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## PROBABLE CLINICAL UTILITY OF CATION EXCHANGE RESINS

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The data which have been presented in the previous papers clearly indicate that the carboxylic cation exchange resins in the hydrogen, ammonium, sodium, and potassium forms individually or in combinations increase the stool excretion of sodium and potassium in man and dog (1-4). In the amounts administered however, 20 to 60 g./day, there was only a limited absolute increase in the stool content of sodium and potassium. The *in vivo* efficiency of these exchangers was usually 1 meq. of sodium or less removed per gram of resin ingested when the diet contained sodium. In addition, potassium excretion per gram of the resin was usually about 50% greater than sodium. Although stool sodium was largest during the administration of the sodium form, and potassium greatest during ingestion of the potassium cycle, it seems clear that these ions were actually being supplied to the body because less was excreted in the stool than was administered.

It may often prove possible to utilize these substances, with the exception of the sodium form of the exchanger, to advantage clinically in conditions in which endogenous sodium is already present in excess or in which exogenous sodium is prescribed. It is logical, for example, to expect that in some borderline situations the resin may serve even without dietary restriction to tilt the balance of sodium sufficiently to prevent further retention or to produce an actual loss of previously retained ions via emunctory pathways other than the gastrointestinal tract. Thus it may well be possible to maintain some patients on a full diet plus resin. It naturally follows that others may only need partial limitation of exogenous sodium. However, the composition of the diet influences the efficiency of the resin. When sodium is rigidly withheld, the amount of sodium removed per gram of the exchanger decreases markedly. Our studies suggest that if essentially complete sodium restriction is achieved only small increments of this cation will be removed in the stool per day and prolonged

therapy may be required for this route of excretion to attain important effects in the removal of endogenous sodium. This is surprising inasmuch as a large pool of endogenous sodium should be available for interchange with the resin but this presumably reflects the greater affinity of the resin for potassium as compared to sodium (5-10).

Since ordinary full diets provide an intake of some 100 to 300 meq. of sodium in the course of 24 hours, it is evident that these agents used alone in amounts up to 60 g./day are incapable of producing negative balances as a result of losses in stools or of preventing the absorption of a major part of the sodium through the intestine. This is particularly true when it is recalled that in the animal experiments and to a lesser degree in the human studies, deviation of sodium excretion to the gastrointestinal tract was accompanied in turn by reduced urinary losses of this ion. A larger intake of resin might of course shift the sodium balance to the negative side, but unfortunately prescriptions in such dosage too often prove burdensome to most patients. This is particularly apt to be true of those who are ill and already anorexic, nauseated or vomiting.

The effects of the hydrogen and ammonium cycle resins are not limited, however, to deviation of sodium to stools. They both produce an acidosis which in the control of edema can be looked upon as a beneficial and a desirable effect in subjects without impaired renal function. This development can induce diuresis by the same mechanisms responsible for increased urine volumes following acidifying diuretic salts (11). It is probable that the hydrogen or ammonium ion attached to the resin is absorbed into the body fluids following displacement from the resin by the other cations present in enteric juice and thereby produces acidosis. This analogy is supported not only by the well-documented changes following ammonium chloride administration but also by the invariable occurrence of hyperchloremia as a se-

quel to the use of any of the so-called acidifying diuretics (11). It is true, as our own findings indicate (4), that frank acidosis and overbreathing may accompany the ingestion of acidifying resins, especially in patients with far-advanced renal failure. Since it is highly dubious that accentuation of a definite acidosis already present as a consequence of renal insufficiency exerts any further stimulus to urinary sodium and water losses, it is well to identify such patients and treat them either with lesser amounts of resin, or with non-acidifying resins in other cycles, or perhaps both. The evidence on hand indicates, however, that the lessened tendency to acidosis recorded with mixtures of hydrogen and potassium, or of ammonium and potassium cycle resins, merely represents the effect of reducing the amount of hydrogen or ammonium ion administered (3). The potential benefits of such mixtures in this regard are minimized by the relatively decreased efficiency of the potassium-bearing resin with respect to sodium exchange (6-10). Further, it is known that potassium deficits in the body are accompanied by alkalosis and that excessive retention of potassium in cells is of itself productive of acidosis (12, 13).

Again, as in the case of the acidosis which follows the use of hydrogen and ammonium carriers, the frequency with which these agents increase stool potassium losses and produce negative balances of potassium may be either undesirable or desirable, depending on the particular patient under treatment. Thus it has been established in previous studies that losses of body potassium in urine, diarrhea, vomitus, or drainage from the intestinal lumen or from fistulae can result, if adequate treatment is not provided, in undesirable deficits of this important cation (14-21). This depletion can be accompanied by hypokalemia, muscular paralysis and electrocardiographic changes, particularly in the S-T and T segments, and prolongation of the Q-T interval (22, 23). Evidence is also available that losses of cell potassium induced experimentally in animals produce myocardial and muscle cell necrosis (24, 25), and that replenishment of depleted stores decreases the mortality in diarrheal infants (15). In view of these facts any agent which can lower body potassium below normal may produce harm. Therefore, factors such as starvation (16), administration of mercurial diuretics (26), or even ACTH

or cortisone (27-29) will increase the requirements of potassium. On the other hand it is obvious that in patients with excessive body stores of potassium this effect would be beneficial (30-32). Certainly ample evidence is available that increased levels of plasma and extracellular potassium will cause cardiac arrest and death (33, 34). This development is most frequently encountered in patients with renal failure, particularly anuria, though it is known to accompany excessive administration of potassium salts (35) and adrenal cortical insufficiency (36), and is even encountered for as yet unexplained reasons in certain newborn infants (37). In some of these patients the hydrogen and ammonium resins can be used to advantage to lower body potassium back toward normal. Admixture of potassium resin would be potentially dangerous in such subjects. It is obvious therefore that the prescription for resin therapy with hydrogen, ammonium, potassium, or any other cycle must be written with these effects and limitations in mind, combined with an adequate knowledge of the patient's status and disease.

