Journal of Clinical Pharmacology and Therapeutics

ISSN: 2766-8347

Research Article

Sodium Zirconium Cyclosilicate-Associated Adverse Events: An Analysis of the FAERS Database

*Lin Yimin and Hong Qingxia**

Department of pharmacy, The People's Hospital of Cangnan, Whenzhou, China

Abstract

Purpose: This study aims to investigate the Adverse Drug Event (ADE) signals associated with potassium ion adhesive sodium cyclozirconate using the United States Food and Drug Administration's Adverse Event Reporting System (FAERS), providing insights for its safe clinical application.

Methods: Adverse reactions related to Sodium Zirconium Cyclosilicate (SZC) were retrieved from the FAERS database, covering the period from May 2018 to September 2023. The analysis utilized several statistical methods, including the Reporting Odds Ratio (ROR), proportional Reporting Odds Ratio (PPR), Bayesian Confidence Propagation Neural Network (BCPNN), and the Multiple Gamma Poisson Distribution Reduction (MGPS) method under the proportional imbalance approach.

Results: A total of 35 positive ADE signals were identified from 1,069 ADE reports where SZC was the primary suspect. These signals encompassed 10 different System Organ Classifications (SOCs).

Conclusion: This study successfully identified and analyzed ADE signals from the FAERS database, contributing valuable insights for evaluating the rationality and safety of clinical medication practices involving SZC.

Keywords: Sodium zirconium cyclosilicate; Adverse drug events; Signal detection; Proportional imbalance method; Safe medication

Introduction

Hyperkalemia is an electrolyte imbalance frequently observed in patients with heart and kidney diseases. Elevated serum potassium levels can significantly affect the excitability of skeletal and cardiac muscles, potentially leading to life-threatening arrhythmias and sudden cardiac death [1,2]. Patients taking Renin-Angiotensin-Aldosterone System (RAAS) inhibitors, such as spironolactone, often experience elevated serum potassium due to disrupted potassium metabolism and excretion caused by the medication [3,4]. Retrospective clinical studies indicate that discontinuing RAAS inhibitors is associated with increased mortality and cardiovascular events in patients with hyperkalemia and chronic kidney disease (CKD) [5]. Among Maintenance Hemodialysis (MHD) patients with acute hyperkalemia, Sodium Zirconium Cyclosilicate (SZC) demonstrated comparable potassium-lowering efficacy to intravenous insulin and glucose at 2 hours, while offering superior convenience and fewer side effects [6]. Recent studies have revealed that SZC, a novel oral potassium binder, has a faster onset of action and is better tolerated in the gastrointestinal tract compared to traditional potassium-lowering resins, positioning it as a preferred treatment for both acute and chronic hyperkalemia [7,8]. SZC works by binding to potassium ions in the gastrointestinal tract, thereby reducing free potassium levels and enhancing fecal potassium excretion, which ultimately decreases serum potassium concentrations [9]. This study utilizes the United States Food and Drug Administration's Adverse Event Reporting System (FAERS) public database to identify and analyze Adverse Drug Event (ADE) signals associated with the potassium-ion binder SZC post-marketing, providing valuable insights for the rational use of this medication in clinical practice.

Citation: Yimin L, Qingxia H. Sodium Zirconium Cyclosilicate-Associated Adverse Events: An Analysis of the FAERS Database. J Clin Pharmacol Ther. 2024;5(3):1062.

Publisher Name: Medtext Publications LLC

Manuscript compiled: Nov 20th, 2024

***Corresponding author:** Hong Qingxia, Department of Pharmacy, The People's Hospital of Cangnan, Whenzhou, China

Information and Methodology

Data sources and filtering

Data for this study were sourced from the Medical Subject Headings (MeSH) module of the National Institutes of Health (NIH) platform in the United States. The keywords "sodium zirconium cyclosilicate," "ZS-9 compound," and "Lokelma" were utilized to retrieve relevant records. Using these terms as the primary suspects, ADE reports from May 2018 to September 2023 were extracted from the drug section of the United States FDA's Open Data Project (openFDA) platform. The extracted data were then processed and cleaned using R software (version 4.4.1) to compile a dataset of ADE reports in which sodium zirconium cyclosilicate was identified as the main suspect [10].

