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MEDICAL PREPARATION FOR REDUCING THE BODY LEVEL OF SODIUM

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This invention relates to a medical preparation for the control of the assimilation of mineral cations by the body.

It is well recognized, by way of example, that restriction of sodium intake as a therapeutic measure has great medical value in the treatment of certain clinical conditions. The value of a diet low in salt content has long been recognized in the treatment of many kinds of conditions, particularly those in which edema is a characteristic, such as, for example, congestive cardiac failure, cirrhosis of the liver, the obesity of pregnancy, and many others, as well as in the treatment of hypertension. Realization, however, of a dietary regimen in which the salt content is sufficiently low to significantly decrease the patient's dietary sodium intake is usually accompanied with many difficulties, not the least of which is lack of acceptability to the patient of a diet so very bland that it is unpalatable.

This invention provides the art with a new, safe, and highly effective therapeutic means by which a patient may be placed, for example, in a very low, or even negative, sodium balance. The degree of sodium restriction is readily controlled by the amount of preparation administered. Further, this invention has utility in correcting a cation deficiency.

The use of ion-exchange resins for restriction of mineral cation intake has been very recently described in the art, but it has been demonstrated that their use in this manner gives rise to certain very undesirable results which have heretofore prevented the adoption of this therapeutic measure to widespread clinical practice. Here again we can, by way of example, consider the removal of sodium ions. It has been observed that the oral administration of ion-exchange resins has resulted in lowered blood levels of cationic minerals other than sodium. Thus, for example, blood levels of calcium and potassium have been observed to have been dangerously depleted below those levels known to be physiologically necessary to the proper metabolism and function of the body. There may result from such a lowering of potassium levels, conditions such as hypokaliemia and eventual shock should such lowered levels be protracted. This effect is due to an affinity of the ion-exchange resin for all cations in varying degree, even though the resin itself may have a preferential affinity for sodium.

Generally speaking, the preparation of this invention comprises a synthetic ion-exchange resin or a combination of such resins combined with

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two or more types of cations. One of these types of cations will be the mineral type.

Preferably, the resin will also be combined with ammonium ions or an amino acid, such as lysine, arginine and histidine, or with any combination of ammonium ions and amino acids. The ammonium ions and the amino acids have a minor physiological effect. Thus, their inclusion in the resin results in insignificant physiological effects in the body while at the same time prevents undesired, and in many cases dangerous, physiological effects which would frequently result, incident to excessively high levels of mineral cations, if only physiologically significant mineral cations were used to charge the resin. This is particularly useful where repeated dosages are required over a protracted period of time.

It will be understood that the particular novelty of this invention is the successful depletion of selected mineral ions such as sodium ions from the body while at the same time there is a replacement of other mineral ions in the body which are depleted by the ion-exchange resins, thus preventing the lowering of body levels of those essential ions. Further, a large depletion of a particular mineral cation can be accomplished without introducing excessively large amounts of replacement mineral cations.

The operation of the preparation in accordance with this invention is believed to be as follows: The resin carrying, for example, ammonium cations and replacement mineral cations are received in the stomach which has a low pH. The high concentration of hydrogen ions present in gastric fluids results in the replacing of the cations with which the resin is charged by hydrogen ions, thus converting the resin to its acid form. Thus, the ammonium cations are released to the stomach fluids and may for all practical purposes be disregarded. The replacement mineral cations are similarly released to the gastro-intestinal tract to be absorbed therein, and thereby increase the concentrations of these physiologically significant mineral cations in the body.

The resin in its acid form proceeds into the intestines, an area of very low acidity or of a pH of approaching 7. Here, the hydrogen ions of the resin are exchanged for mineral cations depending upon the affinity of the resin for these cations and the concentrations of the cations present. Of course, sodium ions will be extracted and, since no replacement sodium ions were in the resin, the level of sodium ions in the body will be reduced. The replacement ions previous-

ly released in the stomach will replenish the amounts of the other mineral cations which are depleted by the resin in the intestines. Thus, the body levels of these cations will be maintained.

