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Synthetic Hydrated Aluminum Silicates as Oral Adsorbents of Potassium Ion

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The adsorption of potassium ion by synthetic hydrated aluminum silicates (zeolites) was studied to examine the feasibility of application of zeolites as oral adsorbents for the treatment of hyper-kalemia. *In vitro* and *in vivo* adsorption studies indicated that one of the zeolites studied (ZPC-10A) had superior physical characteristics as a potassium ion adsorbent, as compared with conventional adsorbents (polystyrene sulfonates). An acute toxicity study also suggested that ZPC-10A is applicable as an oral adsorbent.

Keywords——zeolite; hydrated aluminum silicate; potassium ion adsorption; hyper-kalemia; oral adsorbent

In the previous paper,[1] we reported the application of synthetic hydrated aluminum silicates (zeolites) as oral adsorbents of ammonium ions for the treatment of uremia and ammoniemia. The zeolites studied were found to have uniform structures with pores of constant size adequate to adsorb ammonium ions. The zeolites showed high selectivity for ammonium ion in comparison with other ions such as sodium, calcium and magnesium ions, though potassium ions, the size of which in the hydrated form is close to that of hydrated NH_4^+, were adsorbed by the zeolites as well as ammonium ions. These results suggest the possibility of using the zeolites to reduce plasma potassium level in patients with renal failure.

For the treatment of hyper-kalemia, polystyrene sulfonate resins[2] have been used as oral adsorbents of potassium ions. Polystyrene sulfonates, however, adsorb cations nonselectively through an ion-exchange mechanism, and the extent of adsorption increases with increase in the charge and weight of cations.[3] It is known that the nonselectivity of ion adsorption often causes adverse effects. In particular, sodium polystyrene sulfonate has been reported to adsorb calcium ions preferentially in the gastrointestinal tract and to cause hypocalcemia.[4] Furthermore, these resins are known to cause side effects such as loss of appetite, nausea and vomiting.[4–6] The present investigation was designed to study the *in vitro* and *in vivo* adsorption of potassium ions by zeolites, and to assess the feasibility of application of zeolites as oral adsorbents for the treatment of hyper-kalemia in comparison with polystyrene sulfonates.

Experimental

Materials——The zeolite samples, having the compositions shown in Table I, were prepared as described before.[1] Sodium polystyrene sulfonate (USP XXI, Kayexalate®) and calcium polystyrene sulfonate (JP XI,

TABLE I. Composition of the Zeolites Studied

Zeolite	Composition			Chemical formula	Adsorption capacity[a] (meq/g of zeolite)
	SiO_2	Al_2O_3	Na_2O		
ZPC-10A	10	1.0	1.0	$Na_8Al_8Si_{40}O_{96} \cdot xH_2O$	2.62
ZPC-50A	10	2.1	2.1	$Na_{58}Al_{58}Si_{139}O_{349} \cdot xH_2O$	4.43
Molequlite 401	10	5.0	5.0	$Na_{12}Al_{12}Si_{12}O_{48} \cdot xH_2O$	7.04

a) The theoretical amount of potassium adsorbed by zeolite, calculated from the aluminium (sodium) content in the molecule.

Kalimate®) were used as received. Other chemicals used were of reagent grade.

Assay——For the *in vitro* adsorption study, potassium, sodium, ammonium, calcium and magnesium ions were determined by ion chromatography as described before.[1]

The amount of ions adsorbed on the adsorbent samples was determined after the following pretreatment. The adsorbents were collected on membrane filters (Millipore HAWP 02500, 0.45 μm), transferred into platinum crucibles, heated with sulfuric acid and hydrofluoric acid to evolve silica as SiF_4, and then ignited at 550 °C for 5 h. The residue was dissolved with hydrochloric acid solution. Sodium and calcium polystyrene sulfonates were ignited with sulfuric acid and hydrochloric acid, respectively.

The concentrations of potassium and sodium ions in blood samples were determined by using ion selective electrodes (Hitachi-Horiba, SERA-301A).

***In Vitro* Adsorption**——One gram of adsorbent samples was added to 50 ml of various concentrations of KCl solutions and shaken in a thermostated bath (37 °C) regulated with 0.2 °C precision. At appropriate intervals, samples were filtered through filters. The amount of ions in the filtrate and that adsorbed on the adsorbents were separately determined as described in the assay section.

In order to determine the potential capacity of adsorbents to replace sodium ions in the molecule with potassium ions, 20 g of adsorbents was shaken in 1 l of 1 M KCl solution at 60 °C for 8 h, and the amount of potassium ions adsorbed and the amount of sodium or calcium ions released were determined as described before.