Methodology

The resulting ADE report codes were organized according to the Preferred Term (PT) and System Organ Class (SOC) classifications from the ICH International Dictionary for Regulatory Activities (MedDRA, version 26.0) [11]. The Disproportionality Analysis (DPA) method is currently the most widely used algorithm for ADE data mining, with calculations based on a four-grid table utilizing the ratio imbalance measurement method (Table 1). The proportional imbalance methods include the frequency-based approach, which encompasses the odds ratio (ROR) and the Proportional Reporting Ratio (PPR), as well as Bayesian Trusted Propagation Neural Network (BCPNN) and Multi-Gamma Poisson Distribution Reduction (MGPS) methods. The calculation methods and conditions for

generating positive signals are outlined in Table 2. A positive result from these analysis methods indicates a statistically significant association between the drug and the target ADE. A higher value corresponds to a stronger adverse reaction signal, suggesting a more robust statistical relationship between the target drug and the specific ADE [12].

Table 1: Proportional imbalance method measurement method four-grid table.

	Target ADE	Non-targeted ADE	Add up the total
Target drug	a	b	a+b
Other drugs	c	d	c+d
add up the total	a+c	b+d	a+b+c+d

Results

Overview of the basic situation reported by ADE

SZC was approved in the United States on May 18, 2018, under the trade name Lokelma. Between May 2018 and September 2023, a total of 1,069 ADE reports were retrieved from the FAERS database, identifying sodium zirconium cyclosilicate as the main suspected drug. The year 2023 accounted for the highest number of reports, with 328 cases (30.7%) (Figure 1). Since its approval in May 2018, the reporting trend has consistently increased over the years. Among the reported cases, male patients were more frequently represented, with 521 cases (48.7%) compared to 320 female patients (29.9%), while 228 reports (21.3%) did not specify the patient's sex. The age group of

Table 2: Formula for calculating the proportional imbalance method.

Method	Formula	The criterion for positive signals
ROR	$ROR = \frac{(a/c)}{b/d} = \frac{ad}{bc}$ $SE(LnROR) = \sqrt{\frac{1}{a}+\frac{1}{b}+\frac{1}{c}+\frac{1}{d}}$ $95\%\ CI = e^{Ln(ROR)\pm 1.96\sqrt{\frac{1}{a}+\frac{1}{b}+\frac{1}{c}+\frac{1}{d}}}$	95%*CI*下限＞1，a≥3
MHRA	$PRR = \frac{a/(a/b)}{c/(b+d)}$ $\chi^2 = \frac{(\lvert ab-bc\rvert - N/2)^2 \times N}{(a+b)(a+c)(c+d)(b+d)}$	*PRR*≥2，χ^2≥4，a≥3
MGPS	$RR = a/E_{ij} = \frac{a(a+b+c+d)}{(a+b)(a+c)}$ $EB05 = EBGM_{ij} \times \exp[-2/\sqrt{Nij+1}]$ $EB95 = EBGM_{ij} \times \exp[2/\sqrt{Nij+1}]$	*RR*>1，EB05≥2，a≥3
BCPNN	$IC = \log_2 \frac{a/(a+b+c+d)}{(a+b)(a+c)}$ $IC = E(IC_{ij}),\ SD = \sqrt{V(IC_{ij},)}$ $\gamma = \gamma_{ij} = \frac{(N+\alpha)(N+\beta)}{(C_i+\alpha_i)(C_j+\beta_j)} = 1$ $E(IC_{ij}) = \log_2 \frac{(c_{ij}+\gamma_{ij})(N+\alpha)(N+\beta)}{(N+\gamma)(c_i+\alpha)(c_i+\beta_j)} = 1$ $V(IC_{ij}) = (\frac{1}{\log_2})^2 \frac{N-c_{ij}+\gamma-\gamma_{ij}}{(cij+\gamma ij)(1+N+\gamma)} + \frac{N-c_i+\alpha-\alpha_{ij}}{(c_j+\alpha_{ij})(1+n+a)}$	$95\%IC下限 = IC-2\sqrt{V(IC)} > 0$，a≥3

65 to 85 years had the highest number of reports, totaling 226 cases (21.1%). The majority of reports originated from the United States (827 cases, 77.4%), followed by Japan (17.0%), the United Kingdom (1.5%), and China (1.4%) (Table 3).

