Cation Exchange Resin in the Treatment of Congestive Heart Failure

II. Clinical Effectiveness and Chemical Complications during Prolonged Periods of Use

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

Thirty-four edematous cardiac patients who were being treated with cation exchange resin were studied for its long term effectiveness and for clinical and chemical complications. In 23 of 27 patients the resin was effective in terms of mobilizing edema fluid previously refractory to other forms of treatment, of partial or complete substitution for mercurial diuretics, and of permitting a slight increase in the salt content of the diet. Gastrointestinal intolerance was the chief clinical complication but prevented therapy in only five patients. Chemical complications of sodium depletion, potassium depletion or excess, and severe chloride acidosis were not seen.

In the preceding paper data were presented concerning some of the electrolyte exchanges which result from the use of cation exchange resin in edematous cardiac patients. It was shown that resin will increase the fecal excretion of sodium and potassium, and that in certain patients, previously refractory to treatment with mercurial diuretics, the addition of resin therapy appeared to cause the elimination of their edema. This loss of edema resulted from increased urinary as well as fecal excretion of sodium. These studies, however, gave no information concerning the clinical effectiveness of the administration of resin to such patients over a prolonged period of time, or of the possible complications of such therapy during its long-term use. It is the purpose of this paper to supply such information.

Experimental Material

Observations were made on a total of 34 patients with peripheral edema due to congestive heart failure. The etiologies of the heart disease in these patients were as follows: chronic rheumatic disease, 15; hypertension, 10; arteriosclerosis, 7; and syphilis, 2. In 27 of these patients resin therapy was continued long enough to evaluate its long-term effectiveness, the maximum period of treatment being 62 weeks and the average period being 26.4 weeks. The remaining seven patients of the total series are included in order to give a fair picture of patient tolerance to the preparation.

The 27 patients in whom long-term therapy with resin was evaluated are placed in three classifications for purposes of analysis. Class I is made up of 16 patients in whom congestive heart failure persisted despite intensive treatment by standard methods. These methods included digitalization, sodium deprivation (below 500 mg. daily in most cases), frequent administration of mercurial diuretics, and restricted activity including a period of bed rest in the hospital during the initial period of study. Class II consisted of five patients who had been maintained in an edema-free state on an 800 to 2000 mg. sodium diet by the administration of digitalis and mercurial diuretics. Class III included six edematous patients who were on digitalis but who were unable to take mercurial diuretics due to sensitivity to the drug. Besides the 27 patients included in these three classes, seven patients are tabulated as class IV who were unable to tolerate the resin over a prolonged period or who were not followed closely enough to permit adequate evaluation.
METHOD OF STUDY

Cation exchange resin was administered to these patients as a mixture of ammonium and potassium forms in a 3:1 ratio.* In all but a few patients the daily dosage was 45 Gm. divided into three equal parts. The resin was suspended in a liquid vehicle of the patient's choice and was taken just before, during, or just after meals as preferred. The potential hazard of calcium depletion was met by adding calcium in the form of three glasses of whole or dialyzed milk per day, or 3 Gm. of calcium gluconate (in one patient who was unable to tolerate milk). A mixed vitamin preparation was added because of the possibility of vitamin depletion.

Except for occasional periods of hospitalization, these patients were studied in the outpatient clinic. Positive results are therefore more significant than negative results although every effort was made to ascertain whether or not the patient was following the prescribed regimen. The clinical effectiveness of the resin therapy was assessed as effective, equivocal, or ineffective in a qualitative manner as follows. Resin therapy in patients in class I (edematous despite all other therapy) was judged to be effective if its addition to the other therapeutic agents resulted in a diminution of the edema. In class II (patients maintained in an edema-free state by digitalis and mercurials) the resin was considered to be effective if it was successfully substituted in part or in whole for the mercurial diuretics. In both classes I and II an increase in the salt content of the diet without concomitant fluid retention was taken into account in judging effectiveness of the resin. In class III (patients with edema and with sensitivity to mercurials) the resin was judged to be effective if the edema diminished.

Clinical complications were watched for and recorded. Chemical complications were assessed primarily in terms of changes in concentrations in serum and whole blood of electrolytes and urea nitrogen, respectively;† In the early stages of the study, serum concentration of sodium, potassium, chloride, and total carbon dioxide content were determined every one or two weeks. In the later stages these determinations were made at somewhat longer intervals. The serum calcium concentration was determined periodically in some of the patients.