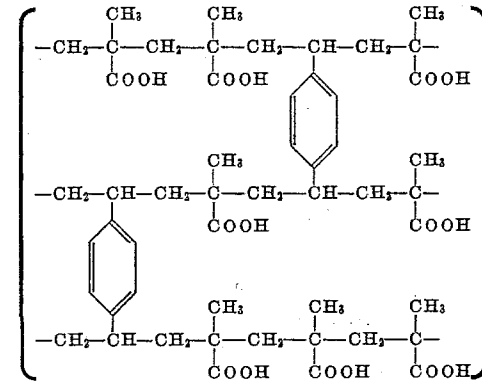
The resin, being insoluble and physiologically and chemically inert, is not susceptible to assimilation by the body. Thus, it passes through the gastro-intestinal tract unaffected by the process of digestion, except for the exchange of cations.

This invention further has the advantage of eliminating the necessity for subsequent, prior, or coadministration of certain supplementary substances, such as, for example, mineral supplements or gastric buffers, in conjunction with ion-exchange resin therapy. It will be further appreciated to have the advantage of minimizing the danger of incurring acidosis usually encountered in the administration of mineral supplements due to the heretofore unavoidable necessity of simultaneous administration, along with the desired mineral cation, of a corresponding, exogenous anion, the presence of which latter may give rise to undesirable acidosis.

The ion-exchange resin of the preparation according to this invention will, generally speaking, be a synthetic cationic resin exhibiting high capacity for mineral cations and particularly for sodium ions. Although the resin will preferably be of a carboxylic type, it may be desirable under certain conditions to utilize a sulfonic resin or even a mixture of carboxylic and sulfonic exchange resins in order to blend the respective affinities and characteristics of those resins in the combining properties of the preparation.

More particularly the ion-exchange resin of this preparation will be a synthetic carboxylic resin with a capacity of greater than 3 meq. per gram of resin. Such a resin, for example, may be prepared by the polymerization of a vinyl-containing carboxylic acid, such as, for example, a derivative of acrylic acid. Such a resin may be copolymerized in various ratios, as may be determined to be necessary to obtain the required characteristics of hardness and permeability of the resulting resin with a molecule containing more than one vinyl group having the ability of participating in the linear polymerization of more than one polymer chain. Such an agent serves to provide cross linkage of the polymer chains in 3 dimensions and serves to provide to the final, polymerized resin its necessary physical characteristics. As exemplary of compounds suitable for such tri-dimensional cross linking and containing more than one vinyl group might be mentioned di-vinyl benzene, butadiene and allyl methacrylate. As exemplary of molecules containing a vinyl group which are suitable for polymerization to form a carboxylic ion-exchange resin may be mentioned such substances as acrylic acid, methacrylic acid, methyl acrylate, ethyl acrylate, methyl methacrylate or in general, derivatives of acrylic acid and lower alkyl esters thereof. In this connection it is to be noted that where an ester of the carboxylic acid is used to form the polymer, the esterifying group must be hydrolyzed off in the preparation of the resin to provide the carboxylic groups in the resin necessary for purposes of cation exchange. The resin as prepared will then be in its hydrogen, or acid, form.

As further illustrative of a high capacity, synthetic, carboxylic ion-exchange resin suitable for utilization in the preparation of this invention is a resin prepared by copolymerization, using techniques well known to the art, of methacrylic acid together with di-vinyl benzene, which substances are reacted together in their monomeric, molar ratios of 10:1 respectively. The polymerized structure may be represented by the following:



where n is an indeterminate number, with monomeric units occurring at random frequency but in an overall molar ratio of 10:1.

The mineral cations with which the resin or resins according to this invention will be combined will be selected, generally, from the group consisting of mono-, di- and trivalent mineral cations occurring naturally in physiological media. Thus, for example, specific mineral cations, with which the resin or resins of this preparation may be combined, will be potassium, calcium, magnesium, iron, cobalt, zinc and manganese. Hydrogen cations can also be used to charge the selected resin in accordance with this invention. It should be noted that the ammonium ion is occasionally considered to be a mineral cation rather than, as is more correct, a non-mineral inorganic ion. It is, therefore, desired to clearly point out that the term "mineral cation," as it is used in the specification and claims, is not intended to include ammonium ions.

Where an amino acid is used, it will have a molecular ratio of ammonium groups to carboxylic groups which is always greater than one.