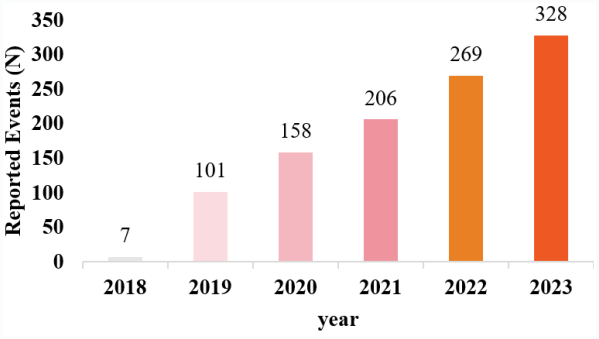

Figure 1: Number of ADE reports for SZC by year.

Table 3: Basic situation of sodium zirconate cyclosilicate ADE report (n=1069).

The project	Subclass	Counts	Percentages
Gender	Male	521	48.70%
	Female	320	29.90%
	Unspecified	228	21.30%
Age/years	18-64	100	9.40%
	65-85	226	21.10%
	>85	76	7.10%
	Unspecified	667	62.40%
Reported countries (the top ranked)	United States	827	77.40%
	Japan	182	17.00%
	United Kingdom	18	1.50%
	China	15	1.40%

ADE signal analysis results

In this study, a total of 413 ADE signals were identified from the 1,069 ADE reports where SZC was the primary suspected drug. Using four proportional imbalance formulas-ROR, PRR, BCPNN, and MGPS-41 positive signals were calculated (Figure 2). After screening and excluding signals related to product issues, poisoning, and operational complications, 35 positive ADE signals were ultimately identified. The top 20 ADE reports are summarized in Table 4 and Figure 3. Among these, the most frequently reported ADE signal was death, with a total of 376 cases. The strongest positive ROR signal was for abnormal serum potassium, which had a lower 95% confidence interval of 130.44.

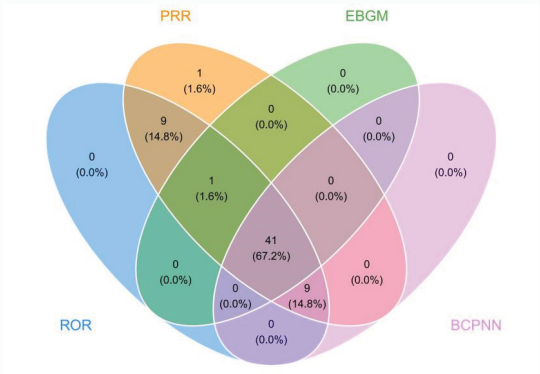

Figure 2: The Venn plot of the number of positive ADE reports for different methods.

SOC and associated ADE signals

In this study, a total of 10 SOC categories were identified in the classification of 35 ADE signals (Table 5). The SOC categories included: investigations, gastrointestinal disorders, metabolism and nutrition disorders, general disorders and administration site conditions, cardiac disorders, reproductive system and breast disorders, renal and urinary disorders, skin and subcutaneous tissue disorders, surgical and medical procedures, and infections. Notably, the following SOC categories were not mentioned in the drug instructions: cardiac disorders, renal and urinary disorders, infections, surgical and medical procedures, and reproductive system and breast disorders.

ADE signaling in the gastrointestinal system

Notably, excluding ADEs related to indications, the SOC with the highest number of reported ADEs associated with SZC was gastrointestinal disorders. Given that SZC is nearly non-absorbable, it reduces blood potassium concentrations by binding to potassium ions (K+) in the gastrointestinal tract. Consequently, the interaction of SZC with the gastrointestinal system may influence the drug's efficacy and the incidence of adverse drug events. A total of 88 ADEs were reported under the SOC of gastrointestinal disorders for SZC, which included conditions such as constipation, intestinal obstruction, gastrointestinal motility disorders, fecal hardness, and fecaloma. Among these, the ADE with the strongest ROR positive signal was ileus (Figure 4), with a total of 14 cases related to intestinal obstruction, including both ileus and intestinal obstruction, which ranked just below "constipation" in frequency.

