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Effect of Using Concomitant Drugs on the Efficacy of Sodium Polystyrene Sulfonate

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Sodium polystyrene sulfonate (SPS) is well used for hyperkalemia. A recent study has shown that SPS may bind to other drugs in the digestive tract. However, there are few reports about the effect of concomitant drug use on serum potassium level variations. Therefore, this study aimed to investigate the effect of concomitant drug use on the variation of serum potassium levels among patients taking SPS. In total, 632 patients were newly prescribed with SPS from 2017 to 2019, and 186 patients were evaluated in this study. Further, the association between increase in serum potassium levels and concomitant drug use was investigated. We classified patients into the Grade 1 (G1) group and the Grade 2–4 (G2–4) group according to baseline serum potassium level by Common Terminology Criteria for Adverse Events (CTCAE) v5.0. There was the significant decrease in serum potassium and chloride levels and the increase in serum sodium levels after SPS treatment. In addition, therapy with SPS might improve renal function. The concomitant use of imidapril in the G1 group (odds ratio: 4.4, 95% confidence interval: 1.1–11.7, $p = 0.0394$) and nifedipine in the G2–4 group (odds ratio: 7.3, 95% confidence interval: 1.5–35.5, $p = 0.0139$) were significantly associated with the increase in serum potassium levels after SPS treatment. These associations might be affected by not only adverse drug reactions but also binding of other drugs to SPS. Hence, concomitant drug use may affect the efficacy of SPS.

Key words sodium polystyrene sulfonate, concomitant drugs, potassium, imidapril, nifedipine

INTRODUCTION

Hyperkalemia is one of the most serious complications among patients with chronic kidney disease (CKD) and it is defined as a serum potassium level of ≥ 5.5 mmol/L.[1,2] Many patients, who have CKD and its complications are treated with different medications. To manage the blood pressure, numerous CKD patients receive treatment with renin-angiotensin-aldosterone system inhibitor (RAAS-I) such as angiotensin-converting enzyme inhibitor (ACE-I) and angiotensin II receptor blocker (ARB). RAAS-Is induce hyperkalemia because they inhibit the aldosterone synthesis and block the ion exchange process of sodium and potassium in the collecting duct.[3] Taken together, the serum potassium levels may be increased by not only the complication of CKD, but also the administration of medicines for CKD. Hyperkalemia causes conditions including arrhythmia and peripheral neuropathy. Moreover, the overall mortality rate of patients with CKD may be increased due to high serum potassium levels (≥ 5.5 mmol/L).[4] Therefore, correction of the serum potassium levels is important in improving the prognosis of CKD patients.

Dialysis, the injection of calcium gluconate and glucose-insulin therapy are used for the treatment to acute and severe hyperkalemia. By contrast, polystyrene sulfonate cationic exchange resin is commonly used for chronic hyperkalemia. Sodium polystyrene sulfonate (SPS) has been used as one of the medicines for hyperkalemia from long ago.[5] SPS decreases serum potassium levels via the ion exchange reaction between sodium and potassium in the digestive tract (specifically in the colon).[6]

The Food and Drug Administration (FDA) reported that SPS may bind to other oral medications, such as amlodipine, metoprolol, amoxicillin, furosemide, warfarin, and phenytoin, in the digestive tract. Further, they announced safety information that recommends treatment with SPS and other oral drugs with an interval of at least 3 h.[7] This information is written in the package inserts of SPS in the US and the EU. However, in Japan, it is not written. Furthermore, there is no report about the influence of concomitant drugs on the SPS efficiency. Elucidating the effect of concomitant drugs on the efficacy of SPS can be an important factor in making prescription proposals for patients with CKD. We focused on the concomitant drugs with SPS and investigated the association between the variation of serum potassium levels after SPS treatment and the use of concomitant drugs in the current study.