The number of cations with which the resin or resins of the preparation will be combined is determined by the number of physiological cationic substances which the resin itself deletes from physiological media and by the clinical condition which it is desired to treat. Thus, for example, if the affinity of the resin for ions of sodium, potassium and calcium is found to be sufficient to delete amounts which are physiologically significant, and if it is desired to place a patient with stomach ulcers in a low sodium balance, it might be desirable to charge the resin or resins with some proportion of cations of potassium, calcium and lysine. The amounts of mineral cations with which the resin will be combined will be such that the levels of those particular cations deleted by the resin in physiologically significant amounts will be replenished and maintained. Thus, upon administration of the preparation, the cations with which the resin is combined would be eluted off from the resin matrix, the mineral cations being in sufficient concentration to replace and maintain the minimum required body levels of those elements; the dibasic amino acid, lysine, being eluted off in the stomach to provide a buffer and neutralizing

agent in the stomach to avoid an undue increase in acidity.

Generally speaking, the multiple cationic ion-exchange resin preparation of this invention will be prepared by either of two methods. The ion-exchange resin as manufactured may be treated with solutions of the various ions with which it is desired to combine the resin, in concentrations such that those ions will be absorbed in and on the resin in quantities appropriate to the desired cationic constitution of the preparation. Thus, for example, were it desired to obtain a preparation containing ammonium and potassium cations in a particular ion-exchange resin in the ratio of 2:1, the resin would be treated with a solution containing those two ions in that same ratio of concentrations. The concentrations of the ions in the solution with which the resin is treated should be sufficiently great to cause the resin to become completely saturated with those two ions; i. e., to charge it with those ions to the extent of its capacity. Thus, in the example mentioned above, if the resin has a capacity of 3 meq. per gram, each gram of resin should contain, after being treated with the charged solution, two meq. of ammonium ion and 1 meq. of potassium ion.

Alternately, the preparation containing multiple cations in combination with the ion-exchange resin may be prepared by physically mixing two or more portions of resin, each of which is saturated with respect to one particular cation, in appropriate proportions. Each of the portions will be prepared by treating that portion of the resin, as received in its hydrogen form, with a solution of that particular cation in the form of a soluble compound.

The resulting resin or combination of resins containing multiple cations as prepared by either of the two methods above may then desirably be subjected to micropulverization in order to render the preparation more pharmaceutically acceptable for purposes of oral ingestion, although this is not necessary to the effective operation of the preparation. It may further be found desirable for the purposes of administration under certain conditions to reaggregate the finely divided resin with such substances as acacia and methylcellulose into larger granules. Such granules, for example, may readily be administered orally in a slurry with fruit juices, water, chocolate milk, and the like.

The pulverization of the resin to a finely divided powder will be readily accomplished through the use of a rotary grinding mill fitted with rotating hammers, geared to operate at a speed of about 12 to 14,000 R. P. M. The rapidly rotating hammers crush the resin particles, which, as initially prepared, may have a particle size of from 4 to 8 mesh, and force the particles through a 60–80 mesh screen fitted into the bottom of the machine.

The following examples will serve to more specifically illustrate preparations according to this invention, as well as the method of making them.

Example 1

12 pounds of carboxylic cation-exchange resin in its hydrogen form, prepared from polymerization of methacrylic acid and di-vinyl benzene and exhibiting an available capacity of from 4.5 to 6.0 meq. per gram in neutral media was weighed into a large battery jar. Having a moisture content of 46%, this was equivalent to 6.5 pounds of the dried resin. Distilled water was added to the jar in sufficient amount to thoroughly soak the resin and the resin was transferred, using suitable wash techniques, into a 5-gallon bottle. 1500 ml. concentrated (15 N) ammonium hydroxide was added to the bottle in portions of 500 ml. each. Following each addition the bottle was thoroughly shaken and when the addition was completed, the bottle containing the resin was placed in a drum and rotated for one hour at room temperature. The resin was then allowed to settle in the bottle, the supernatant liquid was decanted, and the resin was washed onto a Buchner funnel, followed by a successive series of washings using approximately 6 liters of water. After the resin was sucked dry, it was transferred to large wooden trays and dried in an oven at 168° F. Analysis of the resin so prepared determined that it contained 5.0 meq. of ammonia per gram of dry resin.