Discussion

After statistical analysis, we observed a gradual increase in the number of ADE reports (1,069) from May 2018 to September 2023, likely due to the established stability and high safety profile of SZC, coupled with increased promotion and utilization of the drug in clinical practice. Additionally, this trend may be linked to improvements in the adverse reaction reporting system and heightened awareness among both medical and non-medical personnel regarding the monitoring of adverse drug reactions. Notably, the majority of ADE reports with known patient ages were for individuals aged 65 to 85 years, highlighting the age-related onset and progression of kidney disease, with hyperkalemia being more prevalent in older patients [13]. In ADE reports where patient gender is known, the number of reported male patients is nearly twice that of female patients. This finding appears to contradict the conclusions of epidemiological studies on chronic kidney disease both domestically and internationally. However, it is important to note that the majority of these patients are elderly individuals over 65 years of age. This discrepancy may be attributed to several factors, including the faster progression of chronic kidney disease in the male population and the higher incidence of chronic kidney disease observed in men compared to women in older age groups [13,14]. Among the 1,069 ADE reports, over 90% were submitted from the United States and Japan. In contrast, China, which introduced the drug in January 2020-earlier than Japan's approval in March 2020-reported only 13 cases, significantly fewer than Japan's 142 cases. This discrepancy suggests that the number of ADE reports is influenced not only by the timing of drug marketing in different countries but also by the speed and scope of drug promotion in various regions. Additionally, differences in reporting channels and the level of attention given to adverse reactions in different areas may play a crucial role.

Through the analysis of 413 ADEs with SZC as the primary

Table 4: The twenty highest SZC ADE signal strengths.

PT	No.of cases	ROR (95% CI)	PRR (χ2)	IC (IC025)	EBGM(EBGM05)
Death	376	16.98(15.17-19.01)	13.84(4539.84)	3.79(2.12)	13.83(12.58)
Constipation	55	8.69(6.64-11.36)	8.47(363.22)	3.08(1.41)	8.46(6.76)
Blood Potassium Increased	52	124.45(94.36-164.14)	121.1(6137.11)	6.91(5.24)	119.98(95.17)
Oedema	38	28.84(20.91-39.77)	28.28(998.68)	4.82(3.15)	28.23(21.57)
Hypokalaemia	30	22.68(15.81-32.55)	22.34(611.04)	4.48(2.81)	22.31(16.49)
Cardiac Failure	25	10.58(7.13-15.7)	10.46(213.87)	3.39(1.72)	10.45(7.51)
Weight Increased	23	3.62(2.4-5.46)	3.59(43.1)	1.84(0.18)	3.59(2.54)
Cardiac Failure Congestive	21	17.27(11.23-26.55)	17.09(317.87)	4.09(2.43)	17.07(11.91)
Hyperkalaemia	20	20.42(13.14-31.73)	20.21(364.85)	4.34(2.67)	20.18(13.96)
Blood Pressure Increased	17	3.57(2.22-5.76)	3.55(31.24)	1.83(0.16)	3.55(2.38)
Blood Potassium Abnormal	17	211.08(130.44-341.57)	209.21(3466.39)	7.69(6.02)	205.88(137.62)
Oedema Peripheral	16	6.5(3.97-10.63)	6.45(73.73)	2.69(1.02)	6.45(4.27)
Blood Potassium Decreased	13	15.61(9.05-26.95)	15.51(176.37)	3.95(2.29)	15.5(9.81)
Swelling	11	3.53(1.95-6.38)	3.51(19.78)	1.81(0.14)	3.51(2.14)
Metabolic Acidosis	10	10.1(5.42-18.8)	10.05(81.47)	3.33(1.66)	10.04(5.97)
Ileus	9	30.5(15.84-58.76)	30.37(255.03)	4.92(3.25)	30.3(17.5)
Renal Disorder	8	5.51(2.75-11.03)	5.49(29.38)	2.46(0.79)	5.49(3.07)
Hypervolaemia	7	16.08(7.65-33.78)	16.02(98.48)	4(2.33)	16(8.6)
Blood Creatinine Increased	7	3.88(1.85-8.15)	3.87(14.91)	1.95(0.28)	3.87(2.08)
Blood Sodium Increased	6	86.5(38.71-193.29)	86.23(502.09)	6.42(4.75)	85.66(43.71)

Table 5: Signal results of the main systems involved in SZC ADE reports.