The ion selectivity of adsorbents and the effect of coexisting cations on the adsorption ability were determined as described in the previous paper.[1]

***In Vivo* Adsorption**——*In vivo* adsorption was studied as described before.[1] An azotemic dog model was produced by ligating both of ureters of mongrel dogs (8—13 kg). The dogs were allowed to recover for 24 h, and then divided into control and test groups (5 dogs in each group). The dogs were fasted for 24 h prior to experimentation. Adsorbent (10 g) suspended in distilled water was administered to azotemic dogs through catheters connected to the duodenum. Control dogs were given distilled water. The plasma levels of potassium and sodium ions were determined at appropriate intervals.

Acute Toxicity Test——Wistar rats (males weighing 94.8—95.6 g, females 84.3—86.4 g) and ddy mice (males 22.5—22.9 g, females 19.6—20.2 g) were fasted for 16 h prior to experimentation, and divided into control and test groups. Test groups of rats were given 20 or 15 g/kg of ZPC-10A suspended in 5% gum arabic solution through a tube. Test groups of mice were given 50 or 25 g/kg of the ZPC-10A suspension (50% (w/v)). Control groups of animals were given 5% gum arabic solution. Animals were fasted for 6 h after administration. Observation to evaluate acute toxicity was continued for 15 d.

Results and Discussion

In Vitro Adsorption

All of the adsorbents studied (three kinds of zeolites and two types of polystyrene sulfonates) rapidly adsorbed potassium ions, and adsorption equilibrium was attained within 15 min (data not shown). Table II shows the potential capacity of the zeolites and polystyrene sulfonates to replace sodium ions in the molecule with potassium ions in solution. Though the amount of potassium ion adsorbed by ZPC-10A was relatively small, almost all of the sodium ions in ZPC-10A were replaced by potassium ions. Among polystyrene sulfonate resins, Kalimate, which is designed to release calcium ions instead of sodium ions upon adsorption of potassium ions, was found to contain a considerable amount of sodium ions and to release sodium ions as well as calcium ions, contrary to expectation. The amounts of potassium ions adsorbed by the adsorbents are plotted as a function of the concentration of potassium ion

TABLE II. Potential Capacity of Zeolites and Polystyrene Sulfonate Resin (Kayexalate and Kalimate) to Adsorb Potassium Ions[a)]

	Potassium ions adsorbed[b)]	Change in ion contents in the molecule[b)]	
	K^+	Na^+	Ca^{2+}
ZPC-10A	2.05	2.10→0.01	
ZPC-50A	3.48	3.62→0.11	
Molequlite 401	4.48	5.00→0.47	
Kayexalate	3.68	4.19→0.44	
Kalimate	3.10	0.50→0.05	3.50→0.96

a) See the text. *b*) meq/g of adsorbent.

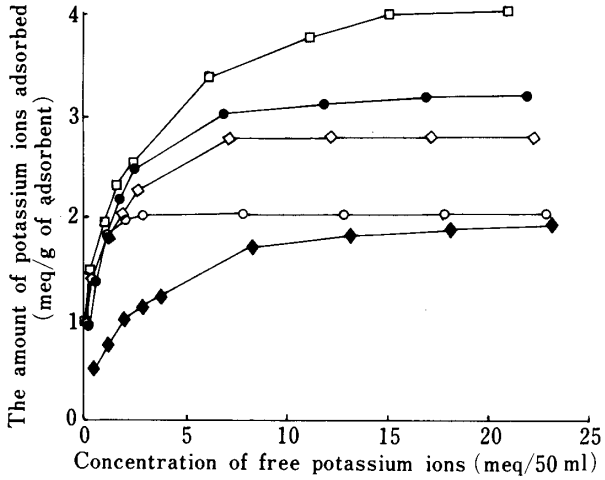

Fig. 1. Adsorption of Potassium Ions by Zeolites and Polystyrene Sulfonate Resins from Solutions Containing Various Concentrations of Potassium Ions

◆, Kalimate; ○, ZPC-10A; ◇, ZPC-50A; □, Molequlite 401; ●, Kayexalate.

TABLE III. Selectivity Coefficient of Zeolites and Polystyrene Sulfonate Resins (Kayexalate and Kalimate)

Concentration of competitive cation (meq/50 ml)		Selectivity coefficient				
		ZPC-10A	ZPC-50A	Molequlite 401	Kayexalate	Kalimate
Na^+	1	6.51	2.25	0.77	2.82	1.17
	5	6.62	2.68	1.06	2.21	1.46
	10	5.76	2.96	1.20	4.91	1.54
NH_4^+	1	1.47	3.41	1.75	0.82	1.31
	5	1.42	3.51	1.35	1.13	1.29
	10	1.31	3.62	2.08	1.50	1.19
Mg^{2+}	1	10.36	1.38	0.52	(0)	0.12
	5	43.78	4.95	4.02	0.35	0.30
	10	33.96	7.65	3.48	0.30	0.41
Ca^{2+}	1	1.80	0.60	0.52	0.12	0.25
	5	6.74	2.30	0.32	0.25	0.46
	10	9.65	3.51	0.51	0.45	0.66

solutions used in Fig. 1. No marked difference in the adsorbed amount was observed among the adsorbents other than Kalimate in the concentration range below 3 meq/50 ml, which is considered to cover the plasma level of patients with hyper-kalemia.

