetic evaluation. Plasma concentrations of tenapanor were below the lower limit of quantification (0.5 ng/mL) in all 128 samples taken.

Safety and tolerability. Tenapanor administered with or without sevelamer to healthy volunteers resulted in no discontinuations because of AEs or serious AEs. Six participants reported a total of 13 AEs during the course of the study, the majority of which were gastrointestinal in nature. The most common AE was flatulence, with 5 events from 3 individuals (2 events with tenapanor and 3 with tenapanor + sevelamer). The other AEs were abdominal pain (1 event with each of tenapanor and tenapanor + sevelamer), headache (2 events with tenapanor + sevelamer), abdominal distension, nausea, and paresthesia (1 event of each with tenapanor + sevelamer), and skin lesion (1 event with tenapanor). All AEs were considered mild or moderate in intensity and resolved by the end of the study.

No clinically significant changes were observed in stool and urinary potassium, urinary creatinine, or

serum calcium following treatment with tenapanor or tenapanor + sevelamer. Any other laboratory values outside the normal range were not considered clinically relevant by the investigator, nor were there any clinically relevant findings in vital signs, ECGs, and physical examinations.

Discussion

Tenapanor is a small-molecule inhibitor of NHE3 that acts locally in the gut to reduce absorption of sodium and phosphate; it is being developed for the treatment of patients with CKD. When developing new drugs, it is important to investigate any potential DDIs that may affect their pharmacodynamic effects or their safety and tolerability profiles. Here, we describe results spanning in vitro, in vivo rat, and healthy volunteer studies designed to investigate potential DDIs between tenapanor and phosphate binders such as sevelamer and calcium-based agents. Results from the in vitro experiments suggested that there may be a drug–drug binding interaction between tenapanor and sevelamer. This warranted further evaluation in vivo, which began with a study in rats. In this study, no evidence of a DDI based on urinary sodium data was observed when tenapanor and sevelamer were coadministered. To further assess the risk of binding between sevelamer and tenapanor in humans, a healthy volunteer study was performed. The human study showed comparable levels of sodium and phosphorus excretion when tenapanor was administered alone or in combination with sevelamer. Stool frequency, consistency, and weight were also similar in both treatment groups. Thus, no evidence of a DDI between tenapanor and sevelamer was found in vivo in our study.

This work is an example of results from in vitro drug–drug binding studies not translating into observable consequences in humans. Predictions of in vivo DDIs from in vitro data are not always reliable, as in vitro experiments cannot take all physiologic complexities into account. In the case of drugs that act locally within the gastrointestinal tract, potential interactions with molecules present in chyme and the role of the mucus layer in allowing access of drugs to the epithelial surface remain poorly understood.[20] Our study highlights the need to follow up findings from in vitro studies to ascertain their relevance to the human situation when it comes to locally acting compounds with the potential for physical binding in the gastrointestinal tract.

It should be noted that this study was designed to assess the effect of sevelamer on tenapanor treatment and not vice versa. It was also not designed to show any additive effects of these drugs in terms of the reduction in intestinal phosphate absorption. To assess these objectives, a sevelamer-only treatment period would have been required. To evaluate fully any additive effect of these drugs, evaluation of serum phosphorus as a clinical end point would be more appropriate than stool and urinary phosphorus. However, using serum phosphorus levels as a pharmacodynamic marker for changes in intestinal phosphate uptake in healthy volunteers (who have full kidney function) is not trivial and would require detailed assessments,[21] which this study was not designed for. Finally, the diet provided to the participants in our study was not standardized for phosphate content, although all participants did receive the same meals on the same respective treatment days of each study period.

Tenapanor is undergoing evaluation for the treatment of patients with hyperphosphatemia in CKD requiring dialysis.[22,23] Patients with CKD often have comorbidities requiring treatment with several concurrent medications, and patients with advanced CKD frequently have a very high tablet burden (which can exceed 25 tablets per day), of which phosphate binders make up a large component.[24] Should tenapanor prove effective in treating hyperphosphatemia in patients with kidney disease, it may have the potential to alleviate the tablet burden on these patients. Further studies are required to evaluate the potential of tenapanor to be coadministered with phosphate binders and other agents used to treat patients with CKD.

In summary, our study showed that coadministration of tenapanor with sevelamer had no clinically relevant effects on the pharmacodynamics of tenapanor in healthy volunteers. This suggests that the interaction between tenapanor and sevelamer observed in vitro does not translate into altered pharmacodynamic effects in humans.

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Declaration of Conflicting Interests

S. Johansson is an employee of and has ownership interest in AstraZeneca. M. Leonsson-Zachrisson and M. Knutsson are employees of AstraZeneca. D. P. Rosenbaum, J. Kohler, and K. Kozuka are employees of and have ownership interest in Ardelyx Inc. A. G. Spencer, E. D. Labonté, D. Deshpande, and D. Charmot were

employees of Ardelyx Inc. at the time the studies were conducted. A. G. Spencer, E. D. Labonté, and D. Charmot maintain ownership interest in Ardelyx Inc.

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