* The resin mixture given to these patients was a carboxylic resin in the ammonium and potassium cycle in the ratio of 3:1, each 45 Gm. containing approximately 60 meq. of potassium. It is marketed under the trade name Resodec, and was supplied for this study through the courtesy of Smith, Kline, and French Company, of Philadelphia.

† The chemical methods used are the same as in the preceding paper.1

RESULTS

The results are presented in tables 1 and 2 and in figures 1 to 3.

Clinical Effectiveness

The effectiveness of the resin therapy in the 27 patients in classes I to III is summarized in table 1. In class I the treatment was considered effective in 13 patients, equivocal in two, and probably ineffective in one. In the effective group the introduction of resin into the therapeutic regimen was followed by a loss of edema, and later by reduction in mercurial dosage. In most of the cases it was also possible to discontinue the severe dietary restriction of sodium and to allow the use of a more easily prepared “low salt” diet containing an estimated 800 to 1600 mg. of sodium per day. The clinical course of one of the patients typical of this group is shown in figure 1. Of the patients rated as showing an equivocal response to resin, one had an encouraging early response to

Table 1.—Clinical Effectiveness and Duration of Resin Therapy

<table>
<thead>
<tr>
<th>Class</th>
<th>I</th>
<th>II</th>
<th>III</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Effectiveness</td>
<td>13</td>
<td>5</td>
<td>5</td>
<td>23</td>
</tr>
<tr>
<td>Equivocal</td>
<td>2</td>
<td>1</td>
<td></td>
<td>3</td>
</tr>
<tr>
<td>Ineffective</td>
<td>1</td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>16</td>
<td>5</td>
<td>6</td>
<td>27</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Duration of Therapy</th>
<th>Minimum, weeks</th>
<th>2</th>
<th>15</th>
<th>5</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximum, weeks</td>
<td>39</td>
<td>62</td>
<td>36</td>
<td>62</td>
<td></td>
</tr>
<tr>
<td>Average, weeks</td>
<td>20.5</td>
<td>43.2</td>
<td>28.2</td>
<td>26.4</td>
<td></td>
</tr>
</tbody>
</table>

Table 2.—Clinical Complications*

<table>
<thead>
<tr>
<th>Condition</th>
<th>Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constipation</td>
<td>7</td>
</tr>
<tr>
<td>Hemorrhoidal bleeding</td>
<td>2</td>
</tr>
<tr>
<td>Abdominal cramps and/or diarrhea</td>
<td>6</td>
</tr>
<tr>
<td>Anorexia or nausea without vomiting</td>
<td>9</td>
</tr>
<tr>
<td>Vomiting</td>
<td>2</td>
</tr>
<tr>
<td>Muscle cramps</td>
<td>2</td>
</tr>
</tbody>
</table>

* Twenty of the 34 patients in classes I to IV had these complaints. Resin therapy was interfered with in 11, and permanently discontinued in 5 patients.
the resin but was forced to discontinue it because of gastrointestinal intolerance; the other improved symptomatically but required the same amount of mercurial diuretic and sodium restriction as before resin therapy. The one patient classed as ineffective developed gastrointestinal intolerance, stopped the resin, and died shortly afterward of progressive cardiac failure.

In class II (patients maintained in a compensated state by digitalis and mercurial diuretics) the resin was considered effective in all five patients in terms of completely or partially replacing the mercurials. Three of these patients have been followed for more than a year on resin and have required only infrequent doses of mercurial diuretics. In the two patients followed for somewhat shorter periods the resin appeared to be a completely adequate substitute for the mercurials. In one of the patients in this class repeated attempts were made to increase the dietary intake of salt from approximately 800 mg. of sodium to approximately 2400 mg. of sodium per day; each time the accumulation of edema fluid promptly occurred.

In class III (edematous patients who were sensitive to mercurials) the resin was effective in five patients and equivocal in one patient. The results were dramatic in one anasarca patient who lost 21 Kg. of weight in one month. The case classified as equivocal was the patient in whom therapy was finally discontinued because of gastrointestinal intolerance and who was suspected of failing to take the recommended dosage of resin.

