Cation Exchange Resin in the Treatment of Congestive Heart Failure

I. Electrolyte Exchanges during Initial Periods of Resin Therapy

By J. R. Elkinton, M.D., R. D. Squires, M.D., and W. C. Klingensmith, Jr., M.D.

Electrolyte balances were measured in four edematous cardiac patients receiving cation exchange resin. It was found that such therapy would increase the fecal loss of sodium and, in some of the cases, would result in the loss of edema which had been refractory to other forms of therapy. In these cases the main route of sodium excretion was through the kidneys and not through the intestinal tract. The resin appeared to potentiate the renal action of simultaneously administered mercurial diuretics.

In 1946 Dock\(^1\) first suggested the use of cation exchange resins for the removal of sodium from the intestinal tract of patients with edema. Since then a series of investigators\(^2\)\(^-\)\(^9\) have demonstrated that such substances will indeed increase the fecal excretion of sodium, and so may be useful in the treatment of edema associated with retention of sodium. On the basis of these studies at least three preparations of cation exchange resin* have been placed on the market by pharmaceutical manufacturers. However, relatively little information as yet is available in the medical literature for the practicing physician, concerning the mode of action, the indications, the contraindications, and the long term results of this therapeutic agent. It is the purpose of these two papers, therefore, to present, in the first, detailed data on the electrolyte exchanges which take place during the initial periods of treatment of edematous cardiacs with resin and, in the second, the clinical results and chemical complications in a large series of patients in whom resin has been an adjunct to therapy over prolonged periods of time.

Theory of Action

Cation exchange resins are extremely stable and insoluble high unit weight polymers. Those used in medicine are usually the phenol-formaldehyde, phenol-methylene or polystyrene types. Their molecular structure resembles that of a crystal lattice due to cross linkages consisting of either phenyl or methyl groups.\(^10\) Attached to this framework are the reactive substituents such as carboxylic or sulfonic groups. The capacity of the resin, or the quantity of ions with which it will exchange, is ultimately determined by the number of cross linkages and the number of reactive substituents per unit weight of resin.\(^11\)

When a resin is placed in a solvent, it tends to swell much the same as does dry gelatin. This facilitates diffusion of the ions to be exchanged throughout the molecular structure of the resin. The reactive substituents behave chemically as if they were a solution of weak acids, the pH of the solvent in which the exchange is taking place determines the extent of their ionization. Therefore, the resin can only


\(^2\) L. S. Public Health Service and the C. Mahlon Kline Fund of the Department of Medicine. The help of the laboratory staff and of the clinical staff of the Hospital is gratefully acknowledged.

\(^3\) J. R. E. is an Established Investigator of the American Heart Association.

\(^4\) R. D. S. is a Fellow in Medicine assigned to the Chemical Section.

\(^5\) W. C. K., Jr., is a Fellow in Medicine assigned to the Robinette Foundation.

\(^*\) Resodex, Smith Kline and French Co.; Natrinil, National Drug Co.; Carbo-Resin, Eli Lilly Co.
saturate its capacity at a pH which permits maximal dissociation of the reactive substituents. In addition, the rate of the reaction depends upon the concentration of the reacting ions. Particle size and adequate mixing are likewise important factors in determining the rate of the reactions as they determine the amount of surface area to be exposed for reaction.

Amberlite IRC-50 is a carboxylic resin and behaves chemically as a weak acid. It is said to have an in vitro capacity, under optimal conditions, of 10 mEq. of base per gram of resin. Maximum capacity for this resin obtains at a pH of 10 to 11. The range of variation of pH in the gut is unknown but it probably averages slightly on the alkaline side of a pH of 7. At pH 7 this resin has a capacity of 6.2 mEq. base per gram, rapidly dropping to 3.5 mEq. at pH 6.12 The time interval required for saturation at this pH is long and therefore the resin perhaps takes up only 2 to 3 mEq. per gram in a few hours it remains in the bowel.12 Sulfinic resins function as stronger acids and have a more rapid rate of exchange than the carboxylic resins. The optimum pH is 3.