TABLE IV. Effect of Cations on Potassium Ion Adsorption by Zeolites and Polystyrene Sulfonate Resins (Kayexalate and Kalimate)

Concentration of competitive cation (meq/50 ml)	Ion content of adsorbent after incubation in potassium ion solution[a]															
	ZPC-10A			ZPC-50A			Molequlite 401			Kayexalate			Kalimate			
	K^+	M^+[b]	Na^+	K^+	M^+	Na^+	K^+	M^+	Na^+	K^+	M^+	Na^+	K^+	M^+	Na^+	Ca^{2+}
Na^+																
1 meq	0.86		1.23	0.81		2.81	0.76		4.24	0.73		3.46	0.19		0.30	3.48
5 meq	0.71		1.39	0.61		3.04	0.60		4.42	0.51		3.71	0.31		0.19	3.50
NH_4^+																
1 meq	0.81	0.66	0.63	0.77	0.57	2.30	0.73	0.46	3.78	0.72	0.58	2.85	0.37	0.22	0.08	3.36
5 meq	0.42	1.22	0.45	0.48	1.35	1.75	0.45	1.54	3.03	0.46	1.82	1.89	0.25	0.75	0.05	3.03
Mg^{2+}																
1 meq	0.87	0.25	0.98	0.76	0.82	2.08	0.92	0.89	3.19	0.68	0.98	2.55	0.31	0.09	0.11	3.52
5 meq	0.80	0.34	0.96	0.62	1.63	1.35	0.84	2.46	1.73	0.28	3.48	0.44	0.18	0.26	0.06	3.49
Ca^{2+}																
1 meq	0.78	0.69	0.65	0.75	0.90	2.02	0.75	0.96	3.26	0.71	0.99	2.50	0.30		0.18	3.52
5 meq	0.63	1.09	0.39	0.46	2.01	1.17	0.44	3.80	0.76	0.25	3.57	0.38	0.17		0.02	3.77

a) 1 meq/50 ml of potassium ions. *b*) Competitive cation.

TABLE V. Decrease in Plasma Concentration of Potassium Ions[a] after Administration of Adsorbents

Time (min)	Control		ZPC-10A			ZPC-50A			Molequlite 401			Kayexalate			Kalimate		
	K^+	S.D.	K^+	S.D.		K^+	S.D.		K^+	S.D.		K^+	S.D.		K^+	S.D.	
0	6.05	(0.24)	6.32	(0.30)		5.95	(0.18)		6.09	(0.31)		6.28	(0.34)		5.99	(0.19)	
15	6.05	(0.24)	5.67	(0.33)	S	5.63	(0.35)	NS	5.90	(0.27)	NS	6.03	(0.15)	NS	5.87	(0.17)	NS
30	6.07	(0.23)	5.54	(0.11)	S	5.44	(0.29)	S	5.63	(0.47)	NS	5.89	(0.22)	NS	5.75	(0.20)	NS
60	6.08	(0.21)	5.38	(0.04)	S	5.25	(0.24)	S	5.42	(0.40)	S	5.60	(0.28)	S	5.46	(0.38)	S
120	6.13	(0.22)	5.18	(0.21)	S	5.04	(0.22)	S	5.13	(0.32)	S	5.31	(0.28)	S	5.18	(0.38)	S
180	6.16	(0.26)	4.98	(0.16)	S	4.85	(0.27)	S	5.01	(0.27)	S	5.10	(0.35)	S	5.08	(0.36)	S

a) Average plasma concentration of potassium ions ($n=5$, meq/l). S.D., standard deviation. S, significant, NS, not significant ($p \leq 0.05$).