Of the 27 patients in classes I, II and III treated for an average period of 26.4 weeks, the resin appeared to be effective as an adjunct to, or partial substitute for, other therapy in 23 patients.

Clinical Complications

The clinical complications in the 34 patients in classes I through IV are summarized in table 2.

Gastrointestinal intolerance was the principal type of complication. Increase in the size and firmness of the stool was noted by almost all the patients. Constipation causing a complaint on the part of the patient was observed in only seven cases. Hemorrhoidal bleeding occurred in two patients and was of sufficient severity in one of these to require temporary discontinuation of the therapy. Abdominal cramps with or without diarrhea were noted.
in six patients and were sufficiently severe to necessitate discontinuation of therapy permanently in two, and temporarily in three patients. Anorexia or nausea without vomiting were observed in nine patients and in two of these were sufficiently severe to stop the therapy. Two patients vomited the resin when initially administered and so could not be treated.

Muscle cramps occurred occasionally in two patients; one of these had had more severe cramps following mercurial diuretics.

Thus, of the total group of 34 patients, 20 displayed one or more undesirable effects of resin therapy. Such therapy was interfered with in 11, and permanently discontinued in five patients.

Chemical Complications

From the observations reported in the preceding paper and by other investigators as well, certain untoward biochemical effects might be anticipated from the prolonged use of cation exchange resins. Data bearing on the incidence of such complications are presented as follows.

Sodium depletion with concomitant peripheral vascular collapse and renal failure was looked for as a possible result of overtreatment with resin. Since this condition in cardiac patients, commonly called the "low salt syndrome," is usually accompanied by hyponatremia, the cardinal chemical index was the serum concentration of sodium. In figure 2 the distribution of 101 determinations of this value obtained during resin therapy in 23 patients is compared with that of 23 determinations in 18 of the same patients before resin therapy as well as with the distribution of such determinations in 21 normal subjects. The mean level of serum sodium before resin therapy was clearly lower than that of the normal group, which is in agreement with the observation made in a previous series of edematous cardiac patients receiving mercurial diuretics. On resin therapy, however, the mean serum level of sodium was higher, not lower, than before therapy, and only four values were 130 mEq.

![Distribution curves of the serum concentrations of sodium and potassium in edematous cardiares before and during resin therapy. The distribution of levels in 21 normal subjects is shown at the top of the figure; the dotted lines represent 2 standard deviations from the mean of the normal group. The mean concentration of sodium is higher and that of potassium lower in the cardiares during resin therapy than before such therapy.](http://circ.ahajournals.org/lookup/fig/00001035)
per liter or below. The small proportion of determinations in this range, which is associated with the "low-salt syndrome," the virtual absence of severe azotemia (see below), and the failure to observe clinical signs and symptoms of peripheral vascular collapse are strong evidence that sodium depletion was not a serious complication in this series of patients.

Potassium deficit and excess are possible complications in view of the known capacity of the ammonium cycle resin to remove potas-
mium and because of the addition of the potassium form of resin to patients with potential renal failure. These two abnormalities in total body potassium are usually mirrored in the serum level of the ion. In figure 2 the distribution of 98 determinations of this value in 23 of the patients during resin therapy is compared with that of 21 determinations in the same patients before resin therapy and with the distribution in 21 normal subjects. On resin the mean value for the whole group of deter-

Chloride acidosis has been reported as a serious complication of the administration of ammonium or hydrogen cycle exchange resins. In figure 3 are presented the distributions of 86 determinations of the serum concentration of chloride and 88 determinations of the total content in serum of carbon dioxide in 22 pa-
tients on resin therapy. These distribution curves are compared with the distribution of such values in most of the patients before resin therapy, as well as with those of a group.
of normal subjects. In the edematous cardiaxes before resin therapy, the serum chloride concentrations tended to be low and the total carbon dioxide contents both low, normal, and high (as previously reported\(^2\)). On resin the mean chloride value rose and that of the carbon dioxide perhaps fell slightly. The concomitant administration of ammonium chloride was not strictly associated with the highest chloride and lowest carbon dioxide levels. Since only one chloride value was above 110 mEq. per liter and one carbon dioxide value below 15 mEq. per liter, chloride acidosis in terms of these measurements was not a serious or frequent complication. pH values were not determined. In none of this group was there any clinical evidence of acidosis.