System organ class	PT	No. of cases	ROR Lower limit of 95% CI	PRR (χ^2)	IC025	EBGM05
Investigations	Blood Potassium Increased	52	94.36	121.1(6137.11)	5.24	95.17
	Weight Increased	23	2.4	3.59(43.1)	0.18	2.54
	Blood Pressure Increased	17	2.22	3.55(31.24)	0.16	2.38
	Blood Potassium Abnormal	17	130.44	209.21(3466.39)	6.02	137.62
	Blood Potassium Decreased	13	9.05	15.51(176.37)	2.29	9.81
	Blood Creatinine Increased	7	1.85	3.87(14.91)	0.28	2.08
	Blood Sodium Increased	6	38.71	86.23(502.09)	4.75	43.71
	Glomerular Filtration Rate Decreased	4	3.8	10.13(32.88)	1.67	4.45
	X-Ray Gastrointestinal Tract Abnormal	3	1279.22	4818.03(10507.71)	9.91	1153.81
Gastrointestinal Disorders	Constipation	55	6.64	8.47(363.22)	1.41	6.76
	Ileus	9	15.84	30.37(255.03)	3.25	17.5
	Ascites	5	2.57	6.18(21.69)	0.96	2.96
	Intestinal Obstruction	5	1.9	4.55(13.86)	0.52	2.18
	Intestinal Perforation	5	6.96	16.7(73.71)	2.39	8
	Gastrointestinal Motility Disorder	3	5.99	18.58(49.82)	2.54	7.19
	Faeces Hard	3	8.06	25(68.98)	2.97	9.66
	Faecaloma	3	6.36	19.73(53.25)	2.63	7.63
Metabolism and Nutrition Disorders	Hypokalaemia	30	22.68	22.34(611.04)	2.81	16.49
	Hyperkalaemia	20	20.42	20.21(364.85)	2.67	13.96
	Metabolic Acidosis	10	10.1	10.05(81.47)	1.66	5.97
	Hypervolaemia	7	16.08	16.02(98.48)	2.33	8.6
	Feeding Disorder	4	5.68	5.67(15.37)	0.83	2.49
	Hypernatraemia	3	21.85	21.81(59.48)	2.78	8.44
General Disorders and Administration Site Conditions	Death	376	15.17	13.84(4539.84)	2.12	12.58
	Oedema	38	20.91	28.28(998.68)	3.15	21.57
	Oedema Peripheral	16	3.97	6.45(73.73)	1.02	4.27
	Swelling	11	1.95	3.51(19.78)	0.14	2.14
Cardiac Disorders	Cardiac Failure	25	7.13	10.46(213.87)	1.72	7.51
	Cardiac Failure Congestive	21	11.23	17.09(317.87)	2.43	11.91
	Ventricular Fibrillation	3	3.86	11.97(30.14)	1.91	4.63
Reproductive System and Breast Disorders	Scrotal Oedema	3	47.9	149.4(437.13)	5.53	56.94
Renal And Urinary Disorders	Renal Disorder	8	2.75	5.49(29.38)	0.79	3.07
Skin And Subcutaneous Tissue Disorders	Rash Pruritic	6	1.81	4.02(13.63)	0.34	2.06
Surgical And Medical Procedures	Dialysis	3	2.84	8.8(20.74)	1.47	3.41
Infections And Infestations	Pneumonia Aspiration	4	2.04	5.44(14.51)	0.78	2.39

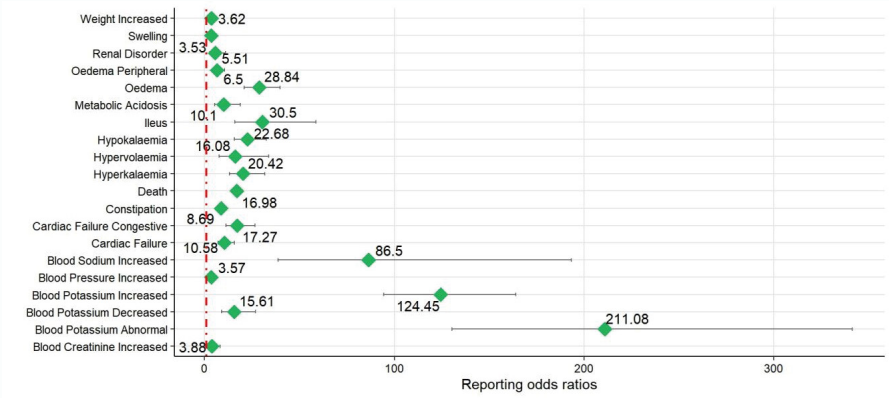

Figure 3: The twenty highest SZC ADE signal strengths in ROR.

