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TREATMENT OF THE OLIGURIC PATIENT WITH A NEW SODIUM-EXCHANGE RESIN AND SORBITOL*

A Preliminary Report

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BOSTON

THE danger of death from acute spontaneous potassium intoxication in patients with severe oliguria is well recognized.[1,2] Because the gastrointestinal secretions are rich in potassium numerous technics have been devised to remove potassium from the oliguric patient by way of the gastrointestinal tract. Most of these technics employed some form of intestinal drainage or lavage and were laborious and only partly successful.[3-5] The development of cation-exchange resins that could be administered to patients suggested a new method for removal of potassium from gastrointestinal secretions. These resins were capable of exchanging cations bound to the resin for other cations present in the solution with which they came in contact. They have been used with some success in the prophylaxis or treatment of hyperkalemia in oliguric patients.[6-11] Although effective, however, the large mesh size of the crosslinked polymers had two decided disadvantages that militated against their widespread use: the large mesh size made them unpalatable to the uremic patient whose major problem frequently is nausea and vomiting; and, when given rectally, they were found to be less effective. The large mesh size again appeared to predispose to concretion of the stool and fecal impaction.[6]

Recently, a new sodium-exchange resin¶ that has decided advantages over the resins previously used has been made available. This resin is a sulfonic polystyrene cation-exchange resin in the sodium cycle. Its mesh size is 5 to 10 microns as compared to 50 to 400 microns of the carboxylic resins previously used. It has the consistence of a powder and when suspended in a small volume of water can be taken by mouth with very little difficulty. Nevertheless, the problem of facilitating the passage of such a resin through the gastrointestinal tract so that it might be eliminated with its bound potassium continued to be troublesome. The problem was particularly difficult in acutely ill uremic patients who are prone to hypotonicity of the bowel and ileus. The use of sorbitol‖ in conjunction with the resin has proved a satisfactory answer to this problem. Sorbitol is a poorly absorbed polyalcohol of the hexose sugar sorbose. Because of its poor absorption from the intestine it produces an osmotic diarrhea, which helps propel the resin through the gastrointestinal tract and thus prevents constipation and ensures adequate contact of the resin with gastrointestinal secretions. The small amount absorbed is metabolized slowly and is nontoxic. This preliminary report is concerned with the clinical evaluation

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¶In the form of Kayexalate, Winthrop Laboratories, New York City.

‖Seventy per cent sorbitol solution in the form of Sorbo, Hercules Powder Company, Wilmington, Delaware.

of the new sodium-exchange resin for the treatment and prophylaxis of hyperkalemia in the patient with severe oliguria, and with the use of sorbitol as an adjunct to resin therapy.

Methods

A total of 10 patients with severe oliguria* were studied. Since many of these patients were transferred from outside hospitals a complete daily record for each patient from the onset of his illness is not available. Therefore, to facilitate analysis the data on each patient are arranged such that day 0 represents control values and day 1 the start of resin therapy. The average values for the serum sodium, serum potassium and serum carbon dioxide combining power for the 10 patients during each day of resin therapy are shown in Figure 1. These data were obtained from the average of the recorded values and the extrapolated values on days when chemical determinations were not obtained. All subjects were treated with the same regimen, which consisted of 500 to 700 ml. of fluid a day in the form of 50 per cent dextrose and water intravenously, or Karo syrup and ginger ale mixed in equal parts and taken by mouth. Other medications such as digitalis, antibiotics and chlorpromazine were assumed not to influence the results of the study.

The exchange resin was suspended in a small volume of water and taken by mouth. The volume of water used was just adequate to make the suspension palatable for the patient. The usual suspension contained 1 gm. of resin per 3 or 4 ml. of water; 15 gm. of resin was given four times a day when it was desired to lower the serum potassium rapidly, and 5 gm. four times a day was given as a maintenance dose until the serum potassium had reached low-normal levels, when it was discontinued. Sorbitol was given as a 70 per cent syrup in doses of 10 to 20 ml. every two hours until a satisfactory diarrhea was produced. The total dose used to produce the diarrhea was then adjusted to each patient and was given once a day in quantities calculated to produce one or two diarrheal stools per day. If oral medication was not possible because of vomiting or paralytic ileus, resin and sorbitol were given as an enema (200 ml. of 25 per cent sorbitol and 40 gm. of resin) every six hours as needed. In a few patients sorbitol was administered orally without the resin.

Serum sodium and potassium concentrations were determined with the Baird atomic flame photometer using a lithium internal standard. The serum carbon dioxide combining power was measured with a Thomas Van Slyke manometer.

The 10 patients studied are divided into three groups: Group 1 — 3 patients treated with sorbitol alone; Group 2 — 5 patients treated with the combination of resin and sorbitol; and Group 3 — 2 patients treated with sorbitol and resin as enemas.