Renal failure, assessed in terms of marked azotemia, was present in only one patient in this series. This patient had intrinsic renal disease of a severe degree (blood urea nitrogen of 50 mg. per 100 ml.) before resin therapy was instituted; on resin the carbon dioxide content fell to 13.5 mEq. per liter (fig. 3). Following discontinuation of his resin therapy, the acidosis responded to treatment with sodium bicarbonate but the azotemia progressed until death two weeks later. In three other patients, one of whom had a normal control value, the blood urea nitrogen increased slightly. In six of eight patients with a mild degree of azotemia before resin, the azotemia decreased during therapy. Thus, despite the report of the production of urinary casts by resin,\(^7\) renal failure was not a direct complication of resin therapy in our series.

Calcium depletion was a possible complication since ammonium cycle resin is known to take up this divalent cation preferentially in vitro. Serum concentrations of calcium were determined 30 times in 12 patients during therapy. No values were found below 9.0 mg. per 100 ml. Although the maintenance of a normal serum level does not rule out a slow depletion of the calcium stores of the body, it does suggest that such did not occur to a serious extent. There was no evidence of tetany. X-ray studies for decalcification were not made.

**Discussion**

The results obtained in this study indicate clearly that the administration of cation exchange resin is a useful adjunct in the treatment of patients with congestive heart failure. It appears to be helpful in the control of such edema over prolonged periods of time as well as in the treatment of edema which has become refractory to other forms of therapy.\(^1\) The term "adjunct" is used advisedly, since the use of resin did not remove the necessity of employing other accepted methods of treatment. Digitalis preparations were administered to all of the patients in the usual doses, and physical activity was restricted. The resin, therefore, modified the previous therapeutic regimen in two ways: (1) the partial or complete elimination of mercurial diuretics, and (2) an increase in the salt content of the diet.

Mercurial diuretics have been such an extremely useful tool in the treatment of cardiac edema that they are unlikely to be supplanted by exchange resins. However, mercurial therapy has its limitations. Some patients are sensitive to these drugs. Some patients become refractory to the diuretic action of mercurials, and in some a "low salt syndrome," characterized by peripheral vascular collapse and progressive renal failure, may ensue.\(^4\) For these reasons cation exchange resin may be a useful adjunct in potentiating the action of mercury in refractory patients,\(^2\) in reducing the number of doses, or in eliminating entirely the necessity for the drug.

Resin therapy in edematous patients was originally introduced with the thought that it would obviate the necessity for an unpalatable salt-free diet. The evidence of other investigators, as well as of our own, supports this concept within certain limits. Resin appears to take up primarily exogenous or dietary sodium, but the degree to which it does so is limited. Thus, in the group of patients reported here it was usually possible during resin therapy to change from a "salt-free" diet (less than 500 mg. of sodium) to a "low-salt" diet (800 to 1600 mg. of sodium). This latter diet contains 35 to 70 mEq. of sodium, an amount which somewhat exceeds the daily fecal sodium excre-
tion observed in patients on ammonium plus potassium resin (Resodex) but which lies within the range of 40 to 90 mEq. of sodium in stools excreted by the usual route by patients receiving ammonium cycle resin.1 When the dietary intake of sodium was increased above this range (2000 to 2400 mg. of sodium or 85 to 100 mEq. of sodium) edema fluid began to reaccumulate. Resin, therefore, does not give a carte blanche for adding salt to the diet. However, the difficulty in preparation of a 500 mg. sodium diet as compared to an 800 to 1600 mg. sodium diet is such that there is a very real advantage in the use of resin on this score.

Against these advantages certain disadvantages must be weighed. One of these is the present high cost of the drug. However, this disadvantage soon may be minimized as a result of improved methods of production and commercial competition. More serious is the problem of gastrointestinal intolerance, the incidence of which was high in this group of patients. Anorexia and nausea may be controlled in the majority of instances by a trial and error attempt at finding the most suitable liquid in which to suspend the resin for administration. In addition, reactions of this type frequently were minimized by permitting the patient to take the resin suspension in small sips during meals, and by guarding against settling of the resin towards the bottom of the suspension. Constipation was a common complication in the series but was usually controlled by the use of mineral oil and a mild laxative. Abdominal cramps and diarrhea were more difficult to treat and sometimes necessitated a period of rest from the resin administration. These difficulties encountered in resin therapy indicate the need for improvement of the agent along lines of increased palatability and increased effectiveness in cation exchange permitting the use of smaller doses of resin. Nevertheless, most of our patients found that the advantages of the resin outweighed the difficulties and were willing to continue the therapy.