MATERIALS AND METHODS

Patients Patients, who were newly prescribed with SPS preparation (Kayexalate® dry syrup) from 2017 to 2019 at Kindai University Hospital, were included in this study. The exclusion criteria were as follows: patients who were prescribed with SPS preparation for < 28 d, those on dialysis treatment, those without laboratory examination data before and after SPS treatment, those not taking concomitant drugs, and those with serum potassium levels of ≤ 4.8 mmol/L. Participants were

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classified into the Grade 1 (G1) group (serum potassium level of 4.9–5.5 mmol/L) and the Grade 2–4 (G2–4) group (serum potassium level of > 5.5 mmol/L) based on the serum potassium levels before receiving SPS treatment. The Grade classification was referred to the standard for hyperkalemia in the Common Terminology Criteria for Adverse Events v5.0.[8]

Evaluation Items We obtained data about the laboratory examination results before and 30 ± 10 d after SPS treatment, and the concomitant drugs at the start of SPS treatment from the medical records. The laboratory examination data were as follows: potassium (K), sodium (Na), chloride (Cl), calcium (Ca), blood urea nitrogen (BUN), estimated glomerular filtration (eGFR), uric acid (UA), aspartate aminotransferase (AST), alanine aminotransferase (ALT), systolic blood pressure (SBP), and diastolic blood pressure (DBP). The serum calcium levels were corrected using the Payne's formula based on Eq. (1).[9]

$$Ca_{corr.} = Ca_{serum} + (4.0 - Alb) \quad (1)$$

where $Ca_{corr.}$ and Ca_{serum} represent corrected and serum calcium levels (mg/dL), respectively, and Alb indicate serum albumin level (mg/dL). The eGFR was calculated using Eq. (2).[10]

$$eGFR = 194 \times Crea^{-1.094} \times Age^{-0.287} \text{ (female: } \times 0.739) \quad (2)$$

where eGFR and Crea represents the estimated glomerular filtration (mL/min/1.73 m^2) and the serum creatinine level (mg/dL), respectively. The use of concomitant drugs was defined as the regular intake of oral medications.

Statistical Analysis Student's *t*-test and Fisher's exact test were used to evaluate differences in background characteristics, variations of laboratory examination data before and after SPS treatment, and the rate of using concomitant drugs between the groups. Comparisons of the laboratory examination data before and after SPS treatment in each group were analyzed using the paired *t*-test. The association between increase in serum potassium levels after SPS treatment and concomitant drug use was evaluated via nominal logistic regression analysis. A p value of < 0.05 was considered statistically significant. All statistical analyses were performed using JMP® Pro version 15.0.0 (SAS Institute Inc., Cary, NC, USA).

Ethical Consideration The study was carried out in accordance with the Ethical Guidelines for Medical and Biological Research Involving Human Subject in Japan and the Declaration of Helsinki and its later amendments, or comparable ethical standards. Its protocol was approved by the ethics committees of Kindai University faculty of medicine and faculty of pharmacy (approval ID: R02-211 and 21-180, respectively). An opt-out consent, rather than a written or oral informed consent, was obtained.

RESULTS

Background Characteristics of Patients Figure 1 shows the flowchart of the participant selection process. In total, 632 patients were newly prescribed with SPS from 2017 to 2019. However, only 186 patients were finally included in the analysis. We excluded patients who were prescribed with SPS for < 28 d (n = 254), those who received dialysis therapy (n = 90), those who had no laboratory examination data (n = 339), those who had no concomitant drug at the start of SPS treatment (n = 39), and those with a serum potassium level of ≤ 4.8 mmol/L, which was the normal upper limit in our facility, before taking SPS (n = 31). We classified participants into 69 of the Grade 1 (G1) group and 117 of the Grade 2–4 (G2–4) group according to baseline serum potassium levels based on the standards for hyperkalemia in the Common Terminology Criteria for Adverse Events (CTCAE) v5.0.[8] Table 1 shows the characteristics of patients. The mean ages of patients in each group were 70 and 71 years old, respectively and ratio of men in each group was 73% and 72%, respectively. There were significant differences in terms of SPS dosage (p = 0.0092), serum albumin level (p = 0.0282) and DBP level (p = 0.0393) between the two groups.