12.5 pounds of the acid form of the same carboxylic resin was weighed into a 5-gallon bottle. The moisture content of this resin being 48.6%, this amounted to 6.425 pounds of dry resin. Sufficient water was added to the bottle to cover the resin to a depth of 3" and 2310 grams of crystalline KCl was added to the slurry in the bottle, followed by thorough shaking. A solution of 1730 grams of KOH in 2 liters of water was added to the 5-gallon bottle containing the resin and the KCl solution, following which the bottle was stoppered and rotated on its side for 5 minutes. The bottle was then allowed to stand for several hours, interrupted only for periodic shaking. The supernatant liquid was then decanted from the resin in the bottle and the resin was rinsed several successive times until all the coloring material had been removed from the resin. Following this the resin was transferred to a large Buchner funnel, washed repeatedly until the rinsings became neutral, i. e., until one drop of 1% phenolphthalein solution, upon addition to 100 ml. of the washings, was decolorized by one drop of 0.1 N HCl. The resin was then transferred to porcelain pans, dried overnight in an oven at 120° C. and was determined to contain 5.88 meq. of potassium per gram of resin.

The ammonium and potassium resins prepared as above, of a particle size of from 4 to 8 mesh, were separately subjected to pulverization techniques such that their particle size was reduced to 80 mesh or less. 2545 grams of powdered potassium resin and 7955 grams of the powdered ammonium resin and 525 grams of powdered acacia, U. S. P. were all placed in a Stokes mixer and thoroughly mixed for from 3 to 5 minutes. An aqueous solution of 0.2% methyl cellulose was prepared by adding sufficient water to obtain a final volume of 23 liters of solution to 46 grams of methyl cellulose, heating to 75° C. and cooling the resultant mixture back to room temperature. The resulting viscous solution was added to the mix in 3-liter portions initially and after 18 liters had been added, in smaller amounts until a doughy consistency was obtained. The material was then scooped out of the mixer, forced through a 16-mesh screen onto large wooden trays and dried in an oven for 20 hours at 125° F. The dried particles were then forced through a 30-mesh screen to obtain the desired granule particle size.

The granules of ion-exchange resin so prepared were determined to contain 1.33 meq. per gram of potassium and 3.33 meq. per gram of ammonium.

Example 2

One pound of wet polyacrylic acid ion-exchange resin was weighed into a 1500 ml. beaker. Inasmuch as the resin had a moisture content of 40%, this was equivalent to 270 grams of dry resin. 600 ml. of water was added to the resin and a solution of 40.5 grams of potassium chloride dissolved in 200 ml. of water was added with constant stirring. 150 ml. of concentrated (15 N) ammonium hydroxide was then added to the beaker with constant stirring, after which the beaker and its contents were set aside for two days, interrupted by occasional stirring. The resin in the beaker was allowed to settle and the supernatant liquid was decanted from the resin. The resin was then rinsed several successive times with distilled water, transferred to a Buchner funnel and washed several times with distilled water. The resin was then sucked dry, transferred to a tray, and dried in a partially evacuated oven at 120° C. for 24 hours. The resin thus prepared was determined to contain 1.3 meq. of potassium and 3.4 meq. of ammonia per gram of resin.

10,500 grams of the ammonium and potassium double salt of the resin prepared as above was pulverized to a 60 to 80 mesh particle size and granulated with acacia and methyl cellulose, using a procedure identical with that described in Example 1 above.

Example 3

3000 grams of polyacrylic acid ion-exchange resin was weighed into a 5-gallon bottle and enough water was added to cover the resin to a depth of one inch. A solution of 6 pounds of $CaCl_2.H_2O$ in 3 liters of water was added to the bottle, followed by intermittent shaking over a period of 2 hours. The supernatant solution was decanted from the resin and the resin was rinsed and decanted several successive times with distilled water. A solution of 3 pounds of anhydrous $CaCl_2$ dissolved in 2 liters of water was then added to the resin followed by the addition of another 5 liters of water. The bottle was stoppered, shaken intermittently for a period of 2 hours and allowed to stand overnight. After decanting the solution from the resin in the bottle, the resin was rinsed several successive times with the distilled water and was transferred onto a Buchner funnel. After successive washings with distilled water, the resin was filtered, dried, transferred to pans and dried in an oven overnight at 105° C. The resin so prepared was determined to contain 5.0 meq. of calcium per gram of resin.