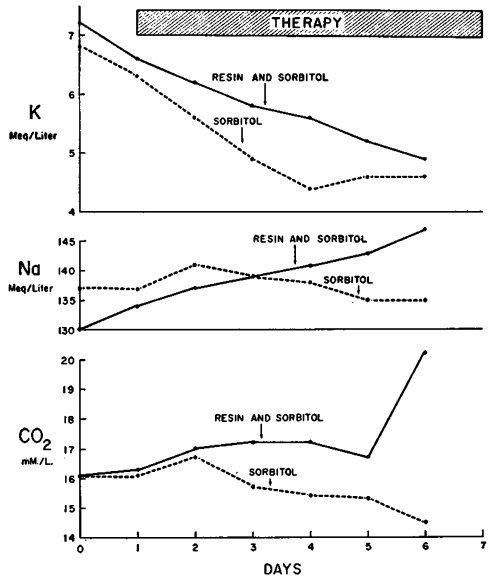

Figure 1. *Average Values for Serum Electrolytes on Combined Resin and Sorbitol Therapy.*

Results

Change in Serum Potassium

Figure 1 shows the average serum potassium, serum sodium and serum carbon dioxide combining power for Groups 1 and 2. The individual values are given in Table 1. It can be seen in Figure 1 that the serum potassium was lowered during the course of continued oliguria over a period of five days. This was

Table 1. *Change in Serum Concentrations in Response to Sorbitol Therapy and Combined Resin and Sorbitol.*

Patient	Sodium		Potassium		Carbon Dioxide	
	day 0	day 5	day 0	day 5	day 0	day 5
	milli-equiv./liter	*milli-equiv./liter*	*milli-equiv./liter*	*milli-equiv./liter*	*milli-equiv./liter*	*milli-equiv./liter*
Orally administered resin with sorbitol:						
K.	120	135	6.2	4.8	15.3	16.4
R.	139	145	6.9	5.6	21.2	21.7
M.	131	150	6.7	4.8	16.4	13.7
W.	135	135	6.0	4.9	12.3	13.4
H.	143	148	7.3	5.9	16.1	18.4
Averages	134	143	6.6	5.2	16.3	16.7
Orally administered sorbitol alone:						
M.C.	136	140	6.2	5.7	13.9	13.9
C.	128	127	6.2	5.0	16.2	15.8
K.	146	139	6.6	3.2	18.1	15.2
Averages	137	135	6.3	4.6	16.1	14.9

*Twenty-four-hour urine volumes less than 400 ml.

true in each of the cases studied (Table 1). The fall was a gradual and continual one. In 1 patient (K.) a fall to subnormal values with oral administration of sorbitol alone made it necessary to discontinue therapy. The values for serum potassium concentration suggest that sorbitol alone was actually more effective than the combined use of resin and sorbitol.

In 2 cases (Table 2) the combination of resin and sorbitol was given as a retention enema, with a good response as evidenced by a fall of serum potassium to an average of 4.5 milliequiv. per liter. In C. the values decreased from 6.8 to 3.5 milliequiv. per liter on the second day. In 1 patient (J.R.) hypokalemia developed (Fig. 2), with electrocardiographic changes of digitalis intoxication, during therapy with the resin and sorbitol, and supplementary potassium chloride was required.

In an effort to correlate the drop in serum potassium with potassium actually moved in the stool we attempted to reclaim and measure potassium by eluting it from the resin in the stool. Previous investigators[6] have demonstrated clearly that much of the potassium removed in the stool is bound to the resin.

TABLE 2. *Response of Anuric Patients to the Exchange Resin and Sorbitol by Enema.*

PATIENT	SODIUM		POTASSIUM		CARBON DIOXIDE	
	DAY 0	DAY 2	DAY 0	DAY 2	DAY 0	DAY 2
	milli-equiv./ liter	*milli-equiv./ liter*	*milli-equiv./ liter*	*milli-equiv./ liter*	*milli-equiv./ liter*	*milli-equiv./ liter*
P.	134	132	7.2	5.4	19.6	22.0
C.	124	121	6.8	3.5	18.0	17.4

Their measurements were facilitated by the fact that the mesh size of the resin used by them was large enough so that the resin could be reclaimed from the stool, dried and suspended in water and the potassium eluted from it with 2N hydrochloric acid. In this study it was not possible to do this since the resin used was of a mesh too fine to be reclaimed from the feces.

Change in Sodium Concentration

The difference between the use of sorbitol alone and the combined use of resin and sorbitol is shown in the data for change in serum sodium concentration in Figure 1. That this rise is caused by the sodium released from the resin in exchange for potassium is evident since there is no elevation of serum sodium when sorbitol is used alone.