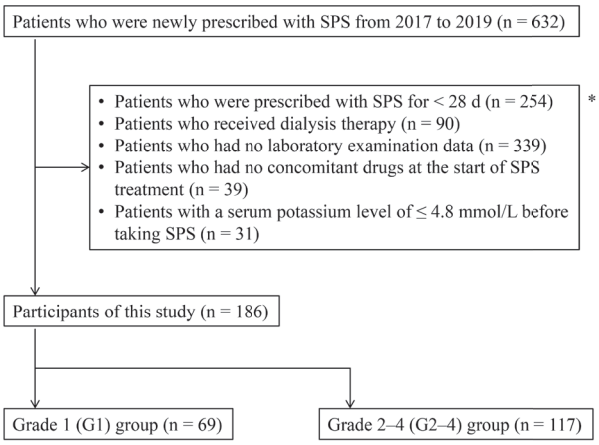

Fig. 1. Flowchart of the Participant Selection Process

* Numbers of patient among the categories overlapped.

Changes in Laboratory Examination Data Before and After SPS Treatment Table 2 shows the laboratory examination data before and after SPS treatment in each group. Results showed similar trends in both groups. There were significant decreases in serum potassium (the G1 group: $p < 0.0001$, the G2–4 group: $p < 0.0001$) and chloride levels (the G1 group: $p = 0.0444$, the G2–4 group: $p = 0.0165$), and the significant increase in serum sodium level (the G1 group: $p = 0.0005$, the G2–4 group: $p < 0.0001$) and the difference between sodium and chloride (Na − Cl, the G1 group: $p < 0.0001$, the G2–4 group: $p < 0.0001$), after SPS treatment. Furthermore, renal function might have improved according to the significant decrease in BUN levels (the G1 group: $p = 0.0208$, the G2–4 group: $p < 0.0001$) and the increase in eGFR level (the G1 group: $p = 0.0072$, the G2–4 group: $p = 0.0030$) after SPS treatment. The comparison of the capacity of variation for serum potassium, chloride and sodium levels, BUN and eGFR, which were recognized significant differences in Table 2, between the groups was shown in Fig. 2. There was the remarkable difference in the capacity of variation for serum potassium levels between the groups ($p < 0.0001$). On the other hand, in other laboratory examination data, there were no significant differences in the capacity of variations.

Concomitant Drugs of SPS Table 3 shows the usage rate of concomitant drugs used with SPS in each group. Almost patients took SPS after a meal. The concomitant drugs were also taken after breakfast and/or dinner. Therefore, in this study, it is considered that SPS and its concomitant drugs were taken together. Febuxostat was the most concomitantly used with SPS in each group (the G1 group: 33%, the G2–4 group: 32%). Amlodipine besylate and furosemide were included as drugs,