The calcium resin prepared as above was then micropulverized to a particle size of 60–80 mesh which was then mixed together with powdered ammonium resin prepared in a manner identical with that described in Example 1, which contained 4.4 meq. of ammonium per gram of resin and with a powdered potassium resin prepared in a manner identical with that described in Example 1, which contained 6.5 meq. of potassium per gram of resin in such a manner that 45 grams of homogeneous resin mixture contained 10 meq. of Ca, 100 meq. K and 121 meq. NH_4.

In the preparation of 1125 grams of a finely divided ion-exchange resin preparation according to the above specifications, 50 grams of Ca resin prepared above and micropulverized, 387.5 grams of the finely divided potassium resin and 687.5 grams of the finely divided ammonium resin were weighed into a large bottle and thoroughly mixed

by prolonged rotation and thorough shaking of the container.

Example 4

A polyacrylic acid cation-exchange resin preparation containing 0.22 meq. of calcium per gram of resin, 2.22 meq. of potassium per gram of resin, and 2.70 meq. of ammonium per gram of resin, was prepared by treating the resin in its free acid form with a solution of $CaCl_2$, KOH, and NH_4OH in a manner similar to the preparation of the double salt of the resin described in Example 2 above. The triple salt of the ion-exchange resin so prepared was then dried, pulverized and granulated according to the procedure described in Example 1 above.

Example 5

0.552 g. of a polyacrylic acid ion-exchange resin having a moisture content of 50%, was treated with a solution of 0.552 g. of lysine in 5.5 ml. of water whose pH was 9.9 according to the techniques described in Example 1 above. The resin so prepared was determined to contain 2.74 millimoles (5.48 meq.) of lysine per gram of resin. The lysine resin was dried, pulverized and granulated according to procedures described above in Example 1.

0.276 g. of the lysine resin was mixed with 0.071 gram of potassium resin, prepared in Example 1 above to contain 5.88 meq. of potassium per gram, to form an ion-exchange resin preparation containing 1.22 meq. of potassium and 2.17 millimoles (4.35 meq.) of lysine per gram of resin preparation. The amino acid capacity of the resin in milliequivalents was calculated on the basis of the molecule containing two active cationic groups.

Example 6

1.004 g. of a polyacrylic ion-exchange resin of a moisture content of 50%, was treated with a solution of 1.004 g. of arginine in 10 ml. of water in a manner identical with that described in Example 5, to yield the arginine resin containing 3.04 millimoles (6.08 meq.) of arginine per gram. This resin was then dried and finely divided.

0.502 g. of the arginine resin was intimately mixed with 0.139 g. pulverized potassium resin prepared in Example 1, and 0.031 g. pulverized calcium resin prepared in Example 3 to yield a homogeneous powdered mixture of resin which was determined to contain 2.27 millimoles (4.54 meq.) arginine, 1.22 meq. of potassium and 0.22 meq. of calcium per gram of the resin powder preparation. The amino acid capacity of the resin in milliequivalents was calculated on the basis of the molecule containing two active cationic groups.

What is claimed is:

1. A medical preparation for reducing the body level of sodium comprising an ion-exchange resin selected from the group consisting of carboxylic and sulfonic ion-exchange resins, said resin being charged with ammonium ions and additionally being charged with potassium ions to maintain the normal body level of potassium, said medical preparation being substantially sodium free.

2. A medical preparation for reducing the body level of sodium comprising a carboxylic ion-exchange resin, said resin being charged with ammonium ions and additionally being charged with potassium ions to maintain the normal body level of potassium, said medical preparation being substantially sodium free.

3. A medical preparation for reducing the body level of sodium comprising a copolymer of methacrylic acid and divinyl benzene, said copolymer being charged with ammonium ions and additionally being charged with potassium ions to maintain the normal body level of potassium, said medical preparation being substantially sodium free.

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