Carbon Dioxide Combining Power

An apparent difference between the effect of sorbitol alone and the combined effect of resin and sorbitol is seen in Figure 1, in which the average values for the serum carbon dioxide combining power are plotted. With the combined use the carbon dioxide combining power rose. With sorbitol alone it decreased. As seen from Table 1 this rise was more pronounced in patients whose initial carbon dioxide combining power was lowest and was seen only in the cases in which resin was used. With sorbitol

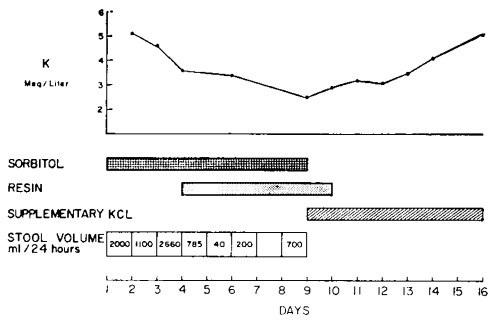

FIGURE 2. *Effects of the Combination of Resin and Sorbitol Therapy in J.R.*

alone there was actually a slight fall in carbon dioxide combining power.

DISCUSSION

The use of a cation-exchange resin in the sodium cycle seemed to us to be the resin of choice in the anuric patient. Danowski et al.,[8-11] in an extensive study of cation-exchange resins in dogs and later in man, demonstrated clearly the biochemical changes caused by the different cations bound to the resin in the use of resins loaded with a variety of cations. They showed preferential binding to the carboxylic acid resin of the bivalent cations, calcium and magnesium, and the monovalent cations, hydrogen, potassium and sodium, in that order. They also demonstrated that the resins of the hydrogen and ammonium cycle caused a marked metabolic acidosis. The production of a metabolic acidosis would tend to offset beneficial effects from the removal of potassium per se since acidosis predisposes to an elevated serum potassium independent of external balances for potassium,[12] and indeed the changes of acidosis per se may mimic those of potassium intoxication.[13] In addition, resins of the hydrogen and ammonium cycle given in large enough quantities predisposed to sodium depletion and serum hypotonicity. The effects of hyponatremia in potentiating potassium intoxication and of serum hypotonicity in aggravating the symptoms of uremia[14,15] are well known.

A rise in serum sodium might reflect simply water loss in excess of sodium. The balance data necessary to rule out this explanation are not available in the present cases; however, the rate of weight loss in the patients studied was not sufficient in itself to account for the rise in sodium. This fact and the properties of the sodium-loaded resin, as well as the contrast

with the data for sorbitol alone, suggest that the resin was primarily responsible for the rise in sodium concentration.

A potential danger of the sodium-cycle resin is overhydration and pulmonary edema. This can be prevented by drastic restriction of water. The data of Evans et al.[6] confirm this belief. The theoretical disadvantages of hypertonicity due to increased serum sodium in the uremic patient have not been a practical disadvantage in our experience. In 1 patient (H.), who was given large doses of resin for a prolonged time in an effort to remove potassium released from a large retroperitoneal hematoma, the serum sodium rose to 154 milliequiv. per liter. We were unable to detect any clinical effects of this change per se.

We were impressed with the rise in serum sodium and carbon dioxide combining power with the use of the resin and the failure of these concentrations to improve when sorbitol alone was used. The lesser rise in serum carbon dioxide combining power undoubtedly represents the accumulation of metabolic acids during the continuing course of oliguria. Serum pH was not measured, but it seems probable that these results reflect a lesser tendency toward acidosis in the cases in which the resin was used. The data suggest that sorbitol alone is as effective as a combination of resin and sorbitol in removing potassium, or more so. However, sorbitol alone necessitated a greater volume of debilitating diarrhea. In either case the predictability of the fall in serum potassium was impressive.

It is difficult to be sure of the correct amount of resin to use in any case. However, on theoretical grounds the obligatory potassium released from catabolic processes in the normal person has been estimated at 40 milliequiv. per day,[16] and this can be reduced to 20 milliequiv. per day if 100 gm. or more carbohydrate is given during a twenty-four-hour period. Furthermore, although the sodium-exchange resin has a theoretical cation-binding capacity of 3.1 milliequiv. of potassium per gram of resin, half to two thirds of this capacity is utilized for other cations such as ammonium, calcium, magnesium and probably organic cations, lipids and protein.[6] For practical clinical purposes, then, an "effective combining capacity" of approximately 1 milliequiv. of potassium per gram of resin remains. Using these figures, therefore, we gave 20 gm. of resin per day in divided doses for maintenance and 60 gm. per day to lower the elevated serum potassium, with satisfactory results. In view of the accentuated protein catabolism of patients with infection, trauma or surgery these calculations must be modified accordingly.

It should be stressed that all patients on resin therapy should be limited to electrolyte-free intake by mouth since the resin will exchange its sodium for other cations in relation to their particular affinity for the resin and to their local concentration.