Table 1. Background Characteristics of Patients

	G1 group (n = 69)	G2–4 group (n = 117)	*p* value
Age (y.o.)	70 ± 16	71 ± 12	0.7871[a]
Sex (Male / Female)	50 / 19	84 / 33	1.0000[b]
Dosage of SPS (g/day)	5.4 ± 4.0	6.9 ± 3.7	0.0092[a]**
Laboratory examination data			
K (mmol/L)	5.2 ± 0.2	6.1 ± 0.5	< 0.0001[a]***
Na (mmol/L)	139.0 ± 3.3	138.3 ± 5.3	0.2929[a]
Cl (mmol/L)	105.8 ± 4.3	105.8 ± 5.3	0.9555[a]
$Ca_{corr.}$ (mg/dL)	9.6 ± 0.6	9.5 ± 0.8	0.3761[a]
Alb (mg/dL)	3.3 ± 0.9	3.6 ± 0.6	0.0282[a]*
P (mg/dL)	4.1 ± 1.0	4.4 ± 1.1	0.1860[a]
BUN (mg/dL)	44.6 ± 22.4	48.4 ± 28.0	0.3423[a]
Crea (mg/dL)	2.8 ± 2.1	2.8 ± 2.3	0.9328[a]
eGFR (mL/min/1.73m^2)	30.6 ± 22.5	30.6 ± 22.1	0.9907[a]
UA (mg/dL)	6.4 ± 1.6	6.4 ± 1.8	0.9382[a]
AST (IU/L)	41.9 ± 127.4	24.1 ± 39.1	0.1679[a]
ALT (IU/L)	29.3 ± 75.3	21.6 ± 22.3	0.3122[a]
SBP (mmHg)	128.5 ± 22.4	125.6 ± 25.0	0.5260[a]
DBP (mmHg)	70.4 ± 13.8	65.0 ± 13.6	0.0393[a]*

Mean ± Standard deviation., SPS: sodium polystyrene sulfonate, K: potassium, Na: sodium, Cl: chloride, $Ca_{corr.}$: corrected calcium, Alb: albumin, P: phosphate, BUN: brood urea nitrogen, Crea: creatinine, eGFR: estimated glomerular filtration rate, UA: uric acid, AST: aspartate aminotransferase, ALT: alanine aminotransferase, SBP: systolic blood pressure, DBP: diastolic blood pressure, *p < 0.05, **p < 0.01, ***p < 0.001, p: statistical significance obtained using [a]Student's t-test, [b]Fisher's exact test.

that may interact with SPS, in the report obtained from the FDA.[7] There was a significantly difference in the rate of concomitant use of furosemide between the two groups (p = 0.0403).

The Association Between the Increase in Serum Potassium Levels After SPS Treatment and Concomitant Drug Use In total, 16 patients (23%) in the G1 group and 7 patients (6%) in the G2–4 group, increased in their serum potassium levels despite receiving SPS treatment. Table 4 shows the association between the increase in serum potassium levels after SPS treatment and the use of concomitant drugs via the logistic regression analysis. Among the patients whose serum potassium levels were increased after SPS treatment, magnesium oxide, atorvastatin calcium and bisoprolol fumarate in the G1 group, and amlodipine besylate and sodium hydrogen carbonate in the G2–4 group, were not used. There was the significant association between the increase in serum potassium levels after SPS treatment and the concomitant use of imidapril in the G1 group (OR: 4.4, 95% CI: 1.1–17.7, p = 0.0394) and nifedipine in the G2–4 group (OR: 7.3, 95% CI: 1.5–35.5, p = 0.0139).

DISCUSSION

The previous study shows that patients, who have the serum potassium levels > 5.5 mEq/L, may increase in the overall mortality rate.[4] In this study, we classified patients into the G1 group (serum potassium level of 4.9–5.5 mmol/L) and the G2–4 group (serum potassium level of > 5.5 mmol/L) based on the severity of hyperkalemia. Moreover, we excluded patients who received dialysis therapy because we could not evaluate the variation of serum potassium levels after receiving dialysis therapy. From the results, there were significantly decrease in serum potassium and chloride levels and the significantly increase in serum sodium levels after SPS treatment. Moreover, the results showed that the renal function may be improved by receiving the SPS treatment. Furthermore, 14 drugs were picked up as the commonly concomitant drugs with SPS. The concomitant use of imidapril in the G1 group and nifedipine in the G2–4 group, were significantly associated with the increase in serum potassium levels after SPS treatment. To the best of our knowledge, this is the first study that evaluated the effect of the use of concomitant drugs on the efficacy of SPS.