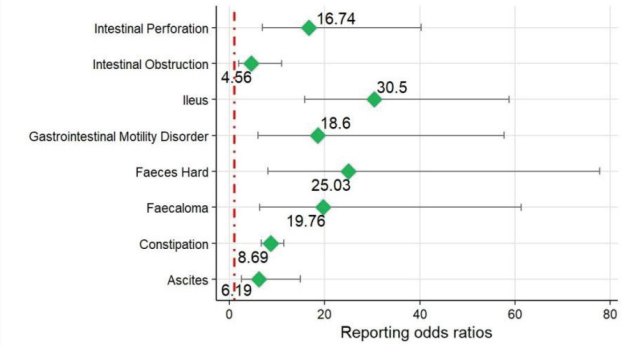

Figure 4: Gastrointestinal system-related ADE signal strengths for SZC in ROR.

suspect, 35 positive ADE signals were identified after screening out signals associated with unrelated SOCs, such as product issues, various injuries, poisoning, and operational complications. These signals were distributed across 10 SOC categories, including systemic diseases and various reactions at the administration site. The top 10 reported ADE signals included death, constipation, elevated serum potassium, edema, hypokalemia, heart failure, weight gain, congestive heart failure, hyperkalemia, and abnormal serum potassium. Notably, hyperkalemia is a known indication for SZC, which is reflected in the drug's labeling. Common ADEs associated with SZC include hypokalemia and edema, aligning with the findings of this study. Clinical studies indicate that excessively low blood potassium levels can often be resolved by adjusting the dose or discontinuing the drug. Edema-related events encompass fluid overload, fluid retention, and generalized edema, with more than half of patients requiring diuretic therapy or adjustments in diuretic dosing. Gastrointestinal adverse reactions, such as constipation and diarrhea, are generally mild; however, the labeling also warns of the risk of intestinal perforation. In the FAERS database, five cases of intestinal perforation were reported, highlighting the need for clinicians to be vigilant regarding signs and symptoms related to this serious complication in clinical practice.

Compared to the current drug insert for SZC (trade name: Lokelma, AstraZeneca Pharmaceuticals LP, Wilmington, April 2020), there are 24 ADE signals that are not included in the label. A review of existing clinical research articles [15-20] indicates that emerging ADE signals such as death, weight gain, heart failure, and elevated blood pressure may be associated with known ADEs listed in the label or with the patients' underlying conditions. In a phase 3 trial conducted by Bruce et al. [15] 76 of the 82 patients who reported hypertensive ADEs had a history of hypertension; among these patients, only one ADE was considered potentially related to sodium zirconium cyclosilicate. In this study, 10 cases of metabolic acidosis were reported as ADE signals. However, previous clinical trials [16,18,19,21,22] indicated that SZC could actually increase serum bicarbonate concentrations in patients with hyperkalemia. This mechanism has been further validated by Donald and Raul et al., who noted that, unlike other potassium binders, SZC binds ammonium ions in the intestine, preventing their reabsorption and urea regeneration, thus enhancing the excretion of ammonium ions in feces (H+ excretion). This action also promotes bicarbonate reabsorption and alleviates metabolic acidosis [17,23], suggesting that clinical attention should be directed toward the association of this adverse event with SZC. Additionally, due to the drug's adherence to the gastrointestinal lumen and its potential to impede radiation transmission, Farid et al. [24] reported a clinical case where a Computed Tomography (CT) scan was disrupted in a patient experiencing intestinal bleeding while taking sodium zirconium cyclosilicate. Therefore, the impact of this medication on imaging examinations should be considered during clinical use.

In this study, the most frequently reported ADEs outside of indications were related to gastrointestinal diseases. Consequently, we focused on the ADE signals within this SOC, which included constipation, ileus, ascites, intestinal obstruction, intestinal perforation, gastrointestinal motility disorders, hard stools, and fecalomas. We observed that conditions such as constipation, intestinal obstruction, and gastrointestinal motility disorders can affect the retention time of contents in the intestine. A recent phase III randomized study evaluating the efficacy and safety of SZC in Chinese patients with hyperkalemia found results broadly consistent with previous studies, except for an imbalance in the incidence of constipation-related adverse events [25]. In addition to impairing the patient's excretory function and potentially inducing intestinal obstruction, these phenomena may also increase the risk of infection [26]. Furthermore, since SZC primarily acts in the intestine, prolonged residence time may result in reduced efficacy. However, there is a lack of controlled studies examining the effects of SZC in patients with constipation. Therefore, the clinical use of this drug should be avoided in patients with severe constipation, intestinal obstruction, or fecal impaction, including those with abnormal postoperative peristalsis disorders. For patients with poor intestinal motility, it is crucial to closely monitor bowel movements, as this may help prevent the occurrence of hypokalemia-related adverse drug reactions.