Insofar as the sodium cycle resin is concerned little need be said even though it can influence cation balances. Thus in sodium depletion states the administration of sodium salts as such is far more certain (38, 39). The resin could be employed, as indicated by our data, to remove potassium. From the theoretical point of view it might be useful in patients with renal disease or Addison's disease where the combination of potassium excess and sodium deficits coexist (36, 40). Other far more effective modes of therapy are, however, available in Addison's disease (41). In the majority of renal disease states the accumulation of potassium is too often accompanied by impending or actual excesses of sodium to permit use of the sodium cycle resin. It should be emphasized that these generalizations do not exclude the possibility that in isolated clinical situations the characteristics of this resin might be considered to be custom-tailored.

Our experience with the calcium cycle resin is as yet too limited to permit any definite statement. If the conclusions drawn from the hydrogen and ammonium cycle studies are valid it should prove gram for gram less effective in inducing diuresis, since the acidifying effect is absent. This attribute may, however, make it useful in cases with renal

failure if it serves to increase losses of sodium and potassium in stools. In this respect it should be remembered that the calcium released in the exchanges with other cations could conceivably be precipitated with phosphate in the intestinal lumen. This event may be useful in modifying the hyperphosphatemia of renal failure and, directly or indirectly, the hypocalcemia. However, bivalence, high ionic diameter, high atomic weight and position in the electromotive series all make calcium elution, in favor of sodium or of potassium, inefficient (6-10). Furthermore the possibility must be considered that the use of milk formulae, because of their relatively high calcium content, may make the other resins less efficient, since the hydrogen, ammonium and potassium resins will tend to take up calcium in preference to sodium, particularly in situations where the concentration of sodium in the medium is minimal, as is the case with sodium-free milk.

Our patients did not show any recognizable evidence of calcium depletion in the relatively short time they received these resins. This problem as well as the one of negative calcium balances and of hypocalcemia during prolonged therapy is still unanswered, although it would seem to be a definite hazard. In addition hypokaliemia might mask the manifestations of tetany (42), and the acidosis defer its onset (43). It might be difficult to prevent this effect by supplying additional dietary calcium during resin therapy since this would reduce the excretion of sodium and potassium in the stool. Similarly we have no information about the quantitative effects of these resins on magnesium metabolism.

Dock has pointed out that the resins as currently used are at best efficient to the extent of 50% of theoretical capacity (44, 45). A number of possibilities exist whereby resin efficiency might be raised and it may be well to list them briefly here. The simplest measure would be to use smaller resin particles, and experiments are now in progress, employing 200 mesh resin in hopes that this may increase sodium uptake. Further, the medium in which the resin is administered requires study. Suspensions of resin in liquid or semi-liquid form in non-ionic vehicles such as cornstarch might well increase exchange and permit ingestion of larger amounts than presently tolerated in capsules or as

a dry powder. Our own data do not include sufficient no-sodium, milk-free cases to evaluate the importance of dietary calcium in blocking resin-acceptors and thus preventing sodium uptake. Finally, it has long been known that ion exchange and uptake is increased by the presence of ethanol in the substrate, leading to the suspicion that a resin elixir might prove to be both effective and acceptable. In addition it may be possible to prevent acidosis resulting from the ingestion and exchange of the ammonium and hydrogen forms by simultaneous administration of an anion exchanger or a salt which would decrease the absorption of or buffer the released ions. It may also be possible to produce resins which contain an organic molecule in the exchange position that would be utilized in large amounts in the body without harmful effects.

In conclusion it seems very clear that these resins provide a valuable additional therapeutic means of controlling body water and electrolytes. Their variety of effects necessitate, however, an adequate understanding of their actions and the status of the patient. It would appear best to prescribe the form of the resin that would most closely meet the needs of the individual, and to periodically determine the various blood constituents during therapy.

At present perhaps the most extensive use of these substances lies in permitting patients requiring salt restriction to ingest a more palatable diet than they could otherwise. The hydrogen and ammonium forms of the exchanger with additional dietary potassium appear to be most useful in patients with edema but with adequate renal function; *i.e.*, congestive heart failure, cirrhosis of the liver, and hypoproteinemia. In addition, *if sufficient potassium is supplied* they may counteract the salt retention, alkalosis and hypochloremia which occur during prolonged ACTH or cortisone therapy.

#### SUMMARY AND CONCLUSIONS

Some of the newer knowledge available concerning the effects, modes of action and clinical usefulness of the carboxylic cation exchange resins has been reviewed and evaluated. Limitations and possible dangers have been emphasized.

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