SPS is one of the medications commonly used for hyperkalemia from the oldest time.[5] In Japan, the standard dosage of SPS is 30 g per day. However, a total of 165 patients (89%) received the SPS treatment at a low dose of ≤ 10 g per day. A previous study showed that the low dose treatment with SPS or calcium polystyrene sulfonate is effective and safe for controlling mild and chronic hyperkalemia over a long time.[11,12] Our study revealed that the long-term treatment with SPS improved the serum potassium levels significantly for at least 30 ± 10 days. SPS decreases the serum potassium levels via exchanging of the sodium ion for the potassium ions in the digestive tract. In this study, the serum potassium levels were significantly decreased (the G1 group: p < 0.0001, the G2–4 group: p < 0.0001) and the serum sodium levels were significantly increased (the G1 group: p = 0.0005, the G2–4 group:

Table 2. Comparisons of the Laboratory Examination Data Before and After SPS Treatment

	G1 group (n = 69)				G2–4 group (n = 117)			
	n (%)	Before	After	*p* value	n (%)	Before	After	*p* value
K (mmol/L)	69 (100)	5.2 ± 0.2	4.6 ± 0.7	< 0.0001***	117 (100)	6.1 ± 0.5	4.8 ± 0.8	< 0.0001***
Na (mmol/L)	69 (100)	139.0 ± 3.3	140.6 ± 3.3	0.0005***	116 (99)	138.3 ± 5.3	140.5 ± 3.5	< 0.0001***
Cl (mmol/L)	69 (100)	105.8 ± 4.3	104.7 ± 4.3	0.0444*	116 (99)	105.8 ± 5.3	104.8 ± 4.2	0.0165*
Na − Cl	69 (100)	33.2 ± 3.0	35.9 ± 3.8	< 0.0001***	116 (99)	32.5 ± 3.4	35.7 ± 3.7	< 0.0001***
$Ca_{corr.}$ (mg/dL)	52 (75)	9.6 ± 0.6	9.5 ± 0.7	0.0877	92 (79)	9.5 ± 0.8	9.5 ± 0.7	0.4683
P (mg/dL)	36 (52)	4.1 ± 1.0	4.0 ± 1.3	0.7548	61 (52)	4.4 ± 1.1	4.2 ± 1.5	0.1127
BUN (mg/dL)	68 (99)	44.6 ± 22.4	40.4 ± 21.8	0.0208*	116 (99)	48.4 ± 28.0	38.7 ± 20.6	< 0.0001***
eGFR (mL/min/1.73 m^2)	68 (99)	30.6 ± 22.5	34.7 ± 27.2	0.0072**	116 (99)	30.6 ± 22.1	33.8 ± 23.2	0.0030**
UA (mg/dL)	59 (86)	6.4 ± 1.6	6.4 ± 1.9	0.6893	95 (81)	6.4 ± 1.8	6.5 ± 1.7	0.6251
AST (IU/L)	67 (97)	41.9 ± 127.4	23.9 ± 14.2	0.2274	114 (97)	24.1 ± 39.1	21.4 ± 12.7	0.4616
ALT (IU/L)	66 (96)	29.3 ± 75.3	21.4 ± 18.7	0.3049	113 (97)	21.6 ± 22.3	20.0 ± 22.5	0.5538
SBP (mmHg)	46 (67)	128.5 ± 22.4	130.4 ± 19.3	0.6232	70 (60)	125.6 ± 25.0	129.5 ± 24.0	0.2251
DBP (mmHg)	46 (67)	70.4 ± 13.8	68.3 ± 12.1	0.4335	70 (60)	65.0 ± 13.6	67.0 ± 15.4	0.2025

Mean ± Standard deviation., K: potassium, Na: sodium, Cl: chloride, $Ca_{corr.}$: corrected calcium, P: phosphate, BUN: brood urea nitrogen, eGFR: estimated glomerular filtration rate, UA: uric acid, AST: aspartate aminotransferase, ALT: alanine aminotransferase, SBP: systolic blood pressure, DBP: diastolic blood pressure. *p < 0.05, **p < 0.01, ***p < 0.001, p: statistical significance obtained by paired-t test.