The affinity the resin manifests toward various ions is peculiar to the resin being considered. However, generally speaking, it may be said that cationic exchange resins have a greater affinity for divalent ions, calcium and magnesium, than monovalent ions, sodium and potassium, and the affinity for potassium is greater than that for sodium. Carboxylic resins have a greater affinity for calcium and magnesium than do sulfinic resins.

Little is known about the variations in the total base concentration throughout the gut. Even less is known regarding the individual concentrations of the various cations comprising the total base. It would appear that the concentration of sodium is high enough to more than compensate for the greater affinity of the resin for potassium. The amount of sodium excreted in the feces is often equal to or greater than that of potassium. The amounts of these ions excreted in the stool per unit time are extremely variable. This variability may be accounted for to some extent by incomplete passage of a 24-hour stool. Much remains to be done in order to ascertain what environmental factors within the gut lumen are most favorable to ion exchange. The precise limits of the exchange capacity of a resin in vivo have yet to be determined. Such limits are probably determined by a variety of factors such as the amount of resin ingested, and its rate of movement through the gastrointestinal tract, variations in pH throughout the course of the bowel lumen, and the amount of sodium in the diet and the rate of exchanges of sodium across the intestinal mucosa.

Both cationic and anionic exchange resins are now in use in medicine. Amberlite IRC-50, a carboxylic resin, or one of its modifications, is the most commonly used (single) resin for cation exchange. It has been given to patients in either the hydrogen cycle or the ammonium cycle. The ammonium cycle resin partially converted to the potassium cycle has also been given. The rationale for giving such a preparation is based on the observation that at the pH of the gastric content the resin will be completely converted to the hydrogen cycle. This reaction free the potassium for absorption into the systemic circulation and thereby helps to compensate for the potassium taken up lower down in the gut.

The ammonium ion released from the resin is absorbed into the enterohepatic circulation and converted to urea by the liver. This reaction produces an acidifying effect similar to that produced by giving ammonium chloride. The base, including sodium, fixed to the insoluble portion of the resin at the higher pH of the small intestine, is excreted in the feces. Thus the amount of sodium absorbed is reduced, tending to produce a negative sodium balance.

Given a negative sodium balance induced by resin, the net effect on the body fluids of the patient will depend in addition upon the associated rates of excretion of water and electrolytes by the kidney. Removal of cation, or base, from the body should result in the renal excretion of water. The tendency to a disturbance in the acid-base equilibrium by the preferential removal of cations, is counterbalanced in the normal kidney by the excretion of a more acid urine containing increased amounts of chloride and ammonia. In patients with dis-
eased kidneys which are unable to produce ammonia, resin administration may lead to relative chloride retention, bicarbonate deficit, and, thus, a metabolic acidosis. Adequate renal function, therefore, is a prerequisite to the successful clinical use of cation exchange resin in edematous patients.

### Table 1.—Average Daily Intake and Output, and Total Period Balances of Electrolytes in Four Edematous Cardiacs Treated with Cation Exchange Resin