The data reported on this series of patients are reassuring in regard to the potential biochemical hazards of the use of cation exchange resins over a prolonged period of time. The occurrence of sodium depletion with peripheral vascular collapse and renal failure has been reported to occur following the use of such resins.8-9 In our series these complications were not observed; this inclines us to the belief that, properly guarded against, such complications are not a common danger. Potassium depletion was reported early in the experimental use of ammonium cycle resin10 and was the reason for adding potassium cycle resin to the ammonium form for ordinary therapeutic use. While carboxylic resin combined in these two cycles is less effective in removing sodium than the ammonium cycle resin alone,1 it does appear not only to have been clinically effective in controlling edema but also to have prevented the development of a serious degree of potassium depletion during prolonged use. On the other hand, another complication was anticipated from the addition of the potassium cycle resin to the regimen, namely, potassium retention and intoxication. Such intoxication is usually the result of renal insufficiency11 and might be anticipated in a group of edematous cardiace whose renal function is generally less than optimum. Nevertheless, in our group of patients this complication was not encountered, its absence probably being due to the usual avoidance of patients with any marked degree of renal failure.

The production of a severe degree of chloride acidosis has been considered to be one of the principal hazards of the use of cation exchange resins,9,13 and has been the reason for the combination of an anion exchanger with the cation exchange resin.14 Such a complication does occur readily in patients with a severe degree of renal disease,15 but did not occur in our group of edematous cardiac patients. In wisely selected patients, therefore, fear of such a complication should not deter the physician from the use of ammonium or hydrogen plus potassium cycle resins. The employment of a combination of anion and cation exchange resins may well have a place in treating edematous patients with advanced renal failure, but such combinations may be less effective in treating edematous cardiac patients without renal failure. The presence of a mild acidosis
has long been known to predispose toward a diuresis, and the data in the preceding paper suggest that it may be one factor in the potentiation by resin of the renal effect of mercurial diuretics.1

Evidence of calcium depletion was not found in this series although the resin has been shown to have a preferential affinity for divalent cations in vitro. In vivo balance studies have indicated that large amounts of calcium are not lost with ammonium and hydrogen cycle resins,16 presumably because of the low concentration of dissolved calcium in comparison with that of sodium in gastrointestinal fluids. The data on this point in this paper, however, are indirect since serum levels may not mirror a calcium depletion and since the patients were maintained on a fairly high calcium intake.

The possibility of the production of other deficiencies, such as magnesium, iron, thiamine, and riboflavin, has been suggested,13 14 but we saw no evidence of this. However, until we are sure they do not occur, supplementary minerals and vitamins should be added during prolonged resin therapy.

Cation exchange resins have given the physician a new tool with which to remove from the body certain constituents which are undesirable. The observations reported in this paper indicate to the authors that such resins have a useful role in the therapy of chronic congestive heart failure but that they must be used with care and with due consideration of their limitations. Like any other manipulation of a biochemical and physiologic disturbance due to a disease state, resin therapy of the edematous cardiac requires careful thought concerning the individual patient. But used in this way, and not as an infallible panacea, it should develop into a dependable item of the physician's armamentarium.

SUMMARY AND CONCLUSIONS

Cation exchange resin, in the ammonium plus potassium cycle, was administered to 34 patients with edema due to chronic congestive heart failure. In 27 of these patients the treatment was sufficiently documented to permit assessment of its long-term effectiveness, the average length of therapy being 26.4 weeks and the maximum being 62 weeks. The results were as follows:

1. In terms of elimination of edema in previously refractory patients or of prevention of reaccumulation of edema during a decrease in mercurial diuretic and salt restriction therapy, the resin was effective in 23 of the 27 patients.

2. Gastrointestinal complications occurred in 20 of the 34 patients but required the discontinuance of the resin in only five patients.

3. No evidence of the following chemical complications were observed: sodium depletion, potassium depletion or intoxication, severe chloride acidosis or calcium depletion.

It is concluded that, with the careful selection of patients, cation exchange resin in this form is a useful and safe adjunct to the treatment of chronic congestive failure over prolonged periods of time.

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