Seventy per cent sorbitol has proved to be an effective osmotic cathartic and will often produce diarrhea within two to four hours. As an adjunct to resin therapy it has proved to be successful in combating hyperkalemia both because of its effect on removing potassium per se and through its ability to facilitate passage of the resin through the gastrointestinal tract. Another advantage of the use of sorbitol is its ability to remove excess fluid from the overhydrated oliguric patient. Excessive electrolyte loss may be replaced in more concentrated solutions, and the net result is loss of edema fluid by way of the bowel.

In patients who are too nauseated to take any medication we do not believe that administration of resin, with or without sorbitol, by a nasogastric tube is of value. The risk of nasopharyngeal irritation and bleeding, as well as the very real hazard of vomiting and aspiration in such cases, we believe, precludes the use of the tube.[17] Under such circumstances the combination of resin and sorbitol given as a retention enema has proved to be effective in lowering the serum potassium. The use of sorbitol in the enema circumvents the danger of fecal impaction. However, the rectal route has proved less effective than the oral route, and since long-term use of continuous enemas is debilitating and difficult, we believe that one should return to the oral route for maintenance therapy whenever possible.

The development of hypokalemia in an oliguric patient and a marked accentuation of digitalis effect by this attests both to the efficacy of this form of therapy and to the necessity for careful control in its use. The gradual drop in serum values suggests that this technic is an extremely effective form of therapy for the prophylaxis of hyperkalemia but that its action is too slow for immediate therapy when the electrocardiographic changes of potassium intoxication are advanced. When the treatment is begun early, however, there is no contraindication to its use by mouth or by rectum. It appears to be an extremely effective method for combating one of the serious complications of acute renal failure.

Summary

A new sodium-cycle sulfonic polystyrene exchange resin has been demonstrated to be an effective and practical method of treating and preventing potassium intoxication in the patient with severe oliguria.

Sorbitol, a polyalcohol of the hexose sugar sorbose, is an effective adjunct to resin therapy in preventing its impaction in the gastrointestinal tract and in promoting fluid and electrolyte losses through the bowel.

Sorbitol alone may be an effective way of promoting dehydration in overhydrated patients.

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MANAGEMENT OF HYPERKALEMIA WITH A CATION-EXCHANGE RESIN*

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IN patients with advanced renal insufficiency hyperkalemia may lead to death by its myocardial effects.[1,2] Glucose and insulin solutions, calcium and hypertonic sodium salts, intestinal and peritoneal lavage, extracorporeal hemodialysis, hormone administration, infusion of alkali salts such as sodium bicarbonate and sodium lactate and cation-exchange resins have been used in the management of this problem.[3-5] This report describes the use of a sulfonic polystyrene cation-exchange resin in the sodium cycle‖ for the control of hyperpotassemia in both acute and chronic renal disease.

Synthetic ion-exchange resins were first made available to industry in 1935 and have since been extensively adapted to biologic and medical purposes.[6] Dock,[7] in 1946, first suggested the use of a cation-exchange resin as a therapeutic agent to reduce the amount of sodium ion available for absorption in the gastrointestinal tract of patients with congestive heart failure. Subsequent clinical studies clearly demonstrated that either carboxylic or sulfonic cation-exchange resins could bind both sodium and potassium ions in the gastrointestinal tract for excretion in the stool.[8] Elkinton and his co-workers,[9] in 1950, successfully employed a carboxylic resin, in the ammonium cycle, in 3 patients with hyperkalemia. Further studies by other investigators have repeatedly demonstrated the effectiveness of polystyrene cation-exchange resins in various cycles in controlling potassium retention associated with either acute or chronic renal disease.[10-15]

PHARMACOLOGY

An ion-exchange resin is a crosslinked polymer containing acidic or basic structural units that can exchange either cations or anions respectively on contact with a solution. Cation-exchange resins have been used to bind sodium, potassium and ammonium ions in congestive heart failure, uremia and hepatic coma, respectively. The sulfonic or carboxylic groups may be saturated initially with hydrogen, ammonium, sodium, potassium or calcium or combinations of these ions, the exact choice depending chiefly on the clinical situation and the palatability of the resultant preparation. In the acid environment of the stomach the original cation of the resin exchanges chiefly for hydrogen ion. As the resin passes into the jejunum, ileum and colon, this ion exchanges for those present in greater concentration, such as sodium, potassium and ammonium, and is then excreted in the stool in this form.[16] The order and effectiveness in which binding will occur in the gastrointestinal tract depends not on the type of resin used but rather on the availability and concentration of the exchanging cations.

Binding of potassium by these resins in the lower gastrointestinal tract has been uniformly effective. Greenman et al.[17] report an in vivo efficiency of potassium binding that is 50 per cent higher than that of sodium, even when the diet contains appreciable amounts of sodium. Presumably, this percentage

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