<table>
<thead>
<tr>
<th>Patient</th>
<th>Period</th>
<th>Daily therapy</th>
<th>Weight</th>
<th>Av. daily intake</th>
<th>Average daily output</th>
<th>Total period balance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Resin</td>
<td>Hg</td>
<td>NH₄Cl</td>
<td>Res</td>
<td>Gm.</td>
</tr>
<tr>
<td>G. B.</td>
<td>11/26</td>
<td>12/6</td>
<td>74.9</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>11/26-28</td>
<td>2</td>
<td>0</td>
<td>75.0</td>
<td>15</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>11/28-12/1</td>
<td>3</td>
<td>25*</td>
<td>75.9</td>
<td>18</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>12/1-12/7</td>
<td>6</td>
<td>37*</td>
<td>76.7</td>
<td>18</td>
<td>27</td>
</tr>
<tr>
<td></td>
<td>12/7-10</td>
<td>3</td>
<td>50*</td>
<td>75.7</td>
<td>30</td>
<td>26</td>
</tr>
<tr>
<td></td>
<td>12/10-16</td>
<td>6</td>
<td>50*</td>
<td>2</td>
<td>68.9</td>
<td>3</td>
</tr>
<tr>
<td>T. M., I</td>
<td>4/24</td>
<td>50</td>
<td>39.2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>4/24-5/4</td>
<td>10</td>
<td>50*</td>
<td>55.6</td>
<td>70</td>
<td>70</td>
</tr>
<tr>
<td></td>
<td>5/4-12</td>
<td>8</td>
<td>50*</td>
<td>56.5</td>
<td>70</td>
<td>70</td>
</tr>
<tr>
<td>H, 1951</td>
<td>2/6</td>
<td>61.6</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2/6-8</td>
<td>2</td>
<td>45*</td>
<td>62.7</td>
<td>70</td>
<td>70</td>
</tr>
<tr>
<td></td>
<td>2/8-10</td>
<td>2</td>
<td>45*</td>
<td>2</td>
<td>59.7</td>
<td>70</td>
</tr>
<tr>
<td>L. J.</td>
<td>11/24</td>
<td>67.5</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>11/24-27</td>
<td>3</td>
<td>2</td>
<td>67.3</td>
<td>60</td>
<td>54</td>
</tr>
<tr>
<td></td>
<td>11/27-30</td>
<td>3</td>
<td>2</td>
<td>68.8</td>
<td>116</td>
<td>57</td>
</tr>
<tr>
<td></td>
<td>11/30-12/3</td>
<td>3</td>
<td>2</td>
<td>70.2</td>
<td>60</td>
<td>57</td>
</tr>
<tr>
<td></td>
<td>12/3-6</td>
<td>3</td>
<td>45†</td>
<td>69.2</td>
<td>42</td>
<td>43</td>
</tr>
<tr>
<td>J. B.</td>
<td>5/25</td>
<td></td>
<td></td>
<td>64.2</td>
<td>48</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>5/25-28</td>
<td>3</td>
<td></td>
<td>64.2</td>
<td>48</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>5/28-6/1</td>
<td>4</td>
<td>50†</td>
<td>52</td>
<td>7</td>
<td>170</td>
</tr>
<tr>
<td></td>
<td>6/1-9</td>
<td>8</td>
<td>50†</td>
<td>2</td>
<td>62.1</td>
<td>46</td>
</tr>
</tbody>
</table>

* Ammonium cycle resin.
† Ammonium plus potassium cycle resin ("Resodec").
‡ Intake approximate.

Data are expressed per individual period rather than cumulatively.

**Experimental Material and Methods**

A carboxylic resin, Amberlite IRC-50, was administered in its ammonium form or in a combination of ammonium and potassium forms (Resodec) to four patients with congestive heart failure and peripheral edema. During the study in each patient, serum and blood were analyzed at the beginning and end of each period for electrolytes and urea nitrogen. Complete balances were measured daily of chloride, sodium, potassium, and nitrogen, in three of the patients; in one patient, the excreta were analyzed but the intake was only approximated. Sodium and potassium in serum and urine were determined by means of a Baray internal standard flame photometer, chloride in serum and urine by the methods of Eisenman and Harvey, respectively. Total carbon dioxide content was measured in serum by the method of Studie and Van Slyke, and nitrogen in urine and feces by macrokjeldahl technic. Representative aliquots of diet and whole stool specimens were digested with concentrated nitric acid and the diluted filtrate poured through the flame photometer for the determination of sodium and potassium. Balances were averaged for three- or two-day periods to eliminate from the results as far as possible the factor of variation in the daily rate of excretion of feces. The two-day periods were necessary in one of the patients, T. M., because of a colostomy irrigation every second day.

* Supplied through the courtesy of Smith, Kline and French Company of Philadelphia.
RESULTS

The results are presented in table 1 and in figures 1 to 4, inclusive.

Exchanges of Sodium and Water. The fecal excretion of sodium was increased in all four of the patients when resin was given (table 1); and in two of the patients (G. B. and T. M.), peripheral edema which previously had been intractable to treatment was eliminated (figs. 1 and 2). During the period when these two patients lost their edema, as much or more sodium was excreted in the urine as in the stools

Fig. 1. Resin therapy plus mercurial diuretic resulting in the partial elimination of edema previously refractory to mercurials alone (patient G. B.). During days 10 to 18 inclusive sodium was lost in the stools in amounts equal to or slightly in excess of the intake, but the largest portion of sodium was excreted in the urine.