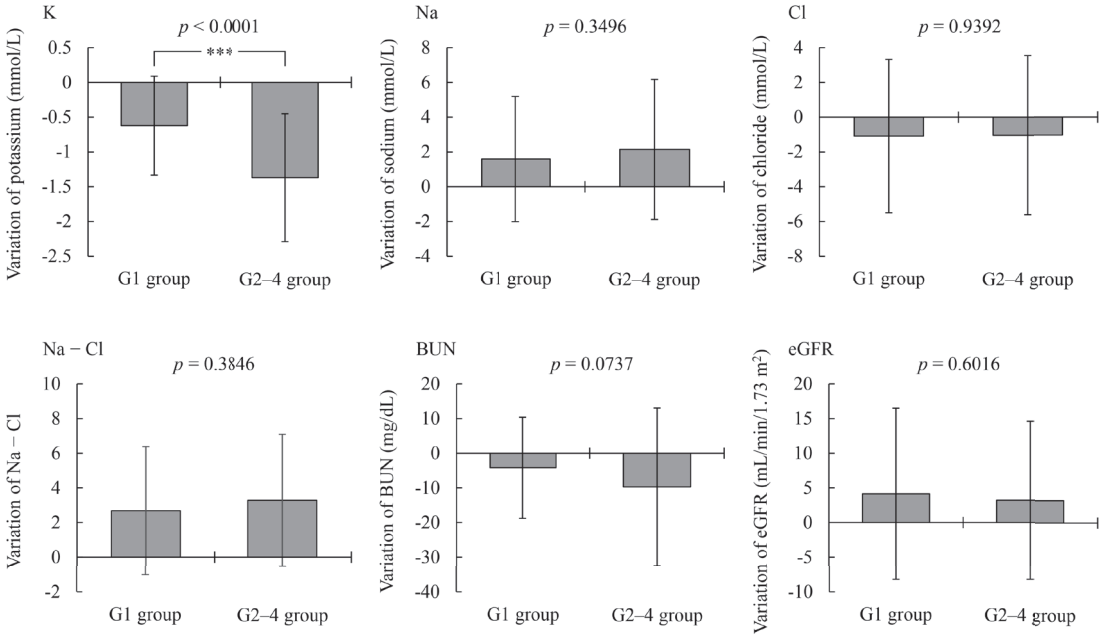

Fig. 2. Differences in the Capacity of Variation of Laboratory Examination Data Before and After SPS Treatment

Mean ± Standard deviation. K: potassium, Na: sodium, Cl: chloride, Na − Cl: the difference between sodium and chloride, BUN: blood urea nitrogen, eGFR: estimated glomerular filtration rate, ***: $p < 0.001$, p refers to statistical significance obtained using the Student's t-test.

Table 3. Concomitant Drugs of SPS

	G1 group (n = 69)	G2–4 group (n = 117)	p value
Febuxostat	23 (33)	38 (32)	1.0000
Azosemide	14 (20)	25 (21)	1.0000
Amlodipine besylate	15 (22)	23 (20)	0.8509
Lansoprazole	14 (20)	20 (17)	0.6949
Magnesium oxide	11 (16)	23 (20)	0.5625
Furosemide	17 (25)	14 (12)	0.0403*
Sodium hydrogen carbonate	11 (16)	20 (17)	1.0000
Nifedipine	9 (13)	21 (18)	0.4169
Carvedilol	12 (17)	16 (14)	0.5282
Aspirin	12 (17)	15 (13)	0.3975
Atorvastatin calcium	12 (17)	13 (11)	0.2676
Azilsartan	9 (13)	13 (11)	0.8147
Bisoprolol fumarate	5 (7)	17 (15)	0.1634
Imidapril	10 (14)	9 (8)	0.2088

n (%), *$p < 0.05$, p: statistical significance obtained using the Fisher's exact test.