The limitations of this study are: (1) The data were exclusively obtained from the FAERS public database in the United States, without incorporating other ADE reporting systems. As FAERS operates as a spontaneous reporting system, the reports are submitted by both medical professionals (e.g., doctors and pharmacists) and non-medical individuals, which may limit the comprehensiveness and reliability of the content. (2) The reported information includes only basic details such as medication timing, indications, gender, age, and country. There is a lack of data regarding patients' clinical diagnoses and concomitant medications, which restricts the ability to establish causal relationships between the reported ADEs and the drug. (3) The proportional imbalance method is designed to illustrate the statistical relationship between drugs and ADEs. While it provides valuable insights for safe drug use, it does not establish a biological causal relationship between the two, indicating a need for further comprehensive research and evaluation. Consequently, the analytical methods employed in this study have inherent limitations.

In summary, while SZC is minimally absorbed by the body [27], contributing to its favorable safety profile, the potential occurrence of adverse reactions should not be underestimated. Continuous monitoring of serum potassium levels during treatment is essential to prevent adverse effects related to hypokalemia. Additionally, attention must be paid to patients' fluid retention to mitigate the risk of exacerbating cardiac burdens. Although SZC exerts significantly less impact on the gastrointestinal tract compared to traditional potassium-lowering resins, there are still reported adverse events, predominantly mild symptoms such as constipation and diarrhea. However, cases of intestinal obstruction have also been documented, warranting greater caution when administering SZC to patients with gastrointestinal dysfunction. This study has its limitations, but the findings regarding adverse drug reactions associated with SZC offer valuable insights for ensuring clinical safety and promoting rational drug use.

Funding

This work was supported by Wenzhou Basic Research Project [Granted No.2024Y2795].