(mercurial diuretics being administered simultaneously). On three occasions when mercurials failed to act on the kidneys, edema fluid was not eliminated, even though the resin resulted in the fecal loss of sodium in amounts equal to, or somewhat in excess of, the dietary intake of the ion (G. B., fig. 1, days 9–12; J. B., table 1, days 4–12). In only one period in one patient, T. M., in whom the fecal excretion of sodium appeared to be greatly in excess of the dietary intake (fig. 2, days 2–4), did the resin remove endogenous sodium (and in this patient feces were eliminated by colostomy irrigation).

Exchanges of Chloride. Chloride was essentially absent from all of the stools of three of the four patients (table 1). In patient T. M., who had the colostomy irrigations, chloride was present in the stools but in smaller amounts than sodium. However, the renal excretion of chloride exceeded that of sodium in all the periods of resin therapy in three patients, and in the last period of the other patient (G. B.) (table 1). The excess of chloride over sodium in the urine frequently was greater than the excess of sodium over chloride in the stools (fig. 3). Presumably the difference was due to the somewhat larger amount of chloride in the diets. The correlation between these two sets of values indicates in these patients an adequate renal response to the removal of sodium by resin through the intestinal tract.

Exchanges of Potassium. The fecal excretion of potassium was increased following the administration of resin in three of the patients studied (table 1, figs. 1, 2). In those patients in whom exact balances were measured, the fecal loss of potassium did not exceed the total in-
take of dietary potassium or of the ion administered as a salt (acetate) or in the resin (Resodec), that is, the potassium balance did not become negative.

**Effect on Serum Electrolyte Concentrations.**

The concentration of sodium in serum was already below normal limits in two patients and fell to slightly lower levels on resin therapy (G. B., T. M.). In one of these patients, T. M., the serum sodium concentration had returned to the upper limits of normal when the patient was studied again after 288 days of resin therapy (fig. 2). In the other two patients the serum concentration of sodium did not fall below the normal range. The serum concentration of potassium was likewise below the normal range in two of the patients before resin therapy was initiated, and in one of these, G. B., the serum potassium fell still further despite the administration of extra potassium acetate and a positive balance of the ion (fig. 1). In patient T. M., the only patient who was treated with ammonium resin without potassium in the resin or supplementing the diet, the serum potassium level fell below the normal range; at the end of 290 days of treatment with ammonium plus potassium resin most of the time, the serum concentration was again normal (fig. 2). The total carbon dioxide content of serum fell below the lower limit of normal (26 mEq. per liter) in two of the four patients on resin (fig. 2), and the chloride concentration rose.

**Fecal Excretion of Sodium and Potassium.**

In all but four periods, sodium in the stools exceeded potassium when the ammonium resin was given, the average daily fecal excretion of sodium being between 28 and 156 mEq. (fig. 4). This range of fecal excretion of sodium represents 0.56 to 3.12 mEq. per gram of resin administered. When ammonium plus potassium resin was given less sodium was lost: 4 to 37 mEq. per day (fig. 4) or 0.08 to 1.48 mEq. per gram of resin administered. On this combined form of resin the potassium in the stool exceeded the sodium. In only two periods, however, did the average daily fecal excretion of potassium exceed the amount administered with the resin (60 mEq.).