$p < 0.0001$) after SPS treatment. The increase in the serum sodium levels may induce hypertension. Therefore, it is known that hypertension is one of the adverse effects of SPS. However, there was no significant change in SBP and DBP before and after SPS treatment. One of the reasons is considered that patients had been using antihypertensive drugs, such as ACE-I, ARB and calcium channel blocker, from before receiving SPS treatment.

The serum chloride levels were significantly decreased after SPS treatment in both groups (the G1 group: $p = 0.0444$, the G2–4 group: $p = 0.0165$). Hyperkalemia induces the metabolic acidosis due to decreasing in ammonia production in the proximal tubule and transport in the collecting duct.[13] This metabolic acidosis is categorized as hyperchloremic acidosis because of the normal anion gap.[14] Kumagai *et al.* reported the clinical usefulness of difference between sodium and chloride (Na − Cl) to evaluate the risk of acid–base valance disorders.[15] This parameter is based on 36, and low values indicate a tendency of metabolic acidosis. In this study, the value of difference between sodium and chloride was improved after SPS treatment in each group (the G1 group: $p < 0.0001$, the G2–4 group: $p < 0.0001$). Results suggest that the SPS treatment may improve the metabolic acidosis via the decrease in serum potassium levels.

CKD develops hyperkalemia due to the decrease in potassium excretion from the kidney. However, it is not clear what kind of influence the high serum potassium levels have on the renal function. In fact, a previous study showed no correlation between changes in the serum potassium levels and the serum creatinine levels in patients taking SPS.[16] Nevertheless, our results suggested that there may be the relationship between the decrease in serum potassium levels by SPS treatment and the improvement of renal function. It is necessary for us to consider the mechanism associated with better renal function.

In this study, almost drugs, used concomitantly with SPS, were therapeutic agents for CKD or its complications. Febuxostat was the drug which used the most concomitantly with SPS in this study. The American College of Rheumatology guideline recommends the urate-lowering therapy among patients with ≥ 3 stage CKD.[17] Sezai *et al*. reported that febuxostat was more effective than allopurinol in protecting renal function in CKD patients who underwent the cardiac surgery.[18] Therefore, febuxostat may be the most useful for the management of serum uric acid levels among CKD patients.

In CKD, diuretics are used to control blood pressure and improve edema. Particularly, loop diuretics and thiazide diuretics are primarily used to manage edema and to control blood pressure, respectively.[19] In loop diuretics, furosemide and azosemide are classified into short- and long-acting types, respectively. The diuretic effects of each drug are almost sim-

Table 4. The Association Between the Increase in Serum Potassium Levels After SPS Treatment and Concomitant Drug Use

Drugs	G1 group			G2–4 group		
	OR	95% CI	*p* value	OR	95% CI	*p* value
Febuxostat	0.6	0.2 – 2.1	0.4227	0.8	0.2 – 4.4	0.8202
Azosemide	0.5	0.1 – 2.5	0.3841	0.6	0.1 – 5.2	0.6407
Amlodipine besylate	0.2	0.0 – 1.5	0.1186	N/A		
Lansoprazole	0.5	0.1 – 2.5	0.3841	0.8	0.1 – 7.0	0.8390
Magnesium oxide	N/A			0.7	0.1 – 5.8	0.7139
Furosemide	0.6	0.2 – 2.6	0.5350	1.2	0.1 – 11.2	0.8456
Sodium hydrogen carbonate	2.2	0.5 – 8.7	0.2665	N/A		
Nifedipine	3.2	0.7 – 13.8	0.1182	7.3	1.5 – 35.5	0.0139*
Carvedilol	0.6	0.1 – 3.1	0.5588	2.7	0.5 – 15.5	0.2538
Aspirin	1.1	0.3 – 4.8	0.8701	1.1	0.1 – 10.2	0.9049
Atorvastatin calcium	N/A			3.6	0.6 – 20.8	0.1524
Azilsartan	1.8	0.4 – 8.2	0.4440	1.4	0.2 – 12.3	0.7836
Bisoprolol fumarate	N/A			2.5	0.5 – 14.3	0.2917
Imidapril	4.4	1.1 – 17.7	0.0394*	2.1	0.2 – 19.9	0.5088