TABLE VI. Mean Body Weight of Rats after Administration of ZPC-10A

Sex	Dose (g/kg)	Number of rats	Time after administration (d)						
			0	2	4	7	9	11	14
Male	Control	10	95.6±2.3	112.7±3.5	124.8±3.4	147.0±4.6	158.9±5.0	164.5±4.7	183.7±5.6
	20	10	94.8±1.9	109.0±6.1	119.7±7.4	141.8±7.3	153.3±6.6	160.6±6.4	179.3±6.1
	15	10	95.5±2.5	112.1±3.0	128.1±3.2	146.1±4.7	157.4±5.6	165.9±5.8	180.9±6.0
Female	Control	10	84.3±1.9	97.8±3.0	102.4±4.5	114.8±3.3	120.6±3.7	122.3±3.0	128.5±4.5
	20	10	84.6±1.7	96.0±1.9	100.5±1.9	112.4±3.0	116.5±3.4	118.9±4.0	126.3±3.9
	15	10	84.4±2.3	97.0±3.4	101.4±3.0	113.4±4.1	118.9±5.7	118.3±4.9	126.3±5.9

Mean ± standard deviation ($n=10$), g.

TABLE VII. Mean Body Weight of Mice after Administration of ZPC-10A

Sex	Dose (g/kg)	Number of mice	Time after administration (d)						
			0	2	4	7	9	11	14
Male	Control	10	22.8±1.2	27.8±1.5	30.0±1.7	30.8±1.9	32.1±1.7	32.8±2.3	33.6±2.2
	50	10	22.5±1.0	27.6±1.1	30.0±1.2	31.0±1.2	32.4±1.2	33.2±1.7	33.9±1.3
	25	10	22.9±1.0	27.4±1.5	30.0±1.8	31.1±2.1	32.7±2.0	33.4±2.1	34.2±2.2
Female	Control	10	20.2±1.4	23.7±1.4	24.5±1.3	25.3±1.3	25.7±1.2	26.6±1.4	26.8±1.5
	50	10	19.6±0.9	23.6±0.5	24.0±1.0	24.8±0.7	25.8±0.8	26.0±1.0	27.1±0.8
	25	10	20.1±1.0	23.6±1.3	24.7±1.7	25.1±1.6	25.9±1.7	26.6±2.0	26.9±1.9

Mean ± standard deviation ($n=10$), g.

The ion selectivity of the zeolites and polystyrene sulfonates was evaluated in terms of selectivity coefficient. Table III shows the selectivity coefficient for potassium ions against sodium, ammonium, magnesium and calcium ions. The zeolites, especially ZPC-10A, showed higher ion selectivity for potassium ions than the polystyrene sulfonates, which adsorbed bivalent cations such as magnesium and calcium ions preferentially through an ion-exchange mechanism. The effect of coexisting cations on the ability of the zeolites and polystylene sulfonates to adsorb potassium ions is shown in Table IV, which lists the amounts of potassium ions adsorbed by the adsorbents in the presence of competitive cations, and the amounts of sodium or calcium ions remaining in the adsorbents after adsorption of potassium

ions. The potassium ion adsorption by the zeolites, especially by ZPC-10A, was inhibited to a smaller extent by coexisting cations in comparison with the potassium ion adsorption by the polystyrene sulfonates.

The results described above suggest that ZPC-10A has superior physical characteristics, adsorbing potassium ions selectively. This can be ascribed to the fact that the pore size of ZPC-10A is similar to the size of the hydrated potassium ion.

In Vivo Adsorption

The plasma concentration of potassium ions of the azotemic dogs decreased with the passage of time after administration of the adsorbents, as shown in Table V. ZPC-10A showed a significant decrease in plasma concentration 15 min after administration, when no significant decrease was observed with other adsorbents. No change in the plasma concentration of sodium ion was observed with any of the adsorbents studied.

Acute Toxicity Test

No detrimental effect of administration of ZPC-10A was observed with either rats or mice. No difference in body weight gain was observed between the test and control groups, as shown in Tables VI and VII. The median lethal dose (LD_{50}) was estimated to be more than 20 and 50 g/kg, for rats and mice, respectively. Pathological study indicated that ZPC-10A had no toxic effect on any tissue.

Conclusion

In vitro and *in vivo* adsorption studies suggest that ZPC-10A has superior characteristics as an oral adsorbent of potassium ions, as compared with polystyrene sulfonates.

It is known that the plasma level of potassium ions of heavy hyper-kalemic patients is about 7 meq/l.[7] Approximately 23—51 meq of potassium ions should be removed per day to reduce the plasma concentration to the normal level (3.6—5.5 meq/l) in the case of a patient weighting 70 kg with 15 l of extracellular water (35% of total body water, *i.e.*, 23% of body weight).[8] Since ZPC-10A showed an adsorption capacity of 1 meq/g, a suitable dose of ZPC-10A for the treatment of hyper-kalemia is estimated to be 23—51 g per day, which is acceptable from the viewpoint of practical therapy.

ZPC-10A showed no toxic effect, as expected on the basis of the fact that it consists of components similar to natural aluminum silicate and bentonite.

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