**Discussion**

These experiments indicate clearly that a carboxylic exchange resin, when ingested by patients with congestive heart failure, will remove sodium and potassium by way of the intestinal tract. They do not show, however, that the amount of sodium so removed will greatly exceed the sodium in the diet. Only in the pa-
tient whose fecal excretion was obtained by colostomy irrigation was there a significant removal of endogenous sodium. Even in this patient, T. M., as well as in patient G. B. (the two patients whose edema was eliminated following the inception of resin therapy), the major portion of the sodium excreted was excreted in the urine (figs. 1 and 2). Since both of these patients had been partially or completely refractory to treatment with mercurial diuretics and other measures prior to the resin,* it appears that in some way the administration of resin potentiated or activated the mercurial diuretics in these two patients. In the other two patients, L. J. and J. B., this did not occur, and these patients did not lose their edema even though resin was removing sodium from the intestinal tract. Resin may prevent the further accumulation of edema by preventing the absorption of dietary sodium, but it is probably a mistake to consider that it causes the elimination of edema by removing endogenous sodium through the intestinal tract.

The factors which control the uptake of sodium by resin in the intestinal tract need further elucidation. One factor is the form or cycle of the resin which is employed. No evidence has yet been presented of a greater efficiency in sodium removal of hydrogen versus ammonium cycle resin. Our studies indicate that the inclusion of potassium cycle with ammonium cycle resin reduces the amount of sodium which is withdrawn. Another factor, however, is the amount of sodium ingested. Less sodium is taken up by the resin on lower sodium intakes.17 But increase in the sodium intake quickly overtaxes the capacity of the resin to remove it, as shown by the inability of cardiae on the resin to take more than 2 to 4 Gm. of sodium chloride without the accumulation of edema.18 Considering the large turnover of sodium in the intestinal fluids, it is surprising that more exogenous and endogenous sodium is not taken up. There must be much to learn concerning the effect of alterations in visceral circulatory dynamics on intestinal fluid exchanges. Endocrine factors must also be considered. The demonstration of a reduction in fecal sodium removal by resin following the injection of desoxycorticosterone19 suggests strongly that the cells of the intestinal mucosa may be analogous in some ways to those of the renal tubule.

Another of the unsolved problems is how the ingestion of cation exchange resin may potentiate the action on the kidneys of a mercurial diuretic. An obvious possibility is that a chloride acidosis is produced similar to that resulting from ammonium chloride administration. The difficulties with this hypothesis in explaining the reactions in these particular patients are several. In patients G. B. and T. M. ammonium chloride given prior to the resin did not potentiate the mercurials, and in patient L. J. much less sodium was excreted by the kidneys when resin was given with mercurials than when ammonium chloride was given with mercurials. This was true despite the fact that the serum carbon dioxide content was at its lowest level after the resin rather than after the ammonium chloride. While these studies are not extensive enough to be definitive on this point, they do suggest that other factors enter into the interactions of these two therapeutic agents.

**Summary and Conclusions**

Electrolyte exchanges were studied in four patients with edema due to congestive heart failure during the administration of cation exchange resin, with the following results:

1. The fecal excretion of sodium and potassium was increased.

2. The pure ammonium resin removed more sodium than the ammonium plus potassium resin.

3. In most periods, the excess of sodium over chloride in the stools was more than equalled by the excess of chloride over sodium in the urine.

4. Except in the patient with the irrigated colostomy, the fecal excretion of sodium did not greatly exceed the dietary intake of the ion.

5. In two of the four patients who were previously refractory to treatment, most or all of their edema was eliminated.

6. The major portion of sodium lost in these

---

* Previous unsuccessful attempts to treat the hyponatremic edematous state of patient G. B. have been described elsewhere.20.
two patients was excreted through the kidneys with the concomitant administration of mercurial diuretics.

It is concluded that carboxylic cation exchange resin, given to patients with congestive heart failure, (1) will prevent the absorption of some sodium from the intestinal tract and so promote a negative balance of the ion, and (2) may be a useful adjunct in the treatment of refractory cases by potentiating or initiating the action on the kidneys of mercurial diuretics. The mechanisms and conditions for such potentiation are at present unknown.

REFERENCES


Cation Exchange Resin in the Treatment of Congestive Heart Failure: I. Electrolyte
Exchanges during Initial Periods of Resin Therapy
J. R. ELKINTON, R. D. SQUIRES and W. C. KLINENSMITH, JR.

Circulation. 1952;5:747-753
doi: 10.1161/01.CIR.5.5.747
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1952 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on
the World Wide Web at:
http://circ.ahajournals.org/content/5/5/747