N/A: not applicable, OR: odds ratio, CI: confidence interval, *$p < 0.05$, *p*: statistical significance obtained via nominal logistic regression analysis.

ilar. However, azosemide is less likely to cause electrolyte imbalance and increase uric acid levels.[20] Komada *et al*. also reported that there is no significant difference in terms of efficacy and safety between furosemide and azosemide among CKD patients.[20]

Hypertension is the risk factor of cardiovascular disease in patients with CKD.[21] Generally, RAAS-Is such as ACE-I and ARB are used primarily for hypertension among patients with CKD. In fact, the KDIGO guideline recommends treatment with RAAS-I among the hypertensive patients who developed CKD.[21] RAAS-Is do not only manage hypertension but also improve renal function, and overall mortality regardless of CKD stage and diabetes complications. However, in this study, we considered that the calcium channel blockers (CCBs) are more commonly prescribed than RAAS-Is due to high background levels of serum potassium in patients.

In our research, there was the significant association between the increase in the serum potassium levels after the SPS treatment and the concomitant use of imidapril in the G1 group and nifedipine in the G2–4 group. Imidapril is one of the ACE-Is. Hyperkalemia is one of the most common adverse effects of ACE-Is because ACE-Is inhibit the aldosterone secretion from the adrenal cortex. Chernin *et al*. showed that the concomitant use of SPS improved hyperkalemia induced by RAAS-Is in patients with CKD and heart disease.[22] However, our study had different results. In addition, almost all patients were prescribed imidapril from before receiving the SPS treatment. Hence, there may be some factors associated with the increase in serum potassium levels other than the adverse effect of imidapril. Nifedipine is one of the CCBs. There are numerous unclear points about the correlation between the serum potassium levels and CCBs. In general, CCBs such as diltiazem, nifedipine, verapamil, and nitrendipine do not affect the serum potassium level.[23] However, some reports showed the effect of CCBs in increasing and decreasing serum potassium levels.[24,25]

FDA showed that SPS might interact with other orally administered drugs such as amlodipine, metoprolol, amoxicillin, furosemide, warfarin, and phenytoin.[7] In our study, a total of 38 patients were treated with amlodipine besylate and a total of 31 patients were treated with furosemide. However, there were no significant association between the increase in serum potassium levels after the SPS treatment and the concomitant use of these drugs with SPS. Ohta *et al*. reported that polystyrene sulfonate drugs adsorbed several drugs such as nifedipine under the artificial intestinal juice condition.[26] Therefore, SPS may bind to other concomitant drugs in the digestive tract and may weaken the effects of not only SPS but also the concomitant drugs.

The current study had several limitations. In this study, it was retrospective research conducted at a single facility, and only a small number of patients were included. Moreover, many participants were outpatients. In inpatients, the drug treatment can be managed by the medical staffs. However, in outpatients, it is necessary for patients to manage drugs themselves. In CKD, medication adherence is one of the most significant factors associated with effective disease management.[27] However, patients with CKD take several drugs for different complications caused by CKD. To evaluate the efficacy of drugs adequately, medical staffs including pharmacists need to check the status of medication such as SPS and its concomitant drugs in detail.

In summary, we showed the feasibility of long-term therapy with low-dose SPS for hyperkalemia. In addition, 14 drugs were concomitantly used with SPS, and nifedipine and imidapril might be correlated with high serum potassium levels among patients receiving SPS. To elucidate the effect of the concomitant drug use on the variation of laboratory examination data after the SPS treatment, it is necessary to carry out the further research including more participants and facilities. Moreover, it is needed to investigate the binding behavior of SPS to the concomitant drugs in the digestive tract with the *in vitro* study.

Conflict of interest The authors declare no conflict of interest.

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