References

1. Montford JR, Linas S. How Dangerous Is Hyperkalemia? J Am Soc Nephrol. 2017;28(11):3155-65.
2. Valdivielso JM, Balafa O, Ekart R, Ferro CJ, Mallamaci F, Mark PB, et al. Hyperkalemia in chronic kidney disease in the new era of kidney protection therapies. Drugs. 2021;81(13):1467-89.
3. De Nicola L, Ferraro PM, Montagnani A, Pontremoli R, Dentali F, Sesti G. Recommendations for the management of hyperkalemia in patients receiving renin-angiotensin-aldosterone system inhibitors. Intern Emerg Med. 2024;19(2):295-306.
4. Hundemer GL, Sood MM. Hyperkalemia with RAAS inhibition: Mechanism, clinical significance, and management. Pharmacol Res. 2021;172:105835.
5. Leon SJ, Whitlock R, Rigatto C, Komenda P, Bohm C, Sucha E, et al. Hyperkalemia-Related Discontinuation of Renin-Angiotensin-Aldosterone System Inhibitors and Clinical Outcomes in CKD: A Population-Based Cohort Study. Am J Kidney Dis. 2022;80(2):164-73.e1.
6. Yao L, Xing X, Li Y, Zhang F, Li P, Liang X, et al. Effects of different potassium-lowering regimens on acute hyperkalemia in hemodialysis patients: a real-world, retrospective study. J Transl Med. 2022;20(1):333.
7. Rastogi A, Hanna RM, Mkrttchyan A, Khalid M, Yaqoob S, Shaffer K, et al. Sodium zirconium cyclosilicate for the management of chronic hyperkalemia in kidney disease, a novel agent. Expert Rev Clin Pharmacol. 2021;14(9):1055-64.
8. Yap DYH, Ma RCW, Wong ECK, Tsui MSH, Yu EYT, Yu V, et al. Consensus statement on the management of hyperkalaemia-An Asia-Pacific perspective. Nephrology (Carlton). 2024;29(6):311-24.
9. Hoy SM. Sodium Zirconium Cyclosilicate: A Review in Hyperkalaemia. Drugs. 2018;78(15):1605-13.
10. He Y, Guan X, Zhang Y, Zhu Z, Zhang Y, Feng Y, et al. Analysis of Inclisiran in the US FDA Adverse Event Reporting System (FAERS): a focus on overall patient population and sex-specific subgroups. Expert Opin Drug Saf. 2024:1-9.
11. Brown EG. Using MedDRA: implications for risk management. Drug Saf. 2004;27(8):591-602.
12. Almenoff JS, Pattishall EN, Gibbs TG, DuMouchel W, Evans SJ, Yuen N. Novel statistical tools for monitoring the safety of marketed drugs. Clin Pharmacol Ther. 2007;82(2):157-66.
13. Zhuang Z, Tong M, Clarke R, Wang B, Huang T, Li L. Probability of chronic kidney disease and associated risk factors in Chinese adults: a cross-sectional study of 9 million Chinese adults in the Meinian Onehealth screening survey. Clin Kidney J. 2022;15(12):2228-36.
14. Wyld MLR, Mata NL, Viecelli A, Swaminathan R, O'Sullivan KM, O'Lone E, et al. Sex-Based Differences in Risk Factors and Complications of Chronic Kidney Disease. Semin Nephrol. 2022;42(2):153-69.
15. Spinowitz BS, Fishbane S, Pergola PE, Roger SD, Lerma EV, Butler J, et al. Sodium Zirconium Cyclosilicate among Individuals with Hyperkalemia: A 12-Month Phase 3 Study. Clin J Am Soc Nephrol. 2019;14(6):798-809.
16. Packham DK, Rasmussen HS, Lavin PT, El-Shahawy MA, Roger SD, Block G, et al. Sodium zirconium cyclosilicate in hyperkalemia. N Engl J Med. 2015;372(3):222-31.
17. Fernandez-Prado R, Villalvazo P, Avello A, Gonzalez-de-Rivera M, Aguirre M, Carrasco-Munoz CG, et al. Sodium zirconium cyclosilicate and metabolic acidosis: Potential mechanisms and clinical consequences. Biomed Pharmacother. 2023;158:114197.
18. Kosiborod M, Rasmussen HS, Lavin P, Qunibi WY, Spinowitz B, Packham D, et al. Effect of sodium zirconium cyclosilicate on potassium lowering for 28 days among outpatients with hyperkalemia: the HARMONIZE randomized clinical trial. JAMA. 2014;312(21):2223-33.
19. Fishbane S, Ford M, Fukagawa M, McCafferty K, Rastogi A, Spinowitz B, et al. A Phase 3b, Randomized, Double-Blind, Placebo-Controlled Study of Sodium Zirconium et al. Cyclosilicate for Reducing the Incidence of Predialysis Hyperkalemia. J Am Soc Nephrol. 2019;30(9):1723-33.
20. Ni Z, Lu R, Xu X, Bian X, Zhou Z, Yang J, et al. DIALIZE China: A Phase IIIb, Randomized, Placebo-Controlled Study to Reduce Predialysis Hyperkalemia With Sodium Zirconium Cyclosilicate in Chinese Patients. Clin Ther. 2023;45(7):633-42.
21. Roger SD, Spinowitz BS, Lerma EV, Fishbane S, Ash SR, Martins JG, et al. Sodium zirconium cyclosilicate increases serum bicarbonate concentrations among patients with hyperkalaemia: exploratory analyses from three randomized, multi-dose, placebo-controlled trials. Nephrol Dial Transplant. 2021;36(5):871-83.
22. Ash SR, Batlle D, Kendrick J, Oluwatosin Y, Kooienga L, Eudicone JM, et al. Sodium Zirconium Cyclosilicate in CKD, Hyperkalemia, and Metabolic Acidosis: NEUTRALIZE Randomized Study. Kidney 360. 2024;5(6):812-20.
23. Wesson DE. Sodium zirconium cyclosilicate for hyperkalemia: a collateral acid-base benefit? Nephrol Dial Transplant. 2021;36(5):756-60.
24. Arman F, Kadosh D, Canetta P. Sodium zirconium cyclosilicate mimicking enteric radiocontrast. Kidney Int. 2024;105(2):394.
25. Liang X, Lu W, Yu X, Cheng H, He Q, Peng Q, et al. HARMONIZE Asia: A Phase III Randomized Study to Investigate the Efficacy and Safety of Sodium Zirconium Cyclosilicate in Patients with Hyperkalemia in China. Clin Ther. 2024;46(9):702-10.
26. Zingone F, Iovino P, Santonicola A, Gallotta S, Ciacci C. High risk of lower urinary tract symptoms in patients with irritable bowel syndrome. Tech Coloproctol. 2017;21(6):433-8.
27. Packham DK, Kosiborod M. Pharmacodynamics and pharmacokinetics of sodium zirconium cyclosilicate [ZS-9] in the treatment of hyperkalemia. Expert Opin Drug Metab Toxicol. 2016;